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AMBIDENTATE PROPERTIES OF ASYMMETRIC SUBSTITUTED IMIDAZOLES. DIRECTION OF BENZYLATION OF 2-[N-(4-CHLOROPHENYL)-CARBAMOYL]METHYLTHIO-4-PHENYL-1H-IMIDAZOLE

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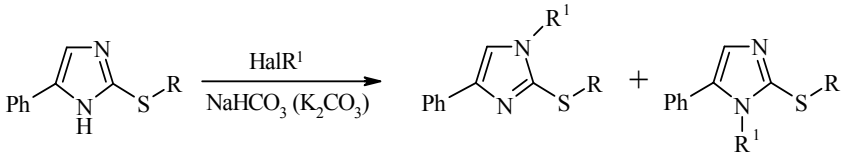
On the basis of ^{1}H-^{1}H two dimensional NMR spectroscopy (NOESY) it has been unambiguously shown that the benzylation of 2-[N-(4-chlorophenyl)carbamoyl]methylthio-4-phenyl-1H-imidazole occurs at the $N_{(1)}$ atom. This data was confirmed by comparison of the properties of the alkylation product obtained with the corresponding $N_{(3)}$-benzylimidazole isomer synthesized independently.

Keywords: imidazole-2-thiols, asymmetric substituted imidazoles, benzylation, ^{1}H-^{1}H two dimensional NMR spectroscopy (NOESY).

4-Arylimidazolyl-2-thione derivatives show a broad spectrum of biological activity [1, 2]. Hence alkylation of 4-arylimidazolyl-2-thiones by reagents having a mobile halogen atom and under mild conditions forms the corresponding sulfide derivatives [1, 2], many of which are immunomodulatory, antitumor, and antihypertensive agents [3-8]. However, despite quite an amount of data reported in the literature regarding the S-alkylation of mercaptoimidazoles, comparatively few reliable publications concern the direction of N-alkylation of the imidazole ring.

The formation of two regioisomers is theoretically possible for the alkylation of asymmetric substituted imidazoles.



We present evidence for the direction of benzylation of the model compound 2-[N-(4-chlorophenyl)-carbamoyl]methylthio-4-phenyl-1H-imidazole (**1**) on the basis of two dimensional ^{1}H-^{1}H NMR spectroscopy and the independent synthesis of a strictly fixed isomer.

The following consecutive reactions have been used to synthesize the sulfide **1**. Initial cyclocondensation of α-aminoacetophenone hydrochloride with potassium thiocyanate in the presence of potassium acetate gave 2-mercapto-4-phenylimidazole which was then alkylated at the sulfur atom by N-(4-chlorophenyl)chloroacetamide to give the sulfide **1**. Sulfide **1** was then alkylated by benzyl chloride in DMF in the presence of excess potassium carbonate.

