Gas-Phase Pyrolysis in Organic Synthesis: A Route for Synthesis of Cyanamides

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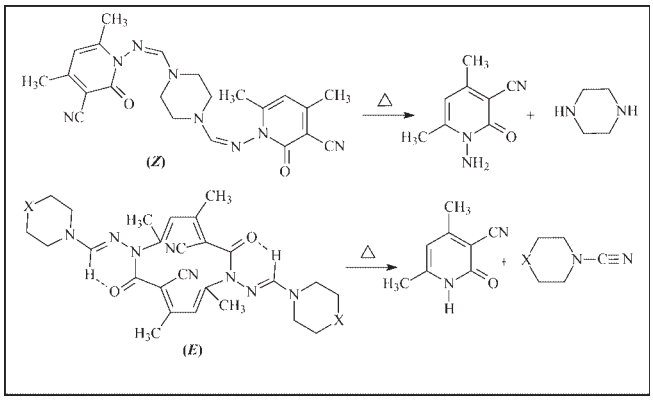

Pyrolysis of 1,7-di-[(*E*)-1-morpholinomethylidene]- and 1,7-di-[(*E*)-1-piperidino-methylidene]-4,6,10,12-tetramethylamino-2,8-dioxo-1,7-diaza-3,5,9,11-cyclododecatetraene-3,9-dicarbonitrile **6a,b** afforded pyridone **10** in addition to cyanamides **11a,b**. On the other hand, pyrolysis of 1-[*E*-(4-(*E*-3-cyano-4,6-dimethyl-2-oxopyridin-1(*2H*)-ylimino) methylpiperazin-1-yl] methylenamino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **8** gave 1-amino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **13** as well as piperazine. The mechanism of pyrolysis and the effect of stereochemistry of pyrolyzed substrates on the nature of the pyrolysates are discussed.

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INTRODUCTION

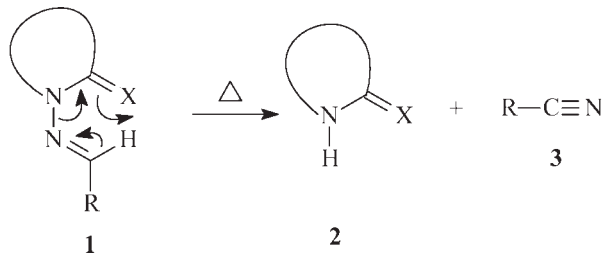
N-Aminoheteroaromatics are readily obtainable precursors [1–5]. The amino function could then be condensed with aromatic aldehydes into **1**. The gas-phase pyrolysis of this derivative produces pyridones **2** and nitriles **3** [6,7]. This approach offers an ideal and environmentally friendly methodology for synthesis of nitriles and related compounds, as no reagents, solvents, or catalysts are used in these thermal gas-phase reactions [8]. It seemed to us quite feasible that simple alternation in the structure of starting substrates could also be adopted as a strategy to synthesize cyanamides as well as organic cyanates (Scheme 1).

RESULTS AND DISCUSSION

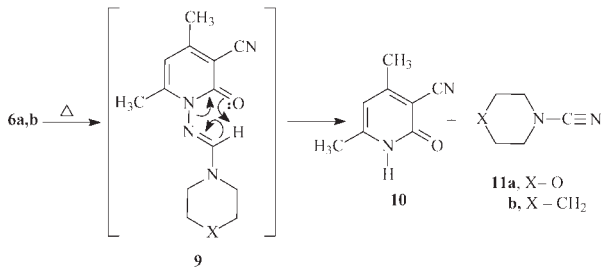
In the present article, we report synthesis of different substituted 1,7-diaza-3,5,9,11-cyclododecatetraene derivatives **4** as well as the results of their pyrolysis in the gas phase. In a recent investigation, we established that the reaction of acetylacetone with 2-cyanoacetohydrazide in the presence of diethylamine gave a dimeric product **4** of $m/z = 327$ ($M^{+\cdot} + 1$) [7]. Here, the reaction of the dimeric product **4** with triethylorthoformate afforded the diiminoformate **5,** which is then converted into **6a,b** and **8** through reaction with secondary amines, namely, morpholine, piperidine, and piperazine. Compound **5** could as well be generated *in situ* in a one-pot synthesis by mixing the three products under reflux in *N*,*N*-dimethylformamide. The reaction is facile, clean, and efficient, and is free from by-products. The structural assignments of compounds **5–8** were inferred from their mass spectra and other analytical data. Formation of **8** is believed to occur via initial conversion of diiminoformate **5** to the intermediate iminoformate **7** and subsequent condensation of two molecules of **7** with one molecule of piperazine (Scheme 2).

