Synthesis of Pharmaceutically Important Heteroaromatics from Methyl Phenyl Sulfone

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Some 5-substituted pyrazoles and pyrimethamine were prepared from 3-methylthio-1-phenyl-4-phenylsulfonyl-2-buten-1-one (**5a**) or (*E*)-1-*p*-chlorophenyl-1-cyano-2-methylthio-3-phenylsulfonylpropene (**6b**) which could be easily synthesized from methyl phenyl sulfone.

Pyrazole derivatives are found in several febrifuges, weed killers, and insecticides. And pyrimethamine is a useful antimalarial agent, which is about 1000 times as active as quinine.[1] Thus, improvement of the synthetic method for these compounds is important. We found that 1,1-bis(methylthio)-2-phenylsulfonylethene (**1**), derived easily from methyl phenyl sulfone, was a useful starting material for the synthesis of these pharmaceutical heteroaromatics. In this paper we describe an efficient method for the synthesis of 5-[(*Z*)-1,3-butadienyl]-3-phenylpyrazole (**2**), 5-methyl-3-phenylpyrazole (**3**), and pyrimethamine (**4**) from methyl phenyl sulfone.

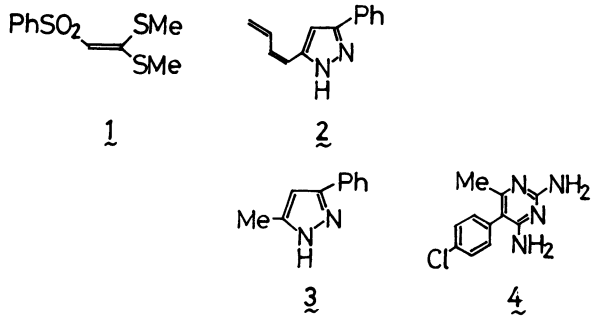


Fig. 1.

Results and Discussion

Reaction of (1) with α-Metalated Ketones or Nitriles. Compound (**1**) was prepared by means of the condensation between methyl phenyl sulfone and methyl trithiocarbonate, followed by methylation in 50% yield. Although Vialle *et al.* have already prepared this compound,[2] our method has a better yield.

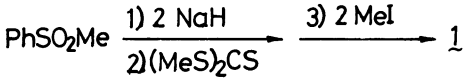
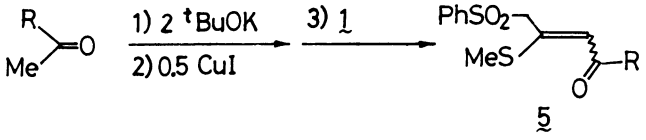


Fig. 2.

When treated with α-metalated ketones[3] or nitriles, **1** was converted to 3-(methylthio)vinyl ketones (**5**) or nitriles (**6**) in moderate yields. The results are summarized in Table 1.



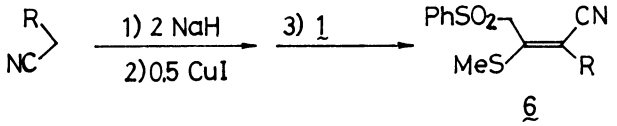


Fig. 3.

TABLE 1. PREPARATION OF **5** AND **6**

Product	R	Yield/%
5a	Phenyl	72
5b	2-Thienyl	64
5c	2-Pyridyl	38
5d	2-Naphthyl	78
5e	Methyl	57
6a	Phenyl	61
6b	*p*-Chlorophenyl	71

In this reaction, copper(I) iodide acted as an inhibitor of the formation of 1,1,2-tris(methylthio)ethene[4] which was generated in the side reaction.[5] But in the case of the reaction with methyl 2-pyridyl ketone, product **5c** could not be obtained in the presence of copper(I) iodide, probably due to the reduced reactivity of the carbanion by chelation of the pyridine nitrogen toward the copper. Compounds (**5**) were obtained as *E,Z* mixtures, while compounds (**6**) were given almost stereoselectively owing to the steric hindrance.

