About the Reaction of β-Dimethylamino-α,β-enones with Active Methylene Nitriles

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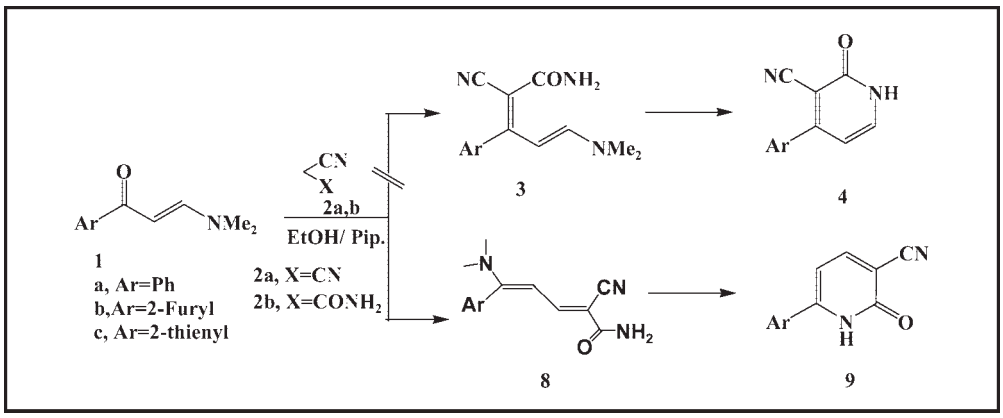

The reaction of 3-dimethylamino-1-arylpropenone derivatives with active methylene nitriles was reinvestigated and a plausible mechanism to account for the results is suggested. X-ray crystallographic study supported the suggested mechanism. Based on these findings, the reaction of 3-acetylamino-4-dimethylaminobut-3-en-2-one with malononitrile was also reinvestigated and the correct structures verified.

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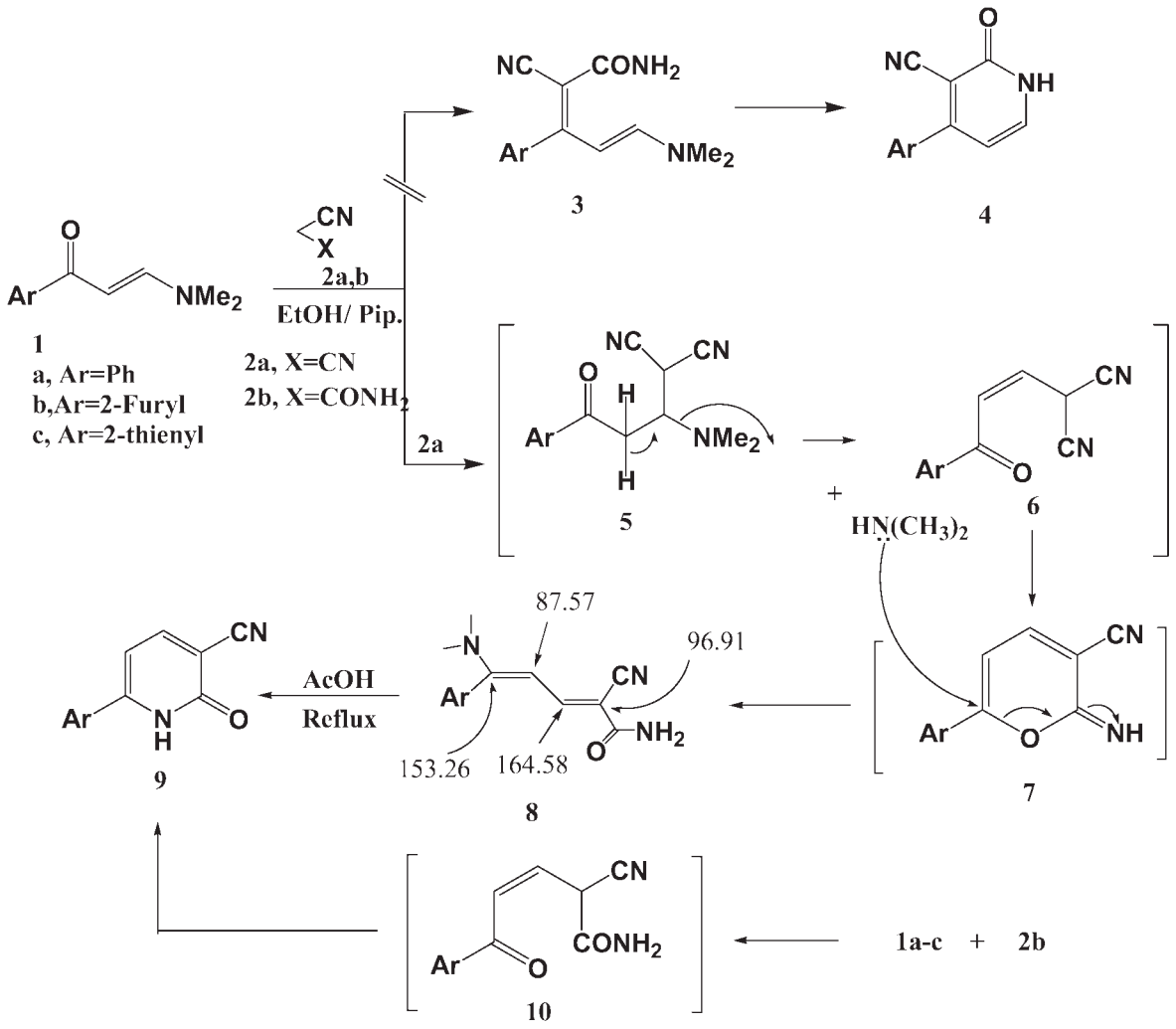
INTRODUCTION

