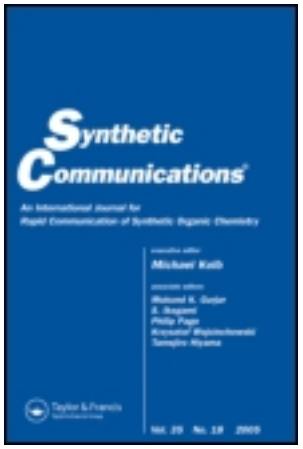

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Novel, Mild, and Highly Efficient Method for the Synthesis of 2-Arylbenzothiazoles by the Oxidation of 2-Arylbenzothiazolines with Silicon Lewis Acids

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Available online: 14 Dec 2010

To cite this article: Sonika, Meenakshi & Rajesh Malhotra (2010): Novel, Mild, and Highly Efficient Method for the Synthesis of 2-Arylbenzothiazoles by the Oxidation of 2-Arylbenzothiazolines with Silicon Lewis Acids, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 41:1, 136-146

To link to this article: http://dx.doi.org/10.1080/00397910903531896

Synthetic Communications®, 41: 136–146, 2011

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910903531896

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NOVEL, MILD, AND HIGHLY EFFICIENT METHOD FOR THE SYNTHESIS OF 2-ARYLBENZOTHIAZOLES BY THE OXIDATION OF 2-ARYLBENZOTHIAZOLINES WITH SILICON LEWIS ACIDS

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Oxidation of structurally diverse 2-arylbenzothiazolines to give the corresponding 2-arylbenzothiazoles has been carried out in benzene using dimethyldichlorosilane and trimethylchlorosilane. Short reaction times, mild reaction conditions, easy and quick isolation of the products, and excellent yields are the main advantages of this procedure.

Keywords: Benzothaizoles; benzothiazolines; dimethyldichlorosilane; silicon Lewis acids; trimethylchlorosilane

INTRODUCTION

Benzothiazoles are a very important group of heterocyclic compounds that have many applications in both pharmaceutical and industrial research. They are widely used in bioorganic and medicinal chemistry with applications in drug discovery.[1] They have also found potent utility as imaging agents for β-amyloid[2] and as luminescent/fluorescent agents.[3]

There are three major routes to synthesize benzothiazoles (Scheme 1). The methodology developed following strategy A involves the reaction of 2-aminothiophenol with aldehydes,[4] carboxylic acids,[5] and esters[6] using a number of oxidants/catalysts. Strategy B includes cyclization of thioanilides or halothioanilides promoted by various reagents.[7] Benzothiazoles have been also prepared by the oxidative cyclization of thiophenolic Schiff's bases/benzothiazolines (strategy C) using various oxidants such as pyridinium chlorochromate[8] and recently via electrooxidation.[9]

However, most of these synthetic approaches suffer from drawbacks such as harsh reaction conditions (strong acids, high temperatures), tedious workup, possibility of side reactions, and generation of acidic/metallic wastes. Therefore, there is a need to overcome these limitations by developing an efficient and convenient methodology for the synthesis of benzothiazoles.

Received September 20, 2009.

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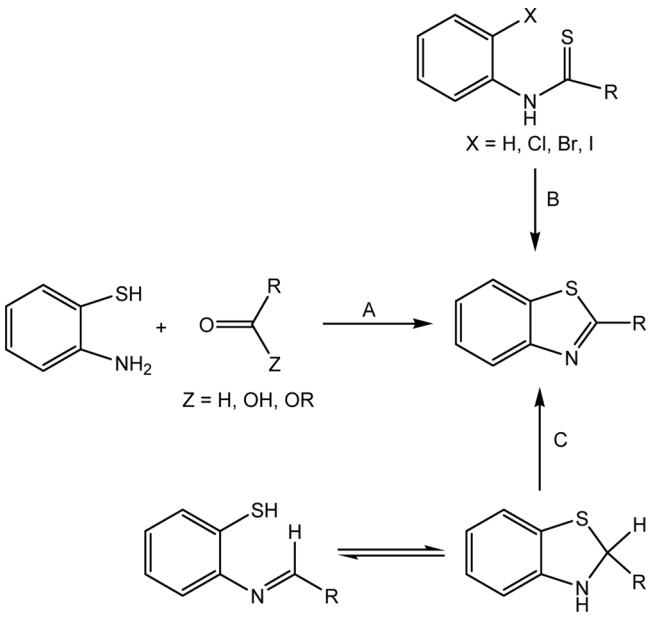


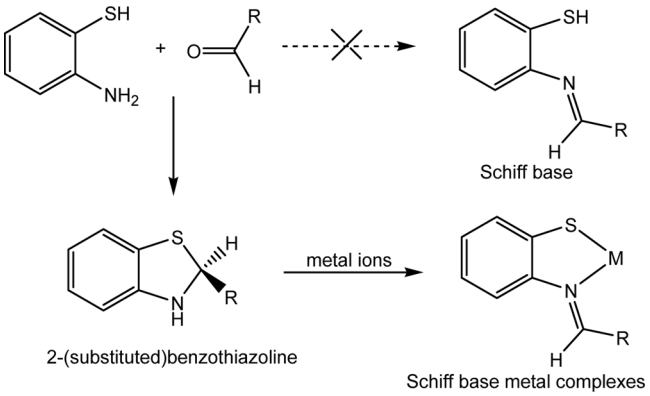
Scheme 1. Synthetic routes to 2-arylbenzothiazoles.

