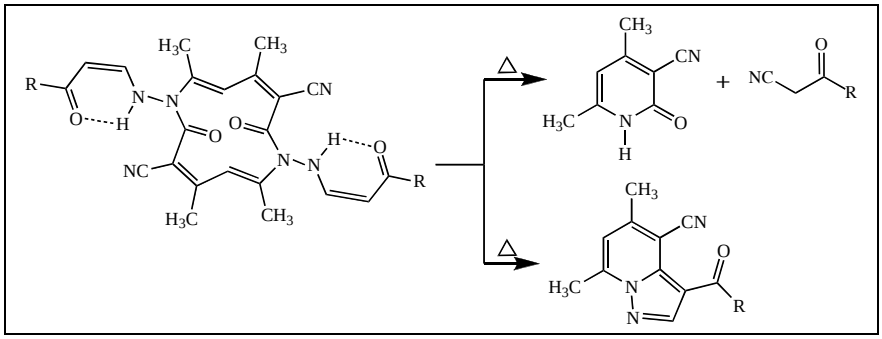
Pyrolytic Behavior of Substituted *N*-Aminoheteroaromatics: Synthesis of Pyrazolo[1,5-*a*]pyridine and 3-Substituted 3-Oxo-propionitrile Derivatives

Nouria A. Al-Awadi,[a] Mervat Abdelkhalik,[b] Mehul Patel[a] and Hicham H. Dib[a]

[a]Chemistry Department, Kuwait University, P.O. Box 5969 Safat, 13060 Kuwait
[b]Applied Science Department, College of Technological Studies, Public Authority for Applied Education and Training, Kuwait

Received April 2, 2006



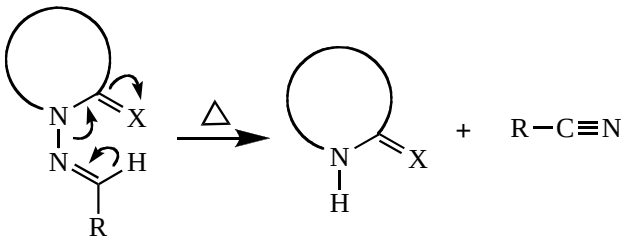
Flash vacuum pyrolysis (FVP) of 1,7-bis-(3-aroylideneamino)-4,6,10,12-tetramethyl-2,8-dioxo-1,7-diazacyclododeca-3,5,9,11-tetraene-3,9-dicarbonitriles **11a-c** at 650 °C and 0.02 Torr yielded 5,7-dimethyl-3-(4-methylbenzoyl)-pyrazolo[1,5-*a*]pyridine-4-carbonitrile **14**, 4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile **16** and 3-aryl-3-oxo-propionitriles **17a,b**. A plausible mechanism is suggested to account for the formation of the products.

J. Heterocyclic Chem., **44**, 989 (2007).

INTRODUCTION

Selective deprotection of the *N*-arylideneamino moiety from hetrocyclic amides of general formula **1** were shown to be an efficient, clean and general synthetic procedure for regioselective synthesis of potential biologically active pyridine, pyrimidines, triazoles and triazines and their derivatives [1-4].

Scheme 1

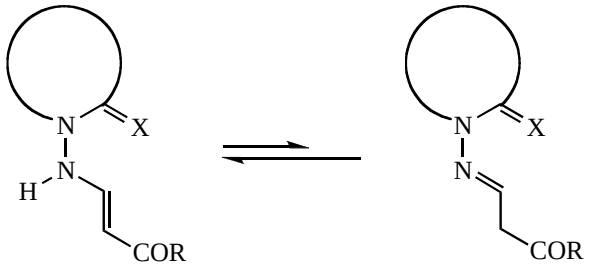


1 X = O, S

In the present study we have extended the investigation to include the thermal behavior of system **2**, which in theory may exist as enamines **2** or imines **3**.