In the past 2 decades, we have been involved in a program aiming to develop new simple routes for the synthesis of heterocyclic compounds of biological interest to be evaluated as biodegradable agrochemicals [1–5]. Pyridines and pyridones represent an important class of these compounds because of their pharmaceutical applications [6–8]. The reaction of enaminones with active methylene nitriles represents one of the strategies for the preparation of 2-1*H*-pyridone [9–11]. 3-Dimethylamino-1-arylpropenones **1a–c** have been extensively used in the last years by Elnagdi and coworkers for the synthesis of pyridones [12–14]. The reaction of **1a–c** with active methylene nitriles (namely malononitrile **2a** and cyanoacetamide **2b**; Scheme 1) in all these and other publications was based on the idea of a Knoevenagel condensation of the active methylene in **2a** or **2b** with the carbonyl groups of **1a–c**. In one article, it was assumed that malononitrile **2a** is first hydrolyzed to cyanoacetamide by the water present in the solvent [12], which then condenses with the carbonyl group of **1a–c** to afford **3a–c**. In the other article, it was assumed that the condensation takes place first and then the water resulting from the condensation hydrolyzes one of the cyano groups in the products of **2a** but do nothing with the products of **2b** to afford the amides **3a–c** [13]. Then, compounds **3a–c** were cyclized to afford the 2-1*H*-pyridones **4a–c**. These assumptions attracted our attention and raised our doubt in the structures of these products. The NMe_2 group is a very good leaving group and the active methylene reagent must substitute it easier and faster than to condense with the carbonyl group. Furthermore, the hydrolysis of a cyano group by the traces of water present in the solvent (ethanol and few drops of piperidine as catalyst), or that resulting from the condensation seemed far unlikely to occur. On the basis of these reservations, we decided to reinvestigate this reaction.

