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Hypervalent Iodine(III) Mediated Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles through Intramolecular Oxidative S−N Bond Formation

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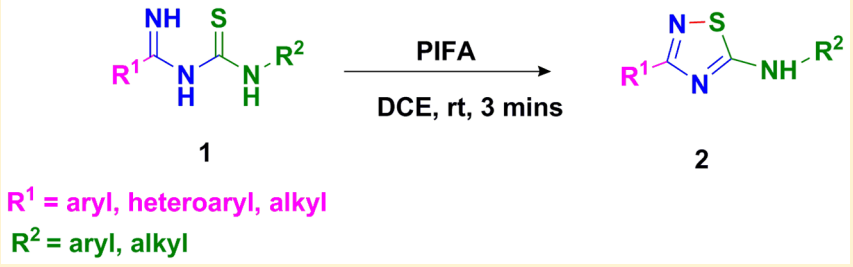
Supporting Information



ABSTRACT: An efficient synthesis of 3-substituted-5-arylamino-1,2,4-thiadiazoles through intramolecular oxidative S−N bond formation of imidoyl thioureas by phenyliodine(III) bis(trifluoroacetate) is reported. The protocol features a metal-free approach, broad substrate scope, very short reaction times, good to excellent yields, and simple starting materials.

INTRODUCTION

Efficient and convenient procedures for the synthesis of heterocycles through heteroatom−heteroatom bond (N−X bond (X = N, O, S)) formation are still in high demand, as only limited examples are available in the literature for N−X[1−3] bond formation in comparison to C−C and C−X bond formation processes. The available metal-catalyzed protocols for N−X bond formation have their own disadvantages, the metal contamination in the desired product and harsh reaction conditions being the main limitations.[4] Some metal-free approaches[1d,5] have been developed for N−X bond formation, in which hypervalent iodine(III) reagents have turned out to be good candidates owing to their environmentally benign nature, low cost, and strong oxidizing power.[6] Hypervalent iodine(III) reagents have been employed in the construction of C−C,[7] C−X,[8] and N−X[1a,b,9−11] (X = N, O, S) bond formation protocols. A careful literature survey reveals that only very few reports describe the synthesis of heterocycles through S−N bond formation using iodine(III) reagents.[11]

1,2,4-Thiadiazole is an important heterocyclic core with a broad spectrum of applications as a pharmacophore, and its derivatives serve as pesticides and corrosion inhibitors.[12] In particular, the substituted 1,2,4-thiadiazoles have been reported to have a wide spectrum of biological activity, including antibacterial,[13] anti-inflammatory,[14] antiulcerative,[15] antirheumatic,[16] and antidiabetic.[17] In view of this importance, numerous methodologies have been developed to construct this skeleton. Among them, the simple oxidative dimerization of thio amides using various oxidants is very common.[18] Smith et al. reported the synthesis of 1,2,4-thiadiazoles by thermolysis of N^3-thiocarbamoylamidrazone ylides.[19] Dürüst et al. reported a cyclocondensation reaction of amidoximes with N-substituted thioureas in the presence of KF/Al_2O_3, but the reaction required more time even at reflux temperature.[20] Wehn et al. reported the synthesis of 3-amino-1,2,4-thiadiazoles via a palladium-catalyzed Suzuki−Miyaura coupling reaction.[21] Many approaches have been reported to construct the 1,2,4-thiadiazole skeleton from imidoyl thioureas.[22−26] Kurzer and Tertiak have employed hydrogen peroxide to prepare 3-alkyl(or aryl)-5-alkyl(or aryl)-amino-1,2,4-thiadiazoles from imidoyl thioureas.[27] Kim et al. developed a copper catalyzed synthesis of 3-substituted-5-amino-1,2,4-thiadiazoles through intramolecular oxidative cyclization.[28] In a continuation of our efforts on the development of useful synthetic methodologies for the construction of heterocycles through mild and eco-friendly protocols using hypervalent iodine(III) reagents,[29] we present an efficient and mild approach for the synthesis of 3-substituted 5-arylamino-1,2,4-thiadiazoles in a very short reaction time at room temperature.

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RESULTS AND DISCUSSION

We initially tested the hypervalent iodine(III) reagent phenyliodine(III) diacetate (PIDA) for the oxidative cyclization of imidoyl thiourea **1a**, which has been obtained by the reaction of amidine and phenyl isothiocyanate. To our delight, the reaction was complete in 5 min, yielding the expected product **2** (Scheme 1) in 70% yield in THF (Table 1, entry 1). Encouraged by this result, we studied this conversion with different hypervalent iodine reagents such as 2-iodoxybenzoic acid, Dess–Martin periodinane, and phenyliodine(III) bis(trifluoroacetate) (Table 1, entries 2–4). We also employed other oxidants such as ceric ammonium nitrate, DDQ, potassium perdisulfate, and oxone. The yields were good with oxone and DDQ (Table 1, entries 5 and 8) but relatively poor with ceric ammonium nitrate and potassium perdisulfate (Table 1, entries 6 and 7). Among all the oxidants investigated, PIFA was found to be the best choice (Table 1, entry 4), though the yield was equally good with DMP (Table 1, entry 2). Increasing the oxidant amount had a negative impact on the reaction (Table 1, entry 9), resulting in a decreased yield of the product. Though the yield was relatively good with all polar solvents (Table 1, entries 10, 11, 13, and 15), the best solvent identified was dichloroethane (Table 1, entry 12). With the optimized reaction conditions in hand, we explored the substrate scope of the reaction. The reaction proceeded well with substrates having both electron-withdrawing as well as electron-donating groups in the aryl rings. Subsequently, we varied the amidine part with heteroaryl rings as well, resulting in good yields of **2**. A library of synthesized compounds is given in Table 2. The structures of products **2** were unambiguously assigned by spectral and analytical data, and that of **2f** was confirmed by single-crystal X-ray analysis (see the Supporting Information).[30]

Scheme 1. Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles

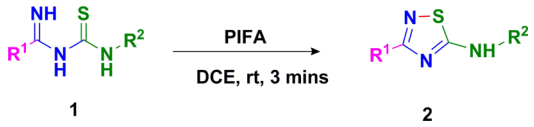

Table 1. Optimisation of Reaction Conditions[a]

entry	oxidant	solvent[b]	time (min)	yield (%)[c]
1	PIDA	THF	5	70
2	DMP	THF	3	76
3	IBX	THF	5	73
4	PIFA	THF	3	80
5	oxone	THF	5	68
6	CAN	THF	5	38
7	$K_2S_2O_8$	THF	3	47
8	DDQ	THF	5	60
9	PIFA[d]	THF	3	62
10	PIFA	DMF	3	65
11	PIFA	MeOH	3	70
12	**PIFA**	**DCE**	**3**	**83**
13	PIFA	MeCN	3	73
14	PIFA	1,4-dioxane	3	46
15	PIFA	TFA	3	66

[a]Reaction conditions unless specified otherwise: reactant **1** (1.0 mmol), oxidant **2** (1.1 mmol), solvent (3 mL), stirred at room temperature for 3–5 min. [b]Abbreviations used in the table: PIDA = phenyliodine(III) diacetate; DMP = Dess–Martin periodinane; IBX = 2-iodoxybenzoic acid; PIFA = phenyliodine(III) bis(trifluoroacetate); CAN = ceric ammonium nitrate; DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DCE = 1,2-dichloroethane; THF = tetrahydrofuran; MeCN = acetonitrile; DMF = *N*,*N*-dimethylformamide; TFA = trifluoroacetic acid. [c]Isolated yield. [d]Oxidant **2** (2.2 mmol).

The scalability of the reaction has been tested with three compounds (Scheme 2), and the results are encouraging.

An attempt to carry out this oxidative cyclization in a one-pot fashion by allowing amidine **3** to react with phenyl isothiocyanate **4** followed by the addition of the hypervalent iodine(III) reagent in the same reaction vessel did not affect the yield significantly (Scheme 3). Under the optimized reaction conditions, when the control experiments were carried out with radical scavengers such as TEMPO (2,2,6,6-tetramethylpiperdine-1-oxide) and hydroquinone, no considerable effect was observed, ruling out a radical mechanism and favoring the ionic mechanism (Scheme 4).

On the basis of this study and a previous literature report,[1c] a mechanism has been proposed for the formation of **2**, as depicted in Scheme 5. The imidoyl thiourea reacts with PIFA to form the intermediate **A**, followed by nucleophilic attack on the sulfur atom by the NH group with the removal of trifluoroacetic acid and iodobenzene resulting in the required product **2**.

CONCLUSION

In summary, we have developed an efficient protocol for the synthesis of 3-substituted 5-amino-1,2,4-thiadiazoles through intramolecular oxidative S–N bond formation by the hypervalent iodine(III) reagent PIFA.

EXPERIMENTAL SECTION

General Methods. All solvents were purchased from commercial sources and used without further purification. The melting points were measured in open capillary tubes and are uncorrected. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 300 MHz spectrometer in $CDCl_3$ and DMSO;d_6 using TMS as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), sept (septet), m (multiplet), bs (broad singlet), bd (broad doublet). ^{13}C NMR spectra were routinely run with broad-band decoupling. Precoated silica gel on aluminum plates was used for TLC analysis with a mixture of petroleum ether (60–80 °C) and ethyl acetate as eluent. Elemental analyses were performed on an Elemental CHNS analyzer.

Synthesis of *N*-(Pyridin-2-yl)benzo[*d*]thiazol-2-amines 2a–z: General Procedure. A mixture of *N*-(phenylcarbamothioyl)-benzimidamide (**1a**; 255 mg, 1.0 mmol) and $PhI(OCOCF_3)_2$ (430 mg, 1.1 mmol) was placed in a 10 mL round-bottom flask in 1,2-dichloroethane (3 mL), and the mixture was stirred at room temperature for 3 min. The completion of the reaction was monitored by TLC. After the completion of the reaction, the solvent was removed. Then the reaction mass was washed with sodium bicarbonate solution and extracted with dichloromethane (three times). After the extract was dried over sodium sulfate, dichloromethane was removed under vacuum. The crude product

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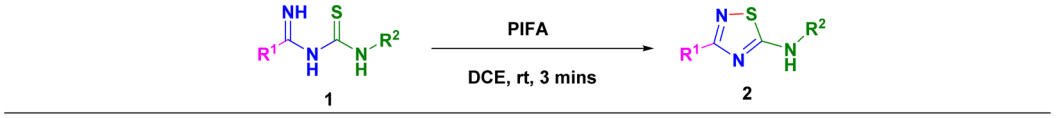
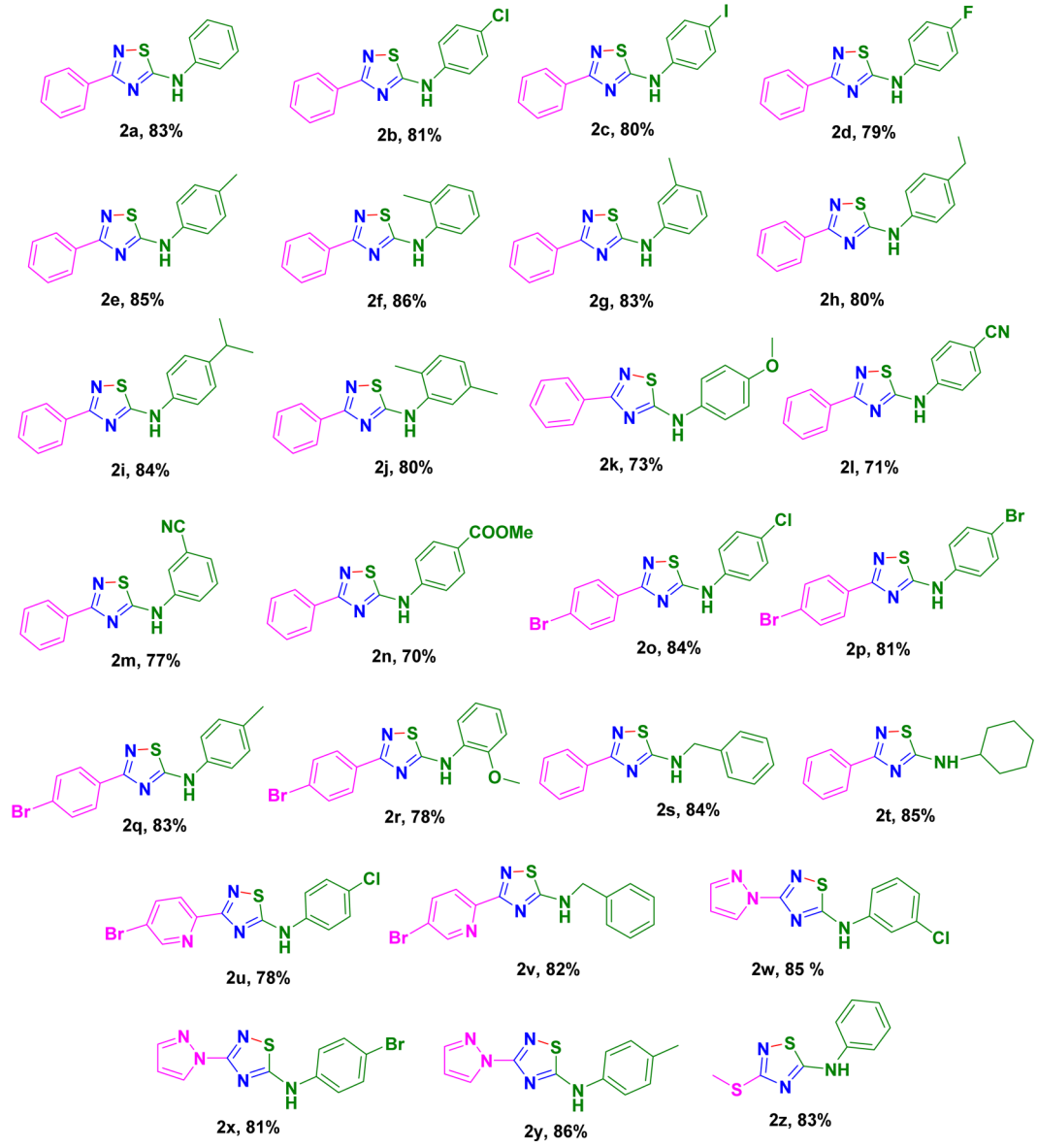
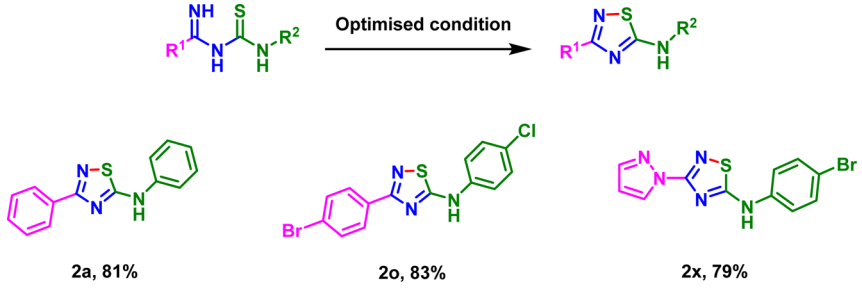
Table 2. Synthesised Compounds 2a–z





Scheme 2. Gram-Scale Synthesis



was purified by column chromatography using petroleum ether/ethyl acetate (70/30) as the eluent to afford compound **2a**.

Characterization data for compounds (2a–2z). *N,3-Diphenyl-1,2,4-thiadiazol-5-amine (**2a**):*[28] isolated as a white solid (210 mg, 83%); mp 170–173 °C; IR (KBr) ν 3231, 2967, 1602, 1566,

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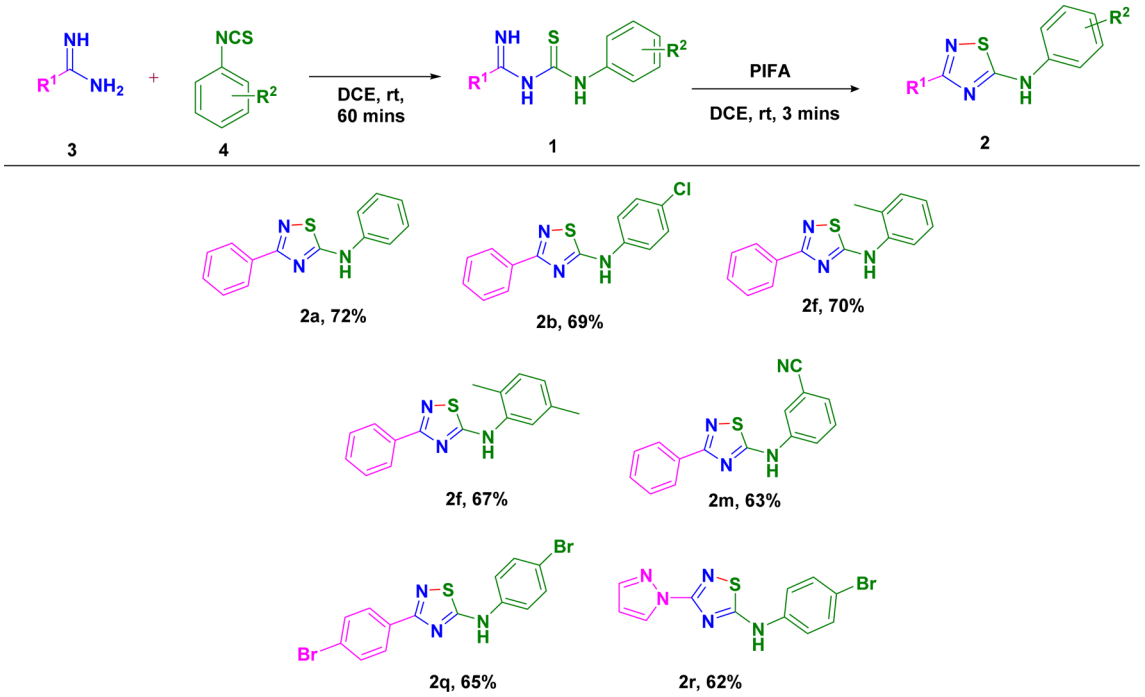
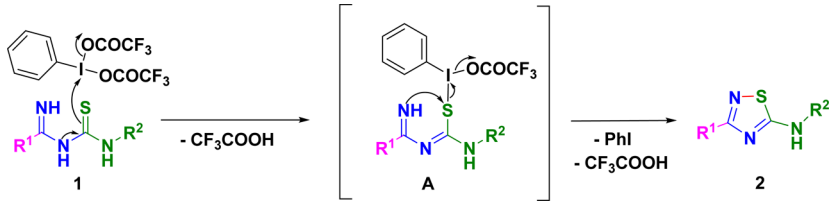
Scheme 3. One-Pot Synthesis of 3-Substituted 5-Amino-1,2,4-thiadiazoles



Scheme 4. Control Experiments

Radical scavenger (mmol)	Yield (%)
TEMPO(1.5)	83
Hydroquinone(1.5)	83

Scheme 5. Proposed Mechanism for the Intramolecular Oxidative S−N Bond Formation



1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.22−8.20 (m, 2H), 7.45−7.41 (m, 3H), 7.39−7.36 (m, 2H), 7.21 (d, J = 7.7 Hz, 2H), 7.15 (t, J = 7.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.8, 169.3, 139.1, 132.8, 130.1, 129.8, 128.6, 128.0, 124.3, 118.4; ESI-MS m/z calcd $[M + H]^+$ 253.07, found 254.12.

N-(4-Chlorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (***2b***)*:*[26] isolated as a white solid (232 mg, 81%); mp 194−196 °C; IR (KBr) ν 3222, 3080, 1604, 1560, 1490 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.31 (s, 1H), 8.26−8.22 (m, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.47- 7.44 (m, 3H), 7.35−7.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.9, 168.9, 138.4, 132.8, 129.5, 128.7, 128.0, 127.5, 127.0, 118.8.

N-(4-Iodophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (***2c***)*:* isolated as a light brown solid (302 mg, 80%) ; mp 180−183 °C; IR (KBr) ν 3220, 3068, 1594, 1551, 1458, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 10.17 (s, 1H), 8.24−8.21 (m, 2H), 7.66 (d, J = 8.8 Hz, 2H), 7.46−7.44 (m, 3H), 7.38 (d, J = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 178.8, 168.9, 139.5, 137.5, 132.7, 129.5, 128.0, 127.5, 119.5, 84.9; ESI-MS m/z calcd $[M + H]^+$ 379.96, found 380.01. Anal. Calcd for $C_{14}H_{10}IN_3S$: C, 44.34; H, 2.66; N, 11.08. Found: C, 44.32; H, 2.69; N, 11.11.

N-(4-Fluorophenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (***2d***)*:* isolated as a white solid (207 mg, 79%); mp 170−173 °C; IR (KBr) ν 3228, 3080, 1597, 1548, 1466 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 10.17 (s, 1H), 8.25−8.22 (m, 2H), 7.60−7.55 (m, 2H), 7.47−7.44 (m, 3H), 7.08 (t, J = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 179.9, 169.2, 158.4(d, $^1J_{C-F}$ = 241.5 Hz) 136.2, 133.1, 129.6, 127.9, 119.6 (d, $^3J_{C-F}$ = 8.5 Hz), 115.6 (d, $^2J_{C-F}$ = 22.5 Hz). Anal. Calcd for $C_{14}H_{10}FN_3S$: C, 61.98; H, 3.72; N, 15.49. Found: C, 61.89; H, 3.68; N, 15.42.

3-Phenyl-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (***2e***)*:* isolated as an off-white solid (225 mg, 85%); mp 120−123 °C; IR (KBr) ν 3234, 3085, 1605, 1564, 1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.20−8.17 (m, 2H), 7.43−7.41 (m, 3H), 7.17 (d, J = 8.2 Hz, 2H), 7.10 (d, J = 8.3 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.7, 169.3, 136.7, 134.4, 132.9, 130.3, 130.1, 128.5, 127.9, 119.0, 20.8; ESI-MS m/z calcd $[M + H]^+$ 268.08, found 268.14. Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.43; H, 4.87; N, 15.76.

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3-Phenyl-N-(o-tolyl)-1,2,4-thiadiazol-5-amine (**2f**):[26] isolated as a white solid (228 mg, 86%); mp 168−171 °C; IR (KBr) ν 3218, 3078, 1605, 1559, 1486 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17−8.13 (m, 2H), 8.04 (bs, 1H), 7.46 (d, J = 7.6 Hz, 2H), 7.41−7.39 (m, 2H), 7.35−7.26 (m, 2H), 7.18 (t, J = 7.4 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.0, 169.4, 137.8, 132.8, 131.4, 130.7, 130.0, 128.4, 127.8, 127.5, 126.2, 121.2, 17.6.

