Studies with functionally substituted enamines: synthesis of new aminoazolo-pyrimidines and -1,2,4-triazines

Said Ahmed Soliman Ghozlan[a], Ismail Abdelshafy Abdelhamid[a], Hatem Gaber[b] and Mohamed Hilmy Elnagdi[a]*

[a]*Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R., Egypt*

[b]*National Organization for Drugs Control and Research (NODCAR), PO Box 29, Cairo, A.R. Egypt*

3-Aminoacrylonitrile derivatives (**1d–g**) coupled with aromatic and heteroaromatic diazonium salts yielding arylhydrazonals and pyrazolo[5,1-*c*]triazines. The enaminonitriles **1d–g** condensed to form dienes **6a–c** on reflux in acetic acid. The latter underwent Diels-Alder type addition to naphthoquinone. Aminopyrazolopyrimidines were obtained from reaction of **1d–g** with heteroaromatic aminoazoles. Enaminonitrile **1d** formed pyran **21** with benzylidenemalononitrile, and dihydropyrimidine **22** with benzaldehyde and urea.

Keywords: enaminonitriles, arylhydrazonals, fused pyrazoles, pyrimidines, 1,2,4-triazines

Introduction

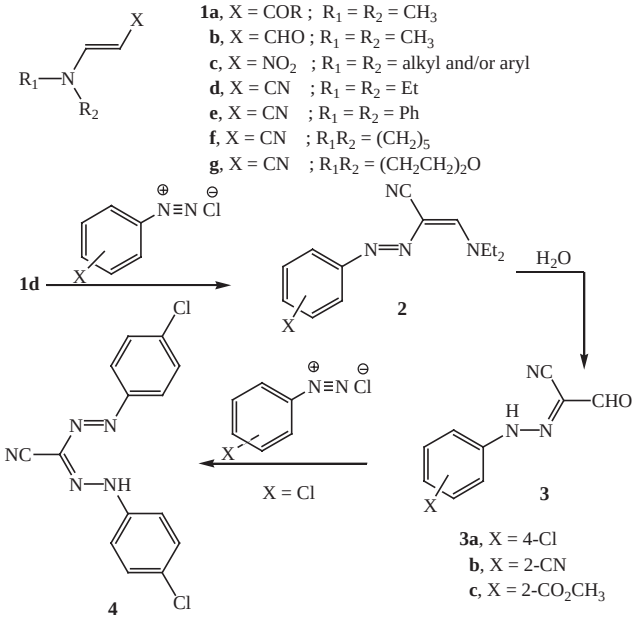
Functionally substituted enamines (**1a–c**) are versatile reagents and their chemistry has recently received considerable interest.[1-6] In previous work from our laboratories the reactivity of enaminones of type **1a** toward both electrophilic[7-10] and nucleophilic[11-15] reagents has been explored. In conjunction of this work we report here the results of our investigations aimed at exploring synthetic potentials of **1d–g**. Although the chemistry of enaminonitriles has been extensively investigated in the past,[16-19] to our knowledge only few data are available on the reactivity of **1d–g** toward electrophilic and nucleophilic reagents.[19-21]

Results and discussion

Compound **1d** was prepared by heating diethylamine, triethylorthoformate and cyanoacetic acid under reflux for two hours, following a reported procedure.[20] The coupling reaction of **1d** with *p*-chlorobenzenediazonium chloride in ethanolic sodium acetate has recently been found to yield a mixture of the hydrazonal **3a** and the formazan **4**.[21] In the present investigation only hydrazonal **3a** was obtained on coupling **1d** with *p*-chlorobenzene diazonium chloride in acetic acid and sodium acetate solution. However, the yield of coupling product was low. We detected the formation of diethylamino-(4-chlorophenyl)diazene on coupling *p*-chlorobenzene diazonium chloride with **1d** (Scheme 1).