RESULTS AND DISCUSSION

Thus, the enaminone compounds **1a–c** were prepared and allowed to react with the active methylene compounds **2a**,**b** according to the method and under the same reaction conditions reported by Elnagdi and coworkers [12]. In our hands, we could isolate the 2-cyano-5-dimethylamino-5-arylpenta-2,4-dienoic amide derivatives **8a–c** from the reaction of **1a–c** with malononitrile **2a**. The mass spectra of these compounds showed

Scheme 1



5-9 : a, Ar=Ph ; b, Ar=2-Furyl ; c, Ar=2-thienyl

m/*z* = 241, 231, and 247, respectively. These masses reveal that 1:1 adducts were obtained and correspond to molecular formulae $C_{14}H_{15}N_3O$, $C_{12}H_{13}N_3O_2$, and $C_{12}H_{13}N_3OS$, respectively, as reported previously [12]. However, the cyclization of these compounds upon reflux in acetic acid led to the 2-1*H*-pyridone derivatives **9a–c**. The ^{1}H NMR spectrum of **9a** revealed two doublets; each integrated for 1H at δ = 6.72 and 8.20 with equal *j* value of 8 Hz, which could be attributed to the pyridone **9a** H-5 and H-4, respectively. A pyridone structure like the claimed **4a** should have revealed these proton signals for H-5 and H-6 at slightly up field values δ ≈ 5.8 and 7.3 ppm. Thus, structures **9a–c** were assigned to these reaction products rather than **4a–c** (*cf*. Experimental).

The formation of the enaminones **8a–c** from the reaction of **1a–c** with **2a** is assumed to take place *via* the sequence depicted in Scheme 1. The active methylene group of malononitrile undergoes addition to the double bond of **1** to give the intermediate **5**, followed by elimination of dimethyl amine to afford 2-(3-oxo-3-aryl-propenyl)-malononitrile **6**, which directly undergoes ring closure *via* its enolized form to afford the iminopyran **7**. This newly born iminopyran is attacked by the dimethyl amine (which is still present in the reaction medium) and undergoes ring opening to afford the isolated 2-cyano-5-dimethylamino-5-arylpenta-2,4-dienoic amides **8a–c**. The ring opening of iminopyran under the effective ammonia and amines is well established in the literature [10]. Elemental analyses and spectral data are

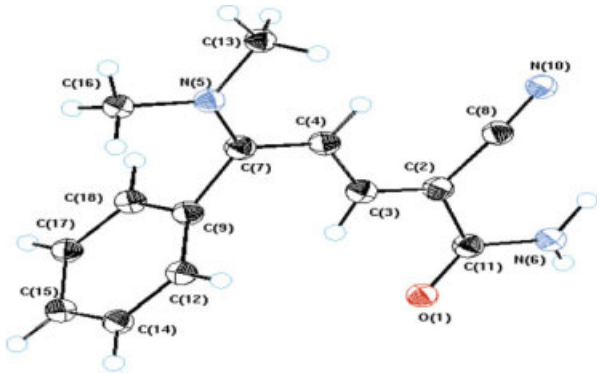


Figure 1. Crystal structure of compound **8a**. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

in complete agreement with structures **8a–c** (*cf.* Experimental).

The X-ray crystallographic picture [15] afforded an unambiguous evidence of structure **8a** (Fig. 1; *cf.* experimental). It shows that the $N(Me)_2$ attached to the same carbon atom (C7) carrying the phenyl group and the other terminus carrying the cyano and the amide group on (C2) as shown in Figure 1 and Scheme 1, which affords a conclusive evidence to the pyridone structures **9**.