Preparation of Pyrazole Derivatives. Compound (**5a**) reacted with hydrazine hydrate in ethanol at refluxing temperature in the presence of a catalytic amount of sulfuric acid to give 3-phenyl-5-(phenylsulfonylmethyl)-pyrazole (**7**)[6] in 98% yield. When **7** was treated with 2 equivalents of *n*-BuLi, followed by addition of allyl bromide, **8** was obtained in 81% yield. Then **8** could easily be converted to 5-[(*Z*)-1,3-butadienyl]-3-phenylpyrazole (**2**) in 89% yield by treatment with 2 equivalents of *t*-BuOK. By the reaction of dianion of **7** with *p*-chlorobenzaldehyde, 5-[2-(*p*-chlorophenyl)-2-hydroxy-1-(phenylsulfonyl)ethyl]-3-phenylpyrazole (**9**) was afforded in 71% yield. Furthermore **7** could also give 5-methyl-3-phenylpyrazole (**3**) in 78% yield on treatment with 5% sodium-amalgam (Na/Hg).[7] In this way, **7** could be converted into various pyrazoles which have an alkadienyl, alkyl, or other functional group at 5-position. This is the principal advantage of the present method over known preparative methods for pyrazoles.[8]

Preparation of Pyrimethamine. When **6b** was treated with 2 equivalents of guanidine, 5-(*p*-chlorophenyl)-2,4-diamino-6-(phenylsulfonylmethyl)pyrimidine (**10**) was obtained in 92% yield. And **10** could be converted to pyrimethamine (**4**) on treatment with

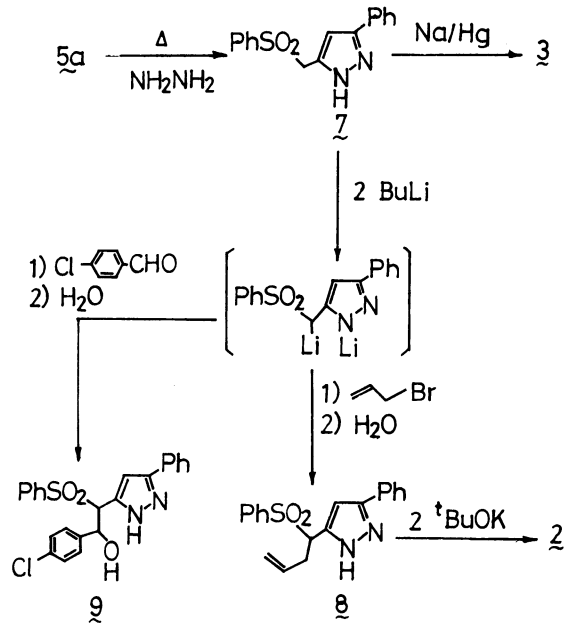


Fig. 4.

Na/Hg quantitatively. The attempts to introduce electrophiles into 6-position failed, owing to low reactivity of the corresponding carbanaion and the presence of free amino groups. However our preparative method for **4** can compete in terms of simple preparation and yield with hitherto known ones.[1]

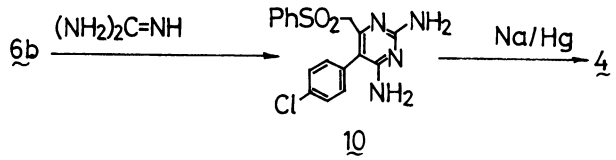


Fig. 5.

Experimental

Microanalyses were performed with Perkin-Elmer 240 elemental analyser at the Chemical Analysis Center of Chiba University. IR, UV, Mass, and ^{1}H-NMR spectra were measured with Japan Spectroscopic Co. DS 403G, Hitachi EPS-3T, RMU 6MC instruments, and Japan Electron Optics Lab. Co. C-60HL instruments, respectively. The silica gel used for TLC was Wakogel B-5F.