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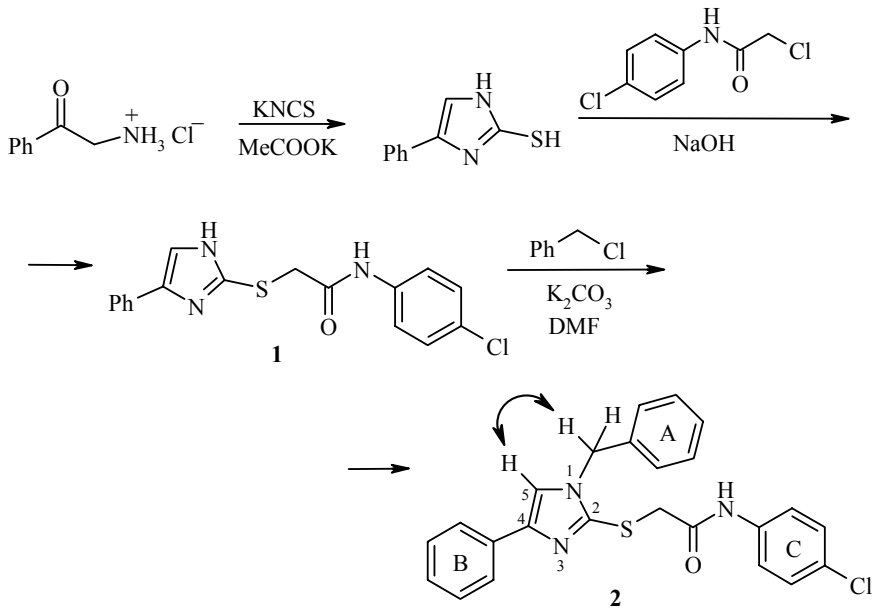
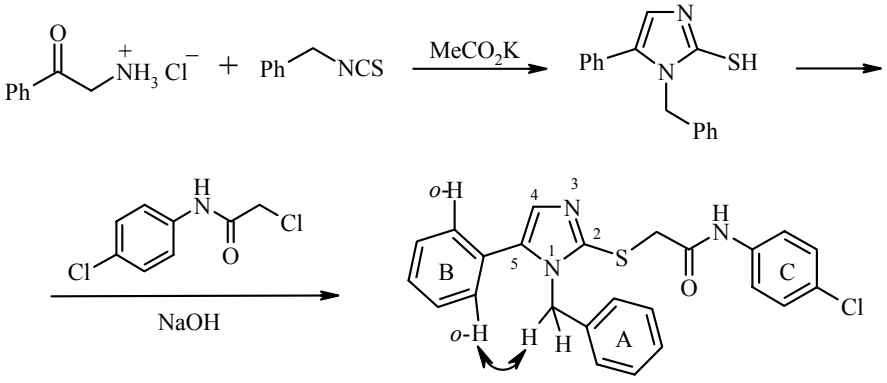


1

2

TLC data for the reaction mixture showed the formation of a single benzylation product, the structure of which was shown to be compound **2** from ^{1}H NMR spectroscopic and mass spectrometric data.

Physicochemical and spectroscopic characteristics for the compound prepared (R_f, mp, ^{1}H NMR chemical shifts) were compared with the constants for compound **3** prepared by an independent route.



3

In this case the starting compound for formation of the imidazole ring in the condensation with α-aminoacetophenone was N-benzylisothiocyanate which gave 1-benzyl-2-mercapto-5-phenyl-1H-imidazole [9]. Alkylation at the sulfur atom using N-(4-chlorophenyl)chloroacetamide gives 1-benzyl-2-[N-(4-chlorophenyl)carbamoyl]methylthio-5-phenyl-1H-imidazole (**3**).

It was found that the R_f, melting point, and solubility of compound **2** differ markedly from the corresponding values for compound **3**. In the ^{1}H NMR spectra the signal for the imidazole H-5 proton in compound **2** was shifted by about 0.4 ppm to lower field when compared with the signal of the analogous proton for compound **3** as a result of the deshielding effect of the aromatic ring **A** and is thus indirect evidence for the structure of compound **2** proposed by us.

However, the final proof that the benzylation of sulfide **1** is really at the $N_{(1)}$ atom of the imidazole ring was obtained by a comparison of the two dimensional ^{1}H-^{1}H NMR (NOESY) spectra of compounds **2** and **3**.