3-Phenyl-N-(m-tolyl)-1,2,4-thiadiazol-5-amine (**2g**): isolated as an off-white solid (220 mg, 83%); mp 110−113 °C; IR (KBr) ν 3228, 3089, 1596, 1548, 1476 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (s, 1H), 8.10 (dd, J = 8.7, 0.9 Hz, 2H), 7.47 (d, J = 7.9 Hz, 1H), 7.38−7.31 (m, 4H), 7.25−7.27 (m, 1H), 7.20−7.15 (m, 1H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.1, 169.2, 139.9, 139.1, 132.8, 130.1, 129.5, 128.5, 128.0, 125.1, 119.5, 115.2, 21.4. Anal. Calcd for $C_{15}H_{13}N_3S$: C, 67.39; H, 4.90; N, 15.72. Found: C, 67.42; H, 4.95; N, 15.69.

N-(4-Ethylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2h**): isolated as a white solid (223 mg, 80%); mp 140−143 °C; IR (KBr) ν 3223, 3070, 1596, 1555, 1513 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.22−8.19 (m, 2H), 7.68−7.44 (m, 3H), 7.24 (d, J = 8.4 Hz, 2H), 7.16 (d, J = 8.5 Hz, 2H), 2.66 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2, 169.4, 140.8, 136.9, 133.1, 130.0, 129.1, 128.5, 128.0, 118.9, 28.0, 15.2; ESI-MS m/z calcd $[M + H]^+$ 282.10, found 282.33. Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.27; H, 5.39; N, 14.97.

N-(4-Isopropylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2i**): isolated as a white solid (246 mg, 84%); mp 130−132 °C; ν 3216, 3092, 1601, 1560, 1520, 1453 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.19 (d, J = 5.3 Hz, 2H), 7.43 (d, J = 2.1 Hz, 3H), 7.26 (d, J = 7.8 Hz, 2H), 7.16 (d, J = 8.0 Hz, 2H), 2.98−2.83 (m, 1H), 1.26 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.4, 169.1, 145.4, 136.9, 132.7, 130.1, 128.5, 128.0, 127.7 119.0, 33.5, 23.9; ESI-MS m/z calcd $[M + H]^+$ 296.11, found 296.33. Anal. Calcd for $C_{17}H_{17}N_3S$: C, 69.12; H, 5.80; N, 14.22. Found: C, 69.16; H, 5.77; N, 14.27.

N-(2,5-Dimethylphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2j**): isolated as a white solid (234 mg, 80%); mp 135−137 °C; IR (KBr) ν 3227, 3026, 1586, 1548, 1442 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.10 (dd, J = 7. 9, 1.6 Hz, 2H), 7.42−7.31 (m, 4H), 7.14 (d, J = 7.7 Hz, 1H), 6.99 (d, J = 7.6 Hz, 1H), 2.37 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 169.6, 137.5, 137.5, 132.9, 131.3, 129.9, 128.4, 127.8, 127.5, 127.0, 121.9, 21.1, 17.2; ESI-MS m/z calcd $[M + H]^+$ 282.10, found 282.17. Anal. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.33; H, 5.39; N, 14.90.

N-(4-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2k**): isolated as a white solid (196 mg, 73%); mp 116−118 °C; IR (KBr) ν 3230, 3079, 1603, 1548, 1512, 1421 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 9.94 (s, 2H), 8.22−8.20 (m, 2H), 7.46−7.43 (m, 5H), 6.93 (d, J = 8.9 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 181.3, 169.3, 156.2, 133.1, 129.7, 128.2, 127.8, 127.1, 120.8, 114.6, 55.4. Anal. Calcd for $C_{15}H_{13}N_3OS$: C, 63.58; H, 4.62; N, 14.83. Found: C, 63.52; H, 4.66; N, 14.78.

4-((3-Phenyl-1,2,4-thiadiazol-5-yl)amino)benzonitrile (**2l**): isolated as a white solid (196 mg, 71%); mp 208−210 °C; IR (KBr) ν 3230, 3091, 2234, 1602, 1560, 1428 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 10.91 (s, 1H), 8.23−8.21 (m, 2H), 7.80 (d, J = 8.7 Hz, 2H), 7.63 (d, J = 8.7 Hz, 2H), 7.45−7.42 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 178.2, 169.3, 143.4, 133.1, 132.7, 129.8, 128.2, 127.7, 119.0, 117.4, 104.4; ESI-MS m/z calcd $[M + H]^+$ 279.06, found 279.14. Anal. Calcd for $C_{15}H_{10}N_4S$: C, 64.73; H, 3.62; N, 20.13. Found: C, 64.70; H, 3.66; N, 20.08.

3-((3-Phenyl-1,2,4-thiadiazol-5-yl)amino)benzonitrile (**2m**):[26] isolated as a yellow solid (213 mg, 77%); mp 223−226 °C; IR (KBr) ν 3236, 2238, 1599, 1540, 1449 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 10.61 (s, 1H), 8.27−8.24 (m, 2H), 8.10 (s, 1H), 7.91 (dd, J = 7.9, 1.7 Hz, 1H), 7.50−7.45 (m, 4H), 7.33 (d, J = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 178.6, 169.1, 140.5, 132.6, 129.7, 129.7, 128.2, 127.6, 125.5, 121.5, 120.3, 118.5, 112.4.

Methyl 4-((3-phenyl-1,2,4-thiadiazol-5-yl)amino)benzoate (**2n**): isolated as a white solid (216 mg, 70%); mp 179−182 °C; IR (KBr) ν 3228, 3068, 1720, 1602, 1556, 1432 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.62 (s, 1H), 8.27−8.26 (m, 2H), 8.07 (d, J = 7.4 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H), 7.48−7.46 (m, 3H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.2, 168.6, 165.8, 143.4, 132.4, 130.3, 129.3, 127.8, 127.2, 123.0, 116.2, 51.2. Anal. Calcd for $C_{16}H_{13}N_3O_2S$: C, 61.72; H, 4.21; N, 13.50. Found: C, 61.76; H, 4.24; N, 13.46.

3-(4-Bromophenyl)-N-(4-chlorophenyl)-1,2,4-thiadiazol-5-amine (**2o**): isolated as a pale yellow solid (307 mg, 84%); mp 174−176 °C; IR (KBr) ν 3226, 3080, 1606, 1557, 1491, 1440 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 10.50 (s, 1H), 8.11 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.2 Hz, 4H), 7.34 (d, J = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 178.6, 167.1, 137.8, 131.3, 130.6, 128.6, 128.1, 126.3, 123.2, 118.3. Anal. Calcd for $C_{14}H_9BrClN_3S$: C, 45.86; H, 2.47; N, 11.46. Found: C, 45.82; H, 2.49; N, 11.40.

N,3-Bis(4-bromophenyl)-1,2,4-thiadiazol-5-amine (**2p**): isolated as a pale yellow solid (331 mg, 81%); mp 179−181 °C; IR (KBr) ν 3231, 3080, 1600, 1554, 1493, 1443 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 10.60 (s, 1H), 8.13 (d, J = 8.5 Hz, 2H), 7.62−7.57 (m, 4H), 7.50 (d, J = 6.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 179.0, 167.8, 138.8, 131.8, 131.5, 131.1, 129.0, 123.7, 119.2, 114.6. Anal. Calcd for $C_{14}H_9Br_2N_3S$: C, 40.90; H, 2.21; N, 10.22. Found: C, 40.96; H, 2.18; N, 10.18.

3-(4-Bromophenyl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2q**): isolated as a white solid (286 mg, 83%); mp 241−243 °C; IR (KBr) ν 3224, 3054, 1592, 1565, 1438 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$+DMSO-d_6) δ 10.30 (s, 1H), 8.11 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.5 Hz, 2H), 7.42 (d, J = 8.3 Hz, 2H), 7.19 (d, J = 8.1 Hz, 2H), 2.28 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 180.3, 168.3, 138.2, 132.9, 132.8, 132.1, 130.2, 130.1, 124.3, 118.7, 21.2. Anal. Calcd for $C_{15}H_{12}BrN_3S$: C, 52.03; H, 3.49; N, 12.14. Found: C, 52.07; H, 3.44; N, 12.17.

N-(2-Methoxyphenyl)-3-phenyl-1,2,4-thiadiazol-5-amine (**2r**): isolated as a white solid (281 mg, 78%); mp 120−123 °C; IR (KBr) ν 3237, 3065, 1600, 1570, 1439 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (s, 1H), 8.12−8.10 (m, 2H), 7.60−7.57 (m, 3H), 7.11−7.08 (m, 2H), 6.96 (d, J = 7.2 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.6, 168.4, 148.0, 132.0, 131.7, 129.6, 128.7, 124.5, 123.7, 121.3, 116.4, 110.7, 55.8. Anal. Calcd for $C_{15}H_{12}BrN_3OS$: C, 49.74; H, 3.34; N, 11.60. Found: C, 49.68; H, 3.30; N, 11.65.

N-Benzyl-3-phenyl-1,2,4-thiadiazol-5-amine (**2s**):[26] isolated as a white solid (223 mg, 84%); mp 101−104 °C; IR (KBr) ν 3218, 3098, 1594, 1570, 1436, 1353 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.15−8.12 (m, 2H), 7.40−7.38 (m, 2H), 7.34−7.26 (m, 6H), 7.01 (s, 1H), 4.47 (d, J = 5.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.7, 169.8, 136.1, 133.1, 129.9, 128.9, 128.4, 128.1, 127.9, 127.6, 50.4; ESI-MS m/z calcd $[M + H]^+$ 268.08, found 268.15.

N-Cyclohexyl-3-phenyl-1,2,4-thiadiazol-5-amine (**2t**):[23b] isolated as a white solid (218 mg, 85%); mp 113−115 °C; IR (KBr) ν 3190, 3062, 2985,1577, 1503, 1450 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17−8.14 (m, 2H), 7.43−7.41 (m, 3H), 5.91 (d, J = 7.7 Hz, 1H), 3.28−3.18 (m, 1H), 2.17−2.09 (m, 2H), 1.82−1.75 (m, 2H), 1.42−1.25 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.4, 169.8, 133.2, 129.8, 128.4, 127.9, 56.2, 32.5, 25.2, 24.5; ESI-MS m/z calcd $[M + H]^+$ 260.11, found 260.33.

3-(5-Bromopyridin-2-yl)-N-(4-chlorophenyl)-1,2,4-thiadiazol-5-amine (**2u**): isolated as a brown solid (285 mg, 78%); mp 228−231 °C; IR (KBr) ν 3179, 3063, 3027, 1590, 1490, 1445 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) δ 10.54 (s, 1H), 8.80 (s, 1H), 8.19 (d, J = 8.3 Hz, 1H), 8.01−7.96 (m, 1H), 7.57 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6)) δ 179.3, 166.8, 150.1, 148.6, 138.8, 138.0, 128.4, 126.9, 124.2, 121.0, 118.7. Anal. Calcd for $C_{13}H_8BrClN_4S$: C, 42.47; H, 2.19; N, 15.24. Found: C, 42.50; H, 2.13; N, 15.28.

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N-Benzyl-3-(5-bromopyridin-2-yl)-1,2,4-thiadiazol-5-amine (**2v**): isolated as a white solid (283 mg, 82%); mp 221−224 °C; IR (KBr) ν 3233, 3088, 3032, 1601, 1534, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) 8.64 (d, J = 2.1 Hz, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.89 (dd, J = 8.5, 2.3 Hz, 1H), 7.37 (m, 5H), 4.56 (d, J = 5.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6)) δ 183.0, 166.2, 149.2, 148.5, 138.2, 136.4, 127.4, 126.6, 126.4, 123.7, 120.1, 48.2. Anal. Calcd for $C_{14}H_{11}BrN_4S$: C, 48.43; H, 3.19; N, 16.14. Found: C, 48.40; H, 3.21; N, 16.11.

N-(3-Chlorophenyl)-3-(1H-pyrazol-1-yl)-1,2,4-thiadiazol-5-amine (**2w**): isolated as an off-white solid (235 mg, 85%); mp 220−222 °C; IR (KBr) ν 3267, 3148, 3087, 1614, 1544, 1473, 1432 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) 10.85 (s, 1H), 8.36 (bd, J = 2.1 Hz, 1H), 7.76 (s, 1H), 7.64 (s, 1H), 7.45−7.44 (m, 1H), 7.31 (t, J = 8.1 Hz, 1H), 7.07 (d, J = 7.8 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO-d_6) δ 179.5, 157.4, 142.3, 140.2, 134.3, 129.9, 129.5, 122.9, 117.9, 115.9, 107.3. Anal. Calcd for $C_{11}H_8ClN_5S$: C, 47.57; H, 2.90; N, 25.22. Found: C, 47.53; H, 2.93; N, 25.27.

N-(4-Bromophenyl)-3-(1H-pyrazol-1-yl)-1,2,4-thiadiazol-5-amine (**2x**): isolated as a white solid (259 mg, 81%); mp 221−224 °C; IR (KBr) ν 3226, 3060, 3025, 1615, 1490, 1430 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + DMSO-d_6) 10.72 (s, 1H), 8.35 (bd, J = 2.4 Hz, 1H), 7.75 (s, 1H), 7.47 (s, 4H), 6.47−6.45 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$+DMSO-d_6) δ 178.9, 156.9, 141.8, 137.8, 131.2, 129.1, 119.1, 114.7, 106.9. Anal. Calcd for $C_{11}H_8BrN_5S$: C, 41.01; H, 2.50; N, 21.74. Found: C, 41.06; H, 2.47; N, 21.69.

3-(1H-Pyrazol-1-yl)-N-(p-tolyl)-1,2,4-thiadiazol-5-amine (**2y**): isolated as a pale yellow solid (219 mg, 86%); mp 180−183 °C; IR (KBr) ν 3220, 3073, 1606, 1548, 1457 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.98 (s, 1H), 8.30 (s, 1H), 7.57 (s, 1H), 7.24−7.15 (m, 4H), 6.41 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 182.7, 158.1, 142.3, 136.6, 135.3, 130.1, 129.1, 120.9, 107.9, 20.9. Anal. Calcd for $C_{12}H_{11}N_5S$: C, 56.01; H, 4.31; N, 27.22. Found: C, 56.06; H, 4.34; N, 27.16.

3-(Methylthio)-N-phenyl-1,2,4-thiadiazol-5-amine (**2z**): isolated as a white solid (184 mg, 83%); mp 80−83 °C; IR (KBr) ν 3223, 2968, 1592, 1545, 1451 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (s, 1H), 7.42−7.37 (m, 2H), 7.34−7.31 (m, 2H), 7.14 (t, J = 7.2 Hz, 1H), 2.63 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 180.2, 168.1, 139.4, 129.4, 123.8, 118.5, 14.3. Anal. Calcd for $C_9H_9N_3S_2$: C, 48.41; H, 4.06; N, 18.82. Found: C, 48.46; H, 4.03; N, 18.78.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01199.

^1H and ^{13}C NMR and ESI mass spectra and X-ray crystal data of compound **2f** (PDF)

X-ray crystal data of compound **2f** (CIF)

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Notes

The authors declare no competing financial interest.

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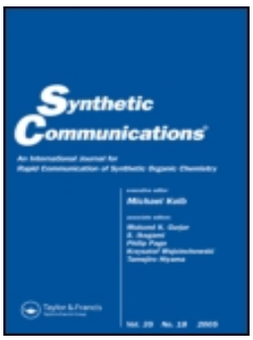

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Microwave-assisted catalyst-free synthesis of tetrasubstituted pyrroles using dialkyl acetylenedicarboxylates and monophenacylanilines

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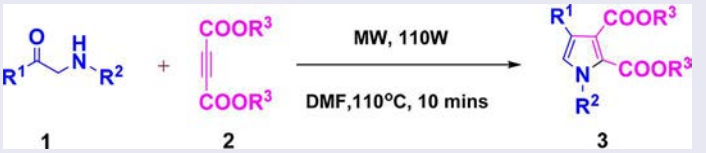
ABSTRACT

An efficient catalyst-free microwave-assisted synthesis of tetrasubstituted pyrroles using dialkyl acetylenedicarboxylates and substituted monophenacylanilines has been developed. Axial chirality has been noticed in some *N*-(α-naphthyl/2-isopropylphenyl)-2,3-dicarbethoxy-4-arylpyrroles, but not with *N*-aryl-2,3-dicarbethoxy-4-(α-naphthyl) pyrrole.

GRAPHICAL ABSTRACT



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KEYWORDS
Axial chirality; diethylacetylene dicarboxylate; microwave synthesis; polysubstituted pyrrole

Introduction

The pyrrole nucleus can be found in many natural bioactive molecules,[1] synthetic pharmaceuticals,[2] and functional materials[3] with varied applications. Several polysubstituted pyrroles, in particular, are effective as antibacterial,[4] anticonvulsant,[5] anticancer,[6] antioxidant,[7] antitumor,[8] and anti-inflammatory[9] agents. It must be pointed out that the pyrrole skeleton has been found as a subunit in heme, chlorophyll, bile pigments, and vitamin B12 apart from alkaloids derived from marine sources. Some popular pyrrole-containing drugs are shown in Fig. 1. Pyrrole derivatives have also been widely used as organic conducting materials.[10]

The pyrrole unit can be generated from routes proposed by Knorr,[11] Paal–Knorr,[12] and Hantzsch[13] and other strategies include the transition-metal-mediated cyclization,[14] reductive coupling,[15] isocyanide-based reactions,[16] rearrangement reactions,[17] and cycloaddition methods.[18] The present investigation reports the synthesis of the polysubstituted pyrroles, dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylates. Though there are many

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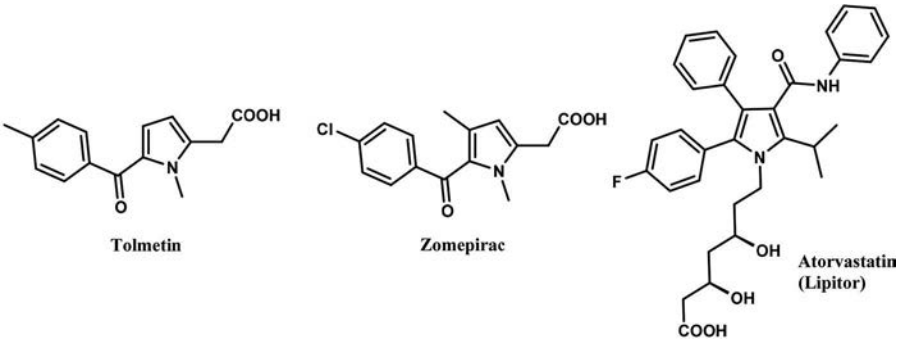
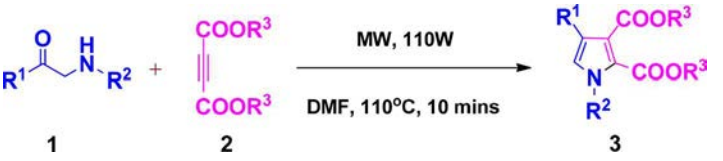


Figure 1. Examples of pyrrole-derived drugs.

reports for the synthesis of the dialkyl 1,5-diaryl-*1H*-pyrrole-2,3-dicarboxylate,[19] only a few reports describe the route for its regioisomer, dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylate. Abbasinejad et al. first reported a two-step strategy involving triphenylphosphine-catalyzed cyclization of α-aminoketones with dialkyl acetylenedicarboxylates followed by chromium trioxide oxidation.[20] Ardakani et al. reported triphenylphosphine-promoted condensation reaction between dialkyl acetylenedicarboxylates and 1-aryl-2-(arylamino)-2-hydroxyethanones.[21] A direct four-component coupling reaction of aldehydes, amines, dialkyl acetylenedicarboxylates, and nitromethane using iodine as a catalyst has been reported[22a] and also an iron(III) chloride–catalyzed three-component reaction of primary amines, dialkyl acetylenedicarboxylates, and β-nitrostyrene.[22b] Very recently, Jeong et al. reported a one-pot, four-component reaction of amines, aldehydes, dialkyl acetylenedicarboxylates, and nitroalkanes using silica-supported ceric ammonium nitrate as a heterogeneous catalyst.[22c] Liu et al. reported a gold-catalyzed cascade hydroamination/cyclization reaction of α-amino ketones with alkynes.[23] These protocols involve either (i) the tedious task of removing the triphenylphosphine oxide, (ii) prefunctionalization of the monophenacylaniline part, (iii) more steps to reach the desired product, (iv) long reaction times, or (v) a cascade hydroamination/cyclization reaction where expensive gold has been used as the catalyst. To overcome these shortcomings and exploit the advantages of microwaves in modern synthetic organic chemistry, the present scheme for pyrrole synthesis has been proposed in continuation of our work[24] on the development of useful synthetic methodologies for the construction of heterocycles. A microwave-assisted, catalyst-free, efficient synthesis of dialkyl 1,4-diaryl-1*H*-pyrrole-2,3-dicarboxylates from α-amino ketones with dialkyl acetylenedicarboxylates has been achieved (Scheme 1).

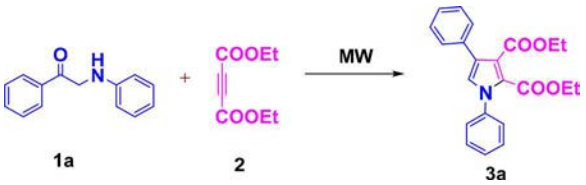


Scheme 1. Synthesis of 1,2,3,4-tetrasubstituted pyrroles.