To circumvent this, we prepared the piperidino and morpholino derivatives (**1f,g**) where the lone pair on nitrogen would be sterically hindered. Better yields of the hydrazonals were obtained in these cases. The formazan **4a** was formed when the coupling was performed with excess of diazonium salt. It is believed that **2a** is an intermediate. In support of this view we could isolate the eneazo compound **2b** on coupling **1d** with diazotised anthranilonitrile. This hydrolysed to **3b** on long reflux in aqueous dimethylformamide. An attempt to isolate other derivatives of **2** as a novel class of eneazo compound failed. Coupling of **3d** with methyl anthranilate was also conducted but in this case only **3c** was isolated.

We attempted to prepare **1e** by reacting cyanoacetic acid and triethyl orthoformate with aniline, but only the bis-cyanovinyl product **5a** was produced. ^{1}H NMR of **5a** indicated that it exists in the *trans* form as it showed two olefinic protons at δ 5.18 and δ 6.75 with a coupling constant J = 16 Hz. Similarly **5b** was obtained, contaminated with some 20% of 3-*p*-tolulidino-acrylonitrile which, according to ^{1}H NMR, exists also in *trans* form, by condensation of triethyl orthoformate, cyanoacetic acid and *p*-toluidine. When this product was warmed with ethanolic hydrochloric acid followed by work-up of the solution pure **5b** could be obtained. The IR spectra of both **5a** and **5b** indicated the presence of a band at around 3240cm^{-1} which is most likely an overtone and combination band (Scheme 2).



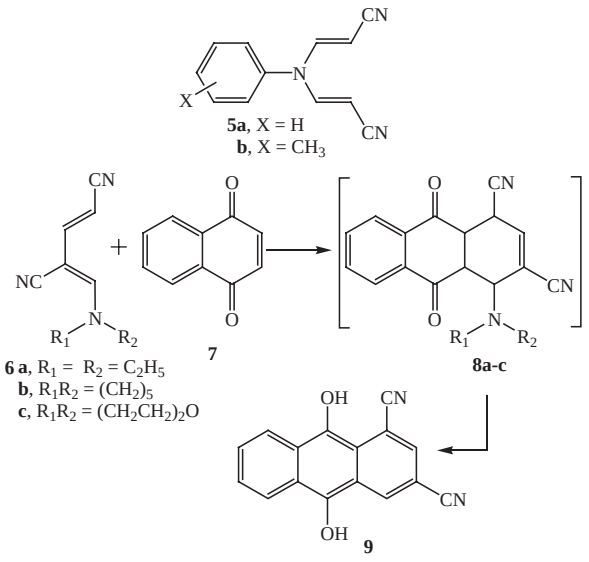
Scheme 1

Refluxing **1d, f, g** in acetic acid afforded the dienes **6a–c** by a self-condensation – elimination route. The electron-rich C-2 in one molecule adds to the electron deficient C-3 in another molecule of **1**, followed by amine elimination. A similar mechanism has been previously suggested by us to account for self condensation of enaminones on reflux in acetic acid.[22, 23]

The dienes **6a,c** reacted with naphthoquinone **7** to yield **9**. It is believed that initially **8a, b** are formed then a secondary amine is eliminated to yield final isolable **9** (Scheme 2).

The condensation of the aminopyrazoles **10a–c** with triethyl orthoformate and cyanoacetic acid afforded oily products that on reflux in acetic acid gave the pyrazolo[1,5-*a*]pyrimidine derivatives **11a–c** (Scheme 3). These same products were obtained upon reacting **1d–g** with **10a–c** in refluxing pyridine. Although these reactants may alternatively provide **12**, structures **11** could be established based on ^{1}H NMR which revealed NH_2 signal at δ 7.57 typical for the amino function in 7-amino-pyrazolo[1,5-*a*]pyrimidines. Isomeric 5-aminopyrazolo [1,5-α]pyrimidines show the NH_2 signal at higher field.[24,25]

