A Novel Synthesis of 5,6-Dihydro-2,3-bisaryl-8*H*-imidazo[2,1-*c*][1,4]thiazine

I. Lantos*, C. Razgaitis and B. M. Sutton

Research and Development Division, Smith Kline and French Laboratories,
Philadelphia, Pennsylvania 19101

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Bisaryl-8*H*-imidazo[2,1-*c*][1,4]thiazines were prepared from the corresponding 2-thiomethylimidazoles. A novel and efficient synthesis is presented for these intermediates based on the condensation of benzils with protected 2-thioacetaldehydes.

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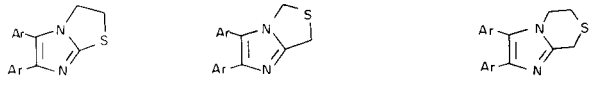
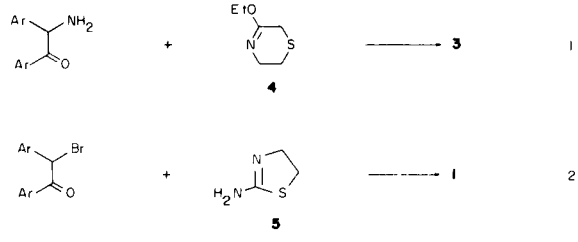
5,6-Diaryl-2,3-dihydroimidazo[2,1-*b*]thiazoles (**1**)represent fused heterocycles with potent antiinflammatory activity (1). Our sustained interest within this biological area required the preparation and evaluation of related heterocycles; the isomeric imidazo[2,1-*c*]thiazoles (**2**), and the homologous 5,6-dihydroimidazo[2,1-*c*][1,4]thiazines (**3**).



1 **2** **3**

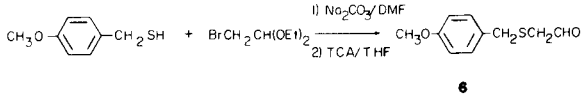
Traditionally, preparation of such compounds involves the condensation of α-aminoketones with cyclic iminoethers (**4**) (2), *e.g.*, reaction 1; or of α-bromoketones with cyclic amidines (**5**) (reaction 2).



4 **5**

Such approaches, however, require the preparation of structurally diverse precursors, **4** or **5**, differing in the size of the sulfur bearing ring. We decided to explore a more general approach based on the common intermediacy of 2-mercaptomethylimidazoles. An important aspect of this approach focused on the functionalization of 2-methylimidazoles which has received only scant attention, despite the abundance of publications dealing with the chemistry of imidazoles and derivatives (3). One simple approach, hydroxymethylation of 4,5-di(4-methoxylphenyl)-imidazole, proved unsuccessful (4).

Scheme I



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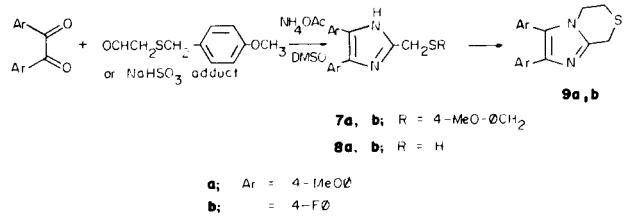

7a, **b**; R = 4-MeO-ØCH$_2$
8a, **b**; R = H

a; Ar = 4-MeOØ
b; Ar = 4-FØ

Scheme I details the successful synthesis of 5,6-dihydroimidazo[2,1-*c*][1,4]thiazines *via* functionalized 2-methylimidazole precursors **7** and **8**. The synthetic strategy involved condensation of *p*-methoxybenzylthioacetaldehyde, prepared in a straightforward manner from *p*-methoxybenzylmercaptan and bromoacetaldehyde diethylketal, with α-diketones and ammonium acetate (5). Application of the standard condensation conditions (5) in refluxing ethanol or acetic acid, failed to furnish imidazole derivatives **7**; 2,4,5-bisarylimidazoles were the only isolable products. Using DMSO as the solvent (6) improved the reaction greatly, affording the desired compounds in 20-25% yields. The imidazole condensation was improved further by utilizing the sodium bisulfite adducts of the aldehyde instead of the aldehyde itself under the DMSO conditions. The desired protected mercaptoimidazoles were obtained in better than 50% crude yields. Purification was accomplished easily by recrystallization. It appears that the aldehyde is released only slowly in this latter procedure, being protected from oxidative degradation until it participates in the condensation.

