Synthesis of 5-Aryl-3-(methylsulfanyl)-1*H*-pyrazoles *via* Three-Component Reaction of 1,1-Bis(methylsulfanyl)-2-nitroethene, Aromatic Aldehydes, and Hydrazine

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An efficient approach for the preparation of functionalized 5-aryl-3-(methylsulfanyl)-1*H*-pyrazoles **2** is described. This three-component reaction between benzaldehydes **1**, $NH_2NH_2 \cdot H_2O$, and 1,1-bis(methylsulfanyl)-2-nitroethene proceeds in EtOH under reflux conditions in good-to-excellent yields. The structures of **2** were corroborated spectroscopically (IR, ^{1}H- and ^{13}C-NMR, and EI-MS). A plausible mechanism for this type of reaction is proposed (*Scheme 2*).

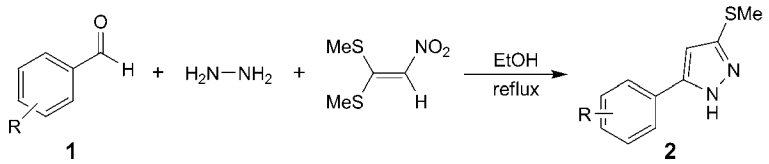
1. Introduction. – Multicomponent reactions (MCRs) are excellent strategies, employed in the synthesis of several natural products. These MCRs are generally defined as reactions where more than two starting materials react to form a product, incorporating more or less all the atoms of the starting materials [1]. Recently, there has been a tremendous development in three- and four-component reactions [2].

As an important type of N-containing heterocycle, pyrazole has been employed as a key structural motif, which widely occurs in nature and exhibits excellent biological activity in pharmaceuticals, such as *Celebrex* [3], *Viagra* [4], and rimonabant [5]. Versatile synthetic routes have been developed for the synthesis of pyrazoles, including cyclocondensation of 1,3-diketones and related derivatives with hydrazines [6], 1,3-dipolar cycloaddition of diazo compounds with alkynes and alkyne equivalents [7], and other procedures [8]. However, it remains a challenge to achieve sufficient regioselectivity for the target pyrazoles. Recently, *Junjappa* and co-workers reported the synthesis of substituted 1-aryl-5(or 3)-*N*-(cycloamino)pyrazoles by condensation of *N*,*S*-acetal precursors with unsymmetrical phenylhydrazines in a regiocontrolled fashion [6c]. *De Kimpe* and co-workers documented the preparation of fluorinated pyrazoles with relatively poor regioselectivity by a similar strategy [6d].

As part of our ongoing work on the synthesis of pharmacologically interesting heterocyclic compounds and development of 1,1-bis(methylsulfanyl)-2-nitroethene in organic synthesis [9], herein we report an efficient protocol for the preparation of substituted pyrazoles by the reaction of 1,1-bis(methylsulfanyl)-2-nitroethene and hydrazones (*Scheme 1*).

2. Results and Discussion. – In a preliminary experiment, we investigated the conversion of a mixture of benzaldehyde (**1a**; 1.0 mmol), $NH_2NH_2 \cdot H_2O$ (2 mmol), and

Scheme 1. *Synthesis of 5-Aryl-3-(methylsulfanyl)-1*H*-pyrazoles*



1,1-bis(methylsulfanyl)-2-nitroethene (1.0 mmol) in refluxing EtOH (5 ml), resulting in the formation of compound **2a** in 85% yield.

In another attempt, when the reaction was carried out at room temperature, only a trace amount of the product was formed. The advantages and limitations of this methodology were investigated by reacting $NH_2NH_2 \cdot H_2O$ and 1,1-bis(methylsulfanyl)-2-nitroethene with various substituted benzaldehydes **1** to give 5-aryl-3-(methylsulfanyl)-1*H*-pyrazoles **2a**–**2g** (*Scheme 1*). Irrespective of the presence of different electron-releasing substituents in the *ortho*-, *meta*-, or *para*-positions, the reactions proceeded fairly well and afforded the desired products in good-to-excellent yields (*Table*). But electron-poor benzaldehydes, such as 2-nitrobenzaldehyde (**1h**), 3-nitrobenzaldehyde (**1i**), and 4-nitrobenzaldehyde (**1j**) did not furnish 5-aryl-3-(methylsulfanyl)-1*H*-pyrazoles (*Entries 8–10*, *Table*).