Pyrolysing **6a,b** in the gas phase gave the expected 1,2-dihydropyridine-3-carbonitrile derivative **10** and cyanamide **11a,b** via the methyleneamino-1,2-dihydropyridine-3-carbonitrile derivative **9** (Scheme 3). Formation of these products was confirmed by LCMS and by TLC, as well as ^{1}H NMR of products of pyrolysis against

Scheme 1



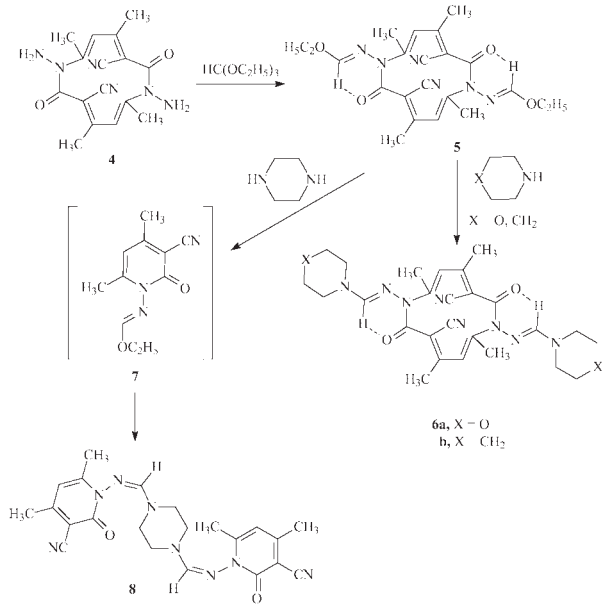
Scheme 3



authentic specimens of pyridone **10**. On the other hand, pyrolysis of **8** afforded **13** without formation of **12** (Scheme 4).

The difference in the pyrolytic behavior of **6a,b** and **8** is most likely a result of their stereochemistry. Thus, the pyrolyzed compounds **6a,b** exist in the (*E*) form, while **8** exists in the (*Z*) form. If one assumes that the pyrolysis of **8** (***E***) occurred via the H-bonded intermediate (Scheme 3), one would obtain pyridine **10** and dicyanamide **12** as pyrolytic products. As the *N*-aminopyridone **13** was the pyrolytic product obtained from **8** and no trace of the dicyanamide **12** was detected, it can thus be expected that **8** exists in the non-H-bonded (*Z*) form. In fact here, hydrolysis of **8** under the pyrolytic reaction conditions took place. To our knowledge such a hydrolysis has not been reported earlier. In conclusion, we could determine structures of pyrolysis products of **6a,b** and **8**. In addition, a new and safe route for synthesis of cyanamide **11a,b** is reported. Although **11a,b** could be obtained by treating cyanogen bromide with Mannich bases [9] and with morpholine compounds [10,11], this route required the use of hazardous and explosive cyanogen bromide reagents.

Scheme 2



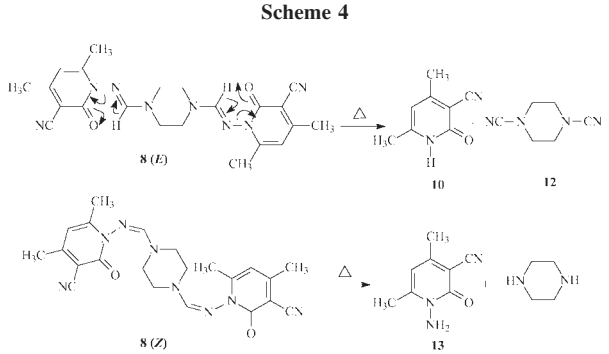
EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analysis was by means of a LECO CHNS-932 Elemental Analyzer. NMR spectra were measured using a Bruker DPX 400 MHz superconducting spectrometer, and FT-IR measurements were from a Perkin Elmer 2000 FT-IR system. Mass spectrometric analysis was carried out on a VG-Autospec-Q high performance tri-sector GC/MS/MS, and the instrument for HPLC was an Agilent 1100 series LC/MSD with an API-ES/APCI ionization mode.