We have attempted to prepare system **2** from the reaction of *N*-aminopyridone **4** and enaminones **5a-c**. According to literature procedure [5] *N*-aminopyridone **4** is reported to be readily obtained from refluxing cyano-acetyl hydrazide **6** with acetylacetone **7** in ethanolic diethylamine solution. Spectroscopic characterization of

Scheme 2



2 **3**

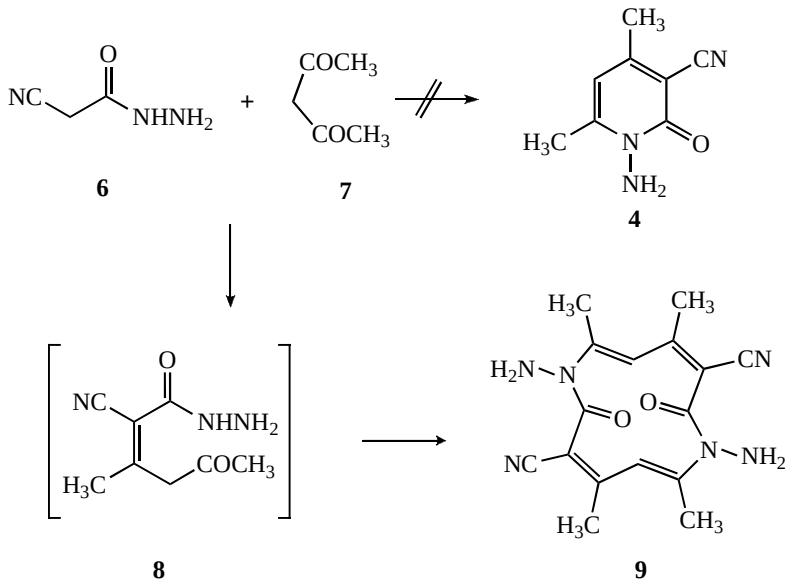
the product by IR and ^{1}H nmr agree well with its reported structure. However the mass spectra of the product by LCMS and GCMS revealed a molecular ion peak at 327 (M^{+1}) corresponding to a diameric product **9**. Formation of the latter could be attributed to the initial formation of condensation product **8**, that would further self condensed to produce **9** (cf. Scheme 3).

Several attempt to prepare **4** were not successful, so we have decided to proceed with **9** by reacting it with enaminones **5a-c**, prepared *via* condensing aryl methyl ketones with dimethylformamide dimethyl acetal under microwave irradiation reported recently [6]. This yielded a dienaminone, which may be represented as imine **10**, *Z* enaminone **11** or *E* enaminone 12 (Scheme 4). ^{1}H nmr data revealed that the product is *Z* enaminone **11a-c**. Two types of products were characterized from the flash

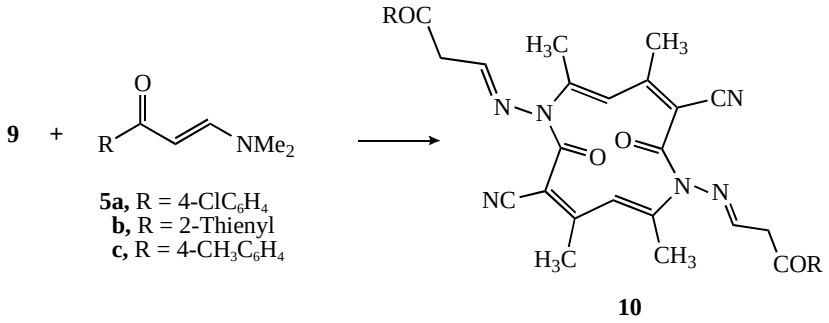
vacuum pyrolysis of **11a-c** depending on the nature of aryl substituents in which an intramolecular reaction takes place leading to intermediates **13** and **15**. Thus **11c** was completely converted into **14** by pyrolytic cyclization, which may arise from the generated enaminone **13** from initial 6π electrocyclization [7] followed by water elimination.

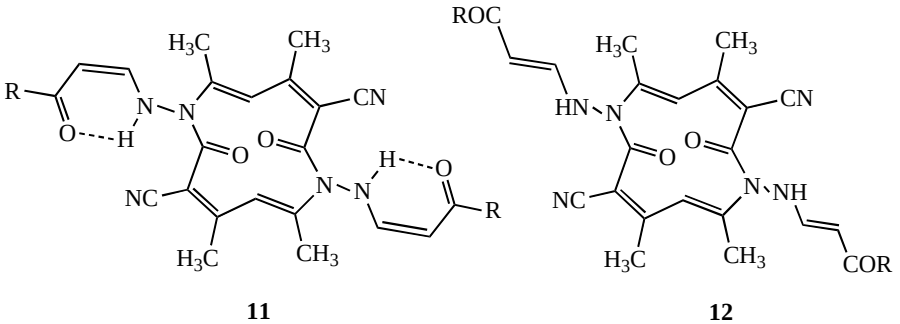
On the other hand, pyrolysis of **11a-b** resulted in the formation of pyridone **16** and oxoalkanonitriles **17a-b**. This could be attributed to the electron withdrawing effect of the *p*-Cl and 2-thienyl substituent which will help facilitate N-N bond breaking *via* enamine formation; although derivatives of **17** can be obtained by reacting haloketones with cyanide ion [8] or reacting ester with