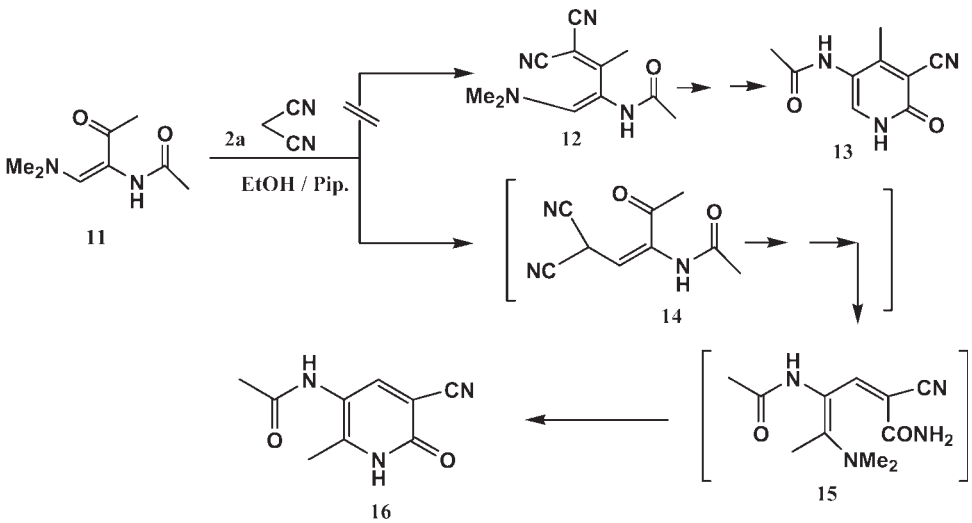
These compounds could be readily cyclized upon reflux in acetic acid to afford the 2-1*H*-pyridinone derivatives **9a–c**, respectively, *via* elimination of dimethyl amine.

The reaction of **1a–c** with cyanoacetamide **2b** afforded the same 2-1*H*-pyridinones **9a–c**, respectively, which represents further evidence to this suggested mechanism. It is apparent that **2b** followed the same addition elimination sequence to afford the intermediate 2-cyano-5-oxo-5-arylpent-3-enoic acid amide **10** (analogous to **6** in the above sequence), which undergoes directly the cyclization *via* elimination of water without passing through the step of the iminopyran, since the amide group is initially present. The identity of the products obtained from the reactions of **1a–c** with either **2a** or **2b** was deduced from the typical melting points and spectral data. It should be also clear that Elnagdi and coworkers [12] have reported that they obtained the same products from the reaction of **2b** with **1a–c**.

Furthermore, Elnagdi and coworkers [13] have reported the reaction of 3-acetylamino-4-dimethylamino-but-3-en-2-one **11** (obtained from the reaction of acetylaminoacetone with DMFDMA) with malononitrile **2a** and assumed the same scenario of condensation to give **12**, which is cyclized to **13** (Scheme 2).

Reinvestigation of this reaction showed that it follows the same mechanistic way shown in Scheme 1. Malononitrile substitutes the dimethylamnino group to give the intermediate **14** followed by cyclization and ring opening of the formed iminopyran to afford **15**, which readily eliminates dimethylamine to afford the final isolable 2-1*H*-pyridinone derivative **16** (in a Dimroth-type rearrangement). Although the claimed structure **13** and our structure **16** have almost the same elemental and spectral data, however, the δ value given by Elnagdi and coworkers [13] to the pyridinone H is 7.95 ppm, which better fits to the H-4 rather than the H-6. A structure like **13** would have revealed this H-6 signal much up field at ≈6–7 ppm. The ^{13}C NMR data given in [13] are wrongly interpreted. They assigned the value 116.64 ppm to the C-4, which points out that no methyl group is attached to this carbon, because attached methyl group at the fourth position would have shifted this

Scheme 2



value dramatically low field (>150 ppm); and the same words can be said on the value given to C-6 δ = 148.54, which is too much down field value to a simple CH (≈90–100 ppm) and this means that the methyl group is attached to this carbon (C-6).

Finally, this confusion of the structures can be excused based on the similarity of analyses and the tiny differences in the spectral interpretation. However, the claim that the pyridinone obtained from this reaction underwent a Michael addition with ylidenemalononitriles to afford diaminoisoquinolines [13] requires revision.

CONCLUSION

Thus, we could suggest a conceivable mechanism that explains the behavior of active methylene nitriles with enaminones and could correct some literature wrong structures.

EXPERIMENTAL

Melting points were measured on an Electrothermal (9100) apparatus and are uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 1430 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian Gemini 300 MHz spectrometer in DMSO-d_6 using TMS as an internal standard and chemical shifts are expressed in δ ppm values. Mass spectra were taken on a Shimadzu GCMS-GB 1000 PX (70 eV). Elemental analyses were carried out at the Microanalytical Center at Cairo University. X-ray data [15] were collected using KappaCCD on a Bruker Nonius apparatus. The structure was solved by direct methods and expanded using Fourier technique *SIR*92 [16]. The structure was refined using maXus [17]. Nonhydrogen atoms are refined anisotropically and the hydrogen atoms were refined according to the theoretical models.