Results and discussion

We started our investigation with **1a** as the model substrate and treated that with diethyl acetylenedicarboxylate (DEAD) in tetrahydrofuran (THF) without catalyst at room temperature. It must be admitted that a related reaction has been reported involving acidic reagent with limited substrate scope after isolating the intermediate.[25a] Our strategy involves no acidic reagent, no isolation of the intermediate, and a wide substrate scope. Similar work yielding 2-trifluoromethyl-substituted pyrrole has been reported very recently.[25b] After 16 h, **3a** was formed in 50% yield (Table 1, entry 1) with 25% of starting material, the remaining being an unrecognizable mass. Increasing the reaction time had no impact on the yield of **3a**. Carrying out the reaction in acetic acid also did not enhance the yield as expected, but resulted in additional by-products as evidenced by thin-layer chromatography (TLC). However, when the reaction was carried out in dimethylformamide (DMF) under reflux without any catalyst, the reaction was completed within 6 h (Table 1, entry 2) with 62% yield of **3a**. When we investigated the reaction by applying microwave (MW) with varying power, temperature, and solvents (Table 1, entries 3–9), we found that **3a** was obtained in good yield with DMF in 110 W at 110 °C (Table 1, entry 9) in 10 min. Increasing the reaction time beyond 10 min did not improve the yield; rather a slight decrease in the yield has been observed as evidenced by TLC. The yield was relatively good with solvents like ethanol, acetonitrile, and water (Table 1, entries 13–15), but it was relatively poor with the other solvents such as toluene, 1,4-dioxane, and 1,2-dichloroethane (Table 1, entries 10–12). The one-pot reaction of all three compounds, as reported in the previous study,[19] resulted in diethyl 1,5-diphenyl-*1H*-pyrrole-2,3-dicarboxylate. Here

Table 1. Optimization of the reaction conditions.[a]

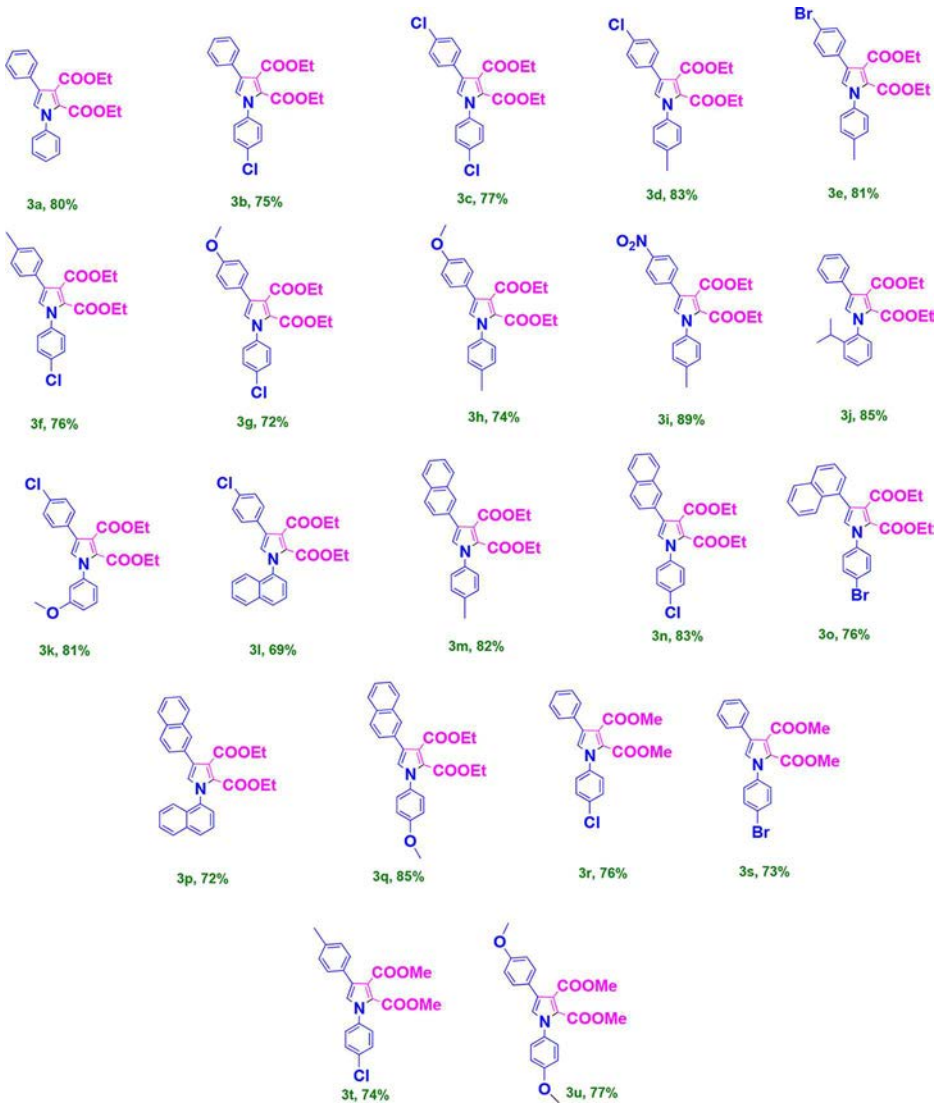


Entry	Solvent	Temp (°C)	MW (W)	Time (min)	Yield[c] of 3 (%)
1	[b]THF	—	—	960	50
2	[d]DMF	140	—	360	62
3	THF	100	100	10	56
4	EtOH	100	120	10	55
5	MeCN	100	110	10	53
6	DMF	110	120	10	68
7	Water	120	100	10	62
8	Toluene	120	110	10	52
9	DMF	110	110	10	80
10	Toluene	110	110	10	48
11	1,4-Dioxane	110	110	10	45
12	1,2-DCE	110	110	10	37
13	MeCN	110	110	10	60
14	EtOH	110	110	10	58
15	Water	110	110	10	65

[a]Reaction conditions: **1a** (1 mmol), **2** (1.1 mmol), solvent (1 ml) for 10 min.
[b]Reaction at room temperature.
[c]Isolated yield.
[d]Reaction at reflux condition.

the reaction of aniline with the diethyl acetylenedicarboxylate was preferred over the formation of monophenacylaniline. The initial reaction between aniline to phenacyl bromide followed by the addition of DEAD could afford the desired product. When we attempted

Table 2. Synthesized compounds (**3a–3u**).



the one-pot synthesis through the addition of aniline to phenacyl bromide under MW for 1 min at 110 °C followed by the addition of DEAD, it resulted in lower yield of the dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylate. This may be due to the initial formation of α,α'-amino ketones, preventing the formation of the pyrrole. After optimization we investigated the scope of the reaction and it worked well with variety of α-aminoketones and different acetylene esters (Table 2). The structures of the products **3** has been unambiguously assigned by spectral and analytical data, and that of **3d** has been confirmed by single-crystal x-ray analysis as well (Fig. 2).[26] A closely related methodology employing gold catalyst has generated a similar skeleton,[23] whereas the present work uses no catalyst, generating a library of 18 compounds.

It is pertinent to note that this cyclization occurred successfully with both electron-withdrawing and electron-donating groups in the aryl ring (Table 2). The presence of electron-withdrawing groups on the carbonyl attached phenyl ring and the electron-donating groups on the aniline ring of the monophenacylaniline promoted the formation of the product, enhancing the yield (Table 2, compounds **3d, 3e, 3i,** and **3q**). All the other monophenacylaniline derivatives differing from the aforementioned combination of electron-withdrawing and electron-donating groups afforded moderate yield (Table 2). Based on the observed results, a plausible mechanism is proposed (Scheme 2). Initially the reaction of α-amino ketones with electron-deficient alkynes afforded the enamine intermediate **A**. Then the nucleophilic attack of the enamine to the carbonyl group afforded intermediate **B,** followed by the elimination of water to provide the desired product **3**.

One out of the two sets of methylene hydrogens in **3j, 3 l,** and **3p** is found to be diastereotopic, indicating that chirality has arisen due to the restricted rotation around the N-(α-naphthyl/N-(2-isopropylphenyl) bond in these cases. In the case of **3i**, the diastereotopic behavior has been felt with the isopropyl methyls as well, both in the ^{1}H and ^{13}C NMR spectra. It must be noted that when a simple methyl is present in the 2-position of the *N*-phenyl ring, no chirality has been noticed.[22c] It is also interesting to note that

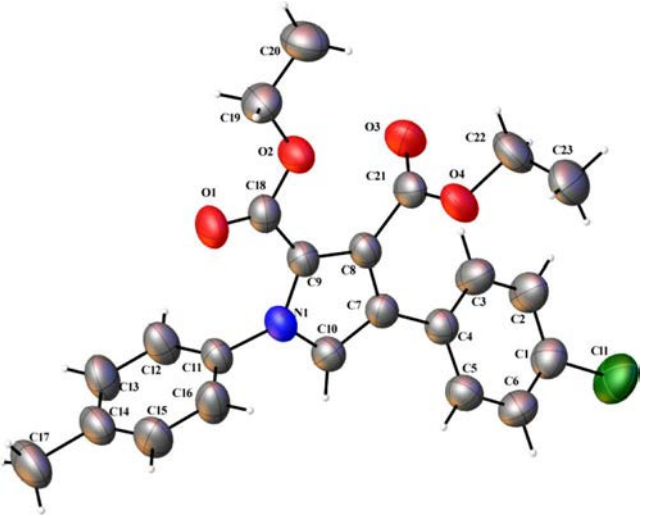
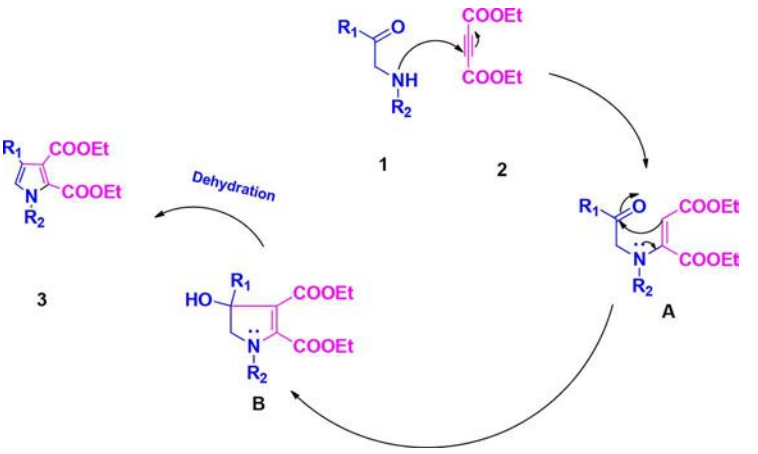


Figure 2. Crystal structure of **3d**.



Scheme 2. Plausible mechanism for the formation of **3**.

the presence of α-naphthyl group in the 4th position of the pyrrole (**3o**) has not raised any chiral characteristics.

Conclusion

In summary, we have developed a microwave-assisted synthesis of dimethyl 1,4-diphenyl-*1H*-pyrrole-2,3-dicarboxylates, and the main advantages of this method are that it is catalyst free with short reaction time, resulting in good to excellent yield. Another interesting feature is the realization of axial chirality in *N*-(α-naphthyl/2-isopropylphenyl)-2,3-dicarbethoxy-4-arylpyrroles but not in *N*-aryl-2,3-dicarbethoxy-4-(α-naphthyl)pyrrole.

Experimental

All solvents were purchased from commercial sources and used without further purification. The melting points were measured in open capillary tubes and are uncorrected. A CEM Discover microwave synthesizer (model no. 908010) operating at 180/264 V and 50/60 Hz with maximum microwave power level of 300 W and microwave frequency of 2455 MHz was employed for the microwave-assisted experiments. Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded on a 300-MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (δ), coupling constants (*J* values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quatret), sept (septet), m (multiplet). ^{13}C NMR spectra were routinely run with broadband decoupling. Elemental analyses were performed on a Perkin-Elmer 2400 Series II Elemental CHNS analyzer.

General procedure for the synthesis of dialkyl 1,4-diaryl-1H-pyrrole-2, 3-dicarboxylate 3

A mixture of substituted monophenacylaniline **1** (1 mmol) and dialkyl acetylenedicarboxylate **2** (1.1 mmol) in DMF (1 mL) was sealed and subjected to microwave irradiation at 110 °C and 110 W for 10 min. The completion of the reaction was monitored by thin-layer

chromatography (TLC). The reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. The crude product was purified by column chromatography using petroleum ether−ethyl acetate (5:95) as the eluent to get **3**.

Selected spectral data for diethyl 4-(4-chlorophenyl)-1-(p-tolyl)-1H-pyrrole-2, 3-dicarboxylate (3d)

Yellow solid; mp 97–100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40–7.31 (m, 4H), 7.27–7.21 (m, 4H), 6.94 (s, 1H), 4.31 (q, $J = 7.1$ Hz, 2H), 4.18 (q, $J = 7.1$ Hz, 2H), 2.41 (s, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.18 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.9, 159.9, 138.5, 136.8, 132.9, 131.8, 129.4, 129.1, 128.6, 125.8, 125.5, 123.9, 123.5, 121.2, 61.3, 60.9, 21.1, 14.0, 13.9. Anal. calcd. for $C_{23}H_{22}ClNO_4$: C, 67.07; H, 5.38; N, 3.40%. Found: C, 67.09; H, 5.33; N, 3.43%. ESI-MS *m/z* calcd. $[M+H]^+$ 412.12; found 412.11.

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Oxidative C–H Functionalization

Hypervalent Iodine Promoted Regioselective Oxidative C–H Functionalization: Synthesis of *N*-(Pyridin-2-yl)benzo[*d*]thiazol-2-amines

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Abstract: Biologically potent *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amines were conveniently synthesized from simple heteroarylthioureas through an oxidative C–S bond formation strategy that employed phenyliodine(III) bis(trifluoroacetate) as the oxidant. This protocol features a metal-free approach, a broad scope of substrates, short reaction times, and a simple product purification procedure.

Introduction

Oxidative C–H bond functionalization is an important atom-economic process for carbon–carbon and carbon–heteroatom bond formation.[1] Transition metals can effectively catalyze these processes,[2] but such reactions have serious drawbacks, such as the use of toxic reagents and harsh reaction conditions. Other disadvantages include metal contamination in the desired product and the requirement of cocatalysts and additives. Therefore, the formation of carbon–heteroatom bonds through metal-free catalysis is highly desirable.[3] Hypervalent iodine(III) reagents are excellent, environmentally friendly metal-free oxidants.[4] They can replace highly toxic, heavy-metal oxidizers, such as lead(IV), mercury(II), and thallium(III) reagents, which are not only costly but also pose problems when purifying the products of a large-scale synthesis.[5] Hypervalent iodine(III) reagents such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) have been employed in the preparation of various heterocyclic compounds that involve C–N,[6] C–O,[7] and C–S[8] bond formations.

The 2-aminobenzothiazole skeleton is a privileged scaffold that is found in pharmaceutically active compounds and natural products that have antidiabetic, antibacterial, anticancer, anti-infective, and herbicidal properties.[9] Biologically important compounds that contain the 2-aminobenzothiazole pharmacophore include riluzole (**I**), a glutamate neurotransmitter,[10] and R116010 (**II**), a potent inhibitor of all-*trans*-retinoic acid (atRA) metabolism.[11] In addition, the 2-aminobenzothiazole nucleus is responsible for enhancing the atRA-induced expression of CYP26B1 (**III**).[12] Similarly, *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amines have been reported as highly potent Lck inhibitors (**IV**)[13] with excellent cellular activity against T-cell proliferation, and molecules that contain this core structure have been shown to have antiproliferative effects on several tumor cell lines (Figure 1).

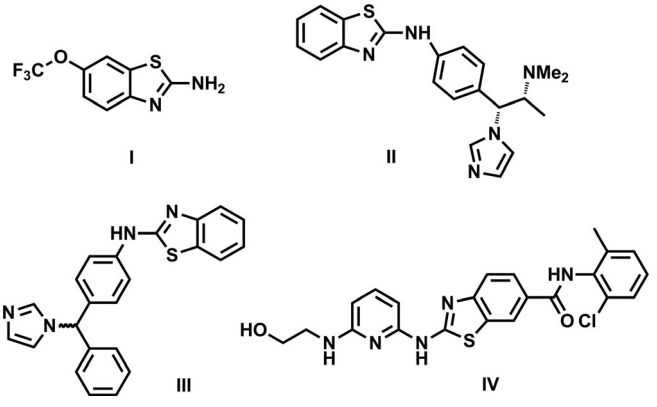

Figure 1. Biologically important molecules that contain the 2-aminobenzothiazole skeleton.

Most reported methods for the synthesis of 2-aminobenzothiazoles involve the transition-metal-catalyzed tandem reaction of 2-haloanilines with isothiocyanates.[14] Heterogeneous catalysis[15] and transition-metal-free synthetic protocols[16] have also been explored, although these methods still require drastic reaction conditions or long reaction times. In contrast with the numerous protocols for the synthesis of 2-aminobenzothiazoles, only few reports exist for the construction of the *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine system.

Yin et al.[17] reported a Pd-catalyzed *N*-(hetero)arylation towards the synthesis of *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine, and Das et al.[13] reported a two-step synthesis accompanied

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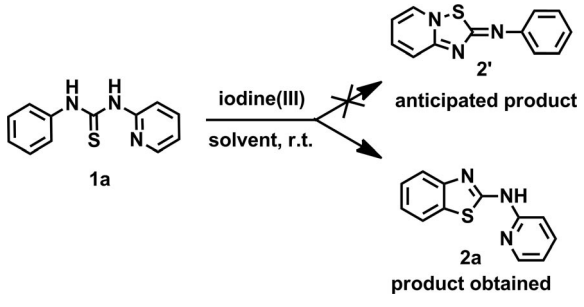
by structure–activity relationship (SAR) studies. A new version of the Hugershoff synthesis has also been developed, but the excess amount of mineral acid needed and the limited substrate scope are both disadvantages of using this route for the preparation of *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amines.[18] Because of the scarcity of protocols to synthesize this heterocyclic skeleton, efficient and environmentally benign methods are desired. Although the formation of a C–S bond through an oxidative cyclization has been achieved by using various metals[19] and metal-free oxidants,[20,8b–8d,16c,16d] the work described herein reports a selective cyclization reaction. Thus, an expedient metal-free oxidative cyclization of a thiourea moiety has been achieved in the presence of phenyliodine(III) bis(trifluoroacetate) (PIFA) to afford *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amines in good yields. A broad substrate scope is a key feature of this C–S bond formation strategy.

Results and Discussion

Zhao et al. reported the synthesis of 1,2,4-triazolo[1,5-*a*]-pyridines through N–N bond formation by using a hypervalent iodine(III) reagent.[21] In continuation of that work, we planned to effect S–N bond formation by using the corresponding thiourea as the starting material. We examined the reaction of thiourea **1a** and phenyliodine diacetate in acetonitrile at room temperature. Upon completion of the reaction, the isolated product was not the anticipated *N*-(2*H*-[1,2,4]thiadiazolo-[2,3-*a*]pyridin-2-ylidene)aniline (**2′**), but *N*-(pyridin-2-yl)benzo-[*d*]thiazol-2-amine (**2a**) had formed instead (Scheme 1). Thus, oxidative C–S bond formation had occurred. The structure of product **2a** was unambiguously assigned by spectral and analytical data, and that of **2b** was confirmed by single-crystal X-ray analysis (Figure 2).[22] It is significant that the cyclization reaction selectively occurred by one of the two possible pathways depicted in Scheme 2.



Scheme 1. Attempt to obtain the S–N bond formation product.

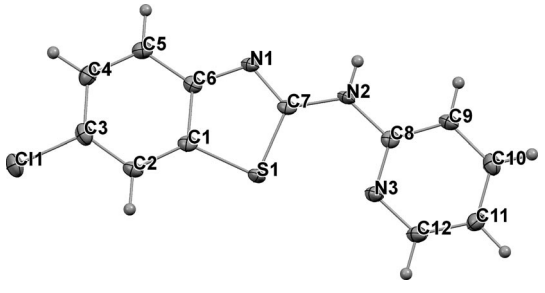
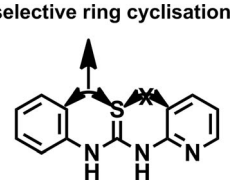


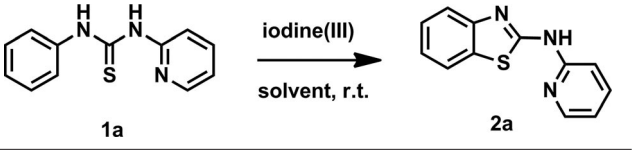
Figure 2. ORTEP diagram of **2b**.



Scheme 2. Selective cyclization of **1a**.

