Synthesis and X-ray crystal structure of pyrrolo[1,2-a]benzimidazoles

Adel M. Awadallah, a,* Konrad Seppeltb and Hashem Shorafab

a Chemistry Department, Faculty of Science, Islamic University of Gaza, PO Box 108, Gaza, Palestine
b Institut für Chemie der Freien Universität, Fabeckstraße 34-36, D-14195 Berlin, Germany

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Abstract—Reaction of nitrilimines 1 with 2-cyanomethylbenzimidazole 2 gave the 3-arylazo-2-methylpyrrolo[1,2-a]benzimidazole 4a rather than the reported 2-arylazo-3-methylpyrrolo[1,2-a]benzimidazole 3a. The correct structure of the product was determined using X-ray crystal structure analysis. The similar reaction of nitrilimines with 2-aminobenzimidazole 5 gave the acyclic nucleophilic addition product 6.

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1. Introduction

Nitrilimines are widely used for the synthesis of heterocycles. They are well known to undergo three types of reactions: 1,3-dipolar cycloaddition leading to five-membered ring heterocycles, cyclocondensation reactions leading to five, six, or larger heterocycles, and nucleophilic addition leading to acyclic adducts. Examples of these modes of reactions were recently reviewed by us for the reactions of hydrazones and oximes with nitrilimines and nitrile oxides.1

Benzimidazoles represent an important heterocyclic system due to their pharmacological activity. The benzo-fused-imidazoles derivative (Rifaximin) is used as antineoplastic and anticancer agents.2

Many efforts have been made to develop methods for preparation of pyrrolo[1,2-a]benzimidazoles. They are prepared via 1,3-dipolar cycloaddition of fluoroalkenes to N-ylikes.3 The reaction between dilithiated 2-methylbenzimidazole and dimidoyl dichlorides gave 1-arylimino-1H-pyrrolo[1,2-a]benzimidazole-2-amines.4

C-Acetyl-N-aryl nitrilimines were recently reported to react with 2-aminonicotinic acid leading to imidazo[1,2-a]pyridines,5 and with 2-aminopyrazines leading to imidazo[1,2-a]pyrazines.6 These reactions start by nucleophilic addition of the lone pair of electrons of nitrilimines to the electrophilic carbon, followed by cyclization of the amino group with C=O.

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* Corresponding author. Tel.: +970 8 2823311; fax: +970 8 2823310; e-mail: awada@iugaza.edu.ps

2. Results and discussion

In this work, we reinvestigated the reaction of 2-cyanomethylbenzimidazole 2 with hydrazonoyl halides 1. This reaction was recently reported by Elwan to give pyrrolo[1,2-a]benzimidazoles 3.7 The reaction of 2-aminobenzimidazoles 5 with hydrazonoyl halides 1 was investigated.

The reaction of hydrazonoyl halides 1 with 2-cyanomethylbenzimidazole 2 was reinvestigated in tetrahydrofuran at room temperature (Scheme 1). The product obtained from 1a is believed to be the same compound 3a that was obtained by Elwan when the reaction was done in refluxing chloroform.7 This is based on the similarity of their physical
2.1. Description of the crystal structure

The structure of 4a·DMF is shown in Figure 1. The substitution pattern is obvious, and the identification of nitrogen atoms versus carbon atoms is straightforward. All ring hydrogen atoms including the aldehydic hydrogen atom have been located in differential Fourier maps, only the methyl group hydrogen atoms have been located by a riding model. Compound 4a and DMF are connected by a C==O...H–N bridge of 185 pm in length. This hydrogen bridge also enlarges the C==O bond length somewhat 123.1(6) pm in length. Another special feature of the molecular unit 4a·DMF is its overall planarity, only the methyl hydrogen atoms are not in plane. The maximal deviation of any non-hydrogen atom from the best plane of the entire unit is only 32 pm (C23 of DMF). Compound 4a alone is even closer to planarity, the largest deviation from this best plane is 26 pm (C3).

A similar reaction of hydrazonoyl halides 1a with 2-aminobenzimidazole 5 was also investigated. This reaction gave the acyclic adduct 6a rather than the imidazobenzimidazole 7a (Scheme 2).

