A Green Mechanochemical Synthesis of New 3,5-Dimethyl-4-(arylsulfanyl)pyrazoles

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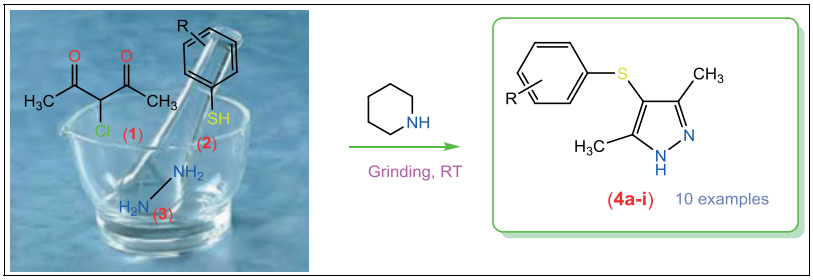

A small series of new 3,5-dimethyl-4-(arylsulfanyl)pyrazoles have been synthesized in good to excellent yields by a grinding-induced, sequential one-pot three-component reaction, of an equimolar mixture of 3-chloro-2,4-pentanedione, differently substituted thiophenols, and hydrazine hydrate in the presence of piperidine under solvent-free conditions.

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INTRODUCTION

Pyrazoles are amongst the best known heterocycles having two nitrogens at adjacent positions and found to have a diversity of applications in the pharmaceutical and agrochemical industries. Pyrazoles constitute the central core of some well-known drugs like celecoxib, a COX-2 selective nonsteroidal anti-inflammatory drug; oxymetazoline, a selective alpha-1 and partial alpha-2 agonist topical decongestant; butazoline; metamizole, an ampyrone sulfonate analgesic, antispasmodic and antipyretic marketed as novalgin; apixaban, an anticoagulant and a direct factor Xa inhibitor; and fipronil, a broad-spectrum insecticide and rimonabant, anorectic anti-obesity drug. Moreover, these are versatile building blocks towards the synthesis of a number of other heterocyclic systems. In view of the fact that a number of books and reviews are available for synthesis and applications of pyrazoles [1–3], there is hardly any need to cite the literature in this connection. However, it is motivating to note that despite the very common occurrence of pyrazole scaffold, a survey of literature indicates only handful reports of sulfur containing pyrazoles. The sulfur containing pyrazole derivatives as blood sugar level-lowering agents had long been patented [4]. Some 1-(2,4-dinitrophenyl)-3-aryl-4-(arylsulfonyl)-1*H*-pyrazoles were prepared by the Vilsmeier reaction of hydrazones under microwave irradiation. The requisite hydrazones were themselves obtained from 2,4-dinitrophenylhydrazine and substituted aryl sulfides [5]. Another report describes the synthesis of pyrazoles by the reaction of the carbanions of 1-aryl-2-(phenylsulphonyl)ethanone with different hydrazonyl halides under ultrasonic conditions. These were shown to exhibit strong antibacterial activity against both gram positive and gram negative bacteria [6]. In addition, some mercaptoheterocyclic compounds were converted into corresponding acylated hydrazines via acetates. The acylated hydrazines on reaction with ketene dithioacetal derivatives afforded the sulphur bridged pyrazoles [7].

Motivated by the aforesaid facts concerning the scarcity of sulfur containing pyrazoles systems coupled with our synthetic and biological experience in the field of heterocycles [8], herein, we report a mechanochemical method for synthesis of title compounds. The grinding-induced method not only reduces the time of reaction from several hours to a few minutes but also improves the yields compared with that of conventional conditions.

RESULTS AND DISCUSSION

The synthetic strategy adopted for the synthesis of the target compounds is depicted in Scheme 1.

Accordingly, an intimate equimolar mixture of 3-chloro-2,4-pentanedione and suitably substituted thiophenols was homogenized in a glass mortar and pestle, in the presence of catalytic amount of piperidine. The mixture was ground further for 5–10 min to afford a semisolid. An equimolar amount of hydrazine hydrate was added, and the grinding was continued for further 10–15 min [9]. The progress of the reaction was monitored by TLC using *n*-hexane ethyl acetate (8:2). On completion, the reaction mixture was diluted with ethyl acetate and filtered; the filtrate was concentrated and recrystallized from ethanol to afford pure products in yields shown in Table 1.