Among various synthetic applications of organosilicon compounds, the transformations utilizing derivatives containing leaving groups at the silicon atom have become especially widespread. Tetravalent triorganosilanes, such as trimethylsilyl chloride, iodide, and triflate, are the standard silylating agents employed for functional-group manipulations in organic synthesis. The Lewis acidity of silicon compounds is attributed mainly to the intrinsic capability of silicon to extend its valence shell, giving rise to five- and six-coordinate intermediates. The latter might dissociate, depending on the strength of the silicon–leaving group bond. Formally, these tetravalent reagents might be understood as silylium ion precursors.

The use of silicon Lewis acids (SLAs) is advantageous over traditional metal-centered activators because they are not prone to aggregation and are compatible with many synthetically valuable C-nucleophiles, such as cuprates, allyl organometallic reagents, and silyl enol ethers. Morever, the reactivity of SLAs can be controlled by varying the steric volume of alkyl substituents. The tendency of silicon to form five- and six-coordinate intermediates is further enhanced upon insertion of two or more electron-withdrawing substituents (i.e., of the type R_2SiX_2 or $RSiX_3$).[10]

RESULTS AND DISCUSSION

It is expected that the reaction of 2-aminothiophenol with several typical aldehydes leads to the corresponding Schiff bases. The actual products are 2-substituted benzothiazolines. However, several metal ions induce rearrangement of these benzothiazolines to yield the corresponding Schiff base–metal complexes. These Schiff bases derived from 2-substituted benzothiazolines act as bidentate ligands and form



Scheme 2. Reaction of 2-substituted benzothiazolines with metal ions.

five-membered N, S-bonded chelate rings. Many researchers have paid attention to reactions classified as "metal ion–induced rearrangement" (Scheme 2).[11]

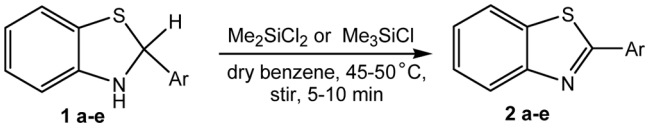
However, when we carried out the reaction of benzothiazoline with dimethyldichlosilane/trimethylchlorosilane (DMSCl/TMSCl) (1.1 eq) in dry benzene, we obtained the corresponding benzothiazoles in excellent yields and purities in short reaction times. Purity of products was further confirmed by thin-layer chromatography (TLC) on silica (fluorescence); under ultravoilet light, benzothiazoles fluoresced bright blue, whereas the benzothiazoline gave quenched spots. Not even a trace of the addition complex was observed in this reaction, as reported previously.[12] To explore the generality and scope of this process, diversified benzothiazolines were studied in the synthesis of benzothiazoles (Scheme 3, Table 1).

We extended our methodology to the oxidation of benzothiazolines of formyl pyrazoles (**3**), which, on treatment with DMSCl or TMSCl, afforded the corresponding 2-pyrazolylbenzothiazoles (**4**) in 90–95% yields. There were no steric hindrances due to the presence of bulky groups (Scheme 4, Table 1).

No significant substituent effect was observed on the yields of the products. The reaction was carried out at different temperatures to evaluate the effect of reaction temperature. At room temperature, the reaction rate was slow (30–40 min), and it increased with temperature. At 45–50 °C, the reaction rate was maximum (5–10 min), and further increase in temperature did not show any enhancement.

Praveen et al.[8] assigned a Schiff base structure to the condensation products of 2-aminothiophenol and various benzaldehydes. However, these compounds have thiazoline structure rather than the Schiff base structure.

The oxidation of benzothiazoline was supported by the disappearance of N-H stretch peaks in the infrared (IR) spectra. Also, in the ^{1}H NMR spectra of



Scheme 3. Synthesis of 2-aryl/heteroarylbenzothiazoles.

Table 1. Synthesis of 2-arylbenzothiazoles by the oxidation of corresponding benzothiazolines with DMSCl and TMSCl

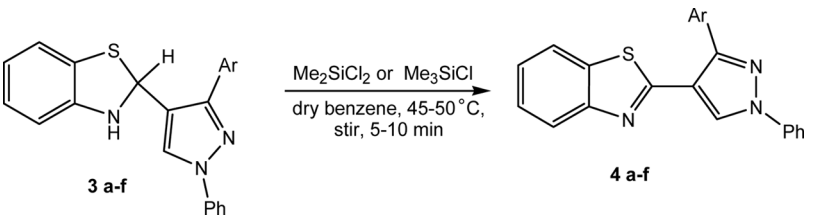
S. no.	Ar	Product	DMSCl yield (%)	TMSCl yield (%)	Ref.
1	C_6H_5	**2a**	92	90	6
2	4-Cl-C_6H_4	**2b**	93	92	4c
3	2-Cl-C_6H_4	**2c**	90	95	4c
4	2-thienyl	**2d**	85	88	4c
5	2-pyridyl	**2e**	86	90	6
6	C_6H_5	**4a**	91	92	—
7	4-CH_3-C_6H_4	**4b**	87	85	—
8	4-OCH_3-C_6H_4	**4c**	95	94	8
9	2-OCH_3-C_6H_4	**4d**	93	90	—
10	4-Cl-C_6H_4	**4e**	92	93	8
11	4-Br-C_6H_4	**4f**	94	93	8
12	4-F-C_6H_4	**4g**	89	92	—

Note. All the products were characterized by IR, NMR, and comparison of melting points with those reported in the literature.