* Correspondence. E-mail: shelmy@access.com.eg



Scheme 2

To establish the structure of the product with certainty we obtained an X-ray crystal structure of compound **11a** (Fig. 1). This compound has been reported earlier in a Japanese patent to be formed by decarboxylation of ethyl 7-amino-2-methylpyrazolo[1,5-*a*]pyrimidine-3-carboxylate.[26]

Compound **1d** also reacted with 2-aminobenzimidazole (**13**) to yield products that can be formulated as **14a** or the isomeric **15a**. Structure **15** was established as ^{1}H NMR revealed absence of any signals at $\delta > 8.4$ ppm. Compound **14a** should reveal H-4 at δ around 9.4 ppm as has been reported earlier by one of us.[11] In **14a, b** H-4 and H-6 experience van der Waals deshielding. Compounds **10a, c** and **13** also condensed with **3** to yield **11d, e** (Scheme 3) and **15b**, respectively.

Consistent with the previously reported[27,28] reactivity of **1a** toward heterocyclic diazonium salts, compound **1d** also coupled with the pyrazolediazonium chlorides **16a–d** to yield the pyrazolo[5,1-*c*]triazines **19a–d** (Scheme 5)**.** Trials to isolate acyclic hydrazones failed. It is believed that direct

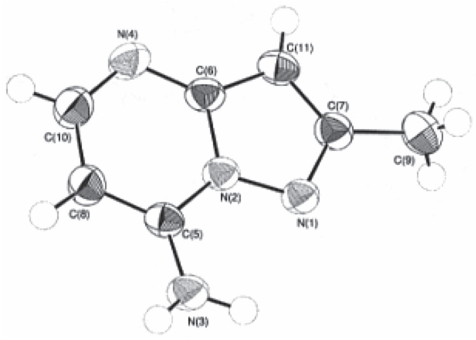
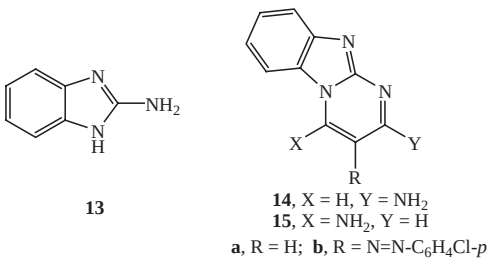
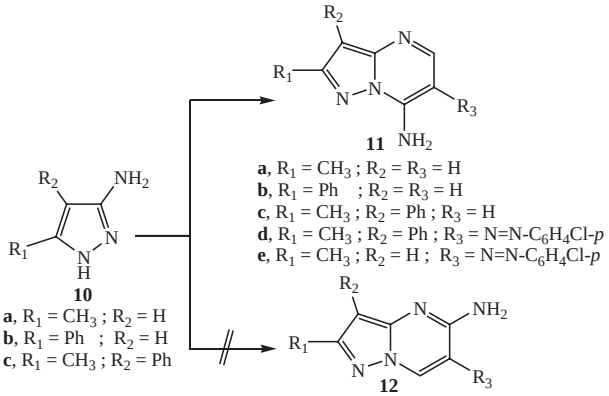


Fig. 1 X-ray structure of compound **11a**.



Scheme 4



Scheme 3

formation of **19** is a result of cycloaddition of the diazo-betaine **17** to **1d** to yield **18,** which then aromatises to form **19.** A similar assumption has been made earlier to account for the direct formation of pyrazolo[5,1-*c*][1,2,4]triazines on reacting **16a–c** with 3-amino-acrylonitrile and naphthols.[29]

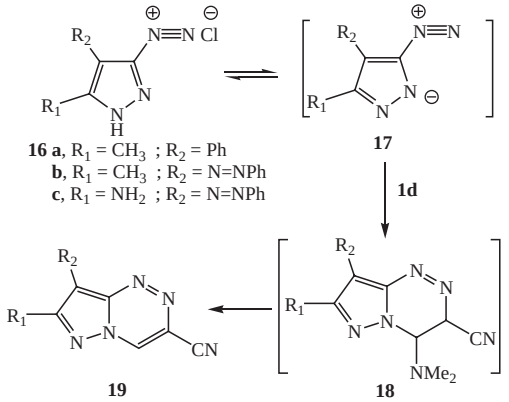
Compound **1d** reacted with benzylidenemalononitrile (**20**) to yield the pyran **21** in good yield. The reaction of **1d** with benzaldehyde and urea in acetic acid afforded dihydropyridine **22** (Scheme 6). Compound **21** has been obtained earlier via an isoxazole ring-opening reaction.[30] Clearly the synthesis reported here is more efficient.