1,7-Diamino-4,6,10,12-tetramethyl-2,8-dioxo-1,7-diazacyclododeca-3,5,9,11-tetraene-3,9-dicarbonitrile 4. This compound was prepared following published procedure. It was obtained as white crystals from ethanol (yield 94%); m.p. 171–172°C, Lit. mp. 174°C [7]; IR (KBr): λ max/cm^{-1}: 3420, 3332 (NH_2), and 2216 (CN); MS: m/z = 327 ($M^{+\cdot}$+1). ^{1}H NMR (DMSO): δ = 2.31 (s, 6H, $2CH_3$), 2.42 (s, 6H, $2CH_3$), 6.15 (br s, 4H, $2NH_2$ D_2O exchangeable), 6.33 (s, 2H). Anal. Calcd. for $C_{16}H_{18}N_6O_2$ (326.36): C 58.89, H 5.56, N 25.75. Found C 59.00, H 5.49, N 25.89.

4,6,10,12-Tetramethyl-1,7-(diethoxy-dimethylene-amino)-2,8-dioxo-1,7-diaza-3,5,9,11-cyclododeca-tetraene-3,9-dicarbonitrile 5. To a stirred mixture of compound **4** (0.01 mol, 3.26g) in 10 mL of *N*,*N*-dimethylformamide was added triethyl orthoformate (0.01 mol, 1.48 g). The resulted mixture was refluxed for 15 min. The solvent was removed and resulting solid was recrystallized from ethanol. Yield 86% (3.77g); m.p. 150°C; IR (KBr): λ max/cm^{-1}: 2218 (CN), 1658 (C=O); MS: m/z = 439 ($M^{+\cdot}$+ 1); ^{1}H NMR (DMSO): δ = 1.35 (t, 6H, J = 7.04 Hz $2CH_3$), 2.28 (s, 6H, $2CH_3$), 2.33 (s, 6H, $2CH_3$), 4.35

Scheme 4



(q, 4H, J = 7.04 Hz $2CH_2$), 6.37 (s, 2H, cycloalkene-H), 8.36 (s, 2H, amidine-H). Anal. Calcd. for $C_{22}H_{26}N_6O_4$ (438.49): C 60.26, H 5.98, N 19.17. Found C 60.06, H 5.94, N 19.25.

General procedure for the preparation of compounds 6a,b and 8. To a stirred mixture of compound **5** (0.01 mol, 4.38 g) in 20 mL of DMF was added the appropriate amine (0.01 mol). The mixture thus obtained was heated under reflux for 20 hours. The solvent was removed and the resulting solid was recrystallized from DMF.

4,6,10,12-Tetramethyl-1,7-di-[(*E*)-1-morpholino-methylidene] amino-2,8-dioxo-1,7-diaza-3,5,9,11-cyclododecatetraene-3,9-dicarbonitrile 6a. Yield 85% (4.42 g); m.p. 190°C, brown crystals from DMF; IR (KBr): ν/cm^{-1}: 2216 (CN), 1647 (C=O); MS: m/z = 521 ($M^{+\cdot}$ + 1); ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.26 (s, 6H, $2CH_3$), 2.30 (s, 6H, $2CH_3$), 3.50–3.54 (m, 8H, morpholino-H), 3.62–3.65 (m, 8H, morpholino-H), 6.30 (s, 2H, cycloalkene-H), 7.93 (s, 2H, amidine-H). Anal. Calcd. for $C_{26}H_{32}N_8O_4$ (520.59): C 59.99, H 6.20, N 21.52. Found C 60.06, H 6.26, N 21.58.

4,6,10,12-Tetramethyl-2,8-dioxo-1,7-di-[(*E*)-1-piperidinomethylidene]amino-1,7-diaza-3,5,9,11-cyclododecatetraene-3,9-dicarbonitrile 6b. Yield 92% (4.75 g); m.p. 115°C, brownish crystals from ethanol; IR (KBr): ν/cm^{-1}: 2213 (CN), 1652 (C=O); MS: m/z = 517 ($M^{+\cdot}$+1); ^{1}H NMR (DMSO-d_6): δ (ppm) = 1.50–1.57 (m, 8H, piperidinyl-H), 1.63–1.66 (m, 4H, piperidinyl-H), 2.25 (s, 6H, $2CH_3$), 2.29 (s, 6H, $2CH_3$), 3.29–3.31(m, 4H, piperidinyl-H), 3.48–3.52 (m, 4H, piperidinyl-H), 6.26 (s, 2H, cycloalkene-H), 7.81 (s, 2H, amidine-H). Anal. Calcd. for $C_{28}H_{36}N_8O_2$ (516.65): C 65.09, H 7.02, N 21.69. Found C 64.67, H 6.71, N 21.57.