The products were characterized on the basis of their FTIR, ^{1}H NMR, mass spectroscopic and microelemental analytical data. The stretchings at 3160 (NH), 528 (C=N), 1597

Scheme 1. Synthetic route to new 3,5-dimethyl-4-(arylsulfanyl)pyrazoles. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

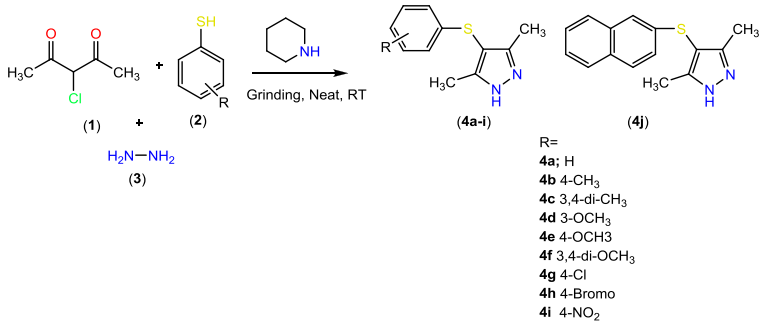
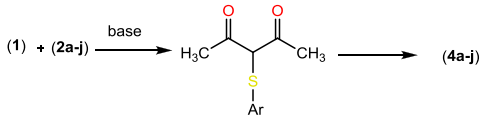


Table 1

Physical data of 3,5-dimethyl-4-(arylsulfanyl)pyrazoles (**4a–j**).

Entry	R	Melting point °C	Time (min)	Yield (%)
4a	H	Oil	13	75
4b	CH_3	95	11	78
4c	3,4-di $(CH_3)_2$	108	15	81
4d	3-CH_3O	Oil	10	79
4e	4-CH_3O	Oil	11	80
4f	3,4-di $(CH_3O)_2$	115	10	83
4g	4-Cl	130	15	72
4h	4-Br	80	10–15	74
4i	4-NO_2	Oil	15–17	88
4j	2-naphthyl	122	10	87

Scheme 2. Mechanistic pathway to 4-(arylsulfanyl)pyrazoles. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



(C=C), and 780 (C–S) cm^{-1} were noted in the FTIR spectra of pyrazoles. In ^1H NMR spectra, the typical sharp singlets were noticed at δ 9.34 for NH at δ 2.42 and 2.32 ppm because of CH_3 protons besides those in the range δ 7.31–7.83 for the aromatic protons, indicating the successful linkage of aryl through sulfur bridge. ^{13}C NMR spectra displayed the signal at δ 156.5 (C=N), 136.1 (C=C), 108.6 (C–S), and 9.6 (CH_3) ppm, in addition to those of aromatic carbons.

Mechanistically, it is likely that first 3-(arylthio)pentane-2,4-dione is formed as an intermediate, which undergoes usual cyclization with hydrazine to afford the target pyrazoles (Scheme 2).

CONCLUSION

An efficient, rapid, one-pot method for the preparation of sulfur containing pyrazoles by a domino multicomponent reaction is described. The outstanding features include crucial shortening of reaction time, effortless separation, and the eco-friendliness. The bioevaluation of the compounds is presently in progress and will be reported in due course.

EXPERIMENTAL

Melting points were recorded using a digital Gallenkamp (SANYO, Moriguchi, Japan) model MPD BM 3.5 apparatus and are uncorrected. ^1H NMR spectra were determined as $CDCl_3$ solutions at 300 MHz using a Bruker AM-300 spectrophotometer (Billerica, MA, USA). FT IR spectra were recorded using Bio-Rad Excalibur FTS 3000 MX spectrophotometer (Madison, WI), Mass Spectra (EI, 70 eV) on a GC-MS instrument. The reactions were carried out in glass mortar and pestle.

General procedure for the preparation of 3,5-dimethyl-4-(arylsulfanyl)pyrazoles (4a–j). A mixture of the appropriate thiophenol (1 mmol), 3-chloro-2,4-pentaned ione (1 mmol), and a catalytic amount of piperidine was ground in a glass mortar and pestle at room temperature. After grinding for 5–10 min, hydrazine hydrate (1 mmol) was added, and the grinding was continued for further 10 min. The progress of the reaction was monitored by TLC using *n*-hexane ethyl acetate (8:2). On completion, the reaction mixture was diluted with ethyl acetate and filtered to remove salts, and the filtrate was concentrated. Recrystal lization from ethanol afforded pure products (**4a–j**).

3,5-Dimethyl-4-phenylsulfanyl-1H-pyrazole (4a). Colorless oil; FTIR (KBr): 3128 (sp^2CH), 2936 (sp^3CH), 1578 (C=N), 1608 (C=C), 693 (C–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.4 (s, 1H, NH), 7.1 (m, 1H, ArH), (m, 2H, ArH), 7.0 (dd, 2H, J = 1.2, Hz, ArH), 2.3 (s, 6H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4 (C=N), 147.5 (C=C), 133.5, 130.3, 127.5 (Ar–C), 108 (C–S), 10.5 (CH_3). *Anal*. Calcd. for $C_{11}H_{12}N_2S$: C, 64.67; H, 5.92; N, 13.71; S, 15.70. Found: C, 64.65; H, 5.93; N, 13.74; S, 15.68. Calcd. (204.29). Found: 204.