Conclusions

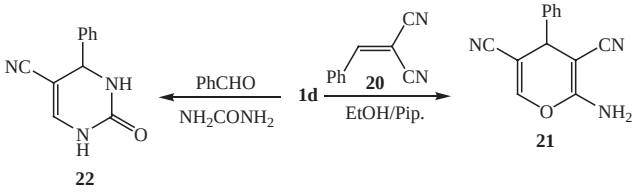
The enamines **1d–g** are readily obtainable starting materials for the synthesis of a variety of novel heterocycles as well as of new dienes and azadienes that seem of interest for their utility in further chemical transformations.

Experimental

The melting points were determined on a Stuart melting point apparatus. The IR spectra were recorded as KBr pellets using a FTIR Bruker-Vector 22 spectrophotometer. The ^{1}H and ^{13}CNMR spectra were recorded in DMSO-d_6 as solvent, the ^{1}H spectra at 200 or



Scheme 5



Scheme 6

300 MHz on Varian Gemini NMR spectrometers using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP-1000 EX mass spectrometer in EI (70 EV) mode. The elemental analyses were performed at the Microanalytical Center, Cairo University. The crystal structure was determined by the X-ray unit at the National Research Center, Dokki, Cairo.

General procedure for the preparation of the cyanoenamines **1d-g**: A mixture of cyanoacetic acid (50 mmol), triethyl orthoformate (50 mmol) and the appropriate amine (50 mmol) was heated under reflux for 2 h, allowed to cool to room temperature, then poured into cold water. The reaction mixture was treated with 1 molar sodium carbonate solution (100 ml), then extracted with dichloromethane (100 ml), and the extract left overnight to dry (Na_2SO_4). The solvent was evaporated *in vacuo*. Enamines **1d, e, g** formed oily residues, while **1f** was obtained as a solid product.

3-Piperidinoacrylonitrile (**1f**): Obtained as buff crystals. Yield: 60%; m.p. 55 °C. IR (KBr) ν_{max}/cm^{-1}: 2220 (CN). MS: *m/z* 137 (M^+). ^1H NMR (DMSO-d_6): δ 1.43–1.56 (m, 6H, piperidinyl–H), 3.12–3.30 (4H, piperidinyl–H), 4.06 (d, 1H, *J* = 14Hz, vinyl–H), 7.13 (d, 1H, *J* = 14Hz vinyl–H). Anal: calcd for $C_8H_{12}N_2$ (136.20): C, 70.55; H, 8.88; N, 20.57. Found: C, 70.52; H, 8.80; N, 21.2 %.

General procedure for the preparation of **2b** *and* **3a**, **3c**: An aryldiazonium salt (10 mmol) solution was prepared by adding sodium nitrite solution (0.7 g in 10 ml H_2O) to a chilled solution of arylamine hydrochloride (10 mmol of arylamine in 5 ml conc. HC1) with stirring. The resulting aryldiazonium solution was then added to a cold solution of enaminonitrile (**1d–g**) in acetic acid (50 ml) containing sodium acetate. The reaction mixture was stirred for 1 h. The solid product so formed was collected by filtration and crystallised from ethanol. Extraction of the filtrate of the reaction of **1d** with *p*-chlorobenzenediazonium salt using chloroform, followed by drying of the non-aqueous layer and evaporation *in vacuo*, afforded 1-(4-chlorophenyl)-3,3-diethyltriazene.