Removal of the protective groups was readily accomplished by the anisole TFA method and the crystalline thiols (**8**) were cyclized by reacting with 1-Br-2-Cl-ethane in DMF overnight to furnish the desired dihydroimidazo-[2,1-*c*][1,4]thiazines (**9**) in excellent yield.

Synthesis of the analogous imidazo[2,1-*c*]thiazoles (**2**) was also attempted. However, the product obtained from the dibromomethane condensation of **8** was too unstable to purify or characterize.

EXPERIMENTAL

The ir spectra were obtained in nujol mulls on a Perkin-Elmer in-

fracord spectrophotometer. The nmr spectra were taken on a Varian T-60 spectrometer in deuteriochloroform solution with internal TMS standard. All melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected.

4-Methoxybenzylthioacetaldehyde (**6**).

2-Bromoacetaldehyde diethylketal (39.4 g, 0.2 mole) and 4-methoxybenzyl mercaptan (31.0 g, 0.2 mole) were dissolved in 500 ml of DMF, anhydrous potassium carbonate (27.6 g, 0.2 mole) was added and the mixture was stirred at ambient temperature for 72 hours under an argon atmosphere. Approximately 150 ml of DMF was distilled from the reaction *in vacuo* and the residue was diluted with water to 1.5 ℓ. After extracting the product into ether, the ethereal solution was dried over anhydrous sodium sulfate, was filtered, and the filtrate was evaporated to an oil (54.0 g, 100%) which was 95% pure by gc.

This oily diethylketal was taken up in 1 ℓ of 15% aqueous THF solution and was stirred under argon with 125 g of TCA over a period of 48 hours. Diluting the solution with water (1 ℓ) furnished a two-phase mixture which was thoroughly extracted with ethyl ether. The ethereal solution was washed with 5% sodium carbonate, brine, and after drying over anhydrous magnesium sulfate, was evaporated to the oily aldehyde; ir: (δ) 5.9, 6.3, 8.1, 9.7, 12.0; nmr: (δ) 9.45 (tr, J = 3 Hz, CHO), 7.05 (q, J = 8 Hz, 8H aromatic), 3.8 (s, 3H, OCH_3), 3.55 (s, 2H, SCH_2), 3.05 (d, J = 3 Hz, 2H, CH_2S).

Anal. Calcd. for $C_{10}H_{12}O_2S$: C, 61.20; H, 6.16. Found: C, 60.95; H, 6.02.

To obtain the sodium bisulfate addition complex, sodium bisulfite (52 g, 0.5 mole) was added in 500 ml of water to the oily aldehyde and the precipitated solid (65 g) was filtered and washed with ether; ir: (μ) 2.9, 6.3, 8.1, 9.6, 9.8, 11.9, 12.2.

Preparation of 4,5-Diaryl-2[(4-methoxybenzylthio)methyl]imidazoles (**7**).

The bisulfite complex of the carboxaldehyde (20 mmoles) was reacted with substituted benzil (10 mmoles) in 100 ml of DMSO in the presence of ammonium acetate (100 mmoles) and concentrated hydrochloric acid (2 ml) at 75° for 20 hours under argon. Diluting the solution to 600 ml with water caused the precipitation of a solid which was taken up in methylene chloride washed with water and brine, and after drying over sodium sulfate was evaporated to an oil. The oily material was crystallized from 2-propanol:ether:hydrogen chloride to yield crystalline imidazoles in 45-50% yield. The 5,6-di(4-methoxybenzyl) derivative (**7a**) had mp 178-181°; ir: (μ) 3.8, 6.2, 6.3, 8.0, 9.75, 12.0; nmr: (δ) 7.0 (2 × q, 12H, aromatic), 4.10 (s, 2H, CH_2S), 3.85 (s, 2H, SCH_2), 3.70 (s, 6H, CH_3O), 3.5 (s, 3H, CH_3O).

Anal. Calcd. for $C_{26}H_{26}N_2O_3S$·HCl: C, 64.65; H, 5.63; N, 5.80. Found: C, 64.78; H, 5.70; N, 6.16.