To improve the yield of **2a**, we optimized the reaction conditions by using **1a** as a model substrate. Initially, the reaction mixture was treated with phenyliodine(III) diacetate in acetonitrile, which afforded **2a** in 40 % yield (Table 1, Entry 1). The other two reagents PIFA and PhIO (Table 1, Entries 2 and 3) were also screened, but PIFA (1.2 mmol) provided the better yield. Upon screening for the appropriate oxidant, we found $K_2S_2O_8$ to give relatively good results (Table 1, Entry 6). However, the yields were negligible with other oxidants such as CAN (ceric ammonium nitrate), DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), and Oxone (Table 1, Entries 4, 5, and 7). Ultimately, PIFA was found to be the reagent of choice for this cyclization reaction. After ascertaining the suitable oxidant, the reaction was optimized for the proper solvent (Table 1, Entries 8–13). From the results, it was clear that the reaction afforded the best yield in tetrahydrofuran (Table 1, Entry 9), although 1,2-dichloroethane (DCE) and other solvents such as MeCN, MeOH, and trifluoroacetic acid (TFA) also provided relatively good yields. Nonpolar solvents such as benzene also performed well and afforded a relatively good yield of 45 % (Table 1, Entry 13). An attempt to carry out the reaction by

Table 1. Optimization of reaction conditions.[a]



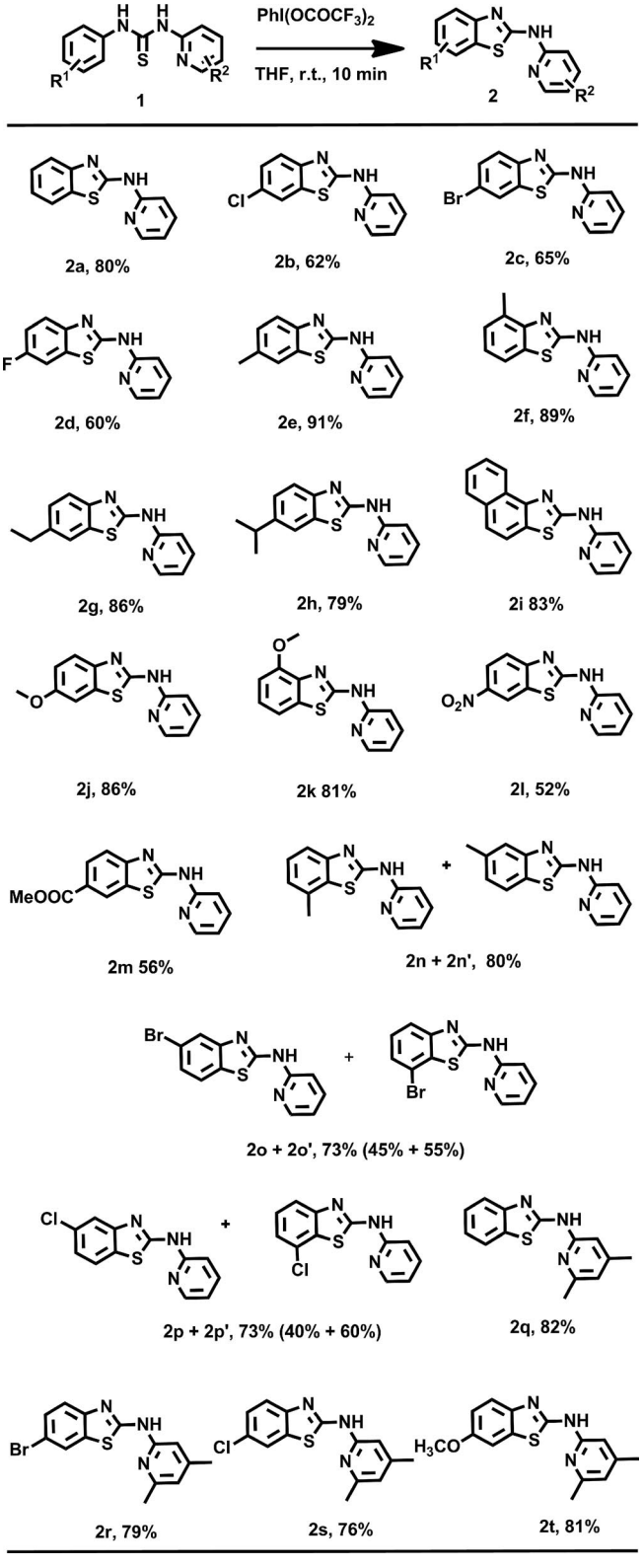
Entry	Oxidant	Solvent	Yield [%][b]
1	PIDA	MeCN	40
2	PhIO	MeCN	26
3	PIFA	MeCN	60
4	CAN	MeCN	trace
5	DDQ	MeCN	20
6	$K_2S_2O_8$	MeCN	45
7	Oxone[c]	MeCN	10
8	PIFA	DCE	72
9	PIFA	THF[d]	80
10	PIFA	TFA	65
11	PIFA	DMF[d]	56
12	PIFA	MeOH	58
13	PIFA	benzene	45
14	PhI/*m*-CPBA[e]	THF	25

[a] Reagents and conditions: thiourea **1a** (1.0 mmol), oxidant (1.2 mmol), and solvent (2 mL). The reaction mixture was stirred at room temperature for 10 min. [b] The obtained yield is provided. [c] The chemical formula of Oxone is $2KHSO_5{\cdot}KHSO_4{\cdot}K_2SO_4$. [d] THF = tetrahydrofuran and DMF = *N*,*N*-dimethylformamide. [e] PhI (20 mol-%) and *meta*-chloroperoxybenzoic acid (*m*-CPBA. 1.5 equiv.) were employed.

generating the catalyst in situ afforded the desired product in a relatively low yield (Table 1, Entry 14).[6i]

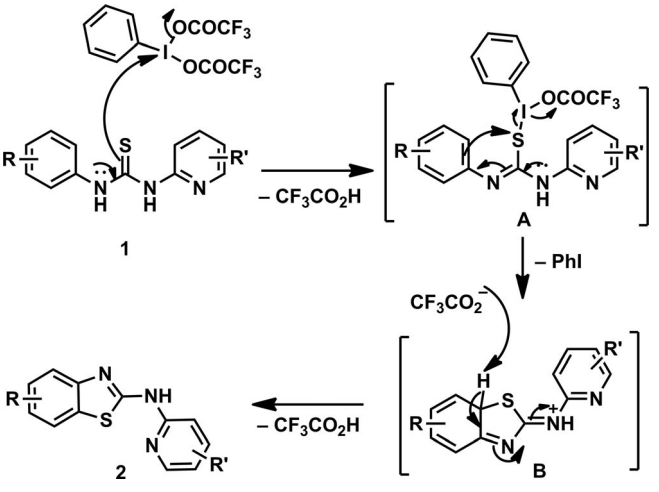
Under the optimized reaction conditions, the scope of the substrates was explored by employing various heteroarylthioureas, which were obtained from different substituted isothiocyanates and 2-aminopyridine. The results show that thioureas that have both electron-withdrawing and electron-donating groups tolerated the reaction conditions. However, the yields were relatively poor for substrates with an electron-withdrawing substituent such as a chloro, nitro, or methoxycarbonyl group compared with those afforded by an electron-rich substrate that has a methyl, ethyl, or methoxy group. From this observation, it is clear that electron-donating groups enhance the nucleophilicity of the ring and, thus, stimulate the rate of the reaction. The library of synthesized compounds is shown in Table 2. In the case of a *meta*-substituted arylthiourea as the starting material (i.e., *meta*-Cl, -Br, or -Me), regioisomeric products were obtained in almost equal amounts. Although the individual isomers were successfully isolated and characterized in the cases of **2o**/**2o′** and **2p**/**2p′**, they could not be separated in the case of **2n** and **2n′**. The substrate scope was also examined by varying the pyridyl unit of the starting material, and good results were obtained (e.g., **2q**–**2t**). With the exception of compounds **2d**, **2i**, **2o**/**2o′**, and **2p**/**2p′**, the purification process of **2** involves a simple trituration with no need for column chromatography.

Table 2. Synthesized compounds **2a**–**2t**.



A double C–H functionalization that occurs through tandem C–N and C–S bond formations by using simple thiourea has been reported by Punniyamoorthy et al.[8b] In the present work, however, C–S bond formation predominates over C–N bond formation, and no further cyclization takes place.

A plausible mechanism for the formation of *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine is shown in Scheme 3.[6k] The first step involves the nucleophilic attack of the sulfur on PIFA to displace one molecule of TFA and give intermediate **A**. The sulfur atom is then attacked by the electron-rich *ortho* position of the benzene ring to provide cationic intermediate **B**, which aromatizes to give *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine.



Scheme 3. Proposed mechanism for the formation of compound **2**.

The addition of a radical scavenger such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) has no effect on the reaction, which suggests that a free radical mechanism is not taking place. Despite the two possible routes for the oxidative cyclization and the formation of the new C–S bond with the phenyl or pyridine ring, this cyclization has regioselectively oc-

curred at the phenyl ring. This selectivity is likely because of the greater nucleophilicity of the *ortho* position of the phenyl ring over that of the 3-position of the pyridine ring.

Conclusions

In summary, we have developed an efficient method for the synthesis of biologically important *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine by using a hypervalent iodine(III) reagent. This reaction has many advantages such as a metal-free approach, a broad substrate scope, a short reaction time, good to excellent yields, an easy purification protocol, and simple starting materials.

Experimental Section

General Methods: The melting points were measured in open capillary tubes. The ^{1}H and ^{13}C NMR spectroscopic data were recorded with a 300 MHz spectrometer (Bruker). $CDCl_3$ or [D_6]dimethyl sulfoxide ([D_6]DMSO) was used as the solvent with TMS as the internal standard. Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are reported in Hertz (Hz). ^{13}C NMR spectra were routinely run with broadband decoupling. Elemental analyses were performed on a Perkin–Elmer 2400 Series II Elemental CHNS analyzer. Mass spectra were recorded with a Thermo Fischer LCMS instrument.

General Procedure for the Syntheses of *N*-(Pyridin-2-yl)-benzo[*d*]thiazol-2-amines (2a–2t): A mixture of the heteroarylthiourea (1.0 equiv.) and $PhI(OCOCF_3)_2$ (1.2 equiv.) were added to a 10 mL round-bottomed flask, and the mixture was stirred at room temperature for 10 min. During this time, the progress of the reaction was monitored by TLC (petroleum ether/ethyl acetate, 2:3). Upon completion, the solvent was removed. The reaction mass was partitioned between dichloromethane and a sodium hydrogen carbonate solution. The aqueous layer was then extracted with dichloromethane (2×). The combined organic layers were dried with sodium sulfate, and the dichloromethane was removed under vacuum to provide a solid. Further trituration with diethyl ether followed by drying in vacuo afforded the product **2a**–**2t**, which was recrystallized (dichloromethane/methanol) to give the pure solid.

***N*-(Pyridin-2-yl)benzo[*d*]thiazol-2-amine (2a):** White solid; m.p. 222–224 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 11.15 (s, 1 H), 8.34 (d, J = 3.6 Hz, 1 H), 7.75 (d, J = 7.7 Hz, 1 H), 7.63 (m, 2 H), 7.35 (t, J = 7.3 Hz, 1 H), 7.15–7.32 (m, 2 H), 6.94–6.90 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 159.5, 151.6, 149.3, 146.0, 137.3, 131.6, 125.1, 121.5, 120.3, 118.8, 116.2, 111.0 ppm. $C_{12}H_9N_3S$ (227.28): calcd. C 63.41, H 3.99, N 18.49; found C 63.44, H 3.95, N 18.53. MS (ESI): calcd. for [M – H]$^+$ 226.05; found 226.04.

6-Chloro-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2b): White solid; m.p. 239–241 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.71 (s, 1 H), 8.42 (d, J = 4.8 Hz, 1 H), 7.76 (d, J = 2.0 Hz, 1 H), 7.64–7.58 (m, 2 H), 7.36 (dd, J = 8.6, 2.1 Hz, 1 H), 7.02–6.95 (m, 1 H), 6.89 (d, J = 8.2 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 160.0, 151.2, 148.0, 145.9, 137.3, 133.2, 126.3, 125.4, 119.8, 119.6, 116.3, 111.0 ppm. $C_{12}H_8ClN_3S$ (261.73): calcd. C 55.07, H 3.08, N 16.05; found C 55.11, H 3.05, N 16.08. MS (ESI): calcd. for [M – H]$^+$ 260.01; found 260.03.

6-Bromo-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2c): White solid; m.p. 187–189 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 11.68 (s, 1 H), 8.32 (dd, J = 5.0, 1.0 Hz, 1 H), 8.11 (d, J = 1.8 Hz, 1 H), 7.77–7.15 (m, 1 H), 7.53–7.44 (m, 2 H), 7.13 (d, J = 8.3 Hz, 1 H), 7.01–6.97 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 160.0, 151.3, 148.6, 146.4, 138.3, 133.9, 128.5, 123.5, 120.5, 117.0, 113.5, 111.2 ppm. $C_{12}H_8BrN_3S$ (306.18): calcd. C 47.07, H 2.63, N 13.72; found C 47.09, H 2.60, N 13.75. MS (ESI): calcd. for [M – H]$^+$ 305.96; found 305.93.

6-Fluoro-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2d): Off-white solid; m.p. 200–202 °C. ^{1}H NMR (300 MHz, [D_6]DMSO): δ = 11.22 (s, 1 H), 8.32 (d, J = 3.9 Hz, 1 H), 7.65–7.55 (m, 2 H), 7.47 (d, J = 8.2 Hz, 1 H), 7.15 (d, J = 8.2 Hz, 1 H), 7.07 (t, J = 9.0 Hz, 1 H), 6.96–6.87 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 159.5, 158.5 (d), 151.6, 146.6, 146.2, 138.5, 133.0 (d), 120.1 (d), 117.1, 113.6 (d), 111.3, 107.8 (d) ppm. $C_{12}H_8FN_3S$ (245.27): calcd. C 58.76, H 3.29, N 17.13; found C 58.72, H 3.31, N 17.17. MS (ESI): calcd. for [M + H]$^+$ 246.04; found 245.98.

6-Methyl-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2e): White solid; m.p. 230–232 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.97 (s, 1 H), 8.41 (d, J = 4.4 Hz, 1 H), 7.61–7.57 (m, 3 H), 7.26–7.21 (m, 1 H), 6.96–6.90 (m, 2 H), 2.48 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.3, 151.4, 146.8, 146.1, 137.3, 131.7, 131.3, 126.5, 120.3, 118.4, 116.1, 110.8, 20.8 ppm. $C_{13}H_{11}N_3S$ (241.31): calcd. C 64.70, H 4.59, N 17.41; found C 64.73, H 4.55, N 17.39. MS (ESI): calcd. for [M + H]$^+$ 242.07; found 242.0.

4-Methyl-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2f): White solid; m.p. 208–210 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 15.53 (s, 1 H), 8.48 (d, J = 4.6 Hz, 1 H), 7.81 (t, J = 7.7 Hz, 1 H), 7.60 (d, J = 6.3 Hz, 1 H), 7.43 (d, J = 8.2 Hz, 1 H), 7.33–7.29 (m, 2 H), 7.19–7.15 (m, 1 H), 2.70 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.7, 149.2, 146.2, 138.9, 135.9, 129.2, 126.1, 125.7, 125.1, 119.8, 119.3, 113.7, 17.6 ppm. $C_{13}H_{11}N_3S$ (241.31): calcd. C 64.70, H 4.59, N 17.41; found C 64.74, H 4.56, N 17.45.

6-Ethyl-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2g): White solid; m.p. 184–187 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.59 (s, 1 H), 8.41 (d, J = 4.5 Hz, 1 H), 7.63–7.60 (m, 2 H), 7.59–7.53 (m, 1 H), 7.26–7.23 (m, 1 H), 6.96–6.90 (m, 2 H), 2.78 (q, J = 7.6 Hz, 2 H), 1.32 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.0, 151.6, 146.8,* 138.8, 137.9, 132.2, 126.2, 119.9, 118.9, 116.9, 111.2, 28.8, 16.0 ppm. * Two carbon signals have merged. $C_{14}H_{13}N_3S$ (255.34): calcd. C 65.85, H 5.13, N 16.46; found C 65.87, H 5.10, N 16.48. MS (ESI): calcd. for [M + H]$^+$ 256.08; found 256.03.

6-Isopropyl-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2h): White solid; m.p. 177–181 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.70 (s, 1 H), 8.41 (d, J = 4.6 Hz, 1 H), 7.62 (d, J = 8.8 Hz, 2 H), 7.52 (t, J = 7.7 Hz, 1 H), 7.27 (dd, J = 7.5, 2.2 Hz, 1 H), 6.96–6.88 (m, 2 H), 3.04 (sept, J = 6.8 Hz, 1 H), 1.34 (d, J = 6.9 Hz, 6 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.1, 151.6, 147.0, 146.8, 143.4, 137.8, 132.2, 124.7, 118.8, 118.4, 116.8, 111.2, 34.1, 24.4 ppm. $C_{15}H_{15}N_3S$ (269.36): calcd. C 66.88, H 5.61, N 15.60; found C 66.85, H 5.57, N 15.63. MS (ESI): calcd. for [M + H]$^+$ 270.10; found 270.03.

***N*-(Pyridin-2-yl)naphtho[1,2-*d*]thiazol-2-amine (2i):** White solid; m.p. 204–206 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.81 (s, 1 H), 8.61 (d, J = 8.8 Hz, 1 H), 8.41 (d, J = 4.7 Hz, 1 H), 7.96–7.93 (m, 1 H), 7.90 (d, J = 8.6 Hz, 1 H), 7.73 (d, J = 8.6 Hz, 1 H), 7.52–7.44 (m, 2 H), 7.31 (t, J = 7.7 Hz, 1 H), 6.87–6.82 (m, 1 H), 6.63 (d, J = 8.3 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 161.1, 151.3, 146.6, 144.3, 137.7, 132.3, 128.2, 127.4, 126.6, 126.2, 125.5, 123.4, 123.0, 119.0, 116.9, 111.3 ppm. $C_{16}H_{11}N_3S$ (277.34): calcd. C 69.29, H 4.00, N 15.15; found C 69.35, H 4.04, N 15.10.

6-Methoxy-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2j): Off-white solid; m.p. 200–202 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 11.25 (s, 1 H), 8.40 (d, J = 4.7 Hz, 1 H), 7.62–7.65 (m, 2 H), 7.32 (br. s, 1 H), 7.02 (d, J = 8.8 Hz, 1 H), 6.92 (d, J = 9.1 Hz, 2 H), 3.89 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.1, 155.7, 151.6, 146.7, 143.0, 137.9, 133.2,

119.6, 116.7, 114.2, 111.0, 104.8, 55.9 ppm. $C_{13}H_{11}N_3OS$ (257.31): calcd. C 60.68, H 4.31, N 16.33; found C 60.63, H 4.35, N 16.37.

4-Methoxy-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2k): Light brown solid; m.p. 196–198 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.25 (s, 1 H), 8.33 (d, J = 4.2 Hz, 1 H), 7.63–7.58 (m, 2 H), 7.16 (d, J = 7.6 Hz, 2 H), 6.92–6.88 (m, 1 H), 6.80 (dd, J = 8.5, 1.5 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 161.0, 158.2, 151.5, 150.6, 146.0, 137.3, 123.5, 120.6, 116.2, 111.0, 110.3, 102.8, 55.0 ppm. $C_{13}H_{11}N_3OS$ (257.31): calcd. C 60.68, H 4.31, N 16.33; found C 60.71, H 4.36, N 16.29.

6-Nitro-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2l): Yellow solid; m.p. 256–258 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 12.13 (s, 1 H), 8.91 (s, 1 H), 8.40 (br. d, J = 4.0 Hz, 1 H), 8.22 (d, J = 8.9 Hz, 1 H), 7.86–7.77 (m, 1 H), 7.71 (d, J = 8.9 Hz, 1 H), 7.20 (d, J = 7.8 Hz, 1 H), 7.13–7.04 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 164.5, 154.7, 150.8, 146.5, 141.7, 138.6, 132.3, 121.7, 118.7, 118.2, 117.8, 111.8 ppm. $C_{12}H_8N_4O_2S$ (272.28): calcd. C 52.93, H 2.96, N 20.58; found C 52.90, H 2.98, N 20.54.

Methyl 2-(Pyridin-2-ylamino)benzo[*d*]thiazole-6-carboxylate (2m): White solid; m.p. 242–244 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 8.44 (d, J = 1.5 Hz, 1 H), 8.37 (d, J = 4.5 Hz, 1 H), 7.99 (dd, J = 8.5, 1.7 Hz, 1 H), 7.73–7.67 (m, 1 H), 7.64 (d, J = 8.5 Hz, 1 H), 7.21 (d, J = 8.3 Hz, 1 H), 7.02–6.98 (m, 1 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 166.2, 162.4, 152.7, 151.0, 145.9, 137.6, 131.6, 126.7, 122.9, 122.4, 118.2, 116.8, 111.4, 51.5 ppm. $C_{14}H_{11}N_3O_2S$ (285.32): calcd. C 58.93, H 3.89, N 14.73; found C 58.98, H 3.85, N 14.70.

7-Methyl-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine and 5-Methyl-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2n and 2n′): Off-white solid. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 11.46 (s, 2 H), 8.45–8.40 (m, 2 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.59–7.53 (m, 4 H), 7.34–7.30 (m, 1 H), 7.06 (t, J = 7.8 Hz, 2 H), 6.95–6.91 (m, 4 H), 2.61 (s, 3 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 160.9, 160.3, 151.4, 149.0, 148.5, 146.2, 137.2, 135.1, 131.6, 130.8, 128.5, 125.3, 123.1, 122.3, 120.0, 119.0, 116.2, 116.1, 110.8, 21.0, 20.3 ppm. Some carbon signals have merged.

5-Bromo-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2o): White solid; m.p. 201–203 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.21 (s, 1 H), 8.35 (d, J = 4.7 Hz, 1 H), 7.77 (s, 1 H), 7.67–7.59 (m, 2 H), 7.27 (d, J = 8.3 Hz, 1 H), 7.14 (d, J = 8.4 Hz, 1 H), 6.97–6.90 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 157.2, 147.7, 147.4, 142.4, 134.1, 127.2, 120.5, 118.6, 117.7, 114.6, 113.1, 107.6 ppm. $C_{12}H_8BrN_3S$ (306.18): calcd. C 47.07, H 2.63, N 13.72; found C 47.11, H 2.60, N 13.68.

7-Bromo-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2o′): White solid; m.p. 216–218 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.46 (s, 1 H), 8.40 (d, J = 6.0 Hz, 1 H), 7.70–7.65 (m, 1 H), 7.59 (dd, J = 7.3, 1.6 Hz, 1 H), 7.32–7.24 (m, 2 H), 7.17 (d, J = 8.3 Hz, 1 H), 7.00–6.95 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 158.8, 151.1, 149.7, 145.9, 137.5, 133.6, 126.5, 124.0, 117.7, 116.4, 112.5, 111.0 ppm. $C_{12}H_8BrN_3S$ (306.18): calcd. C 47.07, H 2.63, N 13.72; found C 47.10, H 2.66, N 13.75.

5-Chloro-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2p): White solid; m.p. 214–216 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.73 (s, 1 H), 8.34 (d, J = 4.0 Hz, 1 H), 7.90 (d, J = 8.2 Hz, 1 H), 7.78–7.73 (m, 1 H), 7.64 (s, 1 H), 7.17 (dd, J = 19.1, 8.1 Hz, 2 H), 7.03–6.99 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 161.2, 151.3, 150.7, 146.5,* 138.4, 130.4, 122.6, 121.8, 118.5, 117.2, 111.4 ppm. * Two carbon signals have merged. $C_{12}H_8ClN_3S$ (261.73): calcd. C 55.07, H 3.08, N 16.05; found C 55.09, H 3.11, N 16.09.

7-Chloro-*N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (2p′): White solid; m.p. 199–201 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.77 (s, 1 H), 8.38 (d, J = 4.0 Hz, 1 H), 7.75 (t, J = 6.8 Hz, 1 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.36 (t, J = 7.9 Hz, 1 H), 7.22 (d, J = 7.7 Hz, 1 H), 7.12 (d, J = 8.2 Hz, 1 H), 7.03–6.99 (m, 1 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.3, 151.2, 150.6, 146.6, 138.7, 131.1, 127.3, 125.3, 121.8, 118.0, 117.4, 111.5 ppm. $C_{12}H_8ClN_3S$ (261.73): calcd. C 55.07, H 3.08, N 16.05; found C 55.11, H 3.04, N 16.01.

***N*-(4,6-Dimethylpyridin-2-yl)benzo[*d*]thiazol-2-amine (2q):** Brown solid; m.p. 232–236 °C. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 11.09 (s, 1 H), 7.76 (d, J = 7.7 Hz, 1 H), 7.62 (d, J = 7.9 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.16 (t, J = 7.5 Hz, 1 H), 6.71 (s, 1 H), 6.59 (s, 1 H), 2.52 (s, 3 H), 2.26 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 160.2, 154.9, 150.7, 149.2, 148.6, 131.9, 124.9, 121.3, 120.3, 118.6, 116.8, 107.8, 23.0, 20.5 ppm. $C_{14}H_{13}N_3S$ (255.34): calcd. C 65.85, H 5.13, N 16.46; found C 65.88, H 5.10, N 16.51.