Reaction of the enaminones 1a–c with malononitrile 2a: Preparation of compounds 8a–c. To a mixture of each of enaminone **1a–c** (10 mmol) and malononitrile (0.66 g; 10 mmol) in ethanol (15 mL) was added few drops of piperidine, which acts as catalyst. The reaction mixture was refluxed for 2 h and then left to cool to room temperature. The solid products thus precipitated were collected by filtration and crystallized from the proper solvent.

2-Cyano-5-dimethylamino-5-phenylpenta-2,4-dienoic acid amide 8a. Canary yellow crystals, yield (1.8 g, 75%); mp 260–262°C (Dioxan) (Lit. 254–256 [12]); υ_{max} = 3435 and 3284 (NH_2), 2193 (CN) and 1665 cm^{-1} (CO); MS: m/z = 241 [M$^+$]; δ_H = 2.92 (s, 6H, 2 CH_3), 5.65 (d, j = 12.75 Hz, 1H, CH), 6.77 (s, 2H, NH_2), 7.13 (d, j = 12.75 Hz, 1H, CH), 7.24–7.55 (m, 5H, Ph). δ_C = 165.08 (s)(amide CO), 164.58 (d)(C-3), 153.26 (s)(C-5), [133.98(s), 129.56(d), 128.76(d), 128.72(d); Phenyl C's], 118.90(s)(CN), 96.91 (s)(C-2), 87.57(d)(C-4), 41.92 (q).

X-ray crystallographic data using *SIR*92 [16] program to solve structure: pale yellow crystals, $C_{14}H_{15}N_3O$ (M_r = 241.294 g mol^{-1}), orthorhombic prismatic, space group Pna-2(1), a = 10.0108(5) Å, b = 18.4003(9) Å, c = 7.1902(3) Å, α[°] = 90.00, β[°] = 90.00, γ[°] = 90.00; V[Å^3] = 1324.45(11). Z = 4, D_x = 1.210 Mg m^{-3}, μ(Mo Kα) = 0.08 nm^{-1}; fine-focus sealed tube. Data were collected using KappaCCD. T[°K] = 298, with graphite monochromator with Mo Kα radiation (λ = 0.71073 Å) min. 91.5%; max 98.2%. Measured reflections 2646, total independent reflections are 1898 were counted with observed reflections 582. R_{int} = 0.024. R(all) = 0.218, R(gt) = 0.101, wR(ref) = 0.197 and wR(all) = 0.224.

Anal. Calcd. for $C_{14}H_{15}N_3O$: (241.12): C, 69.69; H, 6.27; N, 17.41. Found: C, 69.55; H, 6.10; N, 17.30.

2-Cyano-5-dimethylamino-5-furan-2-yl-penta-2,4-dienoic acid amide 8b. Reddish brown crystals, yield (1.75 g, 76%); mp 243–244°C (Dioxan) (Lit 238–240 [12]); υ_{max} = 3330 and 3290 (NH_2), 2187 (CN) and 1665 cm^{-1} (C=O); MS: m/z = 231 [M$^+$]; δ_H = 2.95 (s, 6H, 2 CH_3), 5.6 (d, j = 12.62 Hz, 1H, CH), 6.72 (d, 1H, furan H), 6.78 (d, 1H, furan H), 6.9 (br.s., 2H, NH_2), 7.55 (d, j = 12.62 Hz, 1H, CH), 7.75 (dd, 1H, furan H).

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: (231.25): C, 62.33; H, 5.67; N, 18.17. Found: C, 62.10; H, 5.60; N, 18.20.