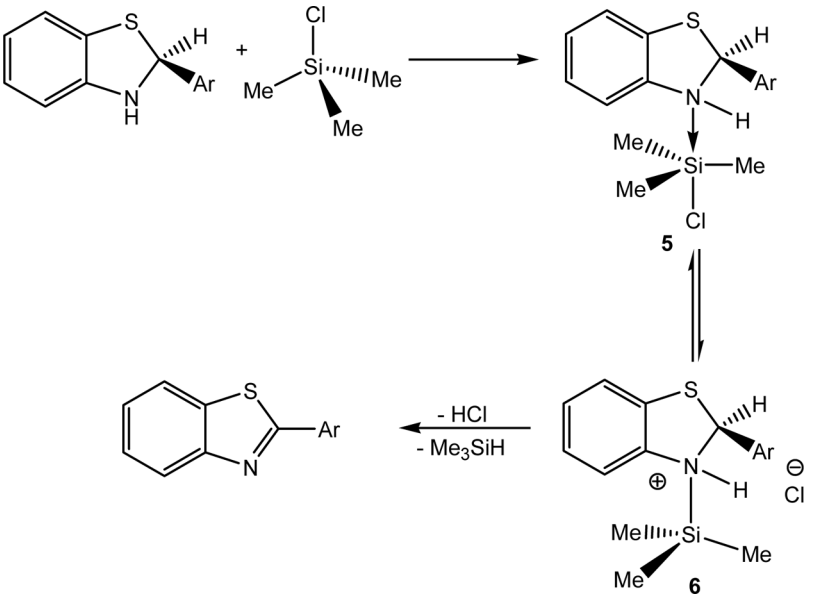
benzothiazoles, the broad singlet at δ 4.3 due to the NH proton and the singlet at δ 6.3 due to the C_2-H proton disappear. In the case of benzothiazolines of formyl pyrazoles, the pyrazolyl-H, which resonated as a singlet at δ 8.2–8.3, showed a significant downfield shift after oxidation and appeared as a singlet at δ 8.6.

Benzothiazoles have been also prepared from 2-aminothiophenol and aldehydes in dimethyformamide (DMF) using TMSCl (2 mol) as a promoter and water-acceptor agent, followed by oxidation with air oxygen.[4a] To exclude the role of air oxygen, we carried out a set of reactions under nitrogen with both DMSCl and TMSCl in dry benzene, and again we got the same oxidized products. This clearly establishes that in our case the oxidation is being carried out by the DMSCl and TMSCl and not by air oxygen.

A mechanistic rationale for this reaction (as shown in Scheme 5) can be given. Initially, the benzothiazoline reacts with TMSCl by the associative mechanism to form a five-coordinate intermediate (**5**). The presence of alkyl groups at the silicon atom makes **5** much less stable for both electronic and stertic reasons, leading to the ionization of a chloride and formation of salt **6**. The complexes **5** and **6** are likely to be short-lived intermediates, which either very rapidly revert to the starting compounds or undergo oxidation to give the benzothiazole. In this case, the equilibrium is shifted to right, probably because of the formation of thermodynamically more stable benzothiazoles.



Scheme 4. Synthesis of 2-pyrazolylbenzothiazoles.



Scheme 5. Proposed mechanism for the SLA-mediated oxidation.

In conclusion, DMSCl and TMSCl have been employed as a novel, mild, and very efficient reagent for the convenient preparation of benzothiazoles from benzothiazolines. The methodology is applicable to a wide variety of structurally diverse substrates and delivers the target products in good yields, excellent homogeneity, and often analytically pure form.

EXPERIMENTAL

Melting points were uncorrected and determined in open capillaries. Fourier transform (FT)—IR spectra were obtained as KBr pellets with a Perkin-Elmer Spectrum RX1 instrument. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance II 400-MHz and 100-MHz NMR spectrometers, respectively, in $CDCl_3$ with tetramethysilane (TMS) as an internal standard. Elemental analyses were carried out on a Perkin-Elmer 2400 instrument. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage MAX instrment. Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany). All the solvents used were dried by conventional methods. Diphenyldichlorosilane and triphenylchlorosilane were obtained through Aldrich and used as such without any further purification.

Synthesis of 2-Aryl/Heteroarylbenzothiazolines (1a–e)

2-Phenylbenzothiazoline (**1a**),[11a] 2-(4-chlorophenyl)-benzothiazoline (**1b**),[11a] 2-(2-chlorophenyl)-benzothiazoline (**1c**),[11b] 2-(2-thienyl)-benzothiazoline (**1d**),[13] and 2-(2-pyridyl)-benzothiazoline (**1e**)[14] were prepared by literature methods.

Synthesis of Benzothiazolines of Formyl Pyrazoles (3a–f): General Procedure

4-Formyl pyrazoles were prepared in two steps. The first was the reaction between acetophenone derivatives and phenylhydrazine. The hydrazone derivatives were treated with the Vilsmeier–Haack reagent (DMF–$POCl_3$), leading to the corresponding 4-carboxaldehyde functionalized pyrazole heterocyclic ring in mild operating conditions. Three equivalents of this reagent, instead of two as described by Kira et al.,[15] were necessary to obtain the aldehydes in good yields.

Equimolar quantities of 2-aminothiophenol (4.0 mmol, 0.50 g) and the appropriate 4-formyl pyrazoles (4.0 mmol) were heated together for 5–10 min at 50–60 °C, the reaction mixture was cooled and triturated with hexane, and the solid was collected and recrystallized with methanol.