6-Bromo-*N*-(4,6-dimethylpyridin-2-yl)benzo[*d*]thiazol-2-amine (2r): Off-white solid; m.p. 217–219 °C. ^{1}H NMR (300 MHz, [D$_6$]-DMSO): δ = 11.13 (s, 1 H), 7.86 (d, J = 1.7 Hz, 1 H), 7.48 (d, J = 8.5 Hz, 1 H), 7.40 (dd, J = 8.5, 1.7 Hz, 1 H), 6.72 (s, 1 H), 6.62 (s, 1 H), 2.51 (s, 3 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 160.3, 154.8, 150.5, 148.7, 148.3, 133.9, 127.9, 122.5, 119.9, 117.0, 113.3, 107.8, 22.9, 20.5 ppm. $C_{14}H_{12}BrN_3S$ (334.23): calcd. C 50.31, H 3.62, N 12.57; found C 50.28, H 3.66, N 12.60.

6-Chloro-*N*-(4,6-dimethylpyridin-2-yl)benzo[*d*]thiazol-2-amine (2s): White solid; m.p. 234–236 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 10.64 (s, 1 H), 7.54 (d, J = 2.0 Hz, 1 H), 7.37 (d, J = 8.6 Hz, 1 H), 7.11 (dd, J = 8.5, 2.1 Hz, 1 H), 6.50 (s, 1 H), 6.44 (s, 1 H), 2.36 (s, 3 H), 2.10 (s, 3 H) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 160.4, 154.8, 150.5, 148.7, 148.0, 133.5, 126.0, 125.2, 119.7, 119.4, 117.0, 107.8, 22.9, 20.5 ppm. $C_{14}H_{12}ClN_3S$ (289.78): calcd. C 58.03, H 4.17, N 14.50; found C 58.01, H 4.20, N 14.54.

***N*-(4,6-Dimethylpyridin-2-yl)-6-methoxybenzo[*d*]thiazol-2-amine (2t):** Brown solid; m.p. 176–178 °C. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 10.55 (s, 1 H), 7.57 (d, J = 8.8 Hz, 1 H), 7.31 (d, J = 2.5 Hz, 1 H), 6.97 (dd, J = 8.8, 2.5 Hz, 1 H), 6.59 (s, 2 H), 3.87 (s, 3 H), 2.53 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 159.5, 155.5, 155.3, 150.8, 149.1, 143.2, 133.2, 119.4, 117.2, 113.7, 107.8, 104.1, 55.5, 23.0, 20.7 ppm. $C_{15}H_{15}N_3OS$ (285.09): calcd. C 63.13, H 5.30, N 14.73; found C 63.10, H 5.35, N 14.69.

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A new facile pyridine-catalyzed hydroacylation of aldehydes with azodicarboxylates under microwave irradiation

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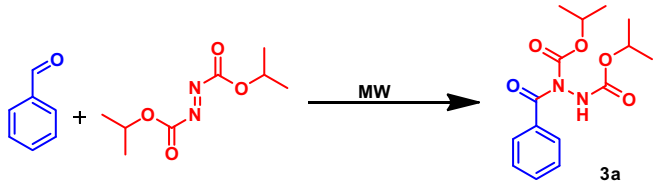
ABSTRACT

An efficient metal free hydroacylation of aromatic aldehydes with azadicarboxylate has been developed using pyridine as a catalyst providing an easy access for hydroacylation products in good yields.

Nitrogen containing compounds are of great significance owing to their wide spectrum of biological activities. The construction of C—N bond is of great importance and several reactions, which includes polar, radical, and pericyclic, have been employed for the construction of C—N bond.[1] The chemistry of dialkyl azodicarboxylates had been of considerable interest, as they behave as good nucleophilic acceptors due to the presence of strong electron withdrawing groups.[1b] The dialkyldiazocarboxylates have successfully subjected to different types of reactions including zwitter ion intermediate reactions,[2] α-amination of carbonyl compounds,[3] the C—H activation at the α position of amines and ethers[4] and the ene type reactions with olefins.[5] The hydroacylation reaction of dialkyldiazocarboxylates with direct C—H functionalization of aldehydic C—H bonds to form hydrazine imides has also been studied. Hydroacylation process is an atom-economic pathway which involves addition of the hydrogen atom and acyl unit across the A–B multiple bond (A = B = C or N).[6] Metals like rhodium, copper, and zinc have been found to catalyze the hydroacylation reactions.[7] Ionic liquid mediated hydroacylation has also been reported by Ni et al.[8] and water mediated hydroacylations are also known.[9] With aromatic aldehydes, the reactivity has been found to be very low with relatively poor yields. Xu and co-workers reported the hydroacylation reaction using co-operative catalysis strategy.[10] Recently, Kokotos et al. reported a photoorganocatalytic hydroacylation[11] and Ramon and Perez reported hydroacylation of azodicarboxylates[12] using a heterogeneous catalyst. In spite of

Table 1
Optimization of the reaction conditions[a]



Entry	Catalyst	Solvent	Yield[b] of 3 (%)
1	Pyridine[c]	DMF	65
2	Pyridine	DMF	85
3	Isoquinoline	DMF	71
4	Quinoline	DMF	63
5	Diethylamine	DMF	Trace
6	DABCO	DMF	Trace
7	Triethylamine	DMF	25
8	Piperidine	DMF	Trace
9	—	DMF	25[d]
10	Pyridine	Water	60
11	Pyridine	Methanol	53
12	Pyridine	Toluene	27
13	Pyridine	Dioxane	23
14	Pyridine	THF	20
15	Pyridine	DCE	Trace

[a] Reaction conditions: Microwave irradiation in the solvent at 140 °C with **1** (1.2 mmol), **2** (1 mmol), catalyst (0.1 mmol), solvent (1 ml) for 10 min.
[b] Isolated yield.
[c] Reaction at reflux condition with pyridine for 5 h.
[d] Reaction without catalyst under microwave condition.

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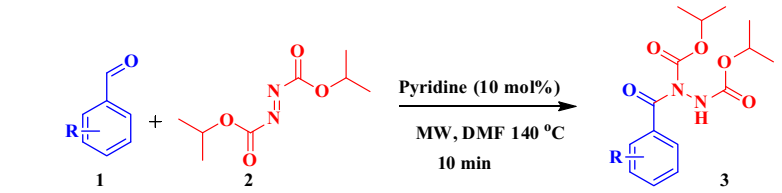
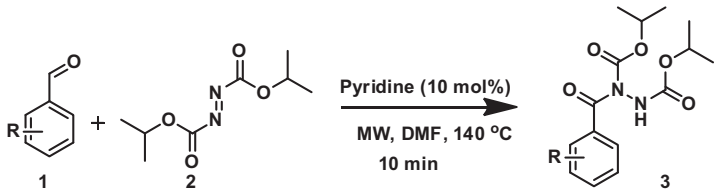
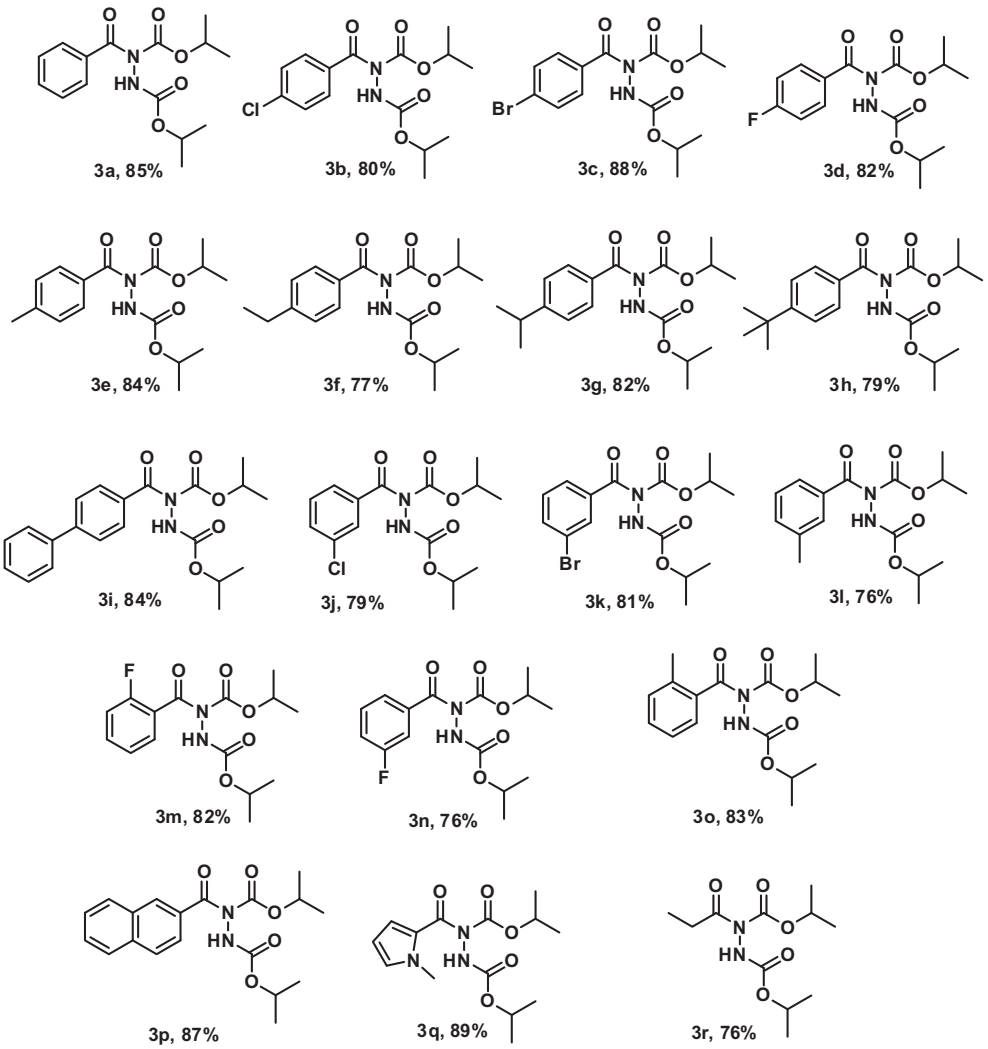


R = H, 4-Cl, 4-Br, 4-F, 4-CH_3, 4-CH_2CH_3, 4-$CH(CH_3)_2$, 4-$C(CH_3)_3$, 4-C_6H_5, 3-Cl, 3-Br, 3-CH_3, 2-F, 3-F, 2-CH_3

Scheme 1. Hydroacylation of azodicarboxylates with aldehydes.

Table 2
Synthesis of **3a–3r**





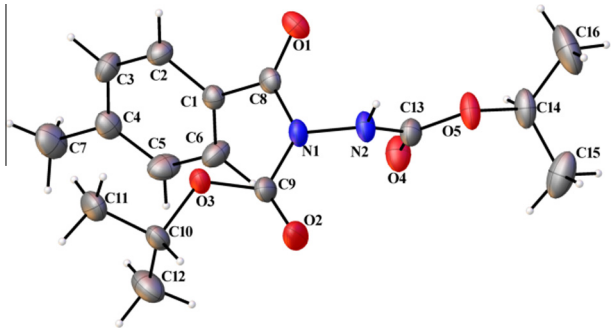


Figure 1. Crystal structure of **3e**.

all these reports, no report has provided a route with reduced reaction time. So it is highly desirable to develop a simple and efficient method for hydroacylation of azodicarboxylates that get completed in shorter reaction time. Pyridine is used as a nucleophilic catalyst in the acylation of alcohols and amines. An unexpected [2+2] cycloaddition of acetylene dicarboxylate with benzaldehyde using pyridine as a catalyst has been reported by Nair et al.[13] The present article summarizes the use of pyridine for a fast hydroacylation of azodicarboxylates.

Initially, we selected a model reaction between benzaldehyde and diisopropyl azodicarboxylate for optimizing the reaction condition (Table 1). We examined the reaction with various solvents and various catalysts (Table 1, entries 1–8). When pyridine is employed as the catalyst, the reaction got completed in 5 h with DMF as the solvent under reflux (Table 1, entry 1). The conversion (45%) was not satisfactory enough and the same reaction under microwave condition got completed within 5 min at 140 °C providing good yield (Table 1, Scheme 1). Encouraged with this result, the reaction was investigated with different nitrogen based catalysts (Table 1, entries 1–8).

However, the yields were relatively poor with isoquinoline and quinoline (Table 1, entries 3 and 4). With nonpyridine based nucleophiles such as diethyl amine and piperidine too (Table 1, entries 5 and 8), the yields were only in trace amounts. Triethylamine and DABCO (Table 1, entries 6 and 7) also failed to affect the reaction significantly and thus pyridine has emerged as the base of choice. Among the solvents tried, the yield was relatively good in DMF, water, and methanol (Table 1, entries 2, 10, and 11), poor in toluene, dioxane, and THF (Table 1, entries 12–14) and negligible in the case of dichloroethane (Table 1, entry 15) under microwave irradiation. The results indicate that the reaction works well at elevated temperature with pyridine as the suitable catalyst in DMF under microwaves (Table 1, entry 2). Under the optimized reaction conditions, the reaction was successfully extended with different aldehydes (Scheme 1, Table 2). As depicted in Table 2, the reaction worked well for a wide range of aldehydes excluding the electron withdrawing and electron donating aromatic aldehydes. Still, a good number of hydroacylated products involving aromatic aldehydes (Table 2, compounds **3a**–**3o**) have been synthesised. The scope of the reaction was then explored with a fused aryl system (Table 2, compound **3p**), a heterocyclic aldehyde (Table 2, compound **3q**), and an aliphatic aldehyde (Table 2, compound **3r**) with encouraging results. The structure of **3e** is confirmed by spectral data[14] and single crystal X-ray analysis as shown in Figure 1.[15]

Though an ionic mechanism as shown in Scheme 2 can be tentatively suggested for the conversion in Scheme 1, it is surprising that the aryl aldehydes with both electron releasing and electron withdrawing substituents have not undergone the reaction successfully.

In conclusion, we report an efficient hydroacylation reaction of aldehydes with azodicarboxylates catalyzed by pyridine under microwave irradiation, which has more advantages over the existing methods in terms of easy workup, less reaction time, and better yield under metal free condition.

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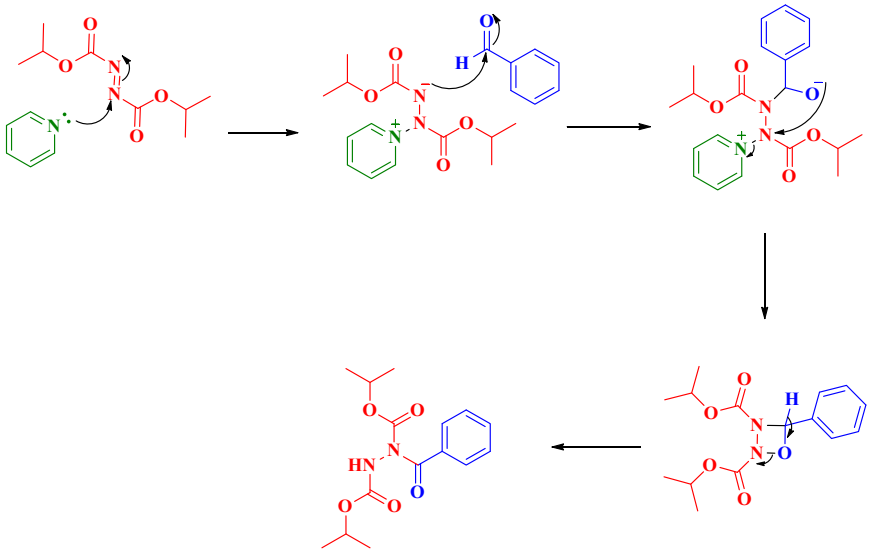
We thank the DST, New Delhi, for assistance under the IRHPA program for the NMR facility. Financial support from the UGC, New Delhi, to A.M. is gratefully acknowledged for the award of a Junior Research Fellowship.



Scheme 2. Tentative mechanism for hydroacylation.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.11.090.

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14. A mixture of substituted benzaldehyde **1** (1.2 mmol), diisopropyl azadicarboxylate **2** (1 mmol), and pyridine (0.1 mmol), in DMF (1 mL) was sealed and subjected to microwave irradiation, programmed at 140 °C and 120 W for 10 min. The completion of the reaction was monitored by TLC. The reaction mixture was then quenched with dilute HCl solution and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous sodium sulfate, and concentrated in vacuum. Crude product was purified by column chromatography using ethyl acetate/hexane (10:90) as the solvent to get **3**. Characterization data for a representative compound, diisopropyl 1-(4-methylbenzoyl) hydrazine-1,2-dicarboxylate (**3e**, Ref. [7b]) are given below:
Isolated as white solid; mp 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60 (bd, 2H), 7.22 (d, J = 7.2 Hz, 2H) 5.06–4.96 (m, 1H), 4.94–4.85 (m, 1H), 2.39 (s, 3H), 1.28 (d, J = 6.1 Hz, 6H), 1.10 (d, J = 5.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.0, 155.3, 152.9, 142.4, 132.0, 128.6, 128.4, 72.1, 70.3, 21.7, 21.3.
15. Crystallographic data (excluding structure factors) for compound **3e** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 1019854. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. [Fax: +44 (0) 1223336033 or e-mail: deposit@ccdc.cam.ac.uk].

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Synthesis and antioxidant characteristic of novel thiazolidinone derivatives

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A series of novel thiazolidinone derivatives have been synthesized by solventless condensation of *N*-alkylamines with arylaldehydes at room temperature followed by a microwave assisted solventless addition of thioglycollic acid to the resultant imines. The synthesized compounds are characterized by ^{1}H NMR, ^{13}C NMR, MS and X-ray techniques and one of the synthesized thiazolidinones has been evaluated for its antioxidant property.

Keywords: Thiazolidinone, solventless condensation, thioglycollic acid, imines, antioxidant property

Thiazolidinones belong to an important group of heterocyclic compounds possessing diverse biological responses such as antimicrobial[1,2], antifungal[3], antiviral[4], antitubercular[5,6] and anticonvulsant activities[7,8]. Literature survey reveal that thiazolidin-4-ones also have potential anticancer[9,10], anti-inflammatory[11] and anti-HIV activities[12,13].

Several methods have been reported in literature for the syntheses of thiazolidinones and the popular method is the cyclocondensation of the appropriate Schiff bases/azomethines with α-mercaptoalkanoic acids such as thioglycollic acid[14-16]. The reaction of thiourea derivatives with chloroacetic acid derivatives[17,18] is another route for this heterocyclic system. A one-pot three component synthesis of 4-thiazolidinones has been developed in aqueous medium[19]. Desai *et al* carried out the microwave assisted synthesis of thiazolidinone from the Schiff's bases using thiolactic acid. Pyridyl substituted thiazolidin-4-ones were employed as chiral ligands in the copper catalyzed aymmetric conjugate addition of diethylzinc to cyclohexenone and chalcone[20]. Anodic partial fluorination of 4-thiazolidinones leads to the synthesis of monofluoro-β-lactams[21].

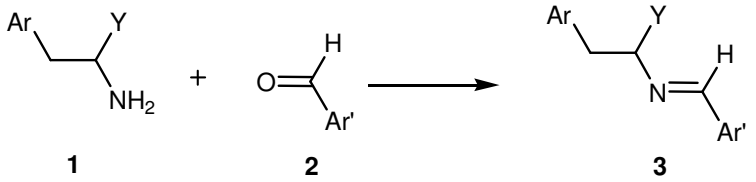
The present work describes a solventless synthetic methodology towards the construction of a series of novel thiazolidinone derivatives **5** in excellent yields along with a preliminary study on one of the synthesized compounds for its antioxidant property on human lung fibroblasts. The N-alkylamines **1** for the present investigation, β-arylethylamines and 1-methyl-2-arylethylamines, have been synthesized from the respective nitroolefins by a complete reduction of the double bond and the nitro group by diborane. The *in situ* generation of diborane by mixing $NaBH_4$ and $BF_3.Et_2O$ was used in excess (1:1.5) for the reduction and the reaction mixture was refluxed in THF for 6 hr. This vigorous condition is essential in order to avoid partial reduction leading to unsaturated amine or saturated hydroxylamine. When the reaction was attempted in the absence of solvent under microwave condition, the reduction has not gone completely. The resultant amines have been used as such for the next step after purification *via* its salt formation.

The imines **3** have been synthesized by the condensation of N-alkyl amines **1** with different arylaldehydes **2** under solvent-free condition by grinding the mixture of amine and aldehyde in equimolar quantity and keeping the mixture at room temperature (**Scheme I**). The reaction got completed in less than 30 min. The condensation is obviously faster here compared to the corresponding nitrone formation[22]. It must be mentioned that a systematic study of solid state condensation of aryl aldehydes and arylamines has been reported by Schmeyers *et al.*[23], in which the course of the reaction was monitored by AFM and SNOM techniques to study the mechanism of conversion. Increasing the temperature of the reaction mixture or irradiation by microwave did not significantly change the yield or the reaction time.

Results and Discussion

The resultant imines **3** have all been characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopic techniques. All the imines have the characteristic C=N stretching frequency around 1640-1690 cm^{-1}. In the mass spectra of all the imines, the base peak appeared at *m/z* M-C_7H_7, indicating the loss of a benzyl radical from the molecular ion peak. This was interesting because in the corresponding nitrones[22], the base peak was different due to the loss of the oxime unit from the molecular ion. The molecular ion peak was also relatively stronger in some cases compared to nitrones. The mass fragmental patterns for N-(2-hydroxy-1-naphthylidene)-1-methyl-2-phenyl)-ethanamine, **3k**, are given in **Scheme II**.