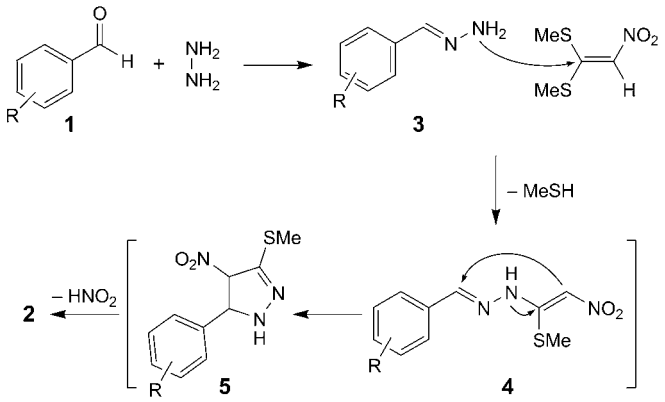
Table. *Synthesis of Pyrazoles* **2**

Entry	Product	R	Time [h]	Yield [%]
1	**2a** [10]	H	6	85
2	**2b** [10][11]	4-MeO	8	70
3	**2c** [12]	4-Cl	7	74
4	**2d**	2-Cl	5	75
5	**2e**	3-OH	9	68
6	**2f**	4-Me	6	80
7	**2g**	3-Br	8	78
8	**2h**	2-NO_2	10	0
9	**2i**	3-NO_2	10	0
10	**2j**	4-NO_2	10	0

The structures of compounds **2a**–**2g** were deduced from their, IR and high-field ^{1}H- and ^{13}C-NMR spectra, and elemental analyses. The mass spectrum of **2a** displayed the molecular-ion peak at *m*/*z* 190, which is in agreement with the proposed structure. The IR spectrum of this compound showed absorption bands due to the NH (3126 cm^{-1}), the CH groups (2930 cm^{-1}), and the Ph group (1560 and 1449 cm^{-1}). The ^{1}H-NMR spectrum of **2a** exhibited three *singlet*s for the MeS, CH, and NH groups (2.47, 6.51, and 7.29 ppm, resp.), and the aromatic moieties gave rise to *multiplet*s in the aromatic region of the spectrum (7.32–7.63 ppm). The ^{1}H-decoupled ^{13}C-NMR spectrum of **2a** showed eight distinct resonances in agreement with the suggested structure.

Although we have not investigated the mechanism of the reaction experimentally, a possible explanation is proposed in *Scheme 2*. Compound **2** could result from the initial

Scheme 2. *Proposed Mechanism for the Formation of Compound* **2**



addition of NH_2NH_2 to the aldehyde and subsequent attack of hydrazone **3** on 1,1-bis(methylsulfanyl)-2-nitroethene, and loss of MeSH produced provides **4**. Cyclization of **4** leads to intermediate **5**, and subsequent elimination of HNO_2 affords compound **2**.

In summary, we have demonstrated that the one-pot three-component reaction of aldehyde **1**, $NH_2NH_2 \cdot H_2O$, and 1,1-bis(methylsulfanyl)-2-nitroethene offers a simple method for the preparation of 5-aryl-3-(methylsulfanyl)-1*H*-pyrazoles **2** of potential synthetic and pharmacological interest. Fairly high yields of the products without any activation, the ready availability of the starting materials, and the reaction's simplicity are the main advantages of this method.

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Experimental Part

General. The reagents and solvents were obtained from *Fluka* (CH-Buchs) and used without further purification. M.p.: *Electrothermal 9100* apparatus. IR Spectra: *Shimadzu IR-460* spectrometer. ^{1}H and ^{13}C-NMR spectra: at 500.1 and 125.7 MHz, resp., on a *BRUKER DRX 500-AVANCE* FT-NMR instrument with $CDCl_3$ as solvent. MS: *FINNIGAN-MAT* 8430 mass spectrometer operating at an ionization potential of 70 eV. Elemental analyses for C, H, and N: *Heraeus CHN-O-Rapid* analyzer.