2-(1-Cyano-2-diethylaminovinylazo)-benzonitrile (**2b**): Obtained as yellow crystals (70%), m.p.: 140 °C. IR (KBr) ν_{max}/cm^{-1}: 2223, 2191 (2 CN). MS: *m/z* 254 (M^+). ^1H NMR (DMSO-d_6): δ 1.58 (t, 6H, *J* = 6Hz, $2CH_3$), 3.85 (q, 4 H, *J* = 6Hz, $2CH_2$), 7.2–7.8 (m, 4H, Ar–H), 7.9 (s, 1H, vinyl-H). ^{13}C NMR (DMSO-d_6) (there are extra carbons indicating the presence of more than one isomer; signals for the carbons of the predominant isomer are underlined): δ 12.0, 14.1, 14.87, 14.90 ($2CH_3$), 44.4, 48.8, 53.0, 53.9 ($2CH_2$), 107.0 (C vinyl) 113.9 (CH aromatic), 118.2, 118.7 (CN), 120.4 (CH aromatic) 127.5, 127.9 (CN), 132.9, 133.9, 149.0, 153.9 (CH aromatic) 158.0 (CH vinyl). Anal. Calcd for $C_{14}H_{15}N_5$ (253.30): C, 66.38; H, 5.96; N, 27.64. Found: C, 66.30; H, 5.95; N, 27.65 %.

2-(4-Chlorophenylhydrazono)-3-oxopropionitrile (**3a**): Obtained as red crystals (78%), mp. 170 °C. IR (KBr): ν_{max}/cm^{-1} 3447 (NH), 3219–3185 (CH), 1680 (CO). MS: *m/z* 207 (M^+). ^1H NMR (DMSO-d_6): δ 7.26–7.41 (m, 4H, Ar–H), 9.4 (s, 1H CHO) 9.6 (s, 1H, NH hydrazone). Anal. Calcd. for $C_9H_6C1N_3O$ (207.60): C, 52.07; H, 2.91; N, 20.24. Found: C, 52.12; H, 2.95; N, 20.21 %.

Methyl 2-[2-(α-cyano-β-oxoethylidene)hydrazino]benzoate (**3c**): Yellow crystals (68%), mp. 126 °C. IR (KBr) ν_{max}/cm^{-1}: 3132 (NH), 2209 (CN), 1692 (CO). MS: *m/z* 231 (M^+). ^1H NMR (DMSO-d_6) (there are extra carbons indicating the presence of more than one isomer; signals for the carbons of the predominant isomer are underlined): δ 3.9, 4.1 (s, 3H, CH_3), 7.5–8.25 (m, 4 H, Ar–H), 9.1, 9.7 (s, 1H, CHO), 13.2 (s, 1H, NH hydrazone). ^{13}C NMR (DMSO-d_6): (there are extra carbons indicating the presence of more than one isomer; signals for the carbons of the predominant isomer are underlined): δ 53.0 (CH_3), 108.9, 114.7, 115.8 (CH aromatic), 116.35 118.5 (CN), 124.7, 126.0, 131.3, 134.96, 134.97 (CH aromatic), 142.6 (CH vinyl), 167.8, 167.9 (COOMe), 182.6, 184.7 (CHO). Anal. Calcd for $C_{11}H_9N_3O_3$ (231.21): C, 57.14; H, 3.92; N, 18.17. Found: C, 57.25; H, 3.82; N, 18.10 %.

(4-Chlorophenylhydrazono)-(4'-chlorophenylazo)acetonitrile (**4**): Sodium nitrite (1.5 g in 10 ml H_2O) was added to a cold solution of arylamine hydrochloride (20 mmol amine in 10 ml concentrated HCl) with stirring. The resulting aryldiazonium salt solution was then added to a cold solution of enaminonitrile **1d–g** (10 mmol) in ethanol (50 ml) containing sodium acetate. The mixture was stirred and the solid product was collected by filtration and crystallised from ethanol. Compound **4** was obtained as yellow crystals (79%), mp. 242 °C. IR (KBr): ν_{max}/cm^{-1} 3427 (NH), 2924 (CH aromatic), 2219 (CN). MS: *m/z* 317 (M^+). ^1H NMR (DMSO-d_6): δ 7.52–7.66 (m, 8H, Ar–H), 12.20 (s, 1H, NH). Anal. Calcd for $C_{14}H_9C1_2N_5$ (318.15): C, 52.85; H, 2.85; N, 22.01. Found: C, 53.00; H, 2.96; N; 21.90 %.