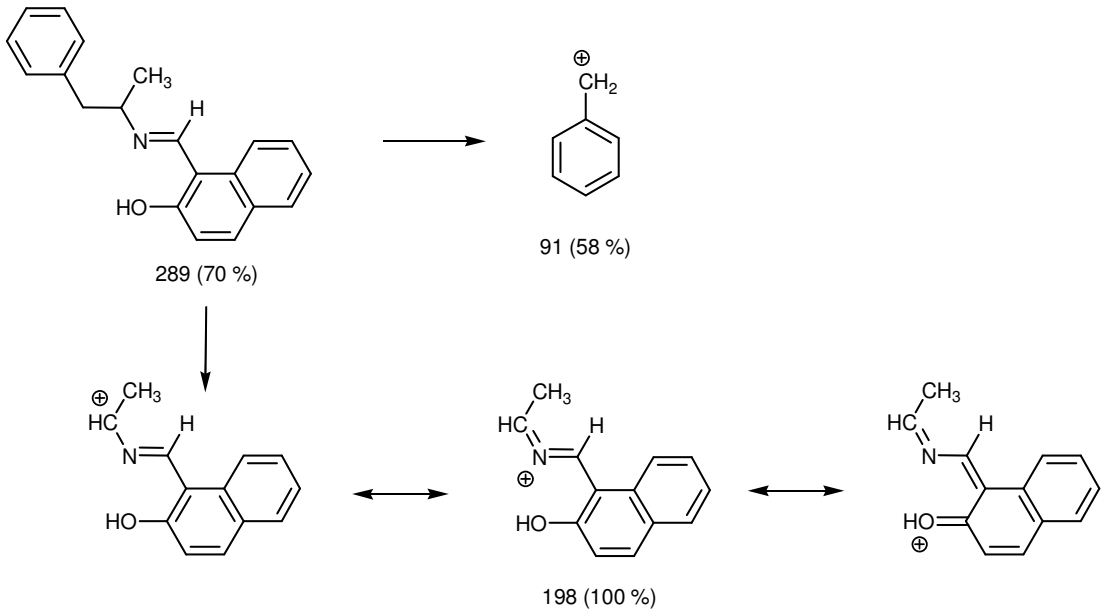
The ^{1}H NMR spectrum of imine N-(4-chlorobenzylidine)-1-methyl-2-(4-hydroxyphenyl) ethanamine **3i** exhibited pairs of doublets at δ 7.55, 7.31, 6.92, 6.67 accounting for the aryl hydrogens. There was a singlet at δ 7.91 which can be attributed to the azomethine proton. The hydroxyl hydrogen appeared at δ 5.30 as a broad signal. There was a three hydrogen doublet (J = 6.3 Hz) and a two hydrogen doublet (J = 6.3 Hz) at δ 1.30 and 2.75, respectively. A symmetrical sextet (J = 6.3 Hz) appeared at δ 3.52. These signal combination proves



1 **2** **3**

Compd	Ar	Y	Ar′
3a	4-Methoxyphenyl	H	4-Chlorophenyl
3b	2,4-Dichlorophenyl	H	4-Chlorophenyl
3c	2-Chlorophenyl	H	4-Chlorophenyl
3d	4-Methylphenyl	H	4-Chlorophenyl
3e	3,4-Methylenedioxy	H	4-Nitrophenyl
3f	2-Methoxyphenyl	H	4-Chlorophenyl
3g	Phenyl	H	Phenyl
3h	2-Thienyl	CH_3	4-Chlorophenyl
3i	4-Hydroxyphenyl	CH_3	4-Chlorophenyl
3j	Phenyl	CH_3	4-Nitrophenyl
3k	Phenyl	CH_3	2-Hydroxy-1-naphthyl

Scheme I — Synthesis of imines



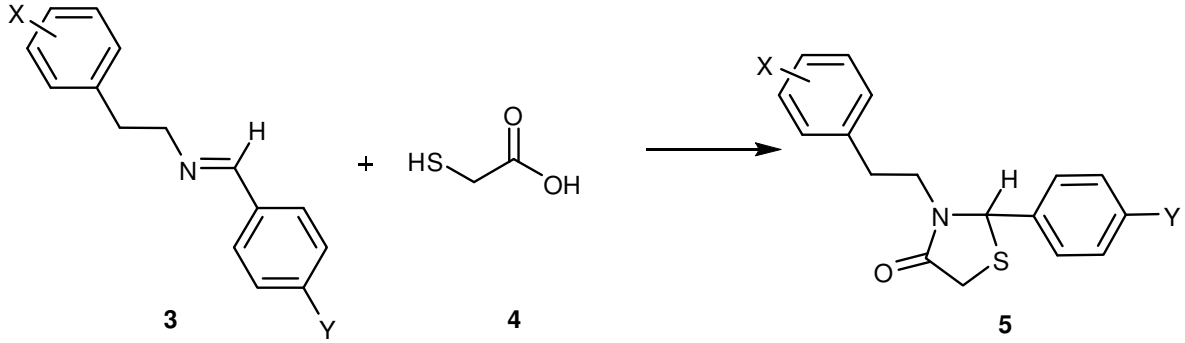
Scheme II — Mass fragmentations of **3k**

the presence of CH_2-CH-CH_3 grouping. The non-equivalence of the diasterotopic methylene hydrogens has not been observed, though in the corresponding nitrones the methylene hydrogens are very much non-equivalent giving different signals[22]. The ^{13}C NMR spectrum of this compound gave signals at δ 115.3, 128.8, 129.5, 130.6, 159.1 for CH carbons, the last one being that of azomethine carbon. The quarternary carbons appeared at δ 130.5, 134.0, 136.6 and 154.5. The methyl carbon appeared at δ 21.9, the methylene carbon at δ 43.3 and the methine carbon at δ 68.6.

Having synthesized the imines under solventless condition, the addition of thioglycollic acid to α-aryl-N-alkyl imines has also been carried out under solventless condition. Equimolar mixture of thioglycollic acid and the imines were mixed together forming a viscous fluid. The fluid was monitored time to time at room temperature for the possible conversion to the heterocyclic compound. The reaction took place slowly, but it has been noticed that the reaction proceeded rapidly to completion under microwaves within three min even in minimum power of microwave. As with other condensation reactions, this reaction also took place efficiently under microwaves. In all the substituted α-aryl-N-alkyl imines subjected to thioglycollic acid addition, a single product **5** has been obtained showing the selectivity of the reaction (**Scheme III**). It may be noticed that imines of the type $ArCH_2CH_2N{=}CHAr'$ alone have been converted to the thiazolidinones and not those of the type $ArCH_2CH(CH_3)N{=}CHAr'$. All the attempts to convert the latter type of imines to the thiazolidinones under different conditions were not successful. This is probably due to the steric effect. All the products isolated have been shown to be 3-[2-arylethyl]-2-(aryl)-4-thiazolidinones **5** by mass and NMR spectral studies. An attempted multicomponent reaction involving **1**, **2** and **4** has led to poor yield of **5**.

The ^1H NMR spectrum of the 3-[2-(3,4-methylene-dioxyphenyl)ethyl]-2-(4-nitrophenyl) -4-thiazolidinone **5e** exhibited a pair of doublets each accounting for two hydrogens with a coupling constant of 8.7 Hz appearing at δ 8.22 and 7.35. These were attributed to the *ortho* and *meta* hydrogens to the nitro group of the *p*-nitrophenyl system. A two hydrogen singlet at δ 5.94 accounts for the methylene hydrogens of –O–CH_2–O– group. There were two bunches of signals each accounting for three hydrogens appearing between δ 3.68-3.98 and 2.60-2.90. The methine hydrogen also did not appear as a sharp signal at δ 5.37. Thus it could be noticed that the isolated –CH_2–CH_2– groups were not giving neat triplets and one of the methylene hydrogens of –CH_2–CH_2– groups was very much deshielded to the tune of δ 1.20, leaving the other three in the upfield region. This Δδ between the diastereotopic hydrogens of the N–CH_2 group was relatively high compared to other systems. The ^{13}C NMR spectrum exhibited equally intense signals at δ 32.5, 33.0, 44.9 and 62.8. The carbonyl carbon appeared at δ 171.0 and the carbon of –O–CH_2–O– appeared at δ 100.9.

The mass spectrum of 3-[2-(2-methoxyphenyl)-ethyl]-2-(4-chlorophenyl)-4-thiazolidinone **5f** exhibited a molecular ion peak at *m/z* 347.2 with 30% abundance. The molecular ion looses methoxy group



Compd	X	Y
5a	4-Methoxy	Cl
5b	2,4-Dichloro	Cl
5c	2-Chloro	Cl
5e	3,4-Methylenedioxy	NO_2
5f	2-Methoxy	Cl
5g	H	H

Scheme III — Synthesis of thiazolidones

giving M-31 signal at *m/z* 316.2. The molecular ion undergoes fragmentation at the C–N bond at the side chain of the thiazolidinone ring and the base peak appears at *m/z* 134 due to $[Ar–CH=CH_2]^+$. The single crystal X ray analysis of one of the thiazolidinones synthesised (**5g**) has been carried out and the ORTEP and packing diagrams are given in **Figure 1**. The crystal data is summarized in **Table I**.

The antioxidant behaviour of 3-phenethyl-2-phenyl-1,3-thiazolan-4-one **5g** was investigated in isoproterenol induced myocardial damage in rats in relation to vitamin C, vitamin E, lipid peroxides and antioxidant enzymes SOD and CAT activities. It has been demonstrated that ISO administration produces free radicals and *via* β-adrenorteceptor mechanism, it affects the cell metabolism to such a degree that cytotoxic free radicals are formed producing myocardial necrosis.

The control rats received physiological saline (1ml/kg body weight) intraperitoneally. Myocardial necrosis was induced by a subcutaneous injection of ISO-HCl (50 mg/kg b.w., 0 h), dissolved in physiological saline. The vehicle control received 10% DMSO (1mL/kg b.w.) intraperitoneally 30 min before ISO administration. The animal has been treated with thiazolidinone with an effective dosage of 5 mg/kg b.w., 30 min after ISO administration. The animals were divided into 4 different groups (5 rats/group) as follows: group 1: saline control (untreated); group 2: ISO induced MN (50 mg/kg), group 3: vehicle control 10% DMSO (1mL/kg) +ISO (50 mg/kg); group 4: thiazolidinone (5 mg/kg)+ISO (50 mg/kg) treated. After 48 hr, the animals were scarified by cerbical decapitation and the serum was collected and used for biochemical assays.

The Superoxidase Dismutase was estimated by monitoring the oxidation of Epinephrine according to the procedure of Misra *et al.*[24] The activity was expressed as units per minute per mg of protein. One unit of enzyme activity was defined as the amount of enzyme required to cause 50% inhibition of epinephrine auto oxidation. The lipid peroxide was estimated by the method of Okhawa *et al.*[25] by monitoring the colour intensity developed by the addition of the reagent, 10% phosphotungstic acid and thiobarbituric acid. Results were expressed in nanomoles of malonaldehyde/ml and for tissue, it was expressed as nanomoles of malonaldehyde per mg protein. Vitamin C and vitamin E have been estimated by spectrophotometric method[26,27]. Enzymatic Assay of Catalase[28] has been studied by observing the time required for the absorbance at 240 nm to get decreased from 0.45 to 0.40.

The results of thiazolidine **5g** treatment on enzymatic and non-enzymatic levels in serum on isoproterenol induced myocardial necrosis are provided in **Table II**.

On isoproterenol administration, the levels of vitamin C, vitamin E, SOD and CAT have been increased significantly ($p<0.001$) and post treatment

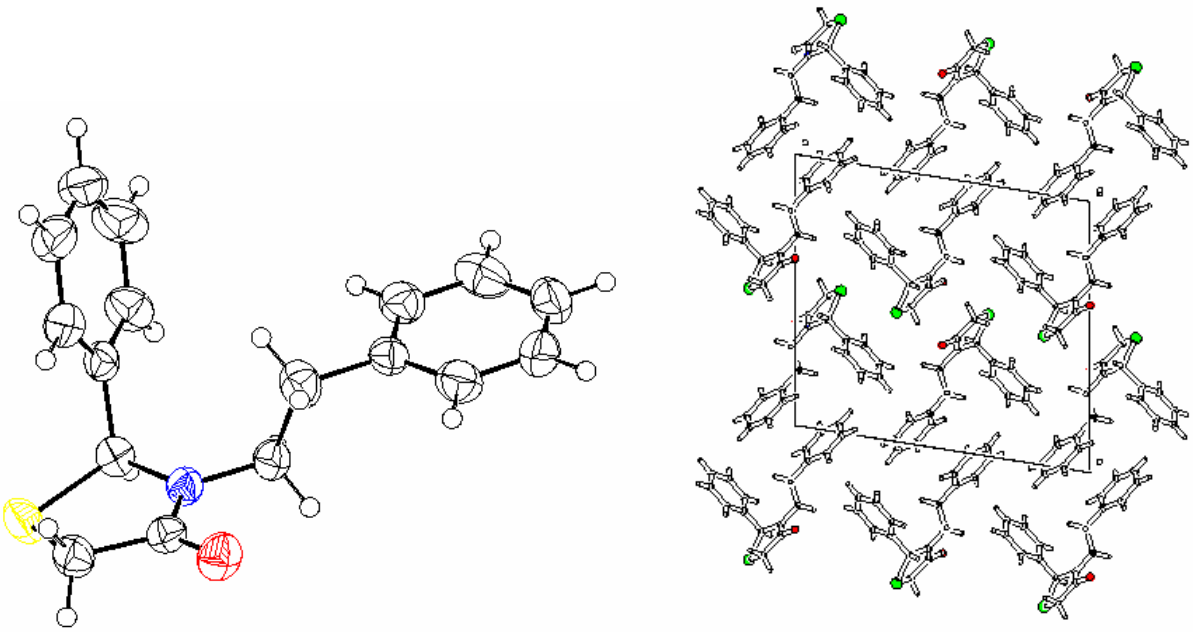


Figure 1 — ORTEP diagram of 3-(2-phenyl)ethyl-2-phenyl-4-thiazolidinones, **5g**

with thiazolidinone significantly retained the levels almost to normal compared to control ($p<0.001$). The levels of serum lipid peroxides increased significantly in the ISO-administered rats and thiazolidinone post treatment ($p<0.05$) reduced the enzymatic lipid peroxide levels significantly.

Experimental Section

Melting points are uncorrected. ^1H, ^{13}C and 2D NMR spectra were recorded on a Bruker 300 MHz instrument in $CDCl_3$ using TMS as internal standard. Chemical shifts are given in δ (ppm) and coupling constants are given in Hz. IR spectra were recorded on a Jasco FTIR instrument using KBr disc method and mass spectra were recorded on a Fennigan GCMS instrument. The single crystal X-ray data were collected on a Nonius MACH3 kappa diffractometer with MoK_α radiation. The structures were solved by direct methods from SHELXS-86 and refined by full matrix least squares on F^2 by SHELXL-93. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 884211). Copies of the data can be obtained, free of charge, by contacting The Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK (email: data_request@ccdc.cam.ac.uk; fax: +44 1223 336033).

Table I — Crystal data and structural refinement for **5g**

Empirical formula	$C_{17}H_{17}NOS$
Formula weight	283.38
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P 21/c
Unit cell dimensions	a = 14.932 Å; α = 90°
	b = 5.995 Å; β = 99.12°
	c = 16.449 Å; γ = 90°
Volume	1453.8 $Å^3$
Z	4
Density (calculated)	1.295 Mg m^{-3}
Absorption coefficient	0.217 mm^{-1}
F(000)	600
Crystal size	0.22 x 0.19 x 0.16 mm
Theta range for data collection	2.51 to 24.97°
Index ranges	0<=h<=17,-1<=k<=7,-19<=l<=19
Reflections collected	3199
Independent reflections	2550 [R_{int} = 0.0120]
Absorption correction	Psi-scans
Max. and min. transmission	0.9614 and 0.9394
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2550 / 0 / 182
Goodness-of-fit on F^2	1.051
Final R indices [I>2□(I)]	R1 = 0.0303, wR2 = 0.0751
R indices (all data)	R1 = 0.0440, wR2 = 0.0821
Largest diff. peak and hole	0.163 and-0.202 e. $Å^{-3}$

General method for the preparation of N-arylidene-2-arylethyanamine

Appropriately substituted arylethanamine (0.001 mole) was mixed with 0.001 mole of appropriately substituted arylaldehyde and ground well in a mortar at RT. The reaction mixture was scratched with petroleum ether (60-80) to remove the impurities. The resulting imine was a viscous liquid.

N-(4-Chlorobenzylidine)- 2 - (4 -methoxyphenyl) ethanamine, 3a. Yield 85%, m.p. 68°C. ^1H NMR (300 MHz, $CDCl_3$): δ 2.94 (t, *J* = 7.2 Hz, 2H), 3.53 (s, 3H), 3.81 (t, *J* = 7.2 Hz, 2H), 6.81 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.1 Hz, 2H), 8.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.8, 55.6, 63.8, 114.1, 129.2, 129.6, 130.3, 132.2, 135.0, 136.9, 158.3, 160.5. Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.00; H, 5.77; N, 5.11%.

N-(4-Chlorobenzylidene)- 2- (2, 4 - dichlorophenyl)- ethanamine, 3b. Yield 80%, Viscous liquid. ^1H NMR (300 MHz, $CDCl_3$): δ 3.10 (t, *J* = 7.2 Hz, 2H), 3.82 (t, *J* = 7.2 Hz, 2H), 7.13-7.15 (m, 2H), 7.32-7.38 (m,

Table II — Effect of thiazolidinone **5g** treatment on the levels of non-enzymatic and enzymatic antioxidants in serum in ISO-induced myocardial necrosis

S.No	Parameter	Vehicle Control	Isoproterenol	Thiazolidinone treated
1.	Vit C mg/dL	1.2880 ± 0.029	0.5700 ± 0.010	1.06000 ± 0.114
2.	Vit E mg/mol	4.4980 ± 0.019	2.2020 ± 0.008	3.5740 ± 0.302
3.	Catalase min/mg protein	14.3740 ± 0.005	10.310 ± 0.010	13.1460 ± 0.125
4.	SOD 50% of epinephrine autoxidation	9.8600 ± 0.089	6.3280 ± 0.031	8.7400 ± 0.167
5.	Lipid peroxide nm of TBA reactants /mg protein	9.1800 ± 0.743	14.9940 ± 0.060	7.6300 ± 0.172

All values are mean ± SD of 5 animals, $p<0.05$ as compared to control by student's unpaired test; $p<0.05$ as compared to isoproterenol control group.

3H), 7.62 (d, *J* = 8.4 Hz, 2H), 8.11 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.5, 60.6, 126.9, 127.4, 128.8, 129.1, 132.0, 132.6, 134.4, 134.7, 135.9, 136.6, 160.4.

N-(4- Chlorobenzylidene)- 2 - (2 - chlorophenyl)-ethanamine, **3c**. Yield 85%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.00 (t, *J* = 7.2 Hz, 2H), 3.72 (t, *J* = 7.2 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.09-7.18 (m, 4H), 7.96 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 59.7, 126.6, 127.7, 128.4, 130.0, 130.2, 133.0, 133.4, 135.4, 135.8, 136.2, 159.2.

N-(4-Chlorobenzylidene)- 2 - (4 - methylphenyl)-ethanamine, **3d**. Yield 90%, m.p. 85°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.95 (t, *J* = 7.2 Hz, 2H), 3.82 (t, *J* = 7.2 Hz, 2H), 7.10 (s, 4H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 36.9, 63.2, 128.8, 128.9, 129.0, 129.2, 134.6, 135.6, 136.4, 136.6, 160.0. Anal. Calcd for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26; N, 5.43. Found: C, 74.23; H, 6.12; N, 5.42%.

N-(4-Nitrobenzylidene)-2- (3, 4 - methylenedioxy-phenyl)ethanamine, 3e. Yield 95%, m.p. 110°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.92 (t, *J* = 7.2 Hz, 2H), 3.82 (t, *J* = 7.2 Hz, 2H), 6.01 (s, 2H), 7.36 (m, 3H), 7.63 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.0 Hz, 2H), 8.10 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 34.9, 62.2, 100.0, 108.2, 109.2, 122.0, 128.3, 128.5, 130.1, 130.4, 131.5, 146.2, 147.6, 160.2. MS (*m/z*): Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.87; H, 4.69; N, 9.32%.

N-(4-Chlorobenzylidene)-2-(2-methoxyphenyl)-ethanamine, 3f. Yield 90%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.95 (t, *J* = 7.2 Hz, 2H), 3.43 (s, 3H), 3.82 (t, *J* = 7.2 Hz, 2H), 6.00-7.36 (m, 6H), 7.63 (d, *J* = 8.4 Hz, 2H), 8.10 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.3, 54.6, 63.1, 113.1, 129.2, 129.6, 130.2, 132.2, 132.5, 132.7, 135.0, 136.9, 158.3, 160.1.

N-Benzylidene-2-phenylethanamine, 3g. Yield 90%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.99 (t, *J* = 7.2 Hz, 2H), 3.80 (t, *J* = 7.2 Hz, 2H), 7.25 (m, 8H), 7.60 (d, *J* = 8.4 Hz, 2H), 8.07 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 35.9, 62.8, 124.8, 128.5, 129.0, 129.2, 134.6, 135.6, 136.4, 136.4, 160.6.

N - (4 - Chlorobenzylidene) - 1 - (Thiophen- 2 - yl)-propan-2-amine, 3h. Yield 85%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (d, *J* = 6.3 Hz, 3H), 3.11 (d, *J* = 6.3 Hz, 2H), 3.55 (sex, *J* = 6.3 Hz, 1H), 6.75-6.85 (m, 2H), 7.05 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 8.03 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.4 38.1, 67.9, 123.7, 125.7, 126.5, 128.7, 129.3, 134.4, 136.4, 141.5, 158.8.

N-(4-Chlorobenzylidene)-1 - (4 - hydroxyphenyl) propan-2-amine, 3i. Yield 80%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.30 (d, *J* = 6.3 Hz, 3H), 2.75 (d, *J* = 6.3 Hz, 2H), 3.52 (sex, *J* = 6.3 Hz, 1H), 5.30 (s, 1H), 6.67 (d, *J* = 8.4 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 8.4 Hz, 2H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9, 43.3, 68.6, 115.3, 128.8, 129.5, 130.5, 130.6, 134.0, 136.6, 154.5, 159.1.

N-(4-Nitrobenzylidene)-1-phenyl propan-2-amine, 3j. Yield 90%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (d, *J* = 6.3 Hz, 3H), 2.82 (d, *J* = 6.3 Hz, 2H), 3.50 (sex, *J* = 6.3 Hz, 1H), 7.00-7.20 (m, 5H), 7.70 (d, *J* = 8.1 Hz, 2H), 8.10 (d, *J* = 8.1 Hz, 2H), 7.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.5, 42.5, 69.0, 124.2, 129.0, 129.1, 129.4, 130.9, 137.1, 139.4, 149.2, 157.9.

N-(2-Hydroxy-1-naphthylidene)-1-phenyl propan-2-amine, 3k. Yield 93%, Viscous liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (d, *J* = 6.3 Hz, 3H), 2.79 (d, *J* = 6.3 Hz, 2H), 3.25 (sex, *J* = 6.3 Hz, 1H), 6.80-7.30 (m, 12H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.22 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1, 44.8, 61.3, 106.5, 118.2, 123.0, 125.4, 127.1, 127.3, 128.2, 129.6 (2C), 129.9, 134.2, 137.6, 137.9, 156.8, 176.8.