Preparation of 1,1-Bis(methylthio)-2-phenylsulfonylethene (1). A solution of methyl phenyl sulfone (9.4 g, 0.06 mol) in 60 ml of THF was added to 60% NaH (5.3 g, 0.13 mol) under nitrogen. After reflux for 1 h and then cooling to 0 °C, methyl trithiocarbonate (8.3 g, 0.06 mol) in 20 ml of THF was added to the mixture. It was stirred for 30 min at 0 °C and at room temperature for an additional 12 h. After addition of methyl iodide (0.12 mol), the resulting mixture was stirred for 3 h, quenched with water, and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated. The yellow powder was obtained and recrystallized from ethanol to give 7.8 g (50% yield) of **1** as white needles, mp 122—123 °C (lit,[2] 119 °C).

Reaction of 1 with α-Metalated Ketones. To a suspension of ketone (1.0 mmol), *t*-BuOK (274 mg, 2.2 mmol), and copper (I) iodide (100 mg, 0.5 mmol) in 5 ml of THF was added a solution of **1** (260 mg, 1.0 mmol) in 5 ml of THF. After stirring for 15 h, water and chloroform were added to the mixture, and acidified with 2M HCl(1 M=1 mol dm^{-3}). The resulting mixture was filtered through Celite, and the organic layer was dried over sodium sulfate and rotary-evaporated. The resulting brown oil was purified by TLC on silica gel using AcOEt–hexane (2:3) as a developing solvent to afford **5**. In the case of methyl 2-pyridyl ketone, copper (I) iodide was not used in the reaction.

3-Methylthio-1-phenyl-4-phenylsulfonyl-2-buten-1-one (5a): Yellow needles (from EtOH); 239 mg (72%); a 1:4 mixture of two stereoisomers; IR (KBr): 3050 (arom CH), 2960, 2900 (CH), 1640 (C=O), 1320 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$): δ=7.85 (2H, m, $PhSO_2$), 7.63 (2H, m, Ph), 7.40 (6H, m, 2Ph), 6.70, 6.58 (1H, s, CH), 5.00, 4.30 (2H, s, CH_2), 2.43, 2.38 (3H, s, CH_3); MS: *m/z* 332 (M^+). Found: C, 61.39; H, 4.86%. Calcd for $C_{17}H_{16}O_3S_2$: C, 61.42; H, 4.85%.

3-Methylthio-4-phenylsulfonyl-1-(2-thienyl)-2-buten-1-one (5b): White prisms (from $CHCl_3$); 217 mg (64%); a 1:4 mixture of two stereoisomers; IR (KBr): 3080 (arom CH), 2950, 2900 (CH), 1620 (C=O), 1320 and 1140 cm^{-1}(SO_2); NMR ($CDCl_3$): δ=7.88 (2H, m, C_6H_5), 7.48 (5H, m, C_6H_5, C_4H_3S), 7.02 (1H, m, C_4H_3S), 6.45 (1H, s, CH), 5.01, 4.25 (2H, s, CH_2), 2.48, 2.38 (3H, s, CH_3); MS: *m/z* 338 (M^+). Found: C, 53.02; H, 4.15%. Calcd for $C_{15}H_{14}O_3S_3$: C, 53.23; H, 4.17%.

3-Methylthio-4-phenylsulfonyl-1-(2-pyridyl)-2-buten-1-one (5c): Greenish brown needles (from acetone); 127 mg (38%); a 1:5 mixture of two stereoisomers; IR (KBr): 3050 (arom CH), 2970, 2890 (CH), 1650 (C=O), 1310 and 1140 cm^{-1}(SO_2); NMR ($CDCl_3$): δ=8.63 (1H, m, C_5H_4N), 7.93 (4H, m, C_6H_5, C_5H_5N), 7.63 (1H, s, CH), 7.47 (4H, m, C_6H_5, C_5H_4N), 5.08, 4.38 (2H, s, CH_2), 2.52, 2.48 (3H, s, CH_3); MS: *m/z* 286 $(M-47)^+$. Found: C, 57.61; H, 4.51; N, 4.13%. Calcd for $C_{16}H_{15}NO_3S_2$: C, 57.64; H, 4.53; N, 4.20%.