General procedure for preparation of compounds **5a, b**: A mixture of cyanoacetic acid (50.0 mmol), triethylorthoformate (50.0 mmol) and primary aromatic amines (50.0 mmol) is heated under reflux for 2 h. The reaction mixture was then poured onto cold water. The solid which separated was collected by filtration and crystallised from ethanol.

3-[(2-Cyanovinyl)phenylamino]acrylonitrile (**5a**): Yellow crystals (82%), mp. 158 °C. IR (KBr) ν_{max}/cm^{-1}: 3243 (olefinic CH), 2223, 2200 (CN). MS: *m/z* 194 (M^+). ^1H NMR (DMSO-d_6): δ 5.185 (d, 2H, 2 vinyl-H), 6.75–8 (d, 2H, 2 vinyl-H), 6.85–7.31 (m, 5H, Ar–H). Anal. Calcd for $C_{12}H_9N_3$ (195.22): C, 73.82; H, 4.64; N, 21.52. Found: C, 73.93; H, 4.69; N, 21.41 %.

3-[(2-Cyanovinyl)-p-tolylamino]acrylonitrile (**5b**): Yellow crystals (54%), m.p. 164 °C. IR (KBr) ν_{max}/cm^{-1}: 3238 (CH olefinic), 2200 (CN). MS: *m/z* 209 (M^+). ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 5.26 (d, 2H, 2 vinyl-H), 7.20–7.80 (m, 4H, Ar–H), 7.25 (d, 2H, 2 vinyl-H). ^{13}C NMR (DMSO-d_6) (there are extra carbons indicating the presence of more than one isomer; signals for the carbons of the predominant isomer are underlined): δ 20.35 (CH_3), 80.2, 80.8, 85.4, 89.25 (C 2 in vinyl moiety), 115.2, 116.6, 117.2, 118.3 (CN), 119.8, 129.9, 133.5, 137.5 (CH aromatic), 142.2, 145.8, 148.7, 150.4 (C 3 in vinyl moiety). Anal. Calcd for $C_{13}H_{11}N_3$ (209.25): C, 74.62; H, 5.30; N, 20.08. Found; C, 74.71; H, 5.38; N, 20.14 %.

General procedure for preparation of compounds **6a–c**: Each of the enamines **1a, d, f** was refluxed alone in glacial acetic acid (20 ml) for 2 h, the reaction mixture was then poured into cold water. The solid product so formed is collected by filtration and crystallised from ethanol.

4-(Diethylaminomethylene)pent-2-enedinitrile (**6a**): Buff crystals (70%), m.p. 107 °C. IR (KBr) ν_{max}/cm^{-1}: 2989 (CH olefinic), 2239, 2197 (2CN). MS: *m/z* (%) = 175 (M^+). ^1H NMR (DMSO-d_6): δ 1.20 (t, 6H, *J* = 6Hz, $2CH_3$), 3.30 (q, 4H; *J* = 6Hz, $2CH_2$), 4.96 (d, 1H, vinyl-H), 7.21 (d, 1H, *J* = 14Hz, vinyl-H), 7.46 (s, 1H, *J* = 14Hz, vinyl-H). Anal. Calcd for $C_{10}H_{13}N_3$ (175.24): C, 68.54; H, 7.48; N, 23.98. Found: C, 68.49; H, 7.50; N, 23.85 %.

