Studies on Isocyanides and Related Compounds. Synthesis of 1-Aryl-2-(tosylamino)-1*H*-imidazoles, a Novel Class of Imidazole Derivatives

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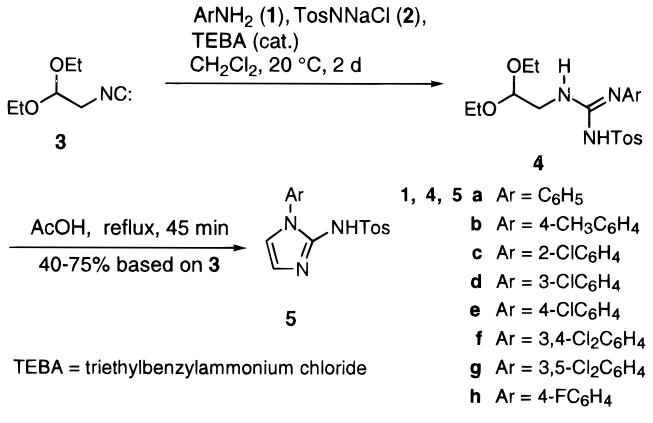
Although 2-aminoimidazoles have received considerable attention, especially with regard to their biological activities,[1] the closely related 2-(sulfonylamino)imidazoles are, to our knowledge, unknown.

In a preliminary communication[2] we reported a novel synthetic route to *N*-tosylguanidines from isocyanides, chloramine T, and anilines. In continuation of our studies on the synthesis of heterocyclic compounds from isocyanides,[3] we decided to investigate the possibility of extending the above reaction to the synthesis of the title compounds starting from anilines **1**, chloramine T (**2**), and 2,2-diethoxy-1-isocyanoethane (**3**), which was recognized to be a useful starting product for the synthesis of imidazole[4] and fused imidazole derivatives.[5]

The reaction between **1**, **2**, and **3** took place easily, under phase transfer catalyzed conditions, to give *N*-tosylguanidines **4**. Attempts to isolate compounds **4** in a pure form failed. Fortunately, the purification of *N*-tosylguanidines **4** was unnecessary, and their cyclization to 1-aryl-2-(tosylamino)-1*H*-imidazoles **5** was accomplished in a satisfactory manner by heating the crude reaction product with acetic acid.



Evidence for the assigned structures **5** was provided by their microanalytical and IR and ^{1}H NMR spectral data. In the IR spectra two strong absorptions at 3251−3371 and 1126−1134 cm^{-1} were detected, due to the NH and SO_2 groups, respectively. In the ^{1}H NMR spectra two singlet signals at about δ 2.33 and 10.40 were detected, due to the CH_3 and NH protons, respectively.

Furthermore, the doublet signal due to the H-4 of the imidazole nucleus was detected at δ 6.85−7.03. The doublet signal due to the H-5 of the imidazole nucleus in many cases was not clearly detectable because of the overlapping due to the aromatic proton signals.

Experimental Section

General. Anilines **1** were purchased from Aldrich. Chloramine T trihydrate (**2**) was purchased from Fluka. 2,2-Diethoxy-1-isocyanoethane (**3**) was prepared according to literature.[4] Anilines **1a**−**d**,**h** were distilled prior to use. Ethanol-free dichloromethane was used in all of the preparations. IR spectra were recorded on a Perkin-Elmer 881 spectrometer, and ^{1}H NMR spectra on a Varian Gemini 200 spectrometer.

1-(4-Methylphenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5a). General Procedure for Synthesis of Imidazoles **5**. A suspension of 2,2-diethoxy-1-isocyanoethane (**3**) (4.44 g, 31 mmol), aniline (**1a**) (2.89 g, 31 mmol), chloramine T trihydrate (**2**) (9.01 g, 32 mmol), and TEBA (100 mg) in dichloromethane (50 mL) was stirred at room temperature for 2 d. The reaction mixture was stirred with water (50 mL), and the phases were separated. The organic layer was dried over Na_2SO_4 and evaporated to dryness. The glasslike residue was stirred with AcOH (50 mL) and the resulting solution refluxed for 45 min. Removal of the solvent left a residue which was stirred with 5% $NaHCO_3$ (30 mL), collected, washed with water, and then recrystallized from EtOH/DMF to give **5a** (4.66 g, 48%): mp 182−183 °C; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.32 (s, 3 H), 6.85 (d, J = 2.4 Hz, 1 H), 7.21 (d, J = 2.4 Hz, 1 H), 7.26−7.72 (m, 9 H), 11.43 (s, 1 H); IR (KBr) 3251, 1140 cm^{-1}. Anal. Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.33; H, 4.83; N, 13.41. Found: C, 61.25; H, 4.86; N, 13.57.