3-Methylthio-1-(2-naphtyl)-4-phenylsulfonyl-2-buten-1-one (5d): Yellow needles (from EtOH); 298 mg (78%); a 2:5 mixture of two stereoisomers; IR (KBr): 3050 (arom CH), 2990, 2900 (CH), 1640 (C=O), 1310 and 1150 cm^{-1}(SO_2); NMR ($CDCl_3$): δ=8.30—7.20 (12H, m, C_6H_5, $C_{10}H_7$), 6.78, 6.72 (1H, s, CH), 5.05, 4.33 (2H, s, CH_2), 2.45, 2.38 (3H, s, CH_3); MS: *m/z* 382 (M^+). Found: C, 65.90; H, 4.82%. Calcd for $C_{21}H_{18}O_3S_2$: C, 65.94; H, 4.74%.

4-Methylthio-5-phenylsulfonyl-3-penten-2-one (5e): White plates (from EtOH); 154 mg (57%); a 3:5 mixture of two stereoisomers; IR (KBr): 3050 (arom CH), 2970, 2900 (CH), 1660 (C=O), 1300 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$): δ=7.88 (2H, m, Ph), 7.23 (3H, m, Ph), 5.93 (1H, s, CH), 4.85, 4.18 (2H, s, CH_2), 2.35 (3H, s, SCH_3), 2.00 (3H, s, CH_3); MS: *m/z* 270 (M^+). Found: C, 53.35; H, 5.18%. Calcd for $C_{12}H_{14}O_3S_2$: C, 53.31; H, 5.22%.

Reaction of 1 with α-Metalated Nitriles. To a solution of nitrile (1.0 mmol) and **1** (260 mg, 1.0 mmol) in 10 ml of THF was added 60% NaH (88 mg, 2.2 mmol) and copper (I) iodide (100 mg, 0.5 mmol). The treatment described above gave **6**.

(E)-3-Methylthio-2-phenyl-4-phenylsulfonyl-2-butenenitrile (6a): Colorless plates; mp 116—118 °C (from EtOH); IR (KBr): 3050 (arom CH), 2900 (CH), 2200 (CN) 1330 and 1160 cm^{-1} (SO_2); NMR ($CDCl_3$): δ=8.03 (2H, m, $PhSO_2$), 7.57 (3H, m, $PhSO_2$), 7.33 (5H, s, Ph), 4.61 (2H, s, CH_2), 2.48 (3H, s, CH_3); MS: *m/z* 329 (M^+). Found: C, 61.94; H, 4.62; N, 4.22%. Calcd for $C_{17}H_{15}NO_2S_2$: C, 61.98; H, 4.59; N, 4.25%.

(E)-2-(p-Chlorophenyl)-3-methylthio-4-phenylsulfonyl-2-butenenitrile (6b): White plates; mp 131—132 °C (from $CHCl_3$); IR (KBr): 3040 (arom CH), 2900 (CH), 2200 (CN), 1330 and 1160 cm^{-1} (SO_2); NMR ($CDCl_3$): δ=8.03 (2H, m, Ph), 7.60 (3H, m, Ph), 7.30 (4H, s, *p*-ClC_6H_4), 4.58 (2H, s, CH_2), 2.50 (3H, s, CH_3); MS: *m/z* 363 (M^+). Found: C, 55.84; H, 3.87; N, 3.79%. Calcd for $C_{17}H_{14}ClNO_2S_2$: C, 56.11; H, 3.88; N, 3.85%.

Preparation of 3-Phenyl-5-(phenylsulfonylmethyl)pyrazole (7). To a solution of **5a** (500 mg, 1.5 mmol) in 40 ml of EtOH was added hydrazine hydrate (150 mg, 3.0 mmol) in 10 ml of

EtOH and a few drops of 5% sulfuric acid. When stirred at refluxing temperature for about 2 h, the yellow solution turned colorless. After being quenched with water, the mixture was extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated. A white powder was obtained (439 mg, 98%) and recrystallized from chloroform to give **7** as white plates, mp 170—171 °C (lit, [6] 173 °C).