General Procedure (exemplified for **2a**). A soln. of *benzaldehyde* (**1a**; 0.106 g, 1 mmol) and $NH_2NH_2 \cdot H_2O$ (2 mmol) was stirred in 5 ml of EtOH for 10 min. Then, 1,1-bis(methylsulfanyl)-2-nitroethene (0.16 g, 1 mmol) was added. The mixture was stirred for 6 h under reflux, and the progress of the reaction was followed by thin layer chromatography. After completion, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (CC; hexane/AcOEt 6 :1). All products gave satisfactory spectroscopic data in accordance with the assigned structures.

*3-(Methylsulfanyl)-5-phenyl-1*H*-pyrazole* (**2a**) [10]. Yield: 0.16 g (85%). Pale-brown oil. IR: 3126 (NH), 2930 (CH), 1624, 1560, 1449 (Ar), 975 (C–S). ^{1}H-NMR: 2.47 (*s*, 3 H); 6.51 (*s*, 1 H); 7.29 (br. *s*, 1 H); 7.32 (*d*, *J* = 7.2, 1 H); 7.35 (*t*, *J* = 7.7, 2 H); 7.63 (*d*, *J* = 7.3, 2 H). ^{13}C-NMR: 16.9; 103.6; 125.1; 127.9; 128.3; 130.1; 146.0; 148.0. EI-MS: 190 (100, M^+), 157.1 (50), 145 (16), 128 (11), 117 (6), 102 (18), 77 (23). Anal. calc. for $C_{10}H_{10}N_2S$ (190.26): C 63.13, H 5.30, N 14.72; found: C 63.24, H 5.35, N 14.85.

*5-(4-Methoxyphenyl)-3-(methylsulfanyl)-1*H*-pyrazole* (**2b**) [10][11]. Yield: 0.15 g (70%). Pale-green oil. IR: 3412 (NH), 1621 (CN), 1517, 1500, 1443 (Ar), 1021 (C–S). ^{1}H-NMR: 2.52 (*s*, 3 H); 3.87 (*s*, 3 H); 6.46 (*s*, 1 H); 6.93 (*d*, *J* = 8.7, 2 H); 7.00 (br. *s*, 1 H); 7.56 (*d*, *J* = 8.7, 2 H). ^{13}C-NMR: 16.8; 54.9; 103.1;

113.8; 126.3; 130.1; 147.3; 148.0; 159.4. EI-MS: 220 (100, M^+), 205 (30), 187 (62), 177 (51), 161 (22), 134 (87), 117 (36), 89 (86), 77 (36), 69 (49), 63 (71). Anal. calc. for $C_{11}H_{12}N_2OS$ (220.29): C 59.97, H 5.49, N 12.72; found: C 59.05, H 5.72, N 12.21.

*5-(4-Chlorophenyl)-3-(methylsulfanyl)-1*H*-pyrazole* (**2c**) [12]. Yield: 0.17 g (74%). Pale-brown oil. IR: 3134 (NH), 1608 (C=N), 1487, 1438 (Ar), 973 (C–S). ^{1}H-NMR: 2.51 (*s*, 3 H); 6.55 (*s*, 1 H); 7.24 (br. *s*, 1 H); 7.38 (*d*, $J = 8.3$, 2 H); 7.61 (*d*, $J = 8.25$, 2 H). ^{13}C-NMR: 17.5; 104.4; 126.3; 128.5; 130.1; 133.7; 147.3; 148.0. EI-MS: *m*/*z* (47, $[M+1]^+$), 224 (100), 191 (30), 181 (7), 149 (3), 138 (7), 128 (4), 84 (4), 71 (2), 57 (2). Anal. calc. for $C_{10}H_9ClN_2S$ (224.71): C 53.45, H 4.04, N 12.47; found: C 53.22, H 4.32, N 12.35.