1,1'-{Piperazine-1,4-diylbis[(*Z*)-methylylidenenitrilo]} bis (4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 8. Yield 62% (2.67 g); m.p. >300 °C, buff crystals from DMF; IR (KBr): ν/cm^{-1}: 2217 (CN), 1642 (C=O); MS: m/z = 433 ($M^{+\cdot}$+1); ^{1}H NMR (DMSO-d_6): δ (ppm) = 2.29 (s, 6H, $2CH_3$), 2.31 (s, 6H, CH_3), 3.44–3.48 (m, 4H, piperidinyl-H), 3.57–3.64 (m, 4H, piperidinyl-H), 6.30 (s, 2H, pyridyl H-5), 8.00 (s, 2H, amidine-H). Anal. Calcd. for $C_{22}H_{24}N_8O_2$ (432.48): C 61.10, H 5.59, N 25.91. Found C 60.69, H 5.72, N 25.68.

General Procedure for Pyrolysis of 6a,b and 8. Each of compounds **6a–c** and **8** was introduced in the reaction tube (1.5 × 12 cm^2 Pyrex), cooled in liquid nitrogen, sealed under vacuum (0.06 mbar) and placed in the pyrolyser for 900 s at a temperature of complete pyrolysis. The pyrolysate was then separated into its constituents by preparative TLC (MERCK, 12 PSC-Platten 20 × 20 cm^2, Silica gel 60 F_{254} 2 mm) using chloroform: petroleum ether (bp 40:60) in 80:20 ratio as eluent, and each constituent was collected, analyzed and characterized. The techniques used include ^{1}H NMR and GC/MS.

Morpholine-4-carbonitrile 11a. MS: m/z = 112 ($M^{+\cdot}$) for $C_5H_8N_2O$ (112.13). IR = 2220 cm^{-1} (CN). ^{1}H NMR ($CDCl_3$): δ (ppm) = 3.05–3.08 (m, 2H, morpholinyl-H), 3.21–3.23 (m, 2H, morpholinyl-H), 3.43–3.49 (m, 2H, morpholinyl-H), 3.59–3.68 (m, 2H, morpholinyl-H). [Lit ^{1}H NMR 90 MHz ($CDCl_3$) [12]: δ (ppm) = 3.2–3.3 (m, 4H), 3.6–3.7 (m, 4H)].

Piperidine-1-carbonitrile 11b. MS: m/z = 110 ($M^{+\cdot}$) for $C_6H_{10}N_2$ (110.16). ^{1}H NMR ($CDCl_3$): δ (ppm) = 1.41–1.52 (m, 6H, piperidinyl-H), 3.56–3.78 (m, 4H, piperidinyl-H). Lit ^{1}H NMR 90 MHz ($CDCl_3$) [13]: δ (ppm) = 1.45–1.68 (m, 6H), 3.2–3.5 (m, 4H)].

4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 10. MS: m/z = 163 ($M^{+\cdot}$) for $C_8H_8N_2O$ (148.16). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.33 (s, 3H, CH_3), 2.40 (s, 2H, CH_3), 3.60 (br s, 1H, NH D_2O exchangeable), 6.21 (s, 1H, pyridyl H-5). [Lit ^{1}H NMR 200 MHz (DMSO/$CDCl_3$ 2:1 [14]): δ (ppm) = 2.23 (s, 3H), 2.32 (s, 3H), 3.40 (br s, 1H), 6.07 (s, 1H)].

1-Amino-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile 13. MS: m/z = 163 ($M^{+\cdot}$) for $C_8H_9N_3O$ (163.18). ^{1}H NMR ($CDCl_3$): δ (ppm) = 2.33 (s, 3H, CH_3), 2.38 (s, 2H, CH_3), 6.15 (br s, 4H, $2NH_2$ D_2O exchangeable), 6.31 (s, 1H, pyridyl H-5).

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