2-Cyano-5-dimethylamino-5-thiophen-2-yl-penta-2,4-dienoic acid amide 8c. Yellow crystals, yield (1.9 g, 78%); mp 253–254°C (Dioxan) (Lit. 250–252 [12]; υ_{max} = 3403 and 3328 (NH_2), 2196 (CN) and 1669 cm^{-1} (CO); MS: m/z = 247 [M$^+$]; δ_H = 2.96 (s, 6H, 2 CH_3), 5.65 (d, j = 12.65 Hz, 1H, CH), 6.90 (br.s., 2H, NH_2), 7.15 (d, 1H, thiophene H), 7.25 (dd, 1H, thiophene H), 7.35 (d, 12.65 Hz, 1H, CH), 7.85 (d,1H, thiophene H).

Anal. Calcd. for $C_{12}H_{13}N_3OS$: (247.32): C, 58.28; H, 5.30; N, 16.99; S, 12.97. Found: C, 58.25; H, 5.35; N, 16.85; S, 12.85.

Cyclization of compounds 8a–c: Synthesis of the 2-1*H*-pyridones 9a–c. Each of compounds **8a–c** (10 mmol) was refluxed in glacial acetic acid (15 mL) for 30 min. The solvent was reduced to one-third of its volume under reduced pressure and left to cool overnight. The solid precipitates that appeared were collected by filtration and crystallized from the proper solvent.

2-Oxo-6-phenyl-1,2-dihydropyridine-3-carbonitrile 9a. Pale yellow crystals, yield (1.7 g, 87%); mp 291–292°C (AcOH) (Lit. 158°C [12]); υ_{max} = 3220, 3151 (NH), 2222 (CN) and 1662 cm^{-1} (CO); MS: m/z = 196 [M$^+$]; δ_H = 6.72 (d, j = 8.57 Hz, 1H, Pyr. H-5), 7.50–7.80 (m, 5H, Ph), 8.20 (d, j = 8.57 Hz, 1H, Pyr. H-4), 12.80 (s, 1H, NH).

Anal. Calcd. for $C_{12}H_8N_2O$: (196.20): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.35; H, 4.00; N, 14.20.

6-(Furan-2-yl)-2-oxo-1,2-dihydropyridine-3-carbonitrile 9b. Pale brownish crystals, yield (1.67 g, 90%); mp 298–300°C (AcOH) (Lit. 314°C [12]); υ_{max} = 3215, 3160 (NH), 2225 (CN) and 1659 cm^{-1} (CO); MS: m/z = 186 [M$^+$]; δ_H = 6.71 (d, j = 12.5 Hz, 1H, Pyr. H-5), 6.77 (t, 1H, Fur. H-4), 7.61 (d, 1H, Fur. H-3), 7.85 (d, 1H, Fur. H-5), 8.15 (d, j = 12.5 Hz, 1H, Pyr. H-4), 12.80 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_6N_2O_2$: (186.17): C, 64.52; H, 3.25; N, 15.05. Found: C, 64.50; H, 3.15; N, 15.10.

2-Oxo-6-(thiophen-2-yl)-1,2-dihydropyridine-3-carbonitrile 9c. Pale yellowish crystals, yield (1.87 g, 93%); mp 295–296°C (AcOH) (Lit. 288°C [12]); υ_{max} = 3215, 3145 (NH), 2228 (CN) and 1655 cm^{-1} (CO); MS: m/z = 202 [M$^+$]; δ_H = 6.65 (d, j = 12.55 Hz, 1H, Pyr. H-5), 7.23 (t, 1H, thienyl H),

7.85 (d, 1H, thienyl H), 7.95 (d, 1H, thienyl H), 8.10 (d, j = 12.55 Hz, 1H, Pyr. H-4), 12.80 (s, 1H, NH).

Anal. Calcd. for $C_{10}H_6N_2OS$: (202.23): C, 59.39; H, 2.99; N, 13.85; S, 15.86. Found: C, 59.35; H, 3.15; N, 13.90; S, 15.70.