Synthesis of 2-Arylbenzothiazoles (2a–e and 3a–f): General Procedure

DMSCl/TMSCl (1.1 mmol) was added dropwise to a stirred solution of 2-arylbenzothiazolines (1.0 mmol) in 5 mL of dry benzene at room temperature. The reaction mixture was warmed to 40–45 °C. The product separated immediately; however, the stirring was continued for an additional 5–10 min to ensure the completion of the reaction. After completion of the reaction, the solvent was removed in vacuo to afford the crude product, which was triturated with dry cyclohexane and recrystallized with methanol.

Spectral and Analytical Data

2-(1,3-Diphenyl-1-H-pyrazol-4-yl)benzothiazoline (3a). White solid; mp 130 °C; $R_f = 0.43$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3350, 3051, 2916, 1598, 1580, 1543, 1503, 1459, 1447, 1396, 1351, 1223, 1121, 1064, 1012, 956, 744. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.33 (bs, 1H, NH), 6.51 (s, 1H, C_2-H), 6.64–6.66 (dd, 1H, $J = 7.68$ & 0.60 Hz, $C_{4'}$-H), 6.76–6.80 (dt, 1H, $J = 7.52$ & 1.04 Hz, C_6-H), 6.92–6.96 (dt, 1H, $J = 7.68$ & 1.20 Hz, C_5-H), 7.06–7.08 (dd, 1H, $J = 7.56$ & 0.96 Hz, C_7-H), 7.23–7.29 (m, 1H, $C_{4'}$-H), 7.35–7.50 (m, 5H, $C_{3''}$-H, $C_{4''}$-H, $C_{5''}$-H, $C_{3'}$-H & $C_{5'}$-H), 7.70–7.80 (m, 4H, $C_{2'}$-H, $C_{6'}$-H, $C_{2''}$-H & $C_{6''}$-H), 8.28 (s, 1H, pyrazolyl-H). Anal. calcd. for $C_{22}H_{17}N_3S$: C, 74.34; H, 4.82; N, 11.82; S, 9.02%. Found: C, 74.00; H, 4.23; N, 11.99; S, 8.58%. ESI-MS $[M + H]^+ = 356.26$; calcd. for $C_{22}H_{17}N_3S = 355.11$.

2-(1-Phenyl-3-p-tolyl-1-H-pyrazol-4-yl)benzothiazoline (3b). White solid; mp 134 °C; $R_f = 0.42$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3310, 3143, 3066, 2920, 2859, 1596, 1581, 1541, 1500, 1469, 1455, 1408, 1363, 1333, 1221, 1058, 960, 826, 735. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H, CH_3), 4.39 (bs, 1H, NH), 6.54 (s, 1H, C_2-H), 6.67–6.69 (m, 1H, C_4-H), 6.77–6.81 (dt, 1H, $J = 7.52$ & 1.02 Hz, C_6-H), 6.93–6.97 (dt, 1H, $J = 7.60$ & 1.16 Hz, C_5-H), 7.08–7.10 (dd, 1H, $J = 7.92$ & 0.80 Hz, C_7-H), 7.25–7.29 (m, 3H, $C_{4'}$-H, $C_{3''}$-H & $C_{5''}$-H), 7.41–7.45 (m, 2H, $C_{3'}$-H & $C_{5'}$-H), 7.60–7.62 (d, 2H, $J = 8.04$ Hz, $C_{2''}$-H & $C_{6''}$-H), 7.71–7.73 (m, 2H, $C_{2'}$-H & $C_{6'}$-H), 8.29 (s, 1H, pyrazolyl-H). Anal. calcd. for

$C_{23}H_{19}N_3S$: C, 74.77; H, 5.18; N, 11.37; S, 8.68%. Found: C, 74.24; H, 5.35; N, 11.03; S, 8.36%. ESI-MS $[M+H]^+ = 370.25$; calcd. for $C_{23}H_{19}N_3S = 369.13$.

2-[3-(4-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]benzothiazoline (3c). White solid; mp 113–114 °C; $R_f = 0.30$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3307, 3141, 3050, 3003, 2931, 2871, 2837, 1611, 1595, 1583, 1540, 1528, 1503, 1471, 1455, 1244, 1174, 1060, 840, 735. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.82 (s, 3H, OCH_3), 4.35 (bs, 1H, NH), 6.48 (s, 1H, C_2-H), 6.64–6.66 (dd, 1H, $J = 7.72$ & 0.64 Hz, C_4-H), 6.76–6.80 (dt, 1H, $J = 7.56$ & 1.04 Hz, C_6-H), 6.91–6.95 (dt, 1H, $J = 7.60$ & 1.20 Hz, C_5-H), 6.96–6.99 (m, 2H, $C_{3''}$-H & $C_{5''}$-H), 7.06–7.08 (dd, 1H, $J = 7.56$ & 1.04 Hz, C_7-H), 7.23–7.27 (m, 1H, $C_{4'}$-H), 7.39–7.43 (m, 2H, $C_{3'}$-H & $C_{5'}$-H), 7.62–7.66 (m, 2H, $C_{2''}$-H & $C_{6''}$-H), 7.68–7.70 (m, 2H, $C_{2'}$-H & $C_{6'}$-H), 8.24 (s, 1H, pyrazolyl-H). Anal. calcd. for $C_{23}H_{19}N_3OS$: C, 71.66; H, 4.97; N, 10.90; S, 8.32%. Found: C, 71.28; H, 4.49; N, 11.18; S, 8.09%. ESI-MS $[M+H]^+ = 386.24$; calcd. for $C_{23}H_{19}N_3OS = 385.12$.