Scheme 3



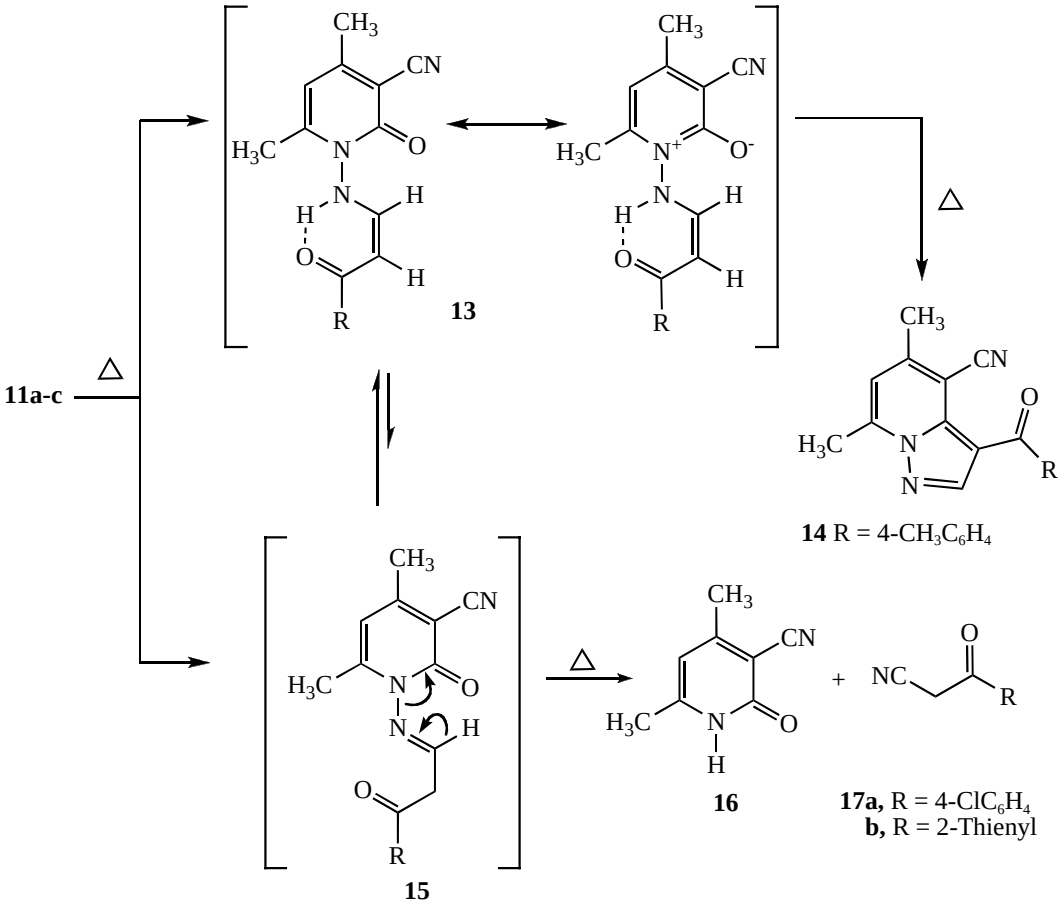
Scheme 4





acetonitrile [9]. These approaches either employ hazardous chemicals (haloketones and cyanide ion) or not readily obtainable substituted acid esters. Formation of **16** and **17** indicates clearly that the reactive species in this case is the intermediate imine form **15** (*cf*. Scheme 5).

Scheme 5



EXPERIMENTAL

Melting points were determined on a Shimadzu-Gallenkamp apparatus and are uncorrected. Elemental analysis was obtained 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 (9). Compound **9** was prepared following published procedure [Lit. mp. 174°C]. This compound was obtained as white crystals from ethanol in yield (94 %, 3.0 g); mp 171-172 °C; ir: 3420, 3332 (NH_2) and 2216 (CN); MS: *m/z* = 327 (M^{+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.

General procedure for the preparation of 11a-c. Compound **9** (3.26 g, 10 mmol) was treated with each of enaminones **5a-c** (10 mmol) in ethanol/hydrochloric acid mixture 8:2 (10 ml). The reaction mixture was heated under reflux for 20 min. and left to cool at room temperature to deposit a solid that was collected by filtration and crystallized from ethanol.