***N*-(5-Cyano-2-methyl-6-oxo-1,6-dihydropyridin-3-yl)-acetamide 16.** To a mixture of **11** (1.7g, 10 mmol; prepared according to the literature method [13]) and malononitrile **2a** (0.66 g, 10 mmol) in ethanol (20 mL) was added a catalytic amount (five drops) of piperidine. The reaction mixture was refluxed for 6 h and then left to cool to room temperature. The contents of the flask were poured into ice-cold water and acidified with few drops of conc. HCl till just neutral (pH paper). The precipitated solid product was filtered off, washed thoroughly with cold water, dried, and recrystallized from ethanol/DMF (4:1) to give **16** as lustrous brown crystals, yield (1.5 g, 78%); mp. 215–217°C (Lit. 200–220°C [13]); υ_{max} = 3340, 3220 (NH), 2195 (CN) and 1655 cm^{-1} (CO); MS: m/z = 191 [M^+]; δ_H = 1.99 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 7.95 (s, 1H, H-4), 9.3 (br.s., 1H, NH), 12.25 (br.s., 1H, NH). δ_C = 169.5 (s), 159.96 (s), 149.75 (d), 148.5 (s), 116.65 (s), 116.05 (s), 99.56 (s), 23.05 (q), 16.43 (q).

Anal. Calcd. for $C_9H_9N_3O_2$: (191.19): C, 56.54; H, 4.74; N, 21.98. Found: C, 56.35; H, 4.90; N, 21.90.

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REFERENCES AND NOTES

[1] (a) Abdelrazek, F. M.; Salah El-Din, A. M.; Mekky, A. E. Tetrahedron 2001, 57, 1813; (b) Abdelrazek, F. M.; Salah El-Din, A. M.; Mekky, A. E. Tetrahedron 2001, 57, 6787.

[2] Abdelrazek, F. M. Synth Commun 2005, 35, 2251.

[3] Abdelrazek, F. M.; Metwally, N. H. Synth Commun 2006, 36, 83.

[4] Abdelrazek, F. M.; Metz, P.; Metwally, N. H.; El-Mahrouky, S. F. Arch Pharm Chem Life Sci (Weinheim) 2006, 339, 456.

[5] Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Arch Pharm Chem Life Sci (Weinheim) 2007, 340, 543.

[6] Meyer, H.; Sitt, R.; Thomas, G.; Kaurse, H. Ger. Offen. 3015 219 (1980), Chem Abstr 1982, 96, 6604d.

[7] Deshang, P.; Cipolina, J. A.; Lowmoster, N. K. J Org Chem 1988, 53, 1356.

[8] Worbel, J.; Li, Z.; Dietrich, A.; McCaleb, M.; Mihan, B.; Serdy, J.; Sullivan, D. J Med Chem 1998, 41, 1084.

[9] Torres, M.; Gil, S.; Parra, M. Curr Org Chem 2005, 9, 1757 (Review).

[10] Abdelrazek, F. M.; Michael, F. A. J Heterocycl Chem 2006, 43, 7.

[11] Yermolayev, S. A.; Gorobets, N. Yu.; Lukinova, E. V.; Shishkin, O. V.; Shishkina, S. V.; Desenko, S. M. Tetrahedron 2008, 64, 4649.

[12] Al-Omran, F.; Al-Awadhi, N.; Abdelkhalik, M. M.; Kaul, K.; Abu El-Khair, A.; Elnagdi, M. H. J Chem Res (S) 1997, 84/85, (M) 601.

[13] Al-Omran, F.; Abu El-Khair, A.; Elnagdi, M. H. J Chem Res (S) 1998, 798.

[14] Abdelkhalik, M. M.; Eltoukhy, A. M.; Agamy, S. M.; Elnagdi, M. H. J Heterocycl Chem 2004, 41, 431.

[15] Crystallographic data (excluding structure factors) for the structure **8a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-722543. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44 1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].

[16] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burl, M. C.; Polidori, G.; Camalli, M. J Appl Crystallogr 1994, 27, 435.

[17] Mackay, S.; Gilmore, C. J.; Edwards, C.; Stewart, N.; Shankland, K. maXus Computer Program for the Solution and Refinement of Crystal Structures; MacScience, Japan/The University of Glasgow: Bruker Nonius, The Netherlands, 1999.