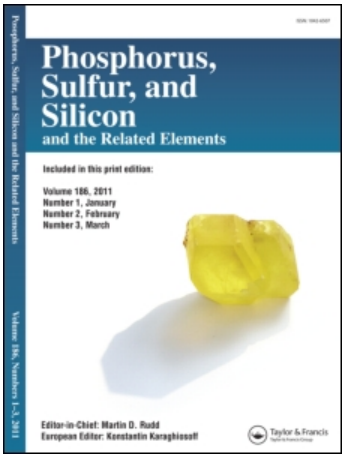


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# Syntheses of 2-Alkylthio-(4,5-Diaryl)imidazoles[1]

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# Syntheses of 2-Alkylthio-(4,5-Diaryl)imidazoles[1]

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*A series of 2-alkylthio-4,5-diarylimidazoles were synthesized in three steps. The reaction of ammonium thiocyanate with benzoylbenzoins **4** gave 4,5-diarylimidazole-2-thiones **5**. Alkylation of compound **5** with alkyl iodide yielded 2-alkylthio-4,5-diarylimidazoles **6**. Chlorosulfonation of compound **6** followed by ammonia gave the desired compounds 4-[2-alkylthio-4(5)-(4-substituted phenyl)imidazole-5(4)-yl]benzensulfonamides **7**.*

**Keywords** 2-Alkylthioimidazole; 4,5-diarylimidazole; imidazole



## INTRODUCTION

Extensive libraries of selective Cox-II inhibitors have been developed by different laboratories in the last 10 years. Most of the compounds fit into three categories: (1) acidic sulfonamide such as NS-398,[2] (2) diarylheterocycles such as rofecoxib and celecoxib[3,4], and (3) modifications of classical nonsteroidal anti-inflammatory drugs (NSAIDs) such as indomethacin derivatives.

Flumizole is one of the early known 4,5-diarylimidazoles showing antiinflammatory activity.[5] Work from a number of laboratories has shown that certain diarylheterocycles have useful antiinflammatory activity. 2-Alkyl-4,5-diaryl-imidazoles, 2-(trifluoromethyl)-4,5-diarylimidazoles, 2,4,5-triarylimidazoles, and 2,3-bis(4-methoxyphenyl)indole have all been reported to have antiinflammatory activity.[6] Further studies have suggested that proper effect could be easily conferred by incorporation of a suitably disposed sulfonamide pharmacophore and alkylthio group.[7,8]

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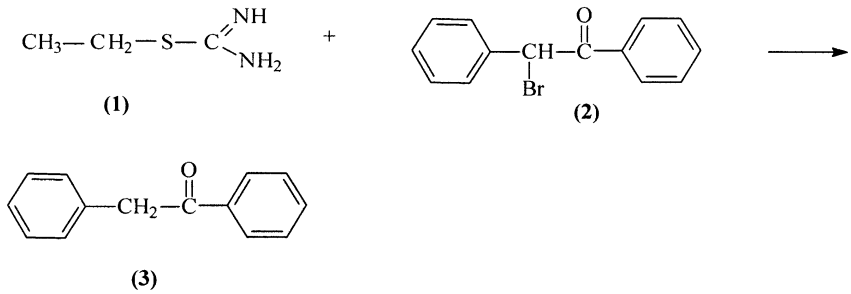
We now report synthesis of a series of 2-alkylthio-4,5-diarylimidazoles as possible Cox-II inhibitors.

## RESLUTS AND DISCUSSION

It has been shown that 2-benzylthio-4(5)-phenylimidazole could be prepared by the reaction of S-benzylthiourea with phenacylbromide.[9] This reaction was extended to the preparation of 1-substituted-2-alkylthio-4-phenylimidazoles by preparation of N-substituted-S-alkylthio ureas with phenacylbromide.[10] The reaction of S-ethylthiourea **1** with $\alpha$-bromoketone **2** (see Scheme 1) did not give the expected imidazole **5**. Instead, the compound **2** was debrominated and deoxybenzoin **3** was isolated. Also, the reaction between compound **2** and ammonium acetate and potassium thiocyanate did not give the desired compounds.[11]




**SCHEME 1** A possible route for synthesis of compounds.

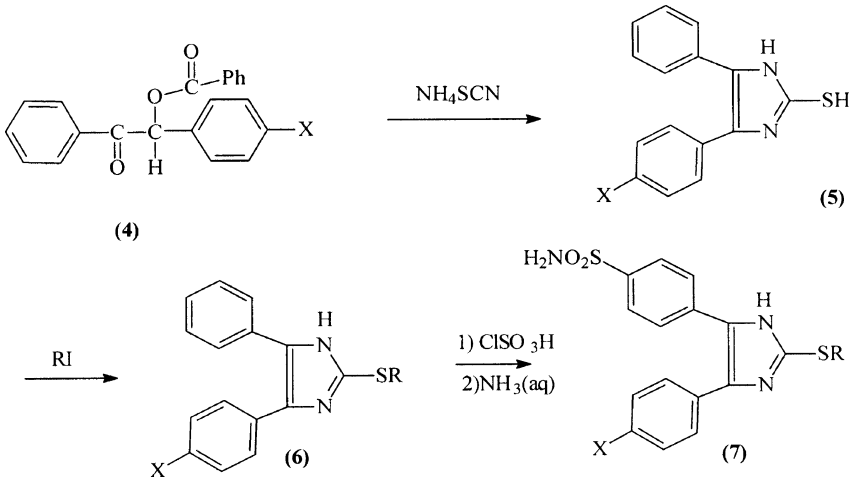
Finally, the reaction of benzoyl acyloins **4** with ammonium thiocyanate in amyl alcohol at 150–200°C gave the 4,5-diarylimidazole-2-thiones **5** in good yield.[12]