Preparation of 3-Phenyl-5-(1'-phenylsulfonyl-3'-butenyl)-pyrazole (8). To a solution of **7** (388 mg, 1.3 mmol) in 10 ml of THF was added 1.4 M solution of *n*-BuLi in hexane (2.0 ml, 2.86 mmol) at −70 °C under nitrogen. After stirring for 30 min, allyl bromide (0.12 ml, 1.43 mmol) was added to the mixture and it was stirred for 10 min at −70 °C, and then for 1 h at room temperature. After being quenched with saturated solution of ammonium chloride, the mixture was extracted with ethyl acetate. The ethyl acetate extract was dried over sodium sulfate and rotary-evaporated. The resulting colorless oil was purified by TLC on silica gel using AcOEt–hexane (1:1) as a developing solvent to give 356 mg (81%) of **8** as a colorless oil; bp 130 °C/13.3 Pa; IR (KBr): 3300 (NH), 1300 and 1150 cm^{-1} (SO_2); NMR ($CDCl_3$): δ= 11.68 (1H, br, NH), 7.55 (10H, m, 2Ph), 6.60 (1H, s, CH), 6.20—5.37 (1H, m, CH_2=C<u>H</u>C<u>H</u>$_2$), 5.10 (1H, dd, J_{trans}=18 Hz, J_{gem}=1 Hz, C<u>H</u>$_2$=CH), 5.02 (1H, dd, J_{cis}=10 Hz, J_{gem}=1 Hz, C<u>H</u>$_2$=CH), 4.59 (1H, t, J=8 Hz, $PhSO_2$C<u>H</u>), 3.07 (2H, m, CH_2=CH-C<u>H</u>$_2$); MS: *m/z* 338 (M^+).

Preparation of 5-[(Z)-1,3-Butadienyl]-3-phenylpyrazole (2). To a solution of **8** (203 mg, 0.6 mmol) in 5 ml of THF was added *t*-BuOK (165 mg, 1.32 mmol), the mixture was stirred for 3 h. The treatment described above gave white powder. It was purified by TLC on silica gel using AcOEt–hexane (2:3) as a developing solvent to give 105 mg (89%) of **2** as white needles; mp 50 °C (decomp.); IR (KBr): 3200 cm^{-1} (NH); NMR ($CDCl_3$): δ=12.15 (1H, br, NH), 7.61 (2H, m, Ph), 7.26 (3H, m, Ph), 6.57 (1H, s, CH), 6.55 (1H, m, CH_2=C<u>H</u>), 6.54 (1H, d, J_{cis}=8 Hz, CH_2=CHCH=C<u>H</u>), 6.20 (1H, dd, J_{cis}=8 Hz, J=10 Hz, CH_2=CHC<u>H</u>=CH), 5.29 (1H, dd, J_{cis}=10 Hz, J_{gem}= 1 Hz, C<u>H</u>$_2$=CH), 5.20 (1H, dd, J_{trans}=17 Hz, J_{gem}=1 Hz, C<u>H</u>$_2$= CH); MS: *m/z* 196 (M^+). Found: C, 79.35; H, 6.21; N, 14.20%. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27%.

Preparation of 5-[2-(p-Chlorophenyl)-2-hydroxy-1-(phenylsulfonyl)ethyl]-3-phenylpyrazole (9). The compound was prepared from **7** (149 mg, 0.5 mmol) in 2 ml of THF by the same method as described in the preparation of **8**; white prisms; mp 164—165 °C (from acetone); IR (KBr): 3650—3010 (NH, OH), 1310 and 1130 cm^{-1}(SO_2); NMR (CD_3CO-CD_3): δ=8.00—6.88 (15H, m, $2C_6H_5$, *p*-ClC_6H_4, NH), 6.72 (1H, s, CH), 6.01 (1H, d, J=2 Hz, C<u>H</u>(OH)), 5.45 (1H, br, OH), 4.78 (1H, d, J=2 Hz, $PhSO_2$C<u>H</u>); MS: *m/z* 421 $(M-17)^+$. Found: C, 62.97; H, 4.39; N, 6.44%. Calcd for $C_{23}H_{19}$-ClN_2O_3S: C, 62.94; H, 4.36; N, 6.38%.