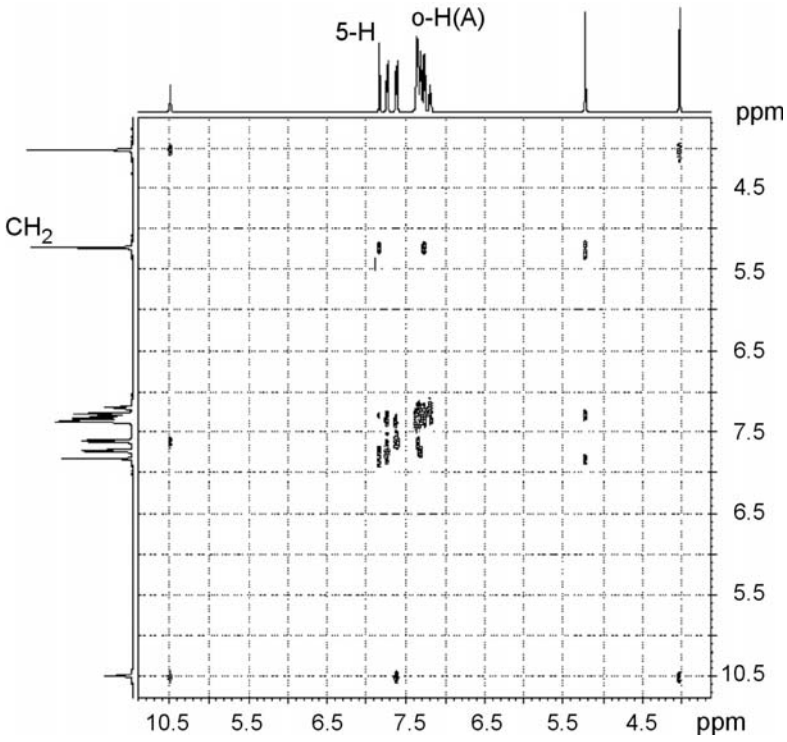


Fig. 1. 2D ^{1}H-^{1}H NOESY NMR Spectrum of Compound **2**.

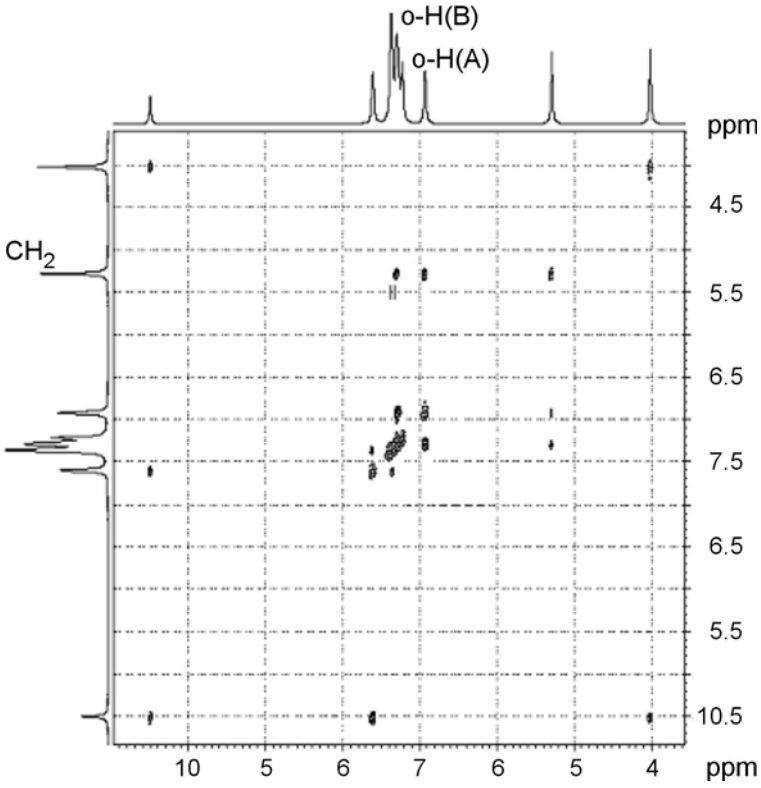


Fig. 2. 2D ^{1}H-^{1}H NOESY NMR Spectrum of Compound **3**.

The 2D ^{1}H-^{1}H NOESY NMR spectrum of compound **2** (Fig. 1) shows cross peak **I** which reflects the interaction of the benzyl CH_2 group protons with the imidazole H-5 proton in compound **2**. In contrast to compound **3** these are closely related sterically.

The 2D ^{1}H-^{1}H NOESY spectrum of compound **3** (Fig. 2) shows cross peak **II** and this reflects the interaction of the benzyl CH_2 group protons with the *o*-H protons of benzene ring **B**. In contrast to compound **2** these are closely related sterically.