1,7-Bis-[3-(4-chlorophenyl)-3-oxo-propylideneamino]-4,6,10,12-tetramethyl-2,8-dioxo-1,7-diazacyclododeca-3,5,9,11-tetraene-3,9-dicarbonitrile (11a). This compound was obtained as yellow crystals from DMF in yield (84 %, 5.5 g); mp 226-227 °C; ir: 3069 (NH) and 2216 (CN), 1668 (CO); MS: *m/z* = 666 (M^{+1}), ^{1}H NMR (DMSO): δ = 2.09 (s, 6H, $2CH_3$), 2.31 (s, 6H, $2CH_3$), 5.83 (d, 2H, 2-H, J = 7.8Hz), 6.45 (s, 2H, 5-H and 11-H), 7.52 (d, 4H, *J* = 8.4 Hz, arom. H), 7.84 (d, 4H, arom. H, J = 8.4 Hz), 7.98 (d, 2H, 3-H J = 7.8Hz), 10.61 (br s, 2H, 2NH). *Anal.*

Calcd. for $C_{34}H_{28}Cl_2N_6O_4$ (655.54): C 62.30, H 4.31, N 12.82. Found C 61.93, H 4.66, N 13.06.

4,6,10,12-Tetramethyl-2,8-dioxo-1,7-bis-(3-oxo-3-thiophen-2-yl-propylideneamino)-1,7-diazacyclododeca-3,5,9,11-tetraene-3,9-dicarbonitrile (11b). This compound was obtained as yellow crystals from DMF in yield (87 %, 5.2 g); mp 188-189 °C; ir: 3258 (NH) and 2216 (CN), 1669 (CO); MS: *m/z* = 599 (M^+). ^{1}H NMR (DMSO): δ = 2.32 (s, 6H, $2CH_3$), 2.40 (s, 6H, $2CH_3$), 5.79 (d, 2H, 2-H, J = 8 Hz), 6.46 (s, 2H, 5-H and 11-H), 7.15 (t, 2H, thienyl 3-H, J = 5.0 Hz), 7.74-7.91 (m, 6H, vinyl 3-H, thienyl 2-H and 4-H), 10.08 (br s, 2H, 2NH). *Anal.* Calcd. for $C_{30}H_{26}N_6O_4S$ (598.69): C 60.18, H 4.38, N 14.04, S 10.71. Found C 59.92, H 4.28, N 14.20, S 10.59.

4,6,10,12-Tetramethyl-2,8-dioxo-1,7-bis-(3-oxo3-p-tolylroylideneamino]-1,7-diazacyclododeca-3,5,9,11-tetraene-3,9-dicarbonitrile (11c). This compound was obtained as yellow crystals from DMF in yield (88 %, 5.4 g); mp 211-212 °C; ir: 3069 (NH) and 2216 (CN), 1671 (CO); MS: *m/z* = 615 (M^{+1}), ^{1}H NMR (DMSO): δ = 2.31 (s, 6H, $2CH_3$), 2.37 (s, 6H, $2CH_3$), 2.51 (s, 6H, $2CH_3$), 5.80 (d, 2H, 2-H, J = 8.0 Hz), 6.46 (s, 2H, 5-H and 11-H), 7.25 (d, 4H, arom. H, J = 8.4 Hz), 7.72 (d, 4H, arom. H, J = 8.4 Hz), 7.87 (d, 2H, 3-H, J = 8.0 Hz), 10.05 (br s, 2H, 2NH). *Anal.* Calcd. for $C_{36}H_{34}N_6O_4$ (614.70): C 70.34, H 5.58, N 13.67. Found C 69.80, H 5.36, N 13.89.

General procedure for Flash Vacuum Pyrolysis (FVP) of 11a-c. The apparatus used is similar to that described in our recent publications [10-11]. The sample was volatilized from a tube in a Büchi Kugelrohr oven through a 30 x 2.5 cm horizontal fused quartz tube. This was heated externally by a Carbolite Eurotherm tube furnace MTF-12/38A to a temperature of 650 °C, the temperature being monitored by a Pt/Pt-13%Rh thermocouple situated at the center of the furnace. The products were collected in a U-shaped trap cooled in liquid nitrogen. The whole system was maintained at a pressure of 10^{-2} Torr by an Edwards Model E2M5 high capacity rotary oil pump, the pressure being measured by a Pirani gauge situated between the cold trap and the pump. Under these conditions the contact time in the hot zone was estimated to be ≅ 10 ms. The different zones of the products collected in the U-shaped trap were analyzed by ^{1}H nmr, LCMS and GC-MS. Relative and percent yields were determined from ^{1}H NMR. Identities of compounds obtained were confirmed by comparison of their ^{1}H-NMR spectra with data of products separated from preparative HPLC.