Compound **8b** had mp 163-164°; ir: (μ) 6.3, 8.0, 8.2, 9.7, 11.9; nmr (δ) 7.0 (m, 12H, aromatic), 3.7 (s, 2H, CH_2S), 3.6 (s, 5H, OCH_3, SCH_2).

Anal. Calcd. for $C_{24}H_{20}F_2N_2OS$: C, 68.23; H, 4.77; N, 6.63. Found: C, 68.42; H, 4.86; N, 6.79.

Preparation of 4,5-Diaryl-2-thiomethylimidazoles (**8**).

The protected mercaptans **8** (2 mmoles) were refluxed in a solution of 20 ml of TFA and 2 ml anisole for 3 hours. Excess solvent was removed by distillation a the residue was taken up in chloroform, washed with 5% sodium carbonate, and the solution was dried over anhydrous sodium sulfate. Evaporation of the chloroform solution yielded an oil which deposited crystalline hydrochloride salt upon trituration with ethereal hydrogen chloride. The 4-methoxyphenyl compound **8a** had mp 210-215°; ir: (μ) 3.7, 6.15, 6.25, 8.0, 8.4, 9.7, 11.9, 12.2; nmr: (δ) 7.36 and 6.75 (2 × q, J = 8 Hz, 8H, aromatic), 4.6 (s, 1H, SH), 4.13 (s, 2H, CH_2S), 3.73 (s, 6H, CH_3O); ms: 326 ($M^{+\cdot}$) 296.

Anal. Calcd. for $C_{18}H_{18}N_2O_2S$·HCl·H_2O: C, 56.76; H, 5.29; N, 7.35. Found: C, 56.78; H, 5.99; N, 7.16.

Compound **8b** had mp 247-250° dec; ir: (μ) 6.1, 6.2, 7.3, 8.1, 8.2, 8.6, 9.1, 12.0; nmr (DMSO): (δ) 7.9-7.3 (m, 8H, aromatic), 4.8 (brs, 1H, SH), 4.3 (s, 2H, CH_2).

Anal. Calcd. for $C_{16}H_{12}F_2N_2S$·HCl: C, 56.72; H, 3.95; N, 8.27. Found: C, 56.38; H, 3.95; N, 8.34.

Preparation of 2,3-Diaryl-5,6-dihydro-8*H*-imidazo[2,1-*c*][1,4]thiazines (**9**).

A solution of the thiol (15 mmoles) and 1-bromo-2-chloroethane (16.5 mmoles) in 200 ml of DMF was stirred overnight at ambient temperature with anhydrous potassium carbonate (33 moles). The reaction mixture was heated to 80-100° for 1.5 hours and poured into an ice-water mixture to cause precipitation of the product. The solid precipitate was taken up in chloroform, washed with water and brine, and after drying the organic extract over anhydrous magnesium sulfate it was evaporated to about 50 ml when crystallization began. Ether (50 ml) was added and crystallization was completed in the refrigerator. The 4-methoxyphenyl compound **9a** (3.8 g) had mp 178-180° ir: (μ) 6.25, 7.3, 8.1, 8.55, 9.7, 11.9; nmr: (δ) 7.43 (2 × q, 8H, aromatic), 4.0 (s, 2H, CH_2S), 3.83 and 3.73 (2 × s, 6H, 2 × CH_3O), 3.80 and 3.0 (2 × tr, J = 6Hz, 4H, CH_2CH_2).

Anal. Calcd. for $C_{20}H_{20}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95. Found: C, 67.73; H, 5.97; N, 7.93.

The 4-fluorophenyl compound **9b** (1.2 g) had mp 137-141°; ir: (μ) 6.25, 8.0, 8.55, 9.2, 11.8; nmr (δ) 7.1 (m, 8H, aromatic), 4.0 (s, 2H, CH_2S), 3.9 and 2.95 (2 × tr, J = 6 Hz, 4H, CH_2CH_2).

Anal. Calcd. for $C_{18}H_{14}F_2N_2S$: C, 65.84; H, 4.30; N, 8.53. Found: C, 65.57; H, 4.49; N, 8.86.

Acknowledgement.

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