3,5-Dimethyl-4-p-tolylsulfanyl-1H-pyrazole (4b). Yellow solid; FTIR (KBr): 3129 (sp^2CH), 2939 (sp^3CH), 1568 (C=N), 1608 (C=C), 735 (C–S) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.3 (s, 1H, NH), 7.2 (d, J = 7.5 Hz, 2H, ArH), 6.8

(d, J = 7.5 Hz, 2H, ArH), 2.4 (s, 1H, CH_3), 2.3 (s, 3H, CH_3), 2.4 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1 (C=N), 146.5 (C=C), 136.6, 132.6, 131.6, 130.4 (Ar–C), 109 (C–S), 22.1, 11.1, 9.5 (CH_3). *Anal*. Calcd. for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83; S, 14.69. Found: C, 66.01; H, 6.45; N, 12.84; S, 14.70. Calcd. (218.09). Found: 218.

4-(3,4-Dimethylphenylsulfanyl)-3,5-dimethyl-1H-pyrazole (4c). Light yellow solid; FTIR (KBr): 3125 (sp^2CH), 2935 (sp^3CH), 1577 (C=N), 1605 (C=C), 757 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.4 (s, 1H, NH), 6.7 (d, J = 8.7 Hz, 1H, ArH), 6.6 (d, J = 2.8 Hz, 1H, ArH), 6.3 (dd, J = 8.7 Hz, 2.8 Hz, 1H, ArH), 2.8 (s, 3H, CH_3), 2.6 (s, 3H, CH_3), 2.4 (s, 3H, CH_3), 2.4 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.1 (C=N), 148.6 (C=C), 145.6, 145.7, 145.6, 132.9, 129.9, 127.9 (Ar–C), 107.3, 108 (C–S), 20.5, 23.5, 10.1, 8.5 (CH_3). *Anal*. Calcd. for $C_{13}H_{16}N_2S$: C, 67.20; H, 6.94; N, 12.06; S, 13.80. Found: C, 67.18; H, 6.92; N, 12.09; S, 13.81. Calcd. (232.10). Found: 232.

4-(3-Methoxyphenylsulfanyl)-3,5-dimethyl-1H-pyrazole (4d). Colourless oil; FTIR (KBr): 3127 (sp^2CH), 2936 (sp^3CH), 1577 (C=N), 1605(C=C), 733 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.3 (s, 1H, NH), 6.51–6.5 (m, 3H, ArH), 6.8–6.9 (m, 1H, ArH), 3.4 (s, 1H, OCH_3), 2.4 (s, 3H, CH_3), 2.3 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (O–Ar), 147.5 (C=N), 145.6 (C=C), 135.3, 130.5, 125.5, 116.5, 113.3 (Ar–C), 107.3 (C–S), 56.5 (OCH_3), 11.0, 9.5 (CH_3). *Anal*. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.49; H, 6.04; N, 11.95; S, 13.69. Calcd. (234.08). Found: 234.

4-(4-Methoxyphenylsulfanyl)-3,5-dimethyl-1H-pyrazole (4e). Colour less oil; FTIR (KBr): 3126 (sp^2CH), 2937 (sp^3CH), 1576 (C=N), 1605 (C=C), 695 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (s, 1H, NH), 7.3 (d, J = 7.5 Hz, 2H, ArH), 6.7 (d, J = 7.5 Hz, 2H, ArH), 3.4 (s, 1H, OCH_3), 2.3 (s, 3H, CH_3), 2.2 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5 (O–Ar), 152.1 (C=N), 144.6 (C=C), 138.6, 135.4, 135.2, 128.9, 121.3 (Ar–C), 106.3 (C–S), 61.1 (OCH_3), 10.1, 8.5 (CH_3). *Anal*. Calcd. for $C_{12}H_{14}N_2OS$: C, 61.51; H, 6.02; N, 11.96; S, 13.68. Found: C, 61.50; H, 6.03; N, 11.95; S, 13.69. Calcd. (234.08). Found: 234.