2-[3-(2-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl]benzothiazoline (3d). Pale yellow solid; mp 128–130 °C; $R_f = 0.38$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3320, 3130, 3050, 2925, 1594, 1580, 1547, 1505, 1475, 1450, 1400, 1360, 1323, 1220, 1060, 950, 830, 738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.85 (s, 3H, OCH_3), 4.51 (bs, 1H, NH), 6.17 (s, 1H, C_2-H), 6.55–6.57 (m, 1H, C_4-H), 6.70–6.74 (dt, 1H, $J = 7.60$ & 0.92 Hz, C_6-H), 6.87–6.91 (dt, 1H, $J = 7.60$ & 1.12 Hz, C_5-H), 6.96–6.98 (d, 1H, $J = 8.28$ Hz, $C_{3''}$-H), 7.03–7.07 (m, 2H, C_7-H & $C_{5''}$-H), 7.21–7.25 (m, 1H, $C_{4'}$-H), 7.34–7.40 (m, 3H, $C_{4''}$-H, $C_{3'}$-H & $C_{5'}$-H), 7.50–7.52 (dd, 1H, $J = 7.48$ & 1.68 Hz, $C_{6''}$-H), 7.66–7.68 (m, 2H, $C_{2'}$-H & $C_{6'}$-H), 8.20 (s, 1H, pyrazolyl-H). Anal. calcd. for $C_{23}H_{19}N_3OS$: C, 71.66; H, 4.97; N, 10.90; S, 8.32%. Found: C, 71.30; H, 5.10; N, 10.78; S, 8.49%. ESI-MS $[M+H]^+ = 386.22$; calcd. for $C_{23}H_{19}N_3OS = 385.12$.

2-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl]benzothiazoline (3e). White solid; mp 124–125 °C; $R_f = 0.36$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3322, 3051, 2923, 1599, 1575, 1558, 1541, 1503, 1466, 1409, 1396, 1211, 1093, 1062, 1007, 831, 743. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.35 (bs, 1H, NH), 6.50 (s, 1H, C_2-H), 6.68–6.70 (dd, 1H, $J = 7.32$ & 0.62 Hz, C_4-H), 6.79–6.83 (dt, 1H, $J = 7.52$ & 1.00 Hz, C_6-H), 6.94–6.98 (dt, 1H, $J = 7.60$ & 1.20 Hz, C_5-H), 7.08–7.10 (dd, 1H, $J = 7.60$ & 0.96 Hz, C_7-H), 7.27–7.31 (m, 1H, $C_{4'}$-H), 7.40–7.49 (m, 4H, $C_{3''}$-H, $C_{5''}$-H, $C_{3'}$-H & $C_{5'}$-H), 7.66–7.73 (m, 4H, $C_{2'}$-H, $C_{6'}$-H, $C_{2''}$-H & $C_{6''}$-H), 8.28 (s, 1H, pyrazolyl-H). Anal. calcd. for $C_{22}H_{16}ClN_3S$: C, 67.77; H, 4.14; N, 10.78; S, 8.22%. Found: C, 67.40; H, 4.31; N, 10.93; S, 8.08%. ESI-MS $[M+H]^+ = 390.21$; calcd. for $C_{22}H_{16}ClN_3S = 389.08$.

2-[3-(4-Bromo-phenyl)-1-phenyl-1H-pyrazol-4-yl]benzothiazoline (3f). White solid; mp 195–196 °C; $R_f = 0.40$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3293, 3111, 3050, 2924, 1597, 1576, 1533, 1505, 1473, 1398, 1360, 1308, 1277, 1200, 1117, 1065, 831, 738. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.29 (bs, 1H, NH), 6.49 (s, 1H, C_2-H), 6.68–6.70 (m, 1H, C_4-H), 6.79–6.83 (m, 1H, C_6-H), 6.94–6.98 (m, 1H, C_5-H), 7.08–7.10 (m, 1H, C_7-H), 7.24–7.31 (m, 1H, $C_{4'}$-H), 7.36–7.46 (m, 2H, $C_{3'}$-H & $C_{5'}$-H), 7.56–7.71 (m, 6H, $C_{2'}$-H, $C_{6'}$-H, $C_{2''}$-H, $C_{3''}$-H, $C_{5''}$-H & $C_{6''}$-H), 8.28 (s, 1H, pyrazolyl-H). Anal. calcd. for $C_{22}H_{16}BrN_3S$: C,

60.83; H, 3.71; N, 9.67; S, 7.38%. Found: C, 60.96; H, 3.58; N, 9.791; S, 7.49%. ESI-MS $[M+H]^+ = 434.17$; calcd. for $C_{22}H_{16}BrN_3S = 433.02$.