4-(Piperidinomethylene)pent-2-enedinitrile (**6b**): Buff crystals (72%), m.p. 145 °C. IR (KBr): ν_{max}/cm^{-1} 2206 (CN). MS: *m/z* 187 (M^+). ^1H NMR (DMSO-d_6): δ 1.61 (m, 6H, piperidinyl-H), 3.30 (m, 4H, piperidinyl-H), 4.8 (d, 1H, *J* = 14Hz, vinyl-H), 7.20 (d, 1H, *J* = 14Hz, vinyl-H), 7.46 (s, 1H, vinyl-H). Anal. Calcd for $C_{11}H_{13}N_3$ (187.24): C, 70.56; H, 7.00; N, 22.44. Found: C, 70.52; H, 6.94; N, 22.48 %.

4-(Morpholinomethylene)pent-2-enedinitrile (**6c**): Buff crystals (70%), m.p. 172 °C. IR (KBr): ν_{max}/cm^{-1} 2208 (CN). MS: *m/z* 189 (M^+). Anal. Calcd for $C_{10}H_{11}N_3O$ (182.19): C, 63.48; H, 5.86; N, 22.21. Found: C, 63.42; H, 5.91; N, 22.35 %.

9,10-Dihydroxyanthracene-1,3-dicarbonitrile (**9**): The diene **6a** (20 mmol) and 1,4-naphthoquinone (20 mmol) were heated under reflux in acetic acid (20 ml) for 1 h, then poured into cold water (50 ml). The solid product which separated was filtered off and crystallised from ethanol. The dinitrile was obtained as grey crystals (80%), m.p: 92 °C. IR (KBr): ν_{max}/cm^{-1} 3426 (OH), 2210 (CN). MS: *m/z* 260 (M^+). ^1H NMR (DMSO-d_6): δ 3.34 (s, 2H, 2OH), 7.1–7.9 (m, 6H, Ar–H), Anal. Calcd for $C_{16}H_8N_2O_2$ (260.25): C, 73.84; H, 3.10; N, 10.76. Found: C, 73.78; H, 2.97; N, 10.74 %.

General procedure for the preparation of pyrazolo[1,5-a] pyrimidines ***11a–c***

Method A: A mixture of enaminonitrile (**1d**) (20 mmol) and each of the aminopyrazoles (**10a–c**) (20 mmol) was refluxed in pyridine (20 ml) for 3 h. The solid product so formed was collected by filtration and crystallised from ethanol.

Method B: A mixture of cyanoacetic acid (20 mmol), triethyl orthoformate (20 mmol) and each of the compounds **10a–c** (20 mmol) was heated under reflux for 2 h. The reaction mixture was treated with aqueous sodium carbonate (1M, 100 ml) then extracted with dichloromethane (100 ml) The extract was dried overnight (Na_2SO_4), then evaporated under vacuum. The resulting product was then refluxed in acetic acid to yield **11a–c**.

2-Methylpyrazolo[1,5-a]pyrimidin-7-amine (**11a**): Brown crystals (60%), mp. 182 °C. IR (KBr): ν_{max}/cm^{-1}: 3310, 3119 (NH_2). MS: *m/z* 148 (M^+). ^1H NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 6.01 (d, 1H, pyrimidine–H), 6.05 (s, 1H, pyrazole–H), 7.57 (s, 2H, NH_2), 7.98 (d, 1H, pyrimidine–H). Anal. Calcd for $C_7H_8N_4$ (148.17): C, 56.74; H, 5.44; N, 37.81. Found: C, 56.70; H, 5.39; N, 37.70 %.

2-Phenylpyrazolo[1,5-a]pyrimidin-7-amine (**11b**): Yellow crystals (61%), m.p. 224 °C. IR (KBr) ν_{max}/cm^{-1}: 3373, 3297 (NH_2). MS: *m/z* 210 (M^+). ^1H NMR (DMSO-d_6): δ 6.11 (d, 1H, pyrimidine–H), 6.85 (s, 1H, pyrazole–H), 7.45–7.72 (m, 5H, Ar–H), 7.70 (s, 2H, NH_2),

8.05 (d, 1H, pyrimidine–H). Anal. Calcd for $C_{12}H_{10}N_4$ (210.24): C, 68.56; H, 4.79; N, 26.65. Found: C, 68.50; H, 4.75; N, 26.80 %.