Preparation of 5-Methyl-3-phenylpyrazole (3). To a solution of **7** (89.1 mg, 0.3 mmol) and anhydrous disodium hydrogenphosphate (170 mg, 1.2 mmol) in 10 ml of dry MeOH was added 5% sodium amalgam (1 g). After stirring for 2 h, water and ether were added to the reaction mixture. The resulting mixture was filtered through Celite, and the organic layer was dried over sodium sulfate and rotary-evaporated. The resulting white powder was purified by TLC on silica gel using AcOEt–hexane (1:1) as a developing solvent to afford 37 mg (78%) of **3** as white crystals, mp 123—124 °C (lit,[9] 127 °C).

Preparation of 5-(p-Chlorophenyl)-2,4-diamino-6-(phenylsulfonylmethyl)pyrimidine (10). NaOEt (74.9 mg, 1.1 mmol) was added to the solution of **6b** (182 mg, 0.5 mmol) and guanidine hydrochloride (105 mg, 1.1 mmol) in 10 ml of absolute EtOH. The resulting mixture was refluxed for 24 h. The reaction was quenched with 10% sodium hydroxide solution. An organic substance was extracted with chloroform, and the extract was dried over sodium sulfate. After removal of the solvent under reduced pressure, the red powder was purified by TLC on silica gel using AcOEt–MeOH (9:1) as a developing solvent to afford 172 mg (92%) of **10** as white needles; mp 206—207 °C (from $CHCl_3$); IR (KBr): 3340, 3150 (NH), 1300 and 1160 cm^{-1}(SO_2); NMR ($CDCl_3$): δ=7.70 (5H, m, Ph), 7.48 (2H, B part of AB quartet, J=8 Hz), 7.12 (2H, A part of AB quartet, J=8 Hz), 5.75, 5.38 (4H, br, $2NH_2$), 4.17 (2H, s, CH_2); MS: *m/z* 374 (M^+). Found: C, 54.40; H, 4.06; N, 15.14%. Calcd for $C_{17}H_{15}ClN_4O_2S$: C, 54.47; H, 4.03; N, 14.95%.

Preparation of 5-(p-Chlorophenyl)-2,4-diamino-6-methylpyrimidine (4). 5% Sodium amalgam (3g) was added to the solution of **10** (150 mg, 0.4 mmol) and anhydrous disodium hydrogenphosphate (227 mg, 1.6 mmol) in 10 ml of dry MeOH. After stirring for 2 h, the reaction was quenched with water and filtered through Celite. The resulting mixture was acidified with 2 M HCl, and washed with ether three times. After neutralization, the solvent was evaporated, and the residue was washed with hot MeOH three times. Removal of MeOH from the washings gave 93.9 mg (100%) of **4** as white needles, mp 269—271 °C (from MeOH) (lit,[1] 264—265 °C).

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5) Phenylsulfonyl group was displaced by methylthio anion which was generated by the nucleophilic substitution as shown bellow.

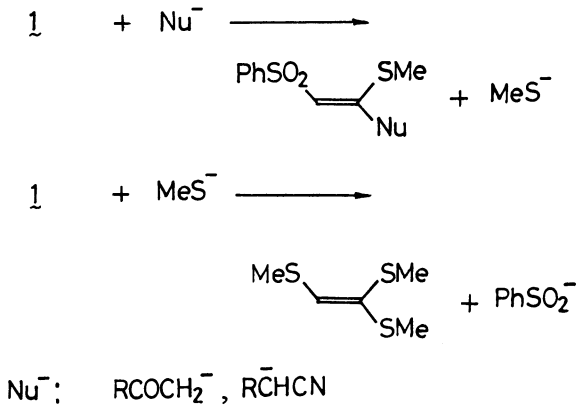

Fig. 6.

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