*5-(2-Chlorophenyl)-3-(methylsulfanyl)-1*H*-pyrazole* (**2d**). Yield: 0.16 g (70%). Pale-brown oil. IR: 3149 (NH), 1621 (C=N), 1569, 1560, 1448 (Ar), 971 (C–S). ^{1}H-NMR: 2.54 (*s*, 3 H); 6.66 (*s*, 1 H); 7.26–7.31 (*m*, 2 H); 7.39 (*d*, $J = 7.50$, 1 H); 7.59 (*d*, $J = 7.5$, 1 H); 8.54 (br. *s.*, 1 H). ^{13}C-NMR: 16.6; 106.8; 126.6; 128.5; 129.0; 129.5; 129.7; 131.2; 143.3; 143.9; 143.9. EI-MS: 224 (100, M^+), 191 (90), 145 (26), 138 (20), 102 (22), 75 (24), 51 (8). Anal. calc. for $C_{10}H_9ClN_2S$ (224.71): C 53.45, H 4.04, N 12.47; found: C 53.30, H 4.53, N 12.47.

*3-[3-(Methylsulfanyl)-1*H*-pyrazol-5-yl]phenol* (**2e**). Yield: 0.14 g (68%). Pale-brown oil. IR: 3250 (NH), 1722 (C=N), 1590, 1455 (Ar), 980 (C–S). ^{1}H-NMR: 2.45 (*s*, 3 H); 6.42 (*s*, 1 H); 6.83 (*d*, $J = 8.1$, 1 H); 7.08 (*d*, $J = 8.1$, 1 H); 7.16 (*t*, $J = 7.8$, 1 H); 7.25 (*s*, 1 H); 9.27 (br. *s*, 2 H). ^{13}C-NMR: 17.2; 104.0; 112.5; 116.2; 118.0; 130.2; 131.0; 145.4; 147.2; 156.4. EI-MS: 206 (45, M^+), 173 (20), 120 (12), 87 (100), 72 (36), 57 (19). Anal. calc. for $C_{10}H_{10}ON_2S$ (206.26): C 58.23, H 4.89, N 13.58; found: C 58.20, H 4. 96, N 13.47.

*5-(4-Methylphenyl)-3-(methylsulfanyl)-1*H*-pyrazole* (**2f**). Yield: 0.16 g (80%). Pale-green oil. IR: 3128 (NH), 1600 (C=N), 1446, 1510 (Ar), 966 (C–S). ^{1}H-NMR: 2.37 (*s*, 3 H); 2.52 (*s*, 3 H); 6.50 (*s*, 1 H); 7.21 (*d*, $J = 7.5$, 2 H); 7.25 (*s*, 1 H); 7.51 (*d*, $J = 7.5$, 2 H). ^{13}C-NMR: 14.1; 22.7; 111.0; 125.4; 129.7; 128.0; 137.0; 148.40 151.2. EI-MS: 205 (14, $[M+1]^+$), 204 (100, M^+), 171 (50), 159 (13), 128 (28), 115 (46), 102 (8), 91 (17), 77 (9), 69 (6), 63 (12), 57 (2), 51 (8). Anal. calc. for $C_{11}H_{12}N_2S$ (204.29): C 64.67, H 5.92, N 13.71; found: C 64.28, H 6.00, N 13.77.

*5-(3-Bromophenyl)-3-(methylsulfanyl)-1*H*-pyrazole* (**2g**). Yield: 0.21 g (78%). Pale-green powder, M.p. 115–119°. IR: 3132 (NH), 1559 (C=N), 1456, 1372 (Ar), 973 (C–S). ^{1}H-NMR: 2.54 (*s*, 3 H); 6.57 (*s*, 1 H); 7.28 (*t*, $J = 7.9$, 1 H); 7.31 (br., 1 H); 7.46 (*dd*, $J = 7.9$, 1 H); 7.61 (*d*, $J = 7.90$, 1 H); 7.85 (*s*, 1 H). ^{13}C-NMR: 14.6; 104.6; 122.5; 123.8; 128.2; 129.9; 130.0; 131.5; 144.3; 148.1. EI-MS: 269 (88, M^+), 267 (100), 236 (32), 128 (23), 104 (60), 86 (73), 72 (86), 51 (6.5). Anal. calc. for $C_{10}H_9BrN_2S$ (269.16): C 44.62, H 3.37, N 10.41; found: C 44.53, H 3.6, N 10.32.

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