1-(4-Methylphenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5b): mp 235−238 °C; yield 40%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.34 (s, 6 H), 6.85 (d, J = 2.6 Hz, 1 H), 7.16 (d, J = 2.6 Hz, 1 H), 7.27−7.73 (m, 8 H), 11.41 (s, 1 H); IR (KBr) 3289, 1137 cm^{-1}. Anal. Calcd for $C_{17}H_{17}N_3O_2S$: C, 62.37; H, 5.24; N, 12.84. Found: C, 62.12; H, 5.37; N, 12.61.

1-(2-Chlorophenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5c): mp 238−241 °C (EtOH/DMF); yield 66%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3 H), 6.86 (d, J = 2.5 Hz, 1 H), 7.03 (d, J = 2.5 Hz, 1 H), 7.25−7.68 (m, 8 H), 11.43 (s, 1 H); IR (KBr) 3289, 1137 cm^{-1}. Anal. Calcd for $C_{16}H_{14}ClN_3O_2S$: C, 55.25; H, 4.06; N, 12.08. Found: C, 55.01; H, 4.18; N, 12.39.

1-(3-Chlorophenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5d): mp 146−147 °C (EtOH); yield 60%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3 H), 6.89 (d, J = 1.8 Hz, 1 H), 7.28−7.73 (m, 9 H), 11.50 (s, 1 H); IR (KBr) 3371, 1126 cm^{-1}. Anal. Calcd for $C_{16}H_{14}ClN_3O_2S$: C, 55.25; H, 4.06; N, 12.08. Found: C, 55.45; H, 3.92; N, 12.15.

1-(4-Chlorophenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5e): mp 271−274 °C (EtOH/DMF); yield 70%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.34 (s, 3 H), 6.88 (d, J = 2.5 Hz, 1 H), 7.23−7.74 (m, 9 H), 11.47 (s, 1 H); IR (KBr) 3280, 1134 cm^{-1}. Anal. Calcd for $C_{16}H_{14}ClN_3O_2S$: C, 55.25; H, 4.06; N, 12.08. Found: C, 55.20; H, 3.97; N, 12.32.

1-(3,4-Dichlorophenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5f): mp 224−225 °C (EtOH/DMF); yield 75%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3 H), 6.90 (d, J = 2.5 Hz, 1 H), 7.25−7.86 (m, 8 H), 11.52 (s, 1 H); IR (KBr) 3269, 1134

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cm^{-1}. Anal. Calcd for $C_{16}H_{13}Cl_2N_3O_2S$: C, 50.28; H, 3.43; N, 10.99. Found: C, 50.35; H, 3.62; N, 10.71.

1-(3,5-Dichlorophenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5g): mp 175−177 °C (EtOH/DMF); yield 70%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3 H), 6.89 (d, J = 1.6 Hz, 1 H), 7.28−7.73 (m, 8 H), 11.55 (s, 1 H); IR (KBr) 3375, 1139 cm^{-1}. Anal. Calcd for $C_{16}H_{13}Cl_2N_3O_2S$: C, 50.28; H, 3.43; N, 10.99. Found: C, 50.01; H, 3.58; N, 11.25.

1-(4-Fluorophenyl)-2-[(4-toluenesulfonyl)amino]-1*H*-imidazole (5h): mp 238−240 °C (EtOH/DMF); yield 62%; ^{1}H NMR (200 MHz, DMSO-d_6) δ 2.33 (s, 3 H), 6.86 (d, J = 2.6 Hz, 1 H), 7.19 (d, J = 2.6 Hz, 1 H), 7.26−7.73 (m, 8 H), 11.44 (s, 1 H); IR (KBr) 3252, 1136 cm^{-1}. Anal. Calcd for $C_{16}H_{14}FN_3O_2S$: C, 58.00; H, 4.26; N, 12.68. Found: C, 57.75; H, 4.02; N, 12.99.

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