2-[3-(4-Fluoro-phenyl)-1-phenyl-1H-pyrazol-4-yl]benzothiazoline (3g). White solid; mp 129 °C; $R_f = 0.33$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3310, 3045, 3305, 1603, 1570, 1500, 1475, 1357, 1268, 1110, 836, 740. ^1H NMR (400 MHz, $CDCl_3$): δ 4.29 (bs, 1H, NH), 6.48 (s, 1H, C_2-H), 6.67–6.69 (d, 1H, $J = 7.64$ Hz, C_4-H), 6.78–6.82 (dt, 1H, $J = 7.60$ & 0.88 Hz, C_6-H), 6.93–6.97 (dt, 1H, $J = 7.64$ & 1.00 Hz, C_5-H), 7.07–7.09 (dd, 1H, $J = 7.60$ & 0.64 Hz, C_7-H), 7.11–7.18 (m, 2H, $C_{3''}$-H & $C_{5''}$-H), 7.26–7.30 (m, 1H, $C_{4'}$-H), 7.36–7.45 (m, 2H, $C_{3'}$-H & $C_{5'}$-H), 7.68–7.71 (m, 4H, $C_{2'}$-H, $C_{6'}$-H, $C_{2''}$-H & $C_{6''}$-H), 8.27 (s, 1H, pyrazolyl-H). Anal. calcd. for $C_{22}H_{16}FN_3S$: C, 70.76; H, 4.32; N, 11.25; S, 8.59%. Found: C, 70.90; H, 4.20; N, 11.37; S, 8.72%. ESI-MS $[M+H]^+ = 374.24$; calcd. for $C_{22}H_{16}FN_3S = 373.10$.

2-(1,3-Diphenyl-1H-pyrazol-4-yl)benzothiazole (4a). Yellow solid; mp 139–140 °C; $R_f = 0.47$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3029, 2923, 1596, 1584, 1544, 1527, 1506, 1448, 1355, 1246, 1065, 962, 930, 752. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30–7.36 (m, 2H, $C_{4'}$-H & C_6-H), 7.44–7.51 (m, 6H, C_5-H, $C_{3'}$-H, $C_{5'}$-H, $C_{3''}$-H, $C_{4''}$-H & $C_{5''}$-H), 7.75–7.77 (m, 3H, C_4-H, $C_{2''}$-H & $C_{6''}$-H), 7.82–7.84 (d, 2H, $J = 8.00$ Hz, $C_{2'}$-H & $C_{6'}$-H), 8.00–8.02 (d, 1H, $J = 8.12$ Hz, C_7-H), 8.64 (s, 1H, pyrazolyl-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 117.36 (C_4-pyrazolyl), 119.30 ($C_{2'}$ & $C_{6'}$), 121.32 (C_4), 122.53 (C_7), 124.79 (C_5), 126.13 (C_6), 127.22 ($C_{4'}$), 128.19 (C_5-pyrazolyl), 128.41 ($C_{2''}$ & $C_{6''}$), 129.06 ($C_{4''}$), 129.53 ($C_{3''}$ & $C_{5''}$), 129.6 ($C_{3'}$ & $C_{5'}$), 131.93 ($C_{1''}$), 134.96 (C_{7a}), 139.34 ($C_{1'}$), 152.12 (C_{4a}), 153.14 (C_2), 160.04 (C_3-pyrazolyl). Anal. calcd. for $C_{22}H_{15}N_3S$: C, 74.76; H, 4.28; N, 11.82; S, 9.07%. Found: C, 74.70; H, 4.41; N, 11.99; S, 8.99%. ESI-MS $[M+H]^+ = 354.27$; calcd. for $C_{22}H_{15}N_3S = 353.10$.

2-(1-Phenyl-3-p-tolyl-1H-pyrazol-4-yl)benzothiazole (4b). White solid; mp 182–183 °C; $R_f = 0.36$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3030, 2936, 2846, 1620, 1605, 1593, 1550, 1522, 1478, 1440, 1305, 1237, 1160, 1012, 950, 745. ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 7.24–7.35 (m, 4H, $C_{4'}$-H, C_6-H, $C_{3''}$-H & $C_{5''}$-H), 7.43–7.50 (m, 3H, C_5-H, $C_{3'}$-H & $C_{5'}$-H), 7.62–7.64 (d, 2H, $J = 7.72$ Hz, $C_{2''}$-H & $C_{6''}$-H), 7.75–7.77 (d, 1H, $J = 7.92$ Hz, C_4-H), 7.81–7.83 (d, 2H, $J = 7.92$ Hz, $C_{2'}$-H & $C_{6'}$-H), 8.00–8.02 (d, 1H, $J = 8.08$ Hz, C_7-H), 8.64 (s, 1H, pyrazolyl-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.45 (C_4-CH_3), 117.36 (C_4-pyrazolyl), 119.30 ($C_{2'}$ & $C_{6'}$), 121.32 (C_4), 122.52 (C_7), 124.74 (C_5), 126.10 (C_6), 127.15 ($C_{4'}$), 128.11 (C_5-pyrazolyl), 129.00 ($C_{1''}$), 129.15 ($C_{2''}$ & $C_{6''}$), 129.52 ($C_{3'}$ & $C_{5'}$), 129.54 ($C_{3''}$ & $C_{5''}$), 135.01 (C_{7a}), 139.02 ($C_{4''}$), 139.42 ($C_{1'}$), 152.24 (C_{4a}), 153.17 (C_2), 160.23 (C_3-pyrazolyl). Anal. calcd. for $C_{23}H_{17}N_3S$: C, 75.18; H, 4.66; N, 11.44; S, 8.73%. Found: C, 75.98; H, 4.39; N, 10.95; S, 8.22%. ESI-MS $[M+H]^+ = 368.30$; calcd. for $C_{23}H_{17}N_3S = 367.11$.