3. Experimental

3.1. General

Melting points were determined on an Electrothermal Mel. Temp apparatus and are uncorrected. IR spectra were obtained by using Perkin–Elmer 237 infrared spectrometer (KBr discs). 1H and 13C NMR spectra were recorded on a Bruker 300 MHz instrument for solutions in DMSO-d6 at 21 °C, using TMS as an internal reference. Electron impact mass spectra were run on Finnigan Mat 8200 spectrometer at 70 eV. Elemental analyses were done at Institut für Chemie der Freien Universität, Berlin. Hydrazonoyl halides 1a and 2a, were prepared as previously described. 2-Cyanomethylbenzimidazole 2 and 2-aminobenzimidazole 5 were purchased from Acros.

3.2. Reaction of nitrilimines with 2-cyanomethylbenzimidazole 2

Triethylamine (0.01 mol, 1.4 mL) was dropwise added to a mixture of hydrazonoyl halides 1 (0.01 mol) and 2-cyanomethylbenzimidazole 2 (0.01 mol, 1.57 g) in tetrahydrofuran.
Yield: 2.5 g, 75%, orange solid, mp 278–280 °C (literature mp 280 °C). The IR, MS, and NMR data for this compound are identical to that reported by Elwan. However, X-ray crystal structure analysis showed it to have structure 4a rather than the reported structure 3a.

3.4. 3-(4-Bromophenylazo)-1-cyano-2-methyl-9H-pyrrolo[1,2-a]benzimidazole 4b

Yield 2.8 g, 65%, orange solid, mp 264–265 °C; [found: C, 56.98; H, 3.29; N, 18.43. C18H12BrN5 requires C, 57.16; H, 3.20; N, 18.52%]; IR (KBr) ν 3151 (NH), 2214 (CN) cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.5 (s, 3H, CH₃), 7.2 (1H, t, J 7.0 Hz, ArC–H), 7.3 (1H, t, J 7.0 Hz, ArC–H), 7.4 (1H, d, J 7.0 Hz, ArC–H), 7.6 (4H, 2d, J 8.0 Hz, 4-BrC₆H₄), 8.5 (1H, d, J 8.0 Hz, ArC–H), 13.3 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 12.0, 112.4, 115.3, 117.60, 117.65, 121.0, 121.5, 123.2, 125.0, 127.3, 132.3, 135.76, 135.83, 144.32, 144.37, 152.7; MS m/z (377/379 M⁺, bromine isotopes).

3.5. 1-(4-Chlorophenylhydrazo)-1-(2-aminobenzimidazol-1-yl)-2-propanone 6a

Yield 2.8 g, 85%, yellow solid, mp 255–257 °C; [found: C, 58.88; H, 4.41; N, 21.51. C₂₁H₁₉Cl₂N₂O requires C, 58.63; H, 4.31; N, 21.37%]; IR (KBr) ν 3416, 3310, 3297 (3NH), 1683 (C=O) cm⁻¹. ¹H NMR (DMSO-d₆) δ 2.5 (s, 3H, CH₃), 6.4 (s, 2H, NH₂), 6.6 (1H, d, J 7.0 Hz, ArC–H), 6.8 (1H, t, J 7.0 Hz, ArC–H), 7.0 (1H, t, J 7.0 Hz, ArC–H), 7.2 (1H, d, J 7.0 Hz, ArC–H), 7.4 (4H, 2d, J 9.0 Hz, 4-ClC₆H₄), 11.0 (s, 1H, NH); ¹³C NMR (DMSO-d₆) δ 191.2 (C=O), 155.1, 144.7 (2C=═N), 142.6, 134.1, 128.8, 126.7 (4ArC), 129.6, 121.7, 118.9, 117.0, 115.4, 108.1 (6ArC–H), 25.6 (CH₃); MS m/z (327/329 M⁺, chlorine isotopes).

3.6. Experimental (of the crystal structure of 4a)

A suitable crystal is mounted on a Bruker Smart CCD-1000 TM diffractometer and measured at 100 °C, with Mo Kα radiation source of λ=71.069 pm and graphite monochromator: scan width of 0.3° in ω, measuring 20 sec/frame, and 1800 frames for a full shell up to θ=28°, no absorption correction. The SHELX programs are used for structure solution and refinement. All atoms except hydrogen are refined with anisotropic displacement parameters. Aromatic hydrogen atoms and the aldehydic hydrogen atom in DMF are refined isotropically with individual displacement parameters, the methyl hydrogen atoms are refined with one combined displacement parameter. Experimental data and results are summarized in Tables 1 and 2, and Figure 1. Further details of the crystal structure determination can be obtained free of charge from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ. Tel.: +44 1223 336 408; fax: +44 1223 336 033. E-mail: deposit@ccdc.com.ac.uk by quoting the depository number CCDC 295742.

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