Available online at www.sciencedirect.com

Tetrahedron 62 (2006) 7744–7746

Tetrahedron

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

Adel M. Awadallah,[a,*] Konrad Seppelt[b] and Hashem Shorafa[b]

[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*

Received 31 January 2006; revised 8 May 2006; accepted 25 May 2006
Available online 19 June 2006

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**.

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]

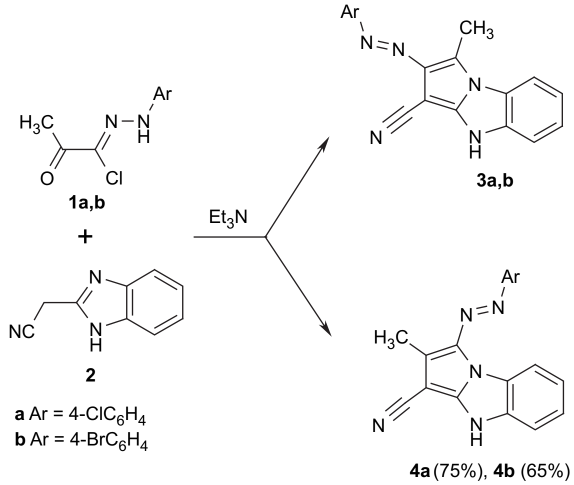
Many efforts have been made to develop methods for preparation of pyrrolo[1,2-*a*]benzimidazoles. They are prepared via 1,3-dipolar cycloaddition of fluoroalkenes to *N*-ylides.[3] The reaction between dilithiated 2-methylbenzimidazole and diimidoyl dichlorides gave 1-arylimino-1*H*-pyrrolo[1,2-*a*]benzimidazole-2-amines.[4]

C-Acetyl-*N*-arylnitrilimines 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.

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.

2. Results and discussion

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



Scheme 1. Synthesis of pyrrolo[1,2-*a*]benzimidazoles **4a**,**b**.

Keywords: Nitrilimines; 2-Cyanomethylbenzimidazole; 2-Aminobenzimidazole; Pyrrolo[1,2-*a*]benzimidazole.

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

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.05.071

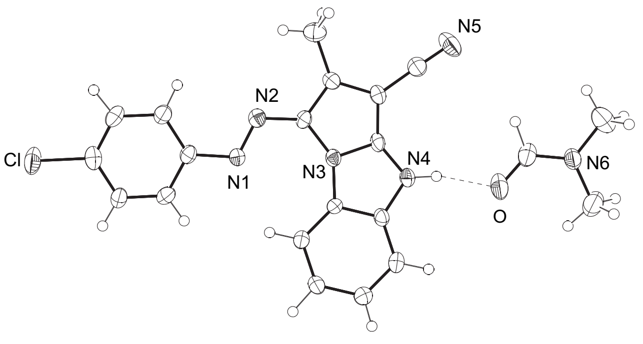


Figure 1. The molecular unit of **4a**·DMF in the crystal, Ortep representation, 50% probability ellipsoids (hydrogen atoms) are represented by cycles of arbitrary size.

properties including mp, MS, IR, ^{1}H NMR, and ^{13}C NMR. However, we suggested that this compound was the regioisomer **4a**. Since the two isomers are very similar, and the spectroscopic analysis (IR, MS, and NMR) cannot differentiate easily between them, we obtained an X-ray structure. The structure revealed that the compound is indeed **4a** rather than **3a** (Fig. 1). Thus the reaction should start by nucleophilic attack of the lone pair of electrons of the benzimidazole nitrogen at the electrophilic carbon of the nitrilimine, followed by cyclization of the carbanion generated at the methylene group at the carbonyl carbon of the nitrilimine. Crystal data and selected bond angles and bond lengths of **4a** are given in Tables 1 and 2, respectively.

Table 1. Crystal data for **4a**·DMF

Formula	$C_{21}H_{19}ClN_6O$
Molecular weight	406.12
Crystal size	0.3×0.3×0.1 mm
Crystal color	Orange red
a	762.0(3) pm
b	2144.5(8) pm
c	1231.7(5) pm
β	96.45(1)°
V	$2000.0\cdot10^6$ pm^3
Space group	$P2_1/c$
Z	4
T	−100 °C
μ	0.22 mm^{-1}
Measured reflections	18899
Unique reflections	4832
R(int)	0.104
$2\theta_{\max}$	56.26°
Parameters	331
Goodness-of-fit	1.049
R_1	0.095
wR_2	0.2238

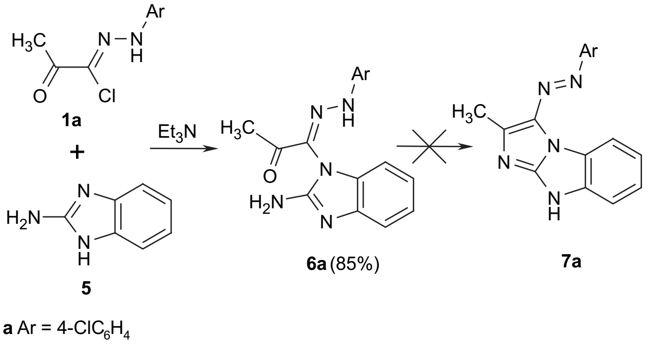
Table 2. Some bond lengths [pm] and angles [°] of **4a**·DMF