2-[3-(4-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl)]benzothiazole (4c). White solid; mp 168–169 °C (lit.[8] mp 167–169 °C); $R_f = 0.34$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3024, 2963, 2930, 2835, 1610, 1598, 1583, 1547, 1515, 1475, 1456, 1293, 1248, 1177, 1023, 963, 840, 750. ^1H NMR (400 MHz, $CDCl_3$): δ 3.87 (s, 3H, OCH_3), 6.99–7.02 (m, 2H, $C_{3''}$-H & $C_{5''}$-H), 7.30–7.35 (m, 2H, $C_{4'}$-H

& C_6-H), 7.43–7.50 (m, 3H, C_5-H, $C_{3'}$-H & $C_{5'}$-H), 7.66–7.68 (m, 2H, $C_{2''}$-H & $C_{6''}$-H), 7.76–7.78 (m, 1H, C_4-H), 7.81–7.83 (m, 2H, $C_{2'}$-H & $C_{6'}$-H), 8.00–8.02 (d, 1H, $J = 8.00$ Hz, C_7-H), 8.66 (s, 1H, pyrazolyl-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.29 (C_4-OCH_3), 113.89 ($C_{3''}$ & $C_{5''}$), 117.24 (C_4-pyrazolyl), 119.25 ($C_{2'}$ & $C_{6'}$), 121.32 (C_4), 122.46 (C_7), 124.21 ($C_{1''}$), 124.75 (C_5), 126.12 (C_6), 127.13 ($C_{4'}$), 128.08 (C_5-pyrazolyl), 129.51 ($C_{3'}$ & $C_{5'}$), 130.97 ($C_{2''}$ & $C_{6''}$), 134.90 (C_{7a}), 139.37 ($C_{1'}$), 151.99 (C_{4a}), 153.07 (C_2), 160.27 (C_3-pyrazolyl), 160.39 ($C_{4''}$). Anal. calcd. for $C_{23}H_{17}N_3OS$: C, 72.04; H, 4.47; N, 10.96; S, 8.36%. Found: C, 71.78; H, 4.39; N, 11.08; S, 8.22%. ESI-MS $[M + H]^+ = 384.28$; calcd. for $C_{23}H_{17}N_3OS = 383.11$.

2-[3-(2-Methoxy-phenyl)-1-phenyl-1H-pyrazol-4-yl)]benzothiazole (4d). White solid; mp 173–174 °C; $R_f = 0.40$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3020, 2970, 2933, 2840, 1608, 1595, 1575, 1540, 1480, 1450, 1290, 1170, 1030, 960, 845, 760. ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.63 (s, 3H, OCH_3), 7.00–7.02 (d, 1H, $J = 8.44$ Hz, $C_{3''}$-H), 7.10–7.14 (t, 1H, $J = 7.28$ Hz, $C_{5''}$-H), 7.24–7.34 (m, 2H, $C_{4'}$-H & C_6-H), 7.41–7.52 (m, 5H, C_5-H, $C_{4''}$-H, $C_{6''}$-H, $C_{3'}$-H & $C_{5'}$-H), 7.71–7.73 (d, 1H, $J = 7.84$ Hz, C_4-H), 7.82–7.84 (d, 2H, $J = 7.80$ Hz, $C_{2'}$-H & $C_{6'}$-H), 7.97–7.98 (d, 1H, $J = 8.04$ Hz, C_7-H), 8.77 (s, 1H, pyrazolyl-H).^{13}C NMR (100 MHz, $CDCl_3$): δ 55.35 (C_2-OCH_3), 111.14 ($C_{3''}$), 118.91 (C_4-pyrazolyl), 119.27 ($C_{2'}$ & $C_{6'}$), 120.88 ($C_{5''}$), 121.16 ($C_{1''}$), 121.28 (C_4), 122.21 (C_7), 124.40 (C_5), 125.96 (C_6), 127.01 ($C_{4'}$), 127.02 (C_5-pyrazolyl), 129.45 ($C_{3'}$ & $C_{5'}$), 130.99 ($C_{6''}$), 131.83 ($C_{4''}$), 134.85 (C_{7a}), 139.45 ($C_{1'}$), 149.63 (C_{4a}), 152.89 (C_2), 158.11 ($C_{4''}$), 160.65 (C_3-pyrazolyl). Anal. calcd. for $C_{23}H_{17}N_3OS$: C, 72.04; H, 4.47; N, 10.96; S, 8.36%. Found: C, 71.80; H, 4.67; N, 10.67; S, 8.19%. ESI-MS $[M + H]^+ = 384.27$; calcd. for $C_{23}H_{17}N_3OS = 383.11$.

2-[3-(4-Chloro-phenyl)-1-phenyl-1H-pyrazol-4-yl)]benzothiazole (4e). White solid; mp 205–206 °C (lit.[8] mp 205–207 °C); $R_f = 0.41$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3060, 2922, 2848, 1598, 1540, 1522, 1506, 1269, 1247, 1091, 1012, 962, 931, 831, 754. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.38 (m, 2H, $C_{4'}$-H & C_6-H), 7.43–7.52 (m, 5H, C_5-H, $C_{3''}$-H, $C_{5''}$-H, $C_{3'}$-H & $C_{5'}$-H), 7.72–7.75 (m, 2H, $C_{2''}$-H & $C_{6''}$-H), 7.79–7.83 (m, 3H, C_4-H, $C_{2'}$-H & $C_{6'}$-H), 8.01–8.03 (d, 1H, $J = 8.12$ Hz, C_7-H), 8.63 (s, 1H, pyrazolyl-H).^{13}C NMR (100 MHz, $CDCl_3$): δ 117.18 (C_4-pyrazolyl), 119.33 ($C_{2'}$ & $C_{6'}$), 121.35 (C_4), 122.67 (C_7), 125.00 (C_5), 126.20 (C_6), 127.39 ($C_{4'}$), 128.56 (C_5-pyrazolyl), 128.62 ($C_{2''}$ & $C_{6''}$), 129.59 ($C_{3'}$ & $C_{5'}$), 130.45 ($C_{1''}$), 130.89 ($C_{3''}$ & $C_{5''}$), 134.88 (C_{7a}), 135.11 ($C_{4''}$), 139.23 ($C_{1'}$), 150.79 (C_{4a}), 153.19 ($C_{2'}$), 159.64 (C_3-pyrazolyl). Anal. calcd. for $C_{22}H_{14}ClN_3S$: C, 68.12; H, 3.64; N, 10.83; S, 8.27%. Found: C, 68.00; H, 3.41; N, 11.16; S, 8.01%. ESI-MS $[M + H]^+ = 388.25$; calcd. for $C_{22}H_{14}ClN_3S = 387.06$.