This data unambiguously confirms the structure of isomer **2** and thus the benzylation of the sulfide **1** at the less sterically hindered nitrogen atom of the imidazole ring.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Bruker MSL-300 (300 MHz) instrument and 2D ^{1}H-^{1}H NOESY NMR spectra on a Bruker DRX-500 (500 MHz) instrument using DMSO-d_6 and TMS internal standard. Mass spectrometric analysis was carried out on a Thermo Finnigan Surveyor MSQ instrument in the electrospray injection mode and positive ions were recorded at 500°C with a needle tip voltage of 3 kV. TLC was carried out in chloroform–methanol (50:1) on Sorbfil plates.

2-[N-(4-Chlorophenyl)carbamoyl]methylthio-4-phenyl-1H-imidazole (1). A 5% aqueous solution of NaOH (8.8 ml, 11 mmol) and N-(4-chlorophenyl)chloroacetamide (2.24 g, 11 mmol) were added to a suspension of 2-mercapto-4-phenyl-1H-imidazole (1.64 g, 10 mmol) in 2-propanol (30 ml) with heating and refluxed for 20 min to the finish of the reaction (TLC monitoring). The white precipitate was filtered off and washed with water and 2-propanol to give compound **1** (2.41 g, 70%); mp 181-182°C, R_f 0.25. Found, %: C 59.05; H 4.48; N 12.03. [M+1] 386.87. $C_{18}H_{17}ClNO_3S$. Calculated, %: C 59.39; H 4.08; N 12.23. [M+1] 386.87.

2-[N-(4-Chlorophenyl)carbamoyl]methylthio-1-benzyl-4-phenyl-1H-imidazole (2). Potassium carbonate (0.207 g, 1.5 mmol) and benzyl chloride (0.151 g, 1.2 mmol) were added to a solution of the sulfide **1** (0.343 g, 1 mmol) in DMF (2 ml) and refluxed for 10 min with vigorous stirring. The cooled reaction mixture was treated with water (3 ml). The crystals formed were filtered, washed with water, and recrystallized from 2-propanol to give compound **2** (0.23 g, 53%); mp 129-130°C, R_f 0.84. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.00 (2H, s, S–CH_2); 5.30 (2H, s, CH_2Ph); 6.93 (2H, d, *J* = 8, H-3,5, Ph_C); 7.20 (1H, s, H-5); 7.22-7.38 (10H, m, Ph_A, Ph_B); 7.59 (2H, d, *J* = 8, H-2,6, Ph_C); 10.44 (1H, s, NH). Found, %: C 66.52; H 4.54; N 9.65. [M+1] 434.96. $C_{24}H_{20}ClN_3OS$. Calculated, %: C 66.43; H 4.65; N 9.68. [M+1] 434.96.

2-[N-(4-Chlorophenyl)carbamoyl]methylthio-1-benzyl-5-phenyl-1H-imidazole (3). A 5% aqueous solution of NaOH (0.88 ml, 1.1 mmol) and N-(4-chlorophenyl)chloroacetamide (0.224 g, 1.1 mmol) were added with heating to a suspension of 1-benzyl-2-mercapto-5-phenyl-1H-imidazole [9] (0.254 g, 1 mmol) in 2-propanol (4 ml) and refluxed for 25 min to the finish of the reaction (TLC monitoring). The white precipitate was filtered off and washed with water and 2-propanol to give compound **3** (0.329 g, 76%); mp 183-184°C, R_f 0.54. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.00 (2H, s, S–CH_2); 5.25 (2H, s, CH_2Ph); 7.18-7.42 (10H, m, Ph_A, Ph_B); 7.58 (2H, d, *J* = 8, H-3,5, Ph_C); 7.73 (2H, d, *J* = 8, H-2,6, Ph_C); 7.81 (1H, s, H-5); 10.41 (1H, s, NH). Found, %: C 66.34; H 4.47; N 9.61. [M+1] 434.96. $C_{24}H_{20}ClN_3OS$. Calculated, %: C 66.43; H 4.65; N 9.68. [M+1] 434.96.

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