C1−Cl	174.3(5)	N1–N2–C4	113.6(4)
N1–N2	128.8(5)	N2–N1–C6	115.3(4)
C–C (ring)	136.5(7)–140.7(6)	C14–C17≡N	178.4(6)
C14–C17(≡N)5	140.9(6)		
C17≡N5	116.1(6)		
C–N(ring)	134.6(6)–141.7(6)		
O(DMF)···H211−N4	185.5(45)		

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).



Scheme 2. Reaction of nitrilimines with 2-aminobenzimidazole.

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). ^{1}H and ^{13}C NMR spectra were recorded on a Brucker 300 MHz instrument for solutions in DMSO-d_6 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**,[8] were prepared as previously described. 2-Cyanomethylbenzimidazole **2** and 2-aminobenzimidazole **5** were purchased from Acros.

3.2. Reaction of nitrilimines 1 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

(50 mL) at room temperature. The reaction mixture was stirred for two days. The precipitated salt was filtered off, and the solvent was then evaporated. The residual solid was washed twice with water, and then triturated with ethanol. The orange solid was collected using suction filtration and crystallized from hot dimethylformamide. Crystals from **4a** were formed upon slow evaporation of a dimethylformamide solution of the compound. An authentic sample of **4a** was also prepared utilizing a procedure similar to that reported by Elwan.[7] Thus, triethylamine (0.005 mol, 0.7 mL) was dropwise added to a mixture of hydrazonoyl halides **1** (0.01 mol) and 2-cyanomethylbenzimidazole **2** (0.005 mol, 0.79 g) in chloroform (50 mL) at room temperature. The reaction mixture was refluxed for 8 h. The precipitated orange product was filtered, and found to be identical with the product **4a** obtained from the above reaction applying THF as a solvent. The identity was based on TLC, mixed melting points, and IR spectra.

3.3. 3-(4-Chlorophenylazo)-1-cyano-2-methyl-9*H*-pyrrolo[1,2-*a*]benzimidazole 4a

Yield: 2.5 g, 75%, orange solid, mp 278–280 °C (literature mp 280 °C).[6] 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-9*H*-pyrrolo[1,2-*a*]benzimidazole 4b

Yield 2.5 g, 65%, orange solid, mp 264–265 °C; [found: C, 56.98; H, 3.29; N, 18.43. $C_{18}H_{12}BrN_5$ requires C, 57.16; H, 3.20; N, 18.52%]; IR (KBr) ν 3151 (NH), 2214 (CN) cm^{-1}. ^1H NMR (DMSO-d_6) δ 2.5 (s, 3H, CH_3), 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-BrC_6H_4), 8.5 (1H, d, J 8.0 Hz, ArC–H), 13.3 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) 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 $M^{+\bullet}$, bromine isotopes).

3.5. 1-(4-Chlorophenylhydrazono)-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. $C_{16}H_{14}ClN_5O$ 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-d_6) δ 2.5 (s, 3H, CH_3), 6.4 (s, 2H, NH_2), 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-ClC_6H_4), 11.0 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) 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 (CH_3); MS m/z (327/329 $M^{+\bullet}$, 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.[9] 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@ccde.com.ac.uk by quoting the depository number CCDC 295742.

Acknowledgements

One of the authors, A.A., is thankful to the ministry of education and higher education of Palestine for financial support, and to Dr. Jalal Ahmed (Jordan University) for measuring the NMR of the new compounds.

References and notes

1. Ferwanah, A. R. S.; Awadallah, A. M. *Molecules* **2005**, *10*, 492–507.
2. *The Merck Index*, 12th ed.; Chapman and Hall: London, 1996; Ver. 12.1.
3. Wu, K.; Chen, Q. *Synthesis* **2003**, 35–40.
4. Langer, P.; Wuckelt, J.; Doering, M.; Schreiner, P.; Goerls, H. *Eur. J. Org. Chem.* **2001**, 2245–2255.
5. Thaher, B. *Abhath Al-Yarmouk Journal (Series of naural studies)* **2003**, *12*, 555–561.
6. Thaher, B. *Journal of the Islamic University of Gaza (Series of natural Studies and Engineering)* **2005**, *13*, 109–115.
7. Elwan, N. *Tetrahedron* **2004**, *60*, 1161–1166.
8. El-Abadelah, M. M.; Hussein, A. Q.; Thaher, B. A. *Heterocycles* **2004**, *10*, 1879–1895.
9. Sheldrick, G. H. *SHELXS-93, Program for Crystal Structure Solution*; Universität Göttingen: Germany; *SHELXL-97, Program for Crystal Structure Refinement*; Universität Göttingen: Germany.