General method for the preparation of thiazolidine derivatives

A mixture of 0.001 mole of N-arylidene-2-arylethanamine and 0.001 mole (0.07 mL) of thioglycollic acid was exposed to microwave radiation for three minutes. The thiazolidinones formed was recrystallised from alcohol.

3-[2-(4-Methoxyphenyl)ethyl]-2-(4 - chlorophenyl)-4-thiazolidinone, 5a. Yield 85%, m.p. 78°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.65-2.88 (m, 3H), 3.65-3.90 (m, 3H), 3.79 (s, 3H), 5.25 (s, 1H), 6.82 (d, *J* = 8.4 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 7.33, d, J = 8.4 Hz, 2H; ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.4, 32.8, 44.7, 55.2, 63.3, 114.0, 128.5, 129.2, 129.6, 130.2, 135.0, 137.8, 158.4, 171.1. Anal. Calcd for $C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.22; N, 4.03. Found: C, 62.30; H, 5.00; N, 4.30%.

3-[2-(2,4-Dichlorophenyl)ethyl]-2-(4-chlorophenyl)-4-thiazolidinone, 5b. Yield 70%, m.p. 80°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.76-3.00 (m, 3H), 3.65-3.84 (m, 3H), 5.36 (d, *J* = 1.2 Hz, 1H), 7.10-7.39 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.4, 32.7, 42.5, 63.4, 127.3, 127.7, 128.2, 128.7, 129.8, 133.3, 134.4, 134.5, 135.1, 137.5, 171.2. Anal. Calcd for $C_{17}H_{14}Cl_3NOS$: C, 52.80; H, 3.65; N, 3.62. Found: C, 52.50; H, 3.50; N, 3.92%.

3-[2-(2-Chlorophenyl)ethyl]-2-(4- chlorophenyl)-4-thiazolidinone, 5c. Yield 85%, m.p. 110°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68-3.89 (m, 3H), 2.79-3.09 (m, 3H), 5.29 (s, 1H), 7.15-7.32 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.0, 32.8, 42.6, 63.4, 127.1, 128.3, 128.6, 129.2, 129.6, 131.0, 133.9, 133.0, 135.9, 137.7, 171.1. Anal. Calcd for $C_{17}H_{15}Cl_2NOS$: C, 57.96; H, 4.29; N, 3.98. Found: C, 57.67; H, 4.00; N, 4.20%.

3-[2-(3,4-Methylenedioxyphenyl)ethyl]-2-(4-nitrophenyl)-4-thiazolidinone, 5e. Yield 95%, m.p. 130°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.68-3.98 (m, 3H), 2.60-2.88 (m, 3H), 5.37 (s, 1H), 5.94 (s, 2H), 6.54 (m, 2H), 6.72 (d, *J* = 8.4 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 8.22 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.5, 33.0, 44.9, 62.8, 100.9, 108.4, 108.8, 121.5, 124.3, 127.7, 131.7, 146.4, 146.8, 147.8, 148.1, 171.0. Anal. Calcd for $C_{18}H_{16}N_2O_5S$: C, 58.05; H, 4.33; N, 7.52. Found: C, 58.60; H, 4.39; N, 7.54%.

3-[2-(2-Methoxyphenyl)ethyl]-2-(4- chlorophenyl)-4-thiazolidinone, 5f. Yield 95%, m.p. 110°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70-2.90 (m, 3H), 3.70 (s, 3H), 3.62-3.90 (m, 3H), 5.28 (s, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.88 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.05-7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 28.1, 32.8, 42.6, 54.9, 63.2, 110.1, 120.6, 126.6, 128.1, 128.6, 129.0, 130.5, 134.8, 137.9, 157.4, 170.9. Anal. Calcd for $C_{18}H_{18}ClNO_2S$: C, 62.15; H, 5.22; N, 4.03. Found: C, 62.56; H, 5.50; N, 3.89%.

3-(2-Phenyl)ethyl-2-phenyl-4-thiazolidinones, 5g. Yield 95%, m.p. 120°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.60-2.90 (m, 3H), 3.65-3.92 (m, 3H), 5.30 (d, *J* = 1.5 Hz, 1H), 7.08-7.35 (m, 10 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.8, 33.3, 44.5, 63.9, 126.6, 127.1, 128.6, 128.7, 129.0, 129.2, 138.4, 139.2, 171.1. Anal. Calcd for $C_{17}H_{17}NOS$: C, 72.05; H, 6.05; N, 4.94. Found: C, 72.30; H, 5.80; N, 4.64%.

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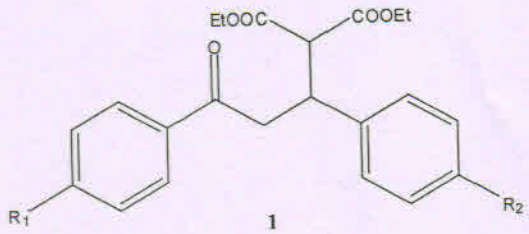
APPENDIX I

BRIEF OBJECTIVE OF THE PROJECT

Pteridine derivatives are the best known anticancer drugs. Several pteridine analogues have been synthesized and tested *in vitro* against three cancer cell lines, MCF7 (breast), NCI-H460 (lung) and SF-268 (CNS) and all the tested pteridines have been shown to serve as novel templates for the anticancer chemotherapy. Flourouracil has also been shown to possess anticancer activities and several structurally modified uracil units posses such activity. Recently, 4-thiazolidones and related heterocycles have been demonstrated to be a perspective source for innovative anticancer agents.



1

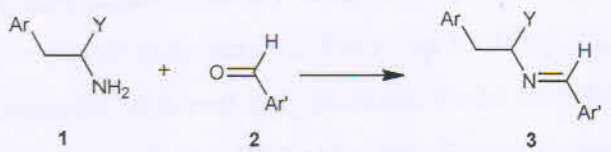
Several derivatives from malono ester **1**, which all can act as good precursors for the generation of 1,3-diazine units, have already been synthesized from our laboratory in another context [Saravanan, S; Sridharan, V; Muthusubramanian S; Synthetic communications, 2006, 36, 849-858]. As there are several functional groups in **1.** which can be effectively transformed to the heterocycles under consideration namely uracil, 4-thiazolidones, pteridine and several others, an intense research towards the synthesis of variety of heterocyclic compounds will be undertaken. The Principal Investigators' expertise in generating more than 1000 new heterocyclic compounds in his laboratory and in publishing more than 100 papers in the synthesis of heterocyclic compounds will be made use of to realize the goals.

All the synthesized compounds by the above schemes will then be tested for their anticancer (in collaboration with Dr Sriram of PITS, Bilani) and other biological activities.

APPENDIX II

WORK DONE SO FAR

It has been proposed in the original work to synthesise thiazoolidines connected to 4-aminopiteridine or fluoro uracil or realted systemes and inspect their anticancer activities. To generalise this idea and carry out a model synthesis of thiazolidines, it has been planned to start with simple system upon whcih the thiazolidine ring could be generated. Nevertheless, we wanted that study to be new one and hence a new set of imines have been synthesized by a simple route (Scheme I).



1 2 3

(11 examples)

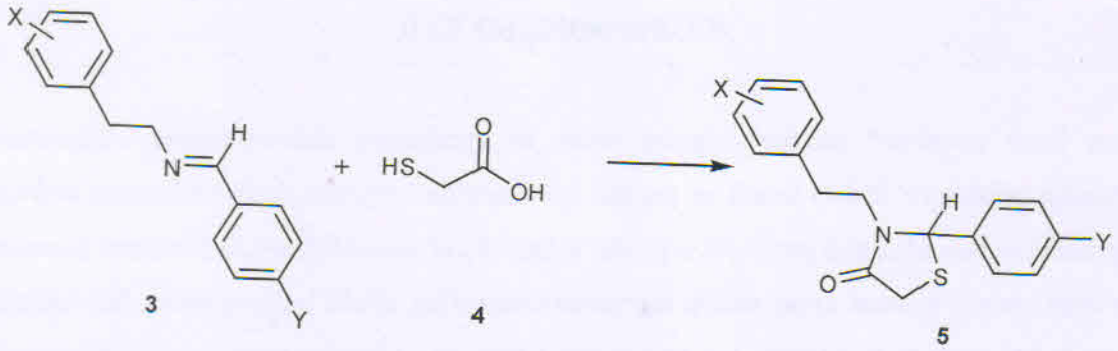
Ar = 4-Methoxyphenyl, 2,4-Dichlorophenyl, 2-Chlorophenyl, 4-Methylphenyl, 3,4-Methylenedioxy, 2-Methoxyphenyl, Phenyl, 2-Thienyl

Ar' = 4-Chlorophenyl, 4-Nitrophenyl, Phenyl, 2-Hydroxy-1-naphthyl

Scheme 1 – Synthesis of imines

Having synthesized the imines under solventless condition, the addition of thioglycollic acid to α-aryl-N-alkyl imines has also been carried out under solventless condition. Equimolar mixture of thioglycollic acid and the imines were mixed together forming a viscous fluid. The fluid was monitored time to time at room temperature for possible conversion to the heterocyclic compound. The reaction took place slowly, but it has been noticed that the reaction proceeded rapidly to completion under microwaves within three min even in minimum power of microwave. In all the substituted α-aryl-N-alkyl imines subjected to thioglycollic acid addition, a single product **5** has been obtained showing the selectivity of the reaction (Scheme II). It may be noticed that imines of the type $ArCH_2CH_2N{=}CHAr'$ alone have been converted to the thiazolidinones and not the type $ArCH_2CH(CH_3)N{=}CHAr.'$ All the attempts to convert the latter type of imines to the thiazolidinones under different conditions were not successful. This is probably due to the steric effect. All the products isolated have been shown to be 3-[2-arylethyl]-2-

(aryl)-4-thiazolidinones **5** by mass and NMR spectral studies. An attempted multicomponent reaction involving **1**, **2** and **4** has led to poor yield of **5**.



Scheme II – Synthesis of thiazolidones.

The results of thiazolidine **5g** treatment on enzymatic and non-enzymatic levels in serum on isoproterenol induced myocardial necrosis is described below:

On isoproterenol administration, the levels of vitamin C, vitamin E, SOD and CAT have been increased significantly ($p<0.001$) and post treatment with thiazolidinone significantly retained the levels almost to normal compared to control ($p<0.001$). The levels of serum lipid peroxides increased significantly in the ISO-administered rats and thiazolidinone post treatment ($p<0.05$) reduced the enzymatic lipid peroxide levels significantly.

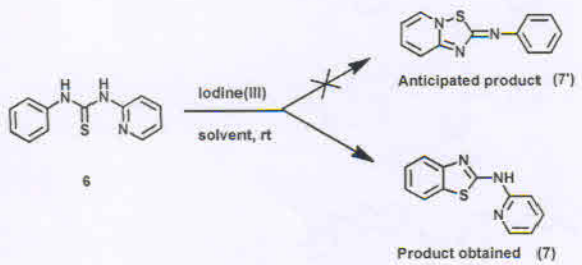
The finding has been published in Indian Journal of Chemistry Section B, 53B, 2014, 377-383.

The construction of C-S bond

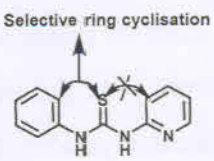
Deviating from our original work, we would like to establish methodologies for some C-X bond formation reactions. To start with, oxidative C-H bond functionalization, which is an important atom-economic process for the carbon-carbon and carbon-heteroatom bond formation, has been investigated. Transition metal catalysts are effective towards this process, but such reactions have serious drawbacks involving toxic reagents and harsh reaction conditions. The other disadvantages include metal contamination in the desired product, the requirement of co-catalysts and additives. So the construction of carbon-heteroatom bond formation through a metal free catalysis is highly desirable. Hypervalent iodine(III) reagents such as phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA) are employed in the construction of various heterocyclic compounds.

The 2-aminobenzothiazole skeleton is a privileged scaffold in pharmaceutically active compounds and natural products owing to their properties such as anti-diabetic, anti-bacterial, anti-cancer, anti-infective and anti-herbicidal. Most of the reported methods for the synthesis of 2-aminobenzothiazole involve transition metal catalyzed tandem reaction of 2-haloanilines with isothiocyanates. Heterogeneous catalysis and transition metal free synthetic protocols have also been explored, though these methods still require drastic reaction conditions or long reaction time. In contrast to the numerous reported protocols for the synthesis of 2-aminobenzothiazoles, only very few reports are available for the construction of *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine system.

Though this type of C-S bond formation using oxidative cyclisation has been achieved through various metals and metal free oxidants, this work reports a selective ring cyclisation when two options are available and thus an expedient metal free oxidative cyclisation of thiourea for the C-S bond formation using PIFA. It has been reported that the synthesis of 1,2,4-triazolo[1,5-α]pyridines can be achieved through N-N bond formation using hypervalent iodine(III) reagent. In continuation of that work, we planned to effect S-N bond formation using the corresponding thiourea as the starting material. We examined the reaction of thiourea **6** and phenyliodine diacetate in acetonitrile at room temperature.

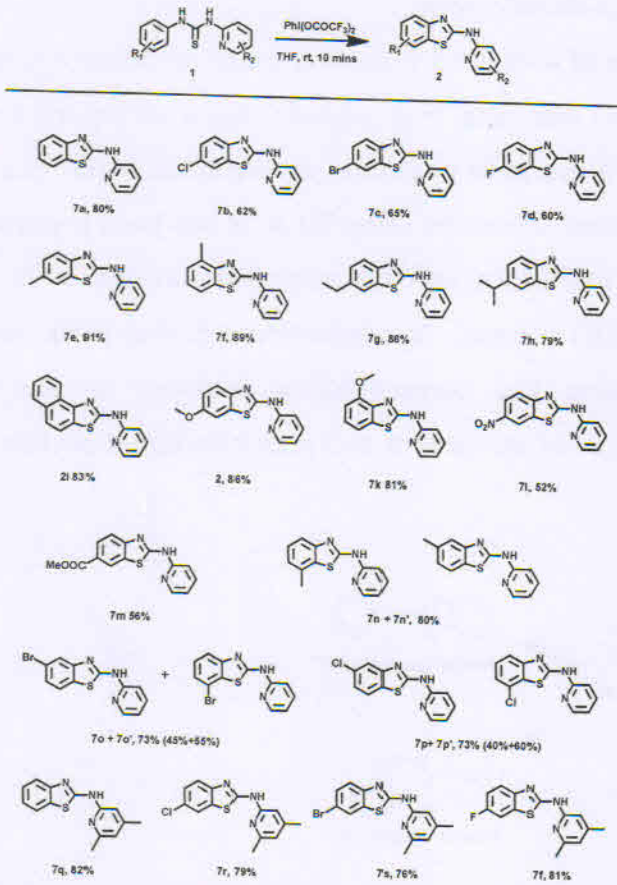


Scheme III. Attempted synthesis for the S-N bond formation product



Scheme IV. Selective ring cyclisation of **6**

After the completion of the reaction, the isolated product was found to be not the anticipated *N*-(2H-[1,2,4]thiadiazolo[2,3-*a*]pyridin-2-ylidene)aniline (**7'**), but *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine (**7**) [Scheme III]. Thus the oxidative C-S bond formation has been noticed. The structure of the product **7a** has been unambiguously assigned by spectral and analytical data, and that of **7b** has been confirmed by single crystal X-ray analysis as well. It is pertinent to note that the selective ring cyclisation occurred out of the two possible oxidative cyclisations as depicted in Scheme IV.

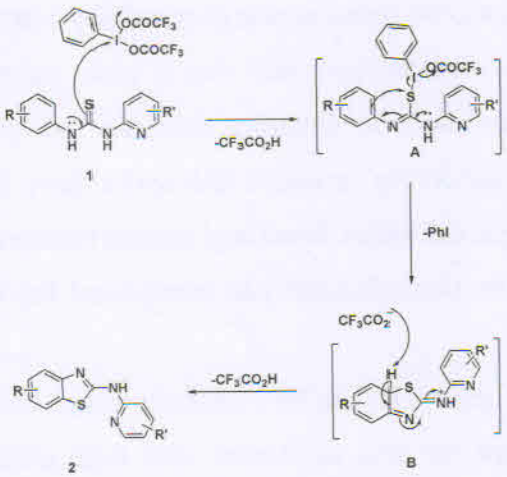


Scheme V. Synthesised compounds **(7a-7t)**

It has been shown that substrates with both electron withdrawing and electron donating groups tolerate the reaction conditions (Scheme V). The yields were relatively poor for the substrates with electron withdrawing groups such as chloro, nitro and methoxycarbonyl groups compared to the electron rich substrates having In conclusion, we have developed an efficient method for the synthesis of biologically important *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine using hypervalent iodine(III) reagent. Advantages of this reaction are metal free approach, substrate scope, short reaction duration and good to excellent yields with easier

purification protocol and simple starting materials. Punniyamoorthy *et al* reported the double C-H functionalization by a tandem C-N and C-S bond formation using the simple thiourea. In the present work, the C-S bond formation predominates over the C-N bond formation and no further cyclisation takes place.

A plausible mechanism for the formation of N-(pyridin-2-yl)benzo[d]thiazol-2-amine has been suggested in Scheme VI.



Scheme VI. Mechanism of formation of **7**

The finding has been published in European Journal of Organic Chemistry, 302–307, 2016.

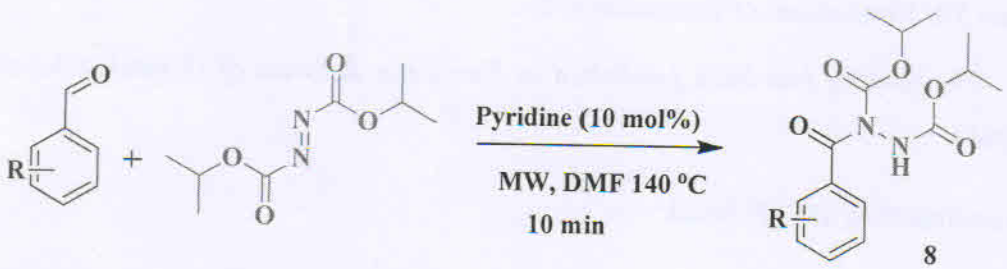
The construction of C-N bond

The construction of C-N bond is of great importance and several reactions, which includes polar, radical and pericyclic, have been employed for the construction of C-N bond. The chemistry of dialkyl azodicarboxylates had been of considerable interest, as they behave as good nucleophilic acceptors due to the presence of strong electron withdrawing groups. The dialkyldiazocarboxylates have been successfully subjected to different types of reactions including zwitter ion intermediate reactions, α-amination of carbonyl compounds, the C-H activation at the α position of amines and ethers and the ene type reactions with olefins. The hydroacylation reaction of dialkyldiazocarboxylates with direct C-H functionalization of aldehydic C-H bonds to form hydrazine imides has been studied. Metals like rhodium, copper and zinc have been found to catalyze the hydroacylation reactions. It is highly desirable to develop a simple and efficient method for hydroacylation of azodicarboxylates that get

completed in shorter reaction time. Pyridine is used as a nucleophilic catalyst in the acylation of alcohols and amines. An unexpected [2+2] cycloaddition of acetylene dicarboxylate with benzadehyde using pyridine as a catalyst has been reported by Nair and co-workers. The present work highlights the use of pyridine for a fast hydroacylation of azodicarboxylates.

Initially, we selected a model reaction between benzaldehyde and diisopropyl azodicarboxylate for optimizing the reaction condition. The results indicate that the reaction works well at elevated temperature with pyridine as the suitable catalyst in DMF under microwaves. Under the optimized reaction conditions, the reaction was successfully extended with different aldehydes (Scheme VII). The reaction worked well for a wide range of aldehydes excluding the electron withdrawing and electron donating aromatic aldehydes. Still, a good number of hydroacylated products involving aromatic aldehydes have been synthesised. The scope of the reaction was then explored with a fused aryl system (compound **8p**), a heterocyclic aldehyde (compound **8q**) and an aliphatic aldehyde (compound **8r**) with encouraging results.

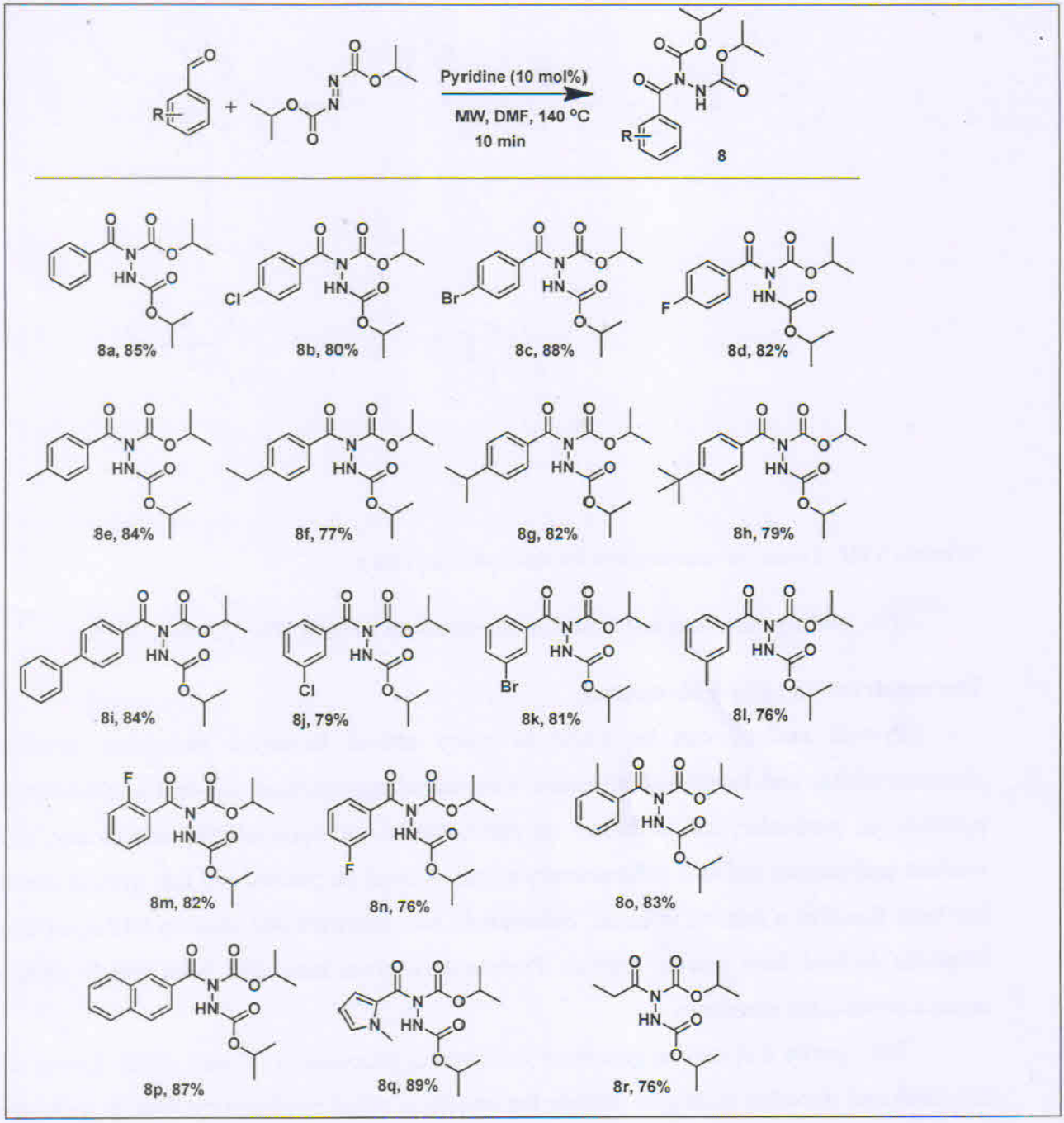
Though an ionic mechanism as shown in Scheme VIII can be tentatively suggested for the conversion in Scheme VII, it is surprising that the aryl aldehydes with both electron releasing and electron withdrawing substituents have not undergone the reaction successfully.

