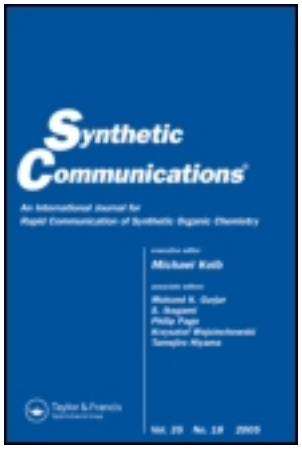

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CONVENIENT AND REGIOSPECIFIC METHOD FOR SYNTHESIS OF 4,5-DIARYL-1-METHYL-2-(METHYLTHIO)-1*H*-IMIDAZOLE

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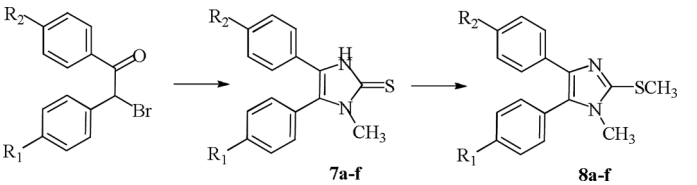
GRAPHICAL ABSTRACT



Abstract *A convenient, high-yielding, regiospecific synthesis of 1H-imidazole-2-thiones ring has been developed. In addition, a series of 4,5-diaryl-1-methyl-2-(methylthio)-1H-imidazoles* ***8*** *were synthesized and characterized. The structure of regioisomers was confirmed through nuclear Overhauser effect spectroscopy and NMR spectroscopy.*

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Keywords 1*H*-Imidazole-2-thione; NOESY; regiospecific synthesis

INTRODUCTION

Imidazoles and imidazole-2-thiones scaffold have been incorporated into a wide variety of pharmacologically active compounds and drug candidates including antifungal, antiulcerative cytotoxic, and anti-inflammatory activities. They include compounds that are inhibitors of phosphodiesterase, cyclooxygenase, lipoxygenase, acyl CoA:cholesterol acyltransferase, and tubulin polymerization.[1–6] In continuation of our research on design and synthesis of the diarylheterocycle scaffold,[7–9]

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we focused on the synthesis of regionspecific 4,5-diaryl-1*H*-imidazole-2-thiones derivatives. Herein we report a fast, convenient, and high-yielding method to regiospecifically synthesize of 4,5-diarly-*N*-methyl-imidazole-2-thione. Furthermore, the structure of two different regioisomers and the position of methyl group in the product were confirmed through nuclear Overhauser (NOESY) and NMR spectroscopy.

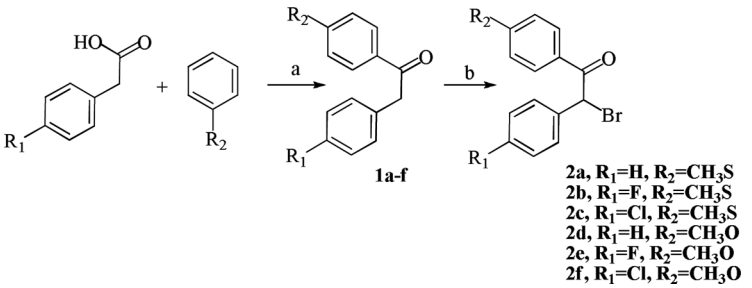
RESULTS AND DISCUSSION

Synthesis of α-bromodesoxybenzoins was carried out by reacting appropriate phenyl acetic acid with various substituted aromatic hydrocarbons. Subsequently, desoxybenzoins **1** were subjected to bromination using bromine in glacial acetic acid to obtain α-bromodesoxybenzoins **2** according to previous reports[10,11] (Scheme 1).