2-[3-(4-Bromo-phenyl)-1-phenyl-1H-pyrazol-4-yl)]benzothiazole (4f). White solid; mp 210–211 °C (lit.[8] mp 210–214 °C); $R_f = 0.42$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3052, 2924, 2854, 1597, 1550, 1517, 1481, 1247, 1071, 960, 829, 753. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.38 (m, 2H, $C_{4'}$-H & C_6-H), 7.46–7.52 (m, 3H, C_5-H, $C_{3'}$-H & $C_{5'}$-H), 7.59–7.61 (d, 2H, $J = 8.40$ Hz, $C_{2''}$-H & $C_{6''}$-H), 7.67–7.69 (d, 2H, $J = 8.40$ Hz, $C_{3''}$-H & $C_{5''}$-H), 7.80–7.82 (d, 3H, $J = 7.60$ Hz, C_4-H, $C_{2'}$-H & $C_{6'}$-H), 8.01–8.03 (d, 1H, $J = 8.00$ Hz, C_7-H), 8.59 (s, 1H, pyrazolyl-H).^{13}C NMR (100 MHz, $CDCl_3$): δ 117.22 (C_4-pyrazolyl), 119.37

($C_{2'}$ & $C_{6'}$), 121.41 (C_4), 122.74 (C_7), 123.44 ($C_{4''}$), 125.06 (C_5), 126.31 (C_6), 127.45 ($C_{4'}$), 128.61 (C_5-pyrazolyl), 129.65 ($C_{3'}$ & $C_{5'}$), 130.96 ($C_{1''}$), 131.20 ($C_{2''}$ & $C_{6''}$), 131.62 ($C_{3''}$ & $C_{5''}$), 134.93 (C_{7a}), 139.27 ($C_{1''}$), 150.82 (C_{4a}), 153.28 (C_2), 159.65 (C_3-pyrazolyl). Anal. calcd. for $C_{22}H_{14}BrN_3S$: C, 61.12; H, 3.26; N, 9.72; S, 7.42%. Found: C, 60.46; H, 3.48; N, 9.31; S, 7.60%. ESI-MS $[M+H]^+ = 432.17$; calcd. for $C_{22}H_{14}BrN_3S = 431.01$.

2-[3-(4-Fluoro-phenyl)-1-phenyl-1H-pyrazol-4-yl)]benzothiazole (4g). White solid; mp 160 °C; $R_f = 0.37$ (AcOEt/petroleum ether 10%). IR (KBr, cm^{-1}): 3040, 2934, 1610, 1555, 1527, 1512, 1487, 1257, 1078, 1019, 970, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13–7.18 (m, 2H, $C_{3''}$-H & $C_{5''}$-H), 7.32–7.37 (m, 2H, $C_{4'}$-H & C_6-H), 7.44–7.51 (m, 3H, C_5-H, $C_{3'}$-H & $C_{5'}$-H), 7.73–7.82 (m, 5H, C_4-H, $C_{2''}$-H, $C_{6''}$-H, $C_{2'}$-H & $C_{6'}$-H), 7.99–8.01 (d, 1H, $J = 8.12$ Hz, C_7-H), 8.60 (s, 1H, pyrazolyl-H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 115.34 & 115.56 ($C_{3''}$ & $C_{5''}$), 117.2 (C_4-pyrazolyl), 119.33 ($C_{2'}$ & $C_{6'}$), 121.34 (C_4), 122.64 (C_7), 124.94 (C_5), 126.23 (C_6), 127.34 ($C_{4'}$), 128.00 & 128.04 ($C_{1''}$), 128.37 (C_5-pyrazolyl), 129.58 ($C_{3'}$ & $C_{5'}$), 131.47 & 131.55 ($C_{2''}$ & $C_{6''}$), 134.88 (C_{7a}), 139.29 ($C_{1'}$), 151.07 (C_{4a}), 153.23 (C_2), 159.77 (C_3-pyrazolyl), 162.19 & 164.66 ($C_{4''}$). Anal. calcd. for $C_{22}H_{14}FN_3S$: C, 71.14; H, 3.80; N, 11.31; S, 8.63%. Found: C, 70.60; H, 3.66; N, 11.68; S, 8.46%. ESI-MS $[M+H]^+ = 372.26$; calcd. for $C_{22}H_{14}FN_3S = 371.09$.

ACKNOWLEDGMENT

The authors are grateful to the Sophisticated Analytical Instrumentation Facility (SAIF), Panjab University, Chandigarh, India, for providing the NMR facility and elemental analysis.

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