Alkylation of compound **5** with alkyl iodide in the presence of sodium hydroxide, sodium carbonate, and sodium alkoxide in methanol gave S and N-dialkylated compounds, and the desired compounds **6** were not obtained. However, alkylation could be accomplished in the presence of triethylamine.

The reaction of compound **6** with chlorosulfonic acid at ice-bath temperature followed by ammonia gave the desired compounds **7** (Scheme 2).

## EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. The IR spectra were obtained using a Nicolet FT-IR




**SCHEME 2** Synthesis of 4-[2-alkylthio-4(5)-(4-substituted phenyl) imidazole-5(4)-yl] benzene sulfonamide (7)



Magna 550 spectrographs; the $^1$HNMR were obtained on a 400 Varian Unity plus spectrometer. Mass spectra were obtained on a Finnigan MAT TSQ 70 spectrometer at 70 eV. Column chromatography was carried out using silica gel (230–400 mesh).

## Preparation of 4,5-Diarylimidazole-2-thiones *5*

### *General Procedure*

A mixture of compound **4** (1 mmol)[13] and ammonium thiocyanate (1 mmol) in amyl alcohol or butyl alcohol was refluxed for 5 h. The product was crystallized on cooling the reaction mixture. The unreacted benzoin was removed from the product by washing with ether and the ammonium thiocyanate by water. The white-to-light yellow solids were separated and crystallized from methanol. The yield was 80–90%.

*Selected data for 4(5)-(4-fluorophenyl)-5(4)-phenylimidazole-2-thione* ***5a***,white solid, m.p. 277–280°C, yield = 90%. $^1$H NMR (DMSO-$d_6$): $\delta$ 7.1–7.3 (m, aromatic), IR (KBr) ($\nu_{max}$, cm$^{-1}$): 1234, 1506, 3047; MS, m/z (%): 270($M^+$, 43), 220 (23), 203 (100), 138 (57), 121 (35); Anal. Calcd. for $C_{15}H_{11}FN_2S$: C, 66.67; H, 4.07; N, 10.37. Found: C, 66.35; H, 4.35; N, 10.54.

Compounds **5b–d** were prepared similar to literature (see Table I).

**TABLE I Data for Compounds 5a–d**

| Comp no. | X | Yield (%) | m.p. °C | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | F | 90 | 277–280 | $C_{15}H_{11}FN_2S$ | 66.67 | 4.07 | 10.37 | 66.35 | 4.35 | 10.54 |
| **5b** | Cl | 89 | 294–296 | $C_{15}H_{11}ClN_2S$ | 62.83 | 3.84 | 9.77 | 62.62 | 3.57 | 9.52 |
| **5c** | Me | 80 | 153–155 | $C_{16}H_{14}N_2S$ | 72.18 | 5.26 | 10.53 | 72.01 | 5.09 | 10.21 |
| **5d** | OMe | 80 | 156–159 | $C_{16}H_{14}N_2OS$ | 68.08 | 4.96 | 9.93 | 68.23 | 5.12 | 10.10 |

## Preparation of 2-Alkylthio-4,5-diarylimidazoles 6

### *General Procedure*

A mixture of compound **5** (1 mmol) in methanol, alkyl iodide (4 mmol), and excess amounts of triethylamine (up to pH = 10) was stirred at room temperature for 24 h. Methanol was removed under reduced pressure and the residue was purified by column chromatography using chloroform-ethyl acetate (5:1) and crystallized from chloroform-petroleum ether. The yield was (16–63%) with methyl iodide and (24–81%) with ethyl iodide.

*Selected data for 2-ethylthio-4(5)-(4-fluorophenyl)-5(4)-phenylimidazole* ***6a*** white solid, m.p. 198–199°C, yield = 81%. $^1$H NMR ($CDCl_3$): $\delta$ 1.3 (t, 3H), 3.1 (q, 2H), 6.9 (m, 2H), 7.3 (m, 7H); MS, *m/z* (%): 298 ($M^+$, 42), 297 (100), 279 (28), 264 (39), 246 (18), 229 (19); Anal. Calcd. for $C_{17}H_{15}FN_2S$: C, 68.46; H, 5.03; N, 9.39. Found: C, 68.21; H, 4.90; N, 9.12.

Compounds **6b–g** were prepared using a similar procedure (see Table II).