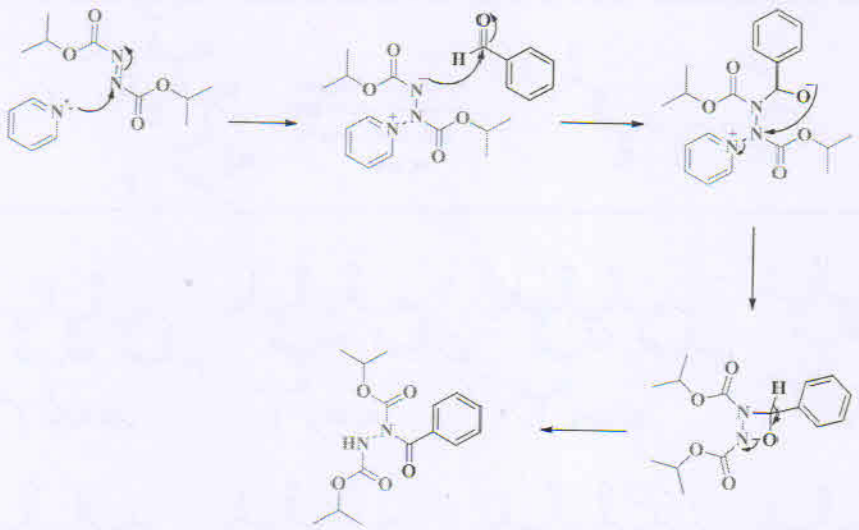


8

R = H, 4-Cl, 4-Br, 4-F, 4-CH_3, 4-CH_2CH_3, 4-$CH(CH_3)_2$, 4-$C(CH_3)_3$, 4-C_6H_5, 3-Cl, 3-Br, 3-CH_3, 2-F, 3-F, 2-CH_3

Scheme VII. Hydroacylation of azodicarboxylates with aldehydes.


Pyridine (10 mol%)
MW, DMF, 140 °C
10 min
8
8a, 85%
8b, 80%
8c, 88%
8d, 82%
8e, 84%
8f, 77%
8g, 82%
8h, 79%
8i, 84%
8j, 79%
8k, 81%
8l, 76%
8m, 82%
8n, 76%
8o, 83%
8p, 87%
8q, 89%
8r, 76%



Scheme VIII. Tentative mechanism for the hydroacylation.

The finding has been published in Tetrahedron Letters, 56, 338-341, 2015.

The construction of pyrrole nucleus

Pyrrole nucleus can be found in many natural bioactive molecules, synthetic pharmaceuticals and functional materials with varied applications. Several polysubstituted pyrroles, in particular, are effective as anti-bacterial, anti-convulsant, anti-cancer, anti-oxidant, anti-tumour and anti-inflammatory agents. It must be pointed out that pyrrole skelton has been found as a subunit in heme, chlorophyll, bile pigments and vitamin B12 apart from alkaloids derived from marine sources. Pyrrole derivatives have also been widely used as organic conducting materials.

The pyrrole unit can be generated from routes proposed by Knorr, Paal–Knorr, and Hantzsch and the other strategies include the transition metal mediated cyclisation, reductive coupling, isocyanide based reactions, rearrangement reaction and cycloaddition methods. The present investigation reports the synthesis of the polysubstituted pyrroles, dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylates. Though there are many reports for the synthesis of the dialkyl 1,5-diaryl-*1H*-pyrrole-2,3-dicarboxylate, only a few reports describe the route for its regioisomer, dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylate. These protocols involve (i) tedious task of removing the triphenylphosphine oxide or (ii) prefunctionalisation of the monophenacylaniline part or (iii) more steps to reach the desired product or (iv) long reaction time or (v) cascade hydroamination/cyclization reaction where expensive gold has been used as the catalyst. To overcome these shortcomings and exploiting the advantages of

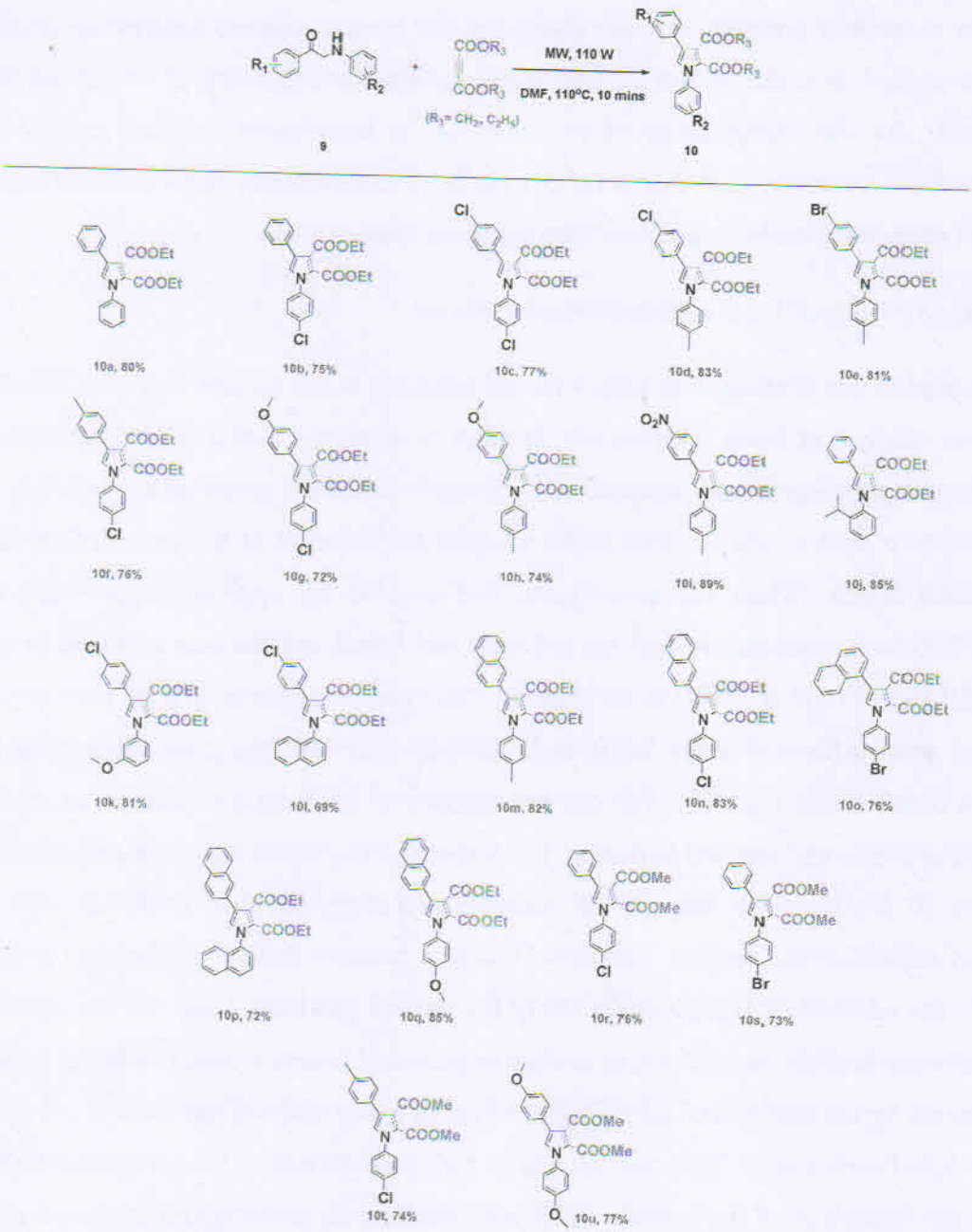
microwaves in modern synthetic organic chemistry, the present scheme for pyrrole synthesis has been proposed in continuation of our work[1] on the development of useful synthetic methodologies for the construction of heterocycles. A microwave assisted catalyst free efficient synthesis of dialkyl **1**,4-diaryl-1*H*-pyrrole-2,3-dicarboxylates from α-amino ketones with dialkyl acetylenedicarboxylates has been achieved (Scheme IX).

Scheme IX: Synthesis of 1,2,3,4 tetrasubstituted pyrrole

We started our investigation with a model substrate **9** and treated that with DEAD in THF without catalyst at room temperature. It must be admitted that a related reaction has been reported involving acidic reagent with limited substrate scope after isolating the intermediate. Our strategy involves no acidic reagent, no isolation of the intermediate and a wide substrate scope. When we investigated the reaction by applying microwave with varying MW power, temperature and the solvents, we found that **10** was obtained in good yield with DMF in 110W at 110°C in 10 minutes. The yield was relatively good with solvents like ethanol, acetonitrile and water, but it was relatively poor with the other solvents such as toluene, 1,4 dioxane and 1,2 DCE. The one pot reaction of all three compounds, as reported in the previous literature,[1] resulted in diethyl 1,5-diphenyl-*1H*-pyrrole-2,3-dicarboxylate. Here the reaction of aniline with the diethyl acetylenedicarboxylate was preferred over the formation of monophenacylaniline. The initial reaction between aniline to phenacyl bromide followed by the addition of DEAD could afford the desired product. When we attempted the one pot synthesis through the addition of aniline to phenacyl bromide under MW for 1 min at 110°C followed by the addition of DEAD, it resulted in lower yield of the dialkyl 1,4-diaryl-*1H*-pyrrole-2,3-dicarboxylate. This may be due to the initial formation of α,α'-amino ketones preventing the formation of the pyrrole. After optimization we investigated the scope of the reaction and it worked well with variety of α-aminoketones and different acetylene esters. The structures of the products **10** have been unambiguously assigned by spectral and analytical data.

9 10

Scheme IX. Synthesis of 1,2,3,4-tetrasubstituted pyrroles



The finding has been accepted for publication in Synthetic Communications. DOI: 10.1080/00397911.2016.1176201.

LIST OF PUBLICATIONS OUT OF THE SCHEME FUNDING

1. Microwave - assisted catalyst- free synthesis of tetrasubstituted pyrroles using dialkyl acetylenedicarboxylates and monophenacylanilines – A Mariappan, K Rajaguru, S Muthusubramanian, N Bhuvanesh - *Synthetic Communications* - *DOI: 10.1080/00397911.2016.1176201.*

2. Hypervalent Iodine Promoted Regioselective Oxidative C–H Functionalization: Synthesis of N-(Pyridin-2-yl)benzo[d]thiazol-2-Amines – A Mariappan, K Rajaguru, S S Roja, **S Muthusubramanian**, N Bhuvanesh, *Eur. J. Org. Chem.*, 302–307, 2016

3. A New facile pyridine-catalyzed hydroacylation of aldehydes with azodicarboxylates under microwave irradiation, A Mariappan, K Rajaguru, **S Muthusubramanian**, N Bhuvanesh, *Tetrahedron Letters*, **56**, 338-341, 2015

4. Synthesis and antioxidant characteristic of novel thiazolidinone derivatives – C Amutha, S Saravanan, **S Muthusubramanian**, *Indian J. Chem.*, **53B**, 377-383, 2014

APPENDIX III

SUMMARY OF THE FINDINGS

Work I

A series of novel thiazolidinone derivatives have been synthesized by solventless condensation of *N*-alkylamines with arylaldehydes at room temperature followed by a microwave assisted solventless addition of thioglycollic acid to the resultant imines. The synthesized compounds are characterized by ^{1}H NMR, ^{13}C NMR, MS and X-ray techniques and one of the synthesized thiazolidinones has been evaluated for its antioxidant property (***Indian Journal of Chemistry Section B, 53B, 2014, 377-383***).

Work II

An efficient method for the synthesis of biologically important *N*-(pyridin-2-yl)benzo[*d*]thiazol-2-amine using hypervalent iodine(III) reagent has been achieved. Advantages of this reaction are metal free approach, substrate scope, short reaction duration and good to excellent yields with easier purification protocol and simple starting materials (***European Journal of Organic Chemistry, 302–307, 2016***).

Work III

In conclusion, we report an efficient hydroacylation reaction of aldehydes with azodicarboxylates catalyzed by pyridine under microwave irradiation, which has more advantages over the existing methods in terms of easy workup, less reaction time and better yield under metal free condition (***Tetrahedron Letters, 56, 338-341, 2015***).

Work IV

We have developed a microwave assisted synthesis of dimethyl 1,4-diphenyl-*1H*-pyrrole-2,3-dicarboxylates, the main advantage of this method being that it is catalyst free with shorter reaction time resulting in good to excellent yield. Another interesting feature is the realisation of axial chirality in *N*-(α-naphthyl/2-isopropylphenyl)-2,3-dicarbethoxy-4-arylpyrroles, but not in *N*-aryl-2,3-dicarbethoxy-4-(α-naphthyl)pyrrole (***Synthetic Communications. DOI: 10.1080/00397911.2016.1176201***).

1. Microwave - assisted catalyst- free synthesis of tetrasubstituted pyrroles using dialkyl acetylenedicarboxylates and monophenacylanilines – A Mariappan, K Rajaguru, S Muthusubramanian, N Bhuvanesh - *Synthetic Communications* - *DOI: 10.1080/00397911.2016.1176201.*

2. Hypervalent Iodine Promoted Regioselective Oxidative C–H Functionalization: Synthesis of N-(Pyridin-2-yl)benzo[d]thiazol-2-Amines – A Mariappan, K Rajaguru, S S Roja, **S Muthusubramanian**, N Bhuvanesh, *Eur. J. Org. Chem.*, 302–307, 2016

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Annexure -VIII

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

NEW DELHI – 110 002.

Annual/Final Report of the work done on the Major Research Project.

(Report to be submitted within 6 weeks after completion of each year)

1. **Project report No. 1st /2nd /3rd /Final** Final

2. **UGC Reference No.** F. 41-265/2012(SR) dated 13th July, 2012

3. **Period of report: from** July 2012 to June 2015

4. **Title of research project** *"Synthesis of heterocycles for evaluation of anticancer behavior"*

5. **(a) Name of the Principal Investigator** Prof. S. Muthusubramanian

   (b) Deptt. School of Chemistry

   (c) University/College where work has progressed Madurai Kamaraj University

6. **Effective date of starting of the project** 01 July 2012

7. **Grant approved and expenditure incurred during the period of the report:**

   a. Total amount approved Rs. 12,96,800/-

   b. Total expenditure Rs. 10,44,152/-

c. Report of the work done: (Please attach a separate sheet)

i. Brief objective of the project Kindly see Appendix I for brief objective of the project.

ii. Work done so far and results achieved and publications, if any, resulting from the work (Give details of the papers and names of the journals in which it has been published or accepted for publication) Kindly see Appendix II for detailed work done report.

iii. Has the progress been according to original plan of work and towards achieving the objective. if not, state reasons

Initially the work has been concentrated on the proposed objective and the preliminary reactions have been optimised on a model system leading to a publication. But we realised, instead of functionalising and generating rings, several new C-X bond formation reactions or new heterocycles generation may be attempted. Ultimately in all the cases, bioactive organic compounds are going to be obtained. These final products may be tested for their medicinal properties including anticancer activities. Thus a slight variation to be the original proposal has been made. Nevertheless the results are very successful yielding good number of publications.

iv. Please indicate the difficulties, if any, experienced in implementing the Project

As the grant has not been released in time, it was very difficult for the PI to manage, especially with the purchase of chemicals.

v. If project has not been completed, please indicate the approximate time by which it is likely to be completed. A summary of the work done for the period (Annual basis) may please be sent to the Commission on a separate sheet.

Does not arise

vi. If the project has been completed, please enclose a summary of the findings of the study. One bound copy of the final report of work done may also be sent to University Grants Commission.

Kindly see Appendix III for summary of the findings.

vii. Any other information which would help in evaluation of work done on the project. At the completion of the project, the first report should indicate the output, such as (a) Manpower trained (b) Ph. D. awarded (c) Publication of results (d) other impact, if any

Kindly see Appendix II for detailed work done. One project assistant, Mr A MARIAPPAN has been engaged out of the finding of the scheme and he has registered for his Ph D in August 2013. He will be submitting his thesis for Doctorate in August 2016.

Details of publications:

1. Microwave - assisted catalyst- free synthesis of tetrasubstituted pyrroles using dialkyl acetylenedicarboxylates and monophenacylanilines – A Mariappan, K Rajaguru, S Muthusubramanian, N Bhuvanesh - *Synthetic Communications* - *DOI: 10.1080/00397911.2016.1176201.*

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4. Synthesis and antioxidant characteristic of novel thiazolidinone derivatives – C Amutha, S Saravanan, **S Muthusubramanian**, *Indian J. Chem.*, **53B**, 377-383, 2014

S Muthusubramanian 5/5/16

SIGNATURE OF THE PRINCIPAL INVESTIGATOR

Professor. S. Muthusubramanian
Principal Investigator
UGC Project
School of Chemistry
Madurai Kamaraj University
Madurai - 625 021. INDIA

31/5/2016

REGISTRAR/PRINCIPAL

(Seal)

REGISTRAR.
MADURAI KAMARAJ UNIVERSITY
MADURAI-625 021

KK
31/5/16

SIGNATURE OF THE CO-INVESTIGATOR

Annexure – IX

UNIVERSITY GRANTS COMMISSION

BAHADUR SHAH ZAFAR MARG

NEW DELHI – 110 002

PROFORMA FOR SUBMISSION OF INFORMATION AT THE TIME OF SENDING THE FINAL REPORT OF THE WORK DONE ON THE PROJECT

1. Title of the Project — Synthesis of heterocycles for evaluation of anticancer behavior

2. NAME AND ADDRESS OF THE PRINCIPAL INVESTIGATOR

Prof. S. Muthusubramanian,

Head, Department of Organic Chemistry,

Madurai Kamaraj University, Madurai – 625021.

3. NAME AND ADDRESS OF THE INSTITUTION

Madurai Kamaraj University, Palkalai Nagar, Madurai – 625021.

4. UGC APPROVAL LETTER NO. AND DATE

F. 41-265/2012(SR)dated 13th July, 2012

5. DATE OF IMPLEMENTATION — 01 July 2012

6. TENURE OF THE PROJECT — 3 YEARS

7. TOTAL GRANT ALLOCATED — Rs. 12,96,800/-

8. TOTAL GRANT RECEIVED — Rs. 10,93,800/-

9. FINAL EXPENDITURE — Rs.10,44,152/-

10. TITLE OF THE PROJECT — Synthesis of heterocycles for evaluation of anticancer behavior

11. OBJECTIVES OF THE PROJECT — Kindly see Appendix I

12. WHETHER OBJECTIVES WERE ACHIEVED (GIVE DETAILS)

Initially the work has been concentrated on the proposed objective and the preliminary reactions have been optimised on a model system leading to a publication. But we realised, instead of functionalising and generating rings, several new C-X bond formation reactions or new heterocycles generation may be attempted. Ultimately in all the cases, bioactive organic compounds are going to be obtained. These final products may be tested for their medicinal properties including anticancer activities. Thus a slight variation to be the original proposal has been made. Nevertheless the results are very successful yielding good number of publications.

13. ACHIEVEMENTS FROM THE PROJECT

Kindly see Appendix II

14. SUMMARY OF THE FINDINGS (IN 500 WORDS)

Kindly see Appendix III

15. CONTRIBUTION TO THE SOCIETY

Several new heterocyclic compounds have been synthesized in the present scheme. These heterocyclic compounds have skelton which are pharmacophore in nature and hence they may be medicinally important. Schematic biological studies may be carried out to identify the active compounds.

16. WHETHER ANY PH.D. ENROLLED/PRODUCED OUT OF THE PROJECT

One project assistant, Mr A MARIAPPAN has been engaged out of the finding of the scheme and he has registered for his Ph D in August 2013. He will be submitting his thesis for Doctorate in August 2016.

17. NO. OF PUBLICATIONS OUT OF THE PROJECT

1. Microwave - assisted catalyst- free synthesis of tetrasubstituted pyrroles using dialkyl acetylenedicarboxylates and monophenacylanilines – A Mariappan, K Rajaguru, S Muthusubramanian, N Bhuvanesh - *Synthetic Communications* - *DOI: 10.1080/00397911.2016.1176201.*

2. Hypervalent Iodine Promoted Regioselective Oxidative C–H Functionalization: Synthesis of N-(Pyridin-2-yl)benzo[d]thiazol-2-Amines – A Mariappan, K Rajaguru, S S Roja, **S Muthusubramanian**, N Bhuvanesh, *Eur. J. Org. Chem.*, 302–307, 2016

3. A New facile pyridine-catalyzed hydroacylation of aldehydes with azodicarboxylates under microwave irradiation, A Mariappan, K Rajaguru, **S Muthusubramanian**, N Bhuvanesh, *Tetrahedron Letters*, **56**, 338-341, 2015

4. Synthesis and antioxidant characteristic of novel thiazolidinone derivatives – C Amutha, S Saravanan, **S Muthusubramanian**, *Indian J. Chem.*, **53B**, 377-383, 2014

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