For regiospecific preparation of 4,5-diaryl-1-methyl-2-methylthio-1*H*-imidazole derivatives, three different methods were considered. In method A, a suspension of α-bromodesoxybenzoin **2f**, *N*,*S*-dimethylisothiourea, and K_2CO_3 in dry CH_3CN were stirred at room temperature for 18 h. However, the expected compound **8f** was not obtaied.[12]

In method B, α-bromodesoxybenzoin **2f** was refluxed with sodium methoxide in methanol. Subsequently, the reaction was quenched with cold 10% hydrochloric acid to obtain benzoin **3**.[13] The 1*H*-imidazole-2-thione **4** was prepared by refluxing benzoin **3** with excess ammonium thiocyanate in *n*-butanol. Finally, compound **5** was prepared by S-methylation of 1*H*-imidazole-2-thione **4** with methyl iodide in methanol with excellent yield. The preferential methylation of the 1*H*-imidazole-2-thiones at the sulfur atom was due to its greater nucleophilicity.[14] On the other hand, N-methylation of imidazole ring using iodomethane in the presence of a base was not successful and obtained products were not regiospecific.[12–15] Our efforts with N-methylation of compound **5** using iodomethane confirm this observation.

Finally, treatment of compounds **5** with excess dimethylformamide–dimethylacetate (DMF-DMA) in toluene under reflux condition afforded two different regioisomer (**8f** and **8f′**) in a 38:62 molar ratio. In ^{1}H NMR of compounds **8f** and **8f′**, the NCH_3 group was observed in 3.42 and 3.40 ppm, and the OCH_3 group was observed in 3.77 and 3.88 ppm respectively. The significantly different chemical shift of methoxy group in two regioisomers **8f** and **8f′** could be due to the presence of a methyl substituent at either nitrogen in the imidazole ring. The regioisomeric structure of

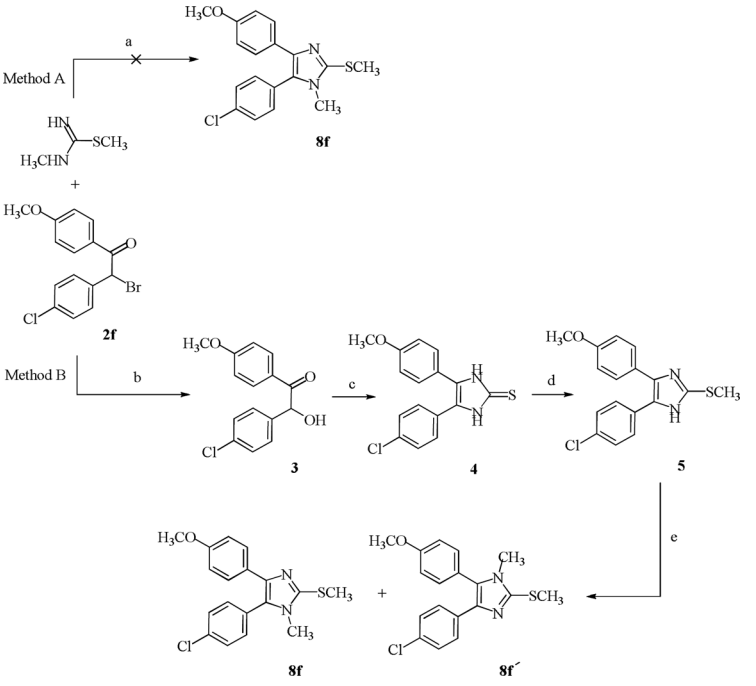


Scheme 1. Reagents and conditions: (a) H_3PO_4, $(CF_3CO)_2O$, 25 °C ; (b) Br_2, glacial AcOH, rt.