**TABLE II Data for Compounds 6a–g**

| Comp no. | R | X | Yield (%) | m.p. °C | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **6a** | Et | F | 81 | 198–199 | $C_{17}H_{15}FN_2S$ | 68.46 | 5.03 | 9.39 | 68.21 | 4.90 | 9.12 |
| **6b** | Me | F | 63 | 242–245 | $C_{16}H_{13}FN_2S$ | 67.60 | 4.58 | 9.86 | 67.34 | 4.30 | 9.55 |
| **6c** | Et | Cl | 80 | 215–218 | $C_{17}H_{15}ClN_2S$ | 64.86 | 4.77 | 8.90 | 64.98 | 4.94 | 8.71 |
| **6d** | Me | Cl | 60 | 270–273 | $C_{16}H_{13}ClN_2S$ | 63.89 | 4.33 | 9.32 | 63.95 | 4.50 | 9.52 |
| **6e** | Et | Me | 76 | 109–111 | $C_{18}H_{18}N_2S$ | 73.47 | 6.12 | 9.52 | 73.21 | 5.90 | 9.32 |
| **6f** | Me | Me | 59 | 102–105 | $C_{17}H_{16}N_2S$ | 72.86 | 5.71 | 10.00 | 72.60 | 5.45 | 9.69 |
| **6g** | Et | OMe | 24 | 112–115 | $C_{18}H_{18}N_2OS$ | 69.68 | 5.81 | 9.03 | 69.43 | 5.55 | 9.23 |

**TABLE III Data for Compounds 7a–j**

| Comp no. | R | X | Yield (%) | m.p. °C | Formula | Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | Me | H | 12 | >350 | $C_{16}H_{15}N_3O_2S_2$ | 55.65 | 4.35 | 12.17 | 55.53 | 4.28 | 12.06 |
| **7b** | Et | H | 12 | >350 | $C_{17}H_{17}N_3O_2S_2$ | 56.82 | 4.73 | 11.70 | 56.70 | 4.57 | 11.59 |
| **7c** | Me | F | 20 | 236–239 | $C_{16}H_{14}FN_3O_2S_2$ | 52.89 | 3.86 | 11.57 | 52.58 | 3.68 | 11.36 |
| **7d** | Et | F | 20 | 232–236 | $C_{17}H_{16}FN_3O_2S_2$ | 54.11 | 4.24 | 11.14 | 54.09 | 4.17 | 11.03 |
| **7e** | Me | Cl | 19 | 135–138 | $C_{16}H_{14}ClN_3O_2S_2$ | 50.59 | 3.69 | 11.07 | 50.49 | 3.71 | 11.16 |
| **7f** | Et | Cl | 19 | 145–148 | $C_{17}H_{16}ClN_3O_2S_2$ | 51.84 | 4.07 | 10.67 | 51.73 | 4.19 | 10.37 |
| **7g** | Me | Me | 16 | oil- | $C_{17}H_{17}N_3O_2S_2$ | 56.82 | 4.37 | 11.70 | 56.68 | 4.57 | 11.90 |
| **7h** | Et | Me | 16 | oil- | $C_{18}H_{19}N_3O_2S_2$ | 57.90 | 5.09 | 11.26 | 57.88 | 5.13 | 11.57 |
| **7i** | Me | OMe | 10 | oil- | $C_{17}H_{17}N_3O_3S_2$ | 54.40 | 4.53 | 11.20 | 54.78 | 4.36 | 11.58 |
| **7j** | Et | OMe | 10 | oil- | $C_{18}H_{19}N_3O_3S_2$ | 55.53 | 4.88 | 10.80 | 55.61 | 4.92 | 11.02 |



## Preparation of 4-[2-Alkylthio-4(5)-(4-substituted Phenyl)imidazole-5(4)-yl]benzensulfonamide 7

### *General Procedure*

To a magnetically stirred solution of compound **6** (1 mmol) was added slowly chlorosulfonic acid (5 mmol) at ice-bath temperature. After 4–5 h cold water was added and yellow solid obtained. After filtration, the residue was dissolved in methanol and excess amounts of ammonia added. The solution stirred for 24 h. Methanol was removed at reduced pressure and the residue purified by preparative thin layer chromatography with solvent system chloroform-methanol (5:1) and crystallized from methanol-petroleum ether.

*Selected data for 4-[2-methylthio-4(5)phenylimidazole-5(4)-yl]benzenesulfonamide* ***7a*** yellow solid, m.p. >350°, yield = 12%. $^1$H NMR (DMSO-$d_6$): $\delta$ 2.5 (s, 3 H), 7.3 (m, 5H), 7.5 (d, 2 H), 7.6 (d, 2 H); MS, m/z (%): 345 ($M^+$, 7), 266 (14), 252 (100), 220 (20), 165 (32); Anal. Calcd. for $C_{16}H_{15}N_3O_2S_2$: C, 55.65; H, 4.35; N, 12.17. Found: C, 55.53; H, 4.28; N, 12.06.

Compounds **7b–j** were prepared using a similar procedure (see Table III).

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