4-(3,4-Dimethoxyphenylsulfanyl)-3,5-dimethyl-1H-pyrazole (4f). Yellow solid; FTIR (KBr): 3125 (sp^2CH), 2935 (sp^3CH), 1577 (C=N), 1602 (C=C), 722 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.3 (s, 1H, NH), 6.8 (d, J = 8.7 Hz, 1H, ArH), 6.6 (d, J = 2.8 Hz, 1H, ArH), 6.3 (dd, J = 8.7 Hz, 2.8 Hz, 1H, ArH), 3.8 (s, 3H, OCH_3), 3.9 (s, 3H, OCH_3), 2.4 (s, 3H, CH_3), 2.3 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.5 (O–Ar), 152.1 (C=N), 148.6 (C=C), 147.6, 135.7, 130.6, 122.9 (Ar–C), 109.3 (C–S), 56.5 (OCH_3), 53.5 (OCH_3), 10.1, 8.5 (CH_3). *Anal*. Calcd. for $C_{13}H_{16}N_2O_2S$: C, 59.07; H, 6.10; N, 10.60; S, 12.13. Found: C, 59.05; H, 6.12; N, 10.59; S, 12.14. Calcd. (264.09). Found: 264.

4-(4-Chlorophenylsulfanyl)-3,5-dimethyl-1H-pyrazole (4g). Light yellow; FTIR (KBr): 3115 (sp^2CH), 2955 (sp^3CH), 1569 (C=N), 1595–1495 (C=C), 727 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.6 (s, 1H, NH), 7.2 (d, J = 9.1 Hz, 2H, ArH), 6.7 (d, J = 9.1 Hz, 2H, ArH), 2.4 (s, 1H, CH_3), 2.3 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8 (C=N), 146.9 (C=C), 137.6, 134, 129.4, 129.2 (Ar–C), 110.4 (C–S), 11.1, 9.7 (CH_3). *Anal*. Calcd. for $C_{11}H_{11}ClN_2S$: C, 55.34; H, 4.64; N, 11.73; S, 13.43. Found: C, 55.32; H, 4.66; N, 11.71; S, 13.45. Calcd. (238.03). Found: 238.

4-(4-Bromophenylsulfanyl)-3,5-dimethyl-1H-pyrazole (4h). Yellow solid, yield 40%, mp 80°C; FTIR (KBr): 3117 (sp^2CH), 2955 (sp^3CH), 1569 (C=N), 1595 (C=C), 695 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.5 (s, 1H, NH), 7.5 (d, J = 7.5 Hz, 2H, ArH), 6.7 (d, J = 7.3 Hz, 2H, ArH), 2.4 (s, 1H, CH_3), 2.7 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.8 (C=N), 144.91 (C=C), 137.63, 134.5, 132.4, 130.4 (Ar–C), 110.4 (C–S), 11.1, 9.50 (CH_3). *Anal*. Calcd. for $C_{11}H_{11}BrN_2S$: C, 46.65; H, 3.92; N, 9.89; S, 11.32. Found: C, 46.63; H, 3.94; N, 9.91; S, 11.30. Calcd. (281.98). Found: 281.

3,5-Dimethyl-4-(4-nitrophenylsulfanyl)-1H-pyrazole (4i). Pink oil, yield 58%; FTIR (KBr): 3115 (sp^2CH), 2955 (sp^3CH), 1569 (C=N), 1595 (C=C), 738 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.33 (s, 1H, NH), 8.0 (d, J = 7.5 Hz, 2H, ArH), 7.1 (d, J = 7.3 Hz, 2H), 2.4 (s, 1H, CH_3), 2.2 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8 (C=N), 147.9 (C=C), 146.6, 142.6, 134.2, 123.5 (Ar–C), 107.4 (C–S), 10.1, 8.5 (CH_3). *Anal*. Calcd. for $C_{11}H_{11}N_3O_2S$; C, 53.00; H, 4.45; N, 16.86; S, 12.86. Found: C, 53.02; H, 4.43; N, 11.95; S, 13.69. Calcd. (234.08). Found: 234.

3,5-Dimethyl-4-(naphthalen-2-ylsulfanyl)-1H-pyrazole (4j). Light pink solid; FTIR (KBr): 3160 (NH), 3057 (sp^2CH), 2917 (sp^3CH), 1528 (C=N), 1597 (C=C), 777 (C–S) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.3 (s, 1H, NH), 7.8–7.7 (m, 2H), 7.7 (qd, J = 7.5, 1.4 Hz, 2H, ArH), 7.5–7.3 (m, 3H, ArH), 2.4 (S, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.5 (C=N), 136.1 (C=C), 134.3, 129.8, 129.6, 127.7, 126.9, 126.6, 124.2, 117.6 (Ar–C), 108.6 (C–S), 9.6 (CH_3). *Anal*. Calcd. for $C_{15}H_{14}N_2S$: C, 70.83; H, 5.55; N, 11.01; S, 12.61. Found: C, 70.81; H, 5.56; N, 11.03; S, 12.60. Calcd. (254.09). Found: 254.

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