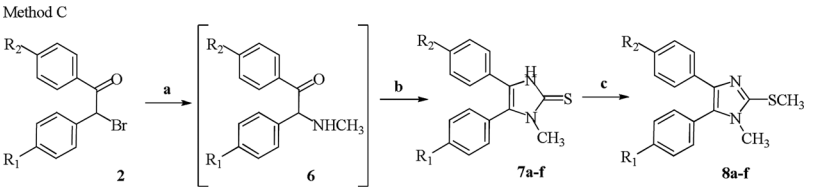
8f and **8f′** were confirmed through NOESY spectroscopy. A correlation between NCH_3 group at 3.42 and H-2, H-6 protons of 4-chlorophenyl ring at 7.26 ppm establishes the regiochemistry of **8f** and correlation between NCH_3 group at 3.40 and H-2, H-6 protons of methoxyphenyl ring at 7.22 ppm establishes the regiochemistry of **8f′** respectivly. This observation was supported by the results from two-dimensional NMR experiments in a series of regioisomeric N-substituted pyridin-4-yl imidazole derivatives,[15] and also the correlation of the NCH_3 group and H-2 and H-6 protons of 4-chlorophenyl in 4,5-diarylimidazole compounds were previously reported based on a NOE experiment[16]

Furthermore, compound **8f**, which was prepared from method C, showed the same spectroscopic data with the one prepared from method B (Scheme 2).

In method C, α-bromodesoxybenzoins **2**, methylamine hydrochloride, and potassium carbonate were refluxed in methanol. After 0.5 h (as monitored by thin-layer chromatography, TLC), starting material disappeared and was completely converted to α-*N*-methyl-desoxybenzoin **6**. The efforts for separation of compounds **6** were not successful because of the instability of the compounds; therefore they were used without further purification and converted to 1*H*-imidazole-2-thione **7** by refluxing with excess ammonium thiocyanate in *n*-butanol. Finally, regioisomers **8** were prepared by S-methylation of 1*H*-imidazole-2-thione **7** with methyl iodide in methanol (Scheme 3, Table 1). The chemical shifts of the aromatic protons were assigned based on comparing ^{1}H NMR of different synthesized compounds **7** and **8a–f** and NOESY

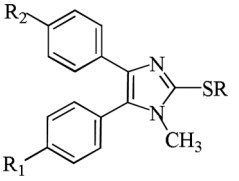


Scheme 2. Reagents and conditions: (a) K_2CO_3, CH_3CN, rt.; (b) CH_3ONa, CH_3OH, reflux, 10% HCl; (c) NH_4SCN, *n*-butanol, reflux; (d) CH_3I, CH_3OH, reflux; (e) DMF-DMA, toluene, reflux.



Scheme 3. Reagents and conditions: (a) $NH_2CH_3 \cdot HCl$, K_2CO_3, CH_3OH, reflux; (b) NH_4SCN, *n*-butanol, reflux; (c) CH_3I, CH_3OH, reflux.

Table 1. Synthesis of **7a–f** and **8a–f**



Compound	R_1	R_2	R	Yield (%)	Mp (°C)
7a	H	SCH_3	H	72	220–223
7b	F	SCH_3	H	75	249–252
7c	Cl	SCH_3	H	74	255–258
7d	H	OCH_3	H	75	203–206
7e	F	OCH_3	H	76	243–246
7f	Cl	OCH_3	H	75	227–230
8a	H	SCH_3	CH_3	82	112–115
8b	F	SCH_3	CH_3	84	96–99
8c	Cl	SCH_3	CH_3	82	135–138
8d	H	OCH_3	CH_3	85	94–95
8e	F	OCH_3	CH_3	84	91–93
8f	Cl	OCH_3	CH_3	84	112–114

spectroscopy of compounds **7d–f** and **8e–f**. For additional support, NOE experiment was used to assign the aromatic chemical shifts. For compounds **8f** and **8f′**, the irradiation of the NCH_3 in 3.42 and 3.40 showed an enhancement of the phenyl hydrogen atoms signals in 7.26 and 7.22 ppm respectively.

In conclusion, we have developed a simple and highly efficient regiospecific synthesis of 1*H*-imidazole-2-thiones derivatives.

EXPERIMENTAL

Reaction of Compound 5 with Dimethylformamide-dimethylacetate

To a solution of compound **5** (2 mmol) in toluene (10 mL), 2 mL DMF-DMA was added, and the reaction was refluxed for 24 h. The solvent evaporated under reduced pressure and the residue was purified by preparative TLC on silica gel using ethyl acetate–petroleum ether (1:2) as mobile phase.