MS and NMR Characterization for Compounds 14, 16 and 17a,b.

5,7-Dimethyl-3-(4-methylbenzoyl)-pyrazolo[1,5-*a*]pyridine-4-carbonitrile (14). MS: *m/z* = 289 (M^+), $C_{18}H_{15}N_3O$ (289.34). ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3H, CH_3), 2.46 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.09 (s, 1H, 6-H), 7.82 (d, 2H, arom. H, J = 8.4 Hz), 8.02 (d, 2H, arom. H, J = 8.4 Hz), 9.05 (s, 1H, 2-H).

4,6-Dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (16). MS: *m/z* = 149 (M^{+1}), $C_8H_8N_2O$ (148.16). ^{1}H NMR ($CDCl_3$): δ = 2.42 (s, 3H, CH_3), 2.51 (s, 3H, CH_3), 6.47 (s, 1H), 12.05 (br s, 1H, NH D_2O exchangeable).

3-(4-Chlorophenyl)-3-oxo-propionitrile (17a). MS: *m/z* = 180 (M^{+1}), C_9H_6ClNO (179.61). ^{1}H NMR ($CDCl_3$): δ = 4.02 (s, 2H, CH_2), 7.54 (d, 2H, arom. H, *J* = 8.0 Hz), 7.88 (d, 2H, arom. H, J = 8.0 Hz).

3-Oxo-3-thiophen-2-yl-propionitrile (17b). MS: *m/z* = 152 (M^{+1}), C_7H_5NOS (151.18). ^{1}H NMR ($CDCl_3$): δ = 4.02 (s, 2H, CH_2), 7.15 (t, 1H, thienyl 3-H, J = 5.0 Hz), 7.74-7.82 (m, 2H, thienyl 2-H and 4-H).

Acknowledgement. This work was supported by Kuwait University through research grant # SC02/03 and ANALAB and SAF grants # GS01/01 and GS03/01. The authors appreciate very much Professor M. H. Elnagdi interest in reading and revising the work.

REFERENCES

[1] Al-Awadi, N. A.; Elnagdi, M. H.; Mathew, T.; El-Gamry, I.; Abdel-Khalik, M. M. *Int. J. Chem. Kinet.* **1996**, *28*, 741-748.

[2] Al-Awadi, N. A.; Ibrahim, Y.; Kaul, K.; Dib, H. *J. Phys. Org. Chem.* **2001**, *14*, 521-524.

[3] Al-Etaibi, A.; Abdullah, M. R.; Al-Awadi, N.; Ibrahim, Y.; Hasan, M. *J. Phys. Org. Chem.* **2004**, *17*, 49-55.

[4] George, B. J.; Dib, H. H.; Abdallah, M. R.; Ibrahim, M. R.; Khalil, N. S.; Ibrahim, Y. A.; Al-Awadi, N. A. *Tetrahedron* **2006**, *62*, 1182-1192.

[5] Ried, M. *Chem. Ber.* **1957**, *90*, 2841-2846.

[6] Al-Saleh, B.; El-Apasery, M. A.; Abdel-Aziz, R. S.; Elnagdi, M. H. *J. Heterocyclic Chem.* **2005**, *42*, 563.

[7] Miller, B. *Advanced Organic Chemistry* 2 nd edition, Prentice hall, upper Saddle River, NJ, 2004, pp 88.

[8] Elnagdi, M. H.; Elmoghayer, M. R. H., Elgemeie, G. E. H. *Synthesis* **1984**, 1-25.

[9] Al-Awadhi, H.; Al-Omran, F.; Elnagdi, M. H.; Infantes, L.; Foces-Foces, C.; Jagerovic, N.; Elguero; J. *Tetrahedron* **1995**, *51*, 12745-12762.

[10] Al-Awadi, N.; Kaul, K.; El-Dusouqui, O. M. E. *J. Phys. Org. Chem.* **2000**, *13*, 499-504.

[11] Ibrahim, Y. A.; Al-Awadi, N. A.; Ibrahim, M. R. *Tetrahedron* **2004**, *60*, 9121-9130.