4-(4-Chlorophenyl)-5-(4-methoxyphenyl)-1-methyl-2-(methylthio)-1*H*-imidazole (8f′). Yield, 52%; mp 108–110 °C; IR (KBr, cm^{-1}): *v*1512, 1246, 1170, 1076, 854; ^1H NMR ($CDCl_3$): δ 2.70 (s, 3H, SCH_3), 3.40 (s, 3H, NCH_3), 3.88 (s, 3H, OCH_3), 6.99 (d, $J = 8.5$, 2H, methoxyphenyl H-3, H-5), 7.16 (d, $J = 8.5$, 2H, chlorophenyl H-2, H-6), 7.22 (d, $J = 8.5$, 2H, methoxyphenyl H-2, H-6), 7.43 (d, $J = 8.5$, 2H, chlorophenyl H-3, H-5). ^{13}C NMR ($CDCl_3$): δ 16.26, 31.40, 55.32, 114.61, 122.67, 127.70, 128.22, 130.68, 131.74, 131.89, 133.15, 136.99, 142.80, 159.95. Anal. calcd. for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; N, 8.12. Found: C, 62.75; H, 4.76; N, 8.33.

5-(4-Chlorophenyl)-4-(4-methoxyphenyl)-1-methyl-2-(methylthio)-1*H*-imidazole (8f). Yield, 25%; mp 112-114 °C; IR (KBr, cm^{-1}): *v* 1510, 1250, 1172, 1087, 846; ^1H NMR ($CDCl_3$): δ 2.71 (s, 3H, SCH_3), 3.42 (s, 3H, NCH_3), 3.78 (s, 3H, OCH_3), 6.78 (d, $J = 8.5$, 2H, methoxyphenyl H-3, H-5), 7.26 (d, $J = 8.5$, 2H, chlorophenyl H-2, H-6), 7.38 (d, $J = 8.5$, 2H, methoxyphenyl H-2, H-6), 7.43 (d, $J = 8.5$, 2H, chlorophenyl H-3, H-5). ^{13}C NMR ($CDCl_3$): δ 16.31, 31.56, 55.19, 113.65, 126.93, 128.03, 128.35, 129.32, 130.68, 129.52, 132.00, 134.50, 138.57, 143.15, 158.39. Anal. calcd. for $C_{18}H_{17}ClN_2OS$: C, 62.69; H, 4.97; N, 8.12. Found: C, 62.83; H, 4.76; N, 8.23.

General Procedure for Regiospecific Synthesis of Compounds 7

Methylamine hydrochloride (2 mmol) and potassium carbonate (4 mmol) were added to a stirring solution of related α-bromodesoxybenzoin 2 (1 mmol) in methanol (50 mL), and the mixture was refluxed for 0.5 h. The solvent was removed under reduced pressure. Water (20 mL) and ehtylacetate (50 mL) were added to the residue. The organic phase was separated, dried (sodium sulfate), filtered, and evaporated under reduced pressure. The residue was disolved in *n*-butanol (50 mL), and 4 mmol ammonium thiocyanate was added. The mixture refluxed for 0.5 h, and then 50 mL water was added. The organic phase was separated, dried (sodium sulfate), filtered, and evaporated under reduced pressure. The residue was crystallized in methanol.

General Procedure for S-Methylation of Compounds 8

Methyl iodide (1.5 mmol) and triethylamine (0.5 mL) were added to a stirring solution of compound **7** (1 mmol) in methanol (50 mL), and the mixture was refluxed for 2 h. The solvent was removed under reduced pressure. Water (20 mL) and ehtylacetate (50 mL) were added to the residue. The organic phase was separated, dried (sodium sulfate), filtered, and evaporated under reduced pressure. The residue was crystallized in petroleum ether.

SUPPLEMENTARY MATERIAL

Full experimental detail, ^1H NMR, ^{13}C NMR, and NOESY spectra can be found via the Supplementary Content section of this article's Web page.

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