2-Methyl-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**11c**): Yellow crystals (69%), m.p. 120 °C. IR (KBr): ν_{max}/cm^{-1} 3299, 3052 (NH_2), 1655 (C=N), 1566 (C=C). MS: *m/z* 224 (M^+). ^{1}H NMR (DMSO-d_6): δ 2.61 (s, 3H, CH_3), 5.71 (s, 2H, NH_2), 6.04 (d, 1H, pyrimidine–H), 7.246–7.71 (m, 5H, Ar–H), 8.80 (d, 1H, pyrimidine–H). Anal. Calcd for $C_{13}H_{12}N_4$ (224.25): C, 69.62; H, 5.39; N, 24.98. Found: C, 69.38; H, 5.58; N, 24.52 %.

General procedure for the preparation of 6-arylazopyrazolo[1,5-c]pyrimidin-7-amines (**11d, e**): An equimolar mixture (0.02 mole) of **3a** with each of the aminopyrazoles **10a** and **10c** was refluxed in pyridine (25 ml) for 3h. The reaction mixture was then poured into cold water and concentrated HCl and boiled for 5 min. The solid that formed was collected by filtration and crystallised from ethanol/DMF (2:1).

6-(4-Chlorophenylazo)-2-methyl-3-phenylpyrazolo[1,5-a]pyrimidin-7-amine (**11d**): Yellow crystals (80%), m.p. 320 °C. IR (KBr): ν_{max}/cm^{-1} 3377 (broad NH_2). MS: 362 (M^+). ^{1}H NMR (DMSO-d_6): δ 2.50 (s, 3H, CH_3), 7.31–7.97 (m, 9H, Ar–H), 8.75 (s, 1H, pyrimidine–H), 9.20–9.60 (br, 2H, NH_2). Anal. Calcd for $C_{19}H_{15}ClN_6$ (362.82): C, 62.88; H, 4.17; N, 23.16; Cl, 9.77. Found: C, 62.82; H, 4.13; N, 23.21; Cl, 9.45 %.

6-(4-Chlorophenylazo)-2-methylpyrazolo[1,5-a]pyrimidin-7-amine (**11e**): Yellow crystals (81%), mp. 310 °C. IR (KBr): ν_{max}/cm^{-1} 3286, 3095 (NH_2). MS: *m/z* 286 (M^+). ^{1}H NMR (DMSO-d_6): δ 2.44 (s, 3H, CH_3), 6.38 (s, 1H, pyrazole–H), 7.53–7.95 (m, 4H, Ar–H), 8.69 (s, 1H, pyrimidine–H), 8.90–9.50 (br, 2H, NH_2). Anal. Calcd for $C_{13}H_{11}ClN_6$ (286.73): C, 54.46; H, 3.87; N, 29.31; Cl, 12.36. Found: C, 54.38; H, 3.75; N, 29.44; Cl, 12.56 %.

Pyrimido[1,2-a]benzimidazol-4-amine (**15a**): The enamine **1d** (0.02 mole) and 2-aminobenzimidazole (**13**) (0.02 mole) were refluxed in pyridine (25 ml) for 3 h. The reaction mixture was then poured into water (100 ml) and concentrated HCl (10 ml) and boiled for 5 min. The solid that formed was collected by filtration and crystallised from ethanol. Compound **15a** was obtained as Brown crystals (57%), mp. 272 °C. IR (KBr): ν_{max}/cm^{-1} 3424 (NH_2), 1681 (C=N). MS: *m/z* 185 (M^+). ^{1}H NMR (DMSO-d_6): δ 3.20 (s, 2H, NH_2), 6.15 (d, 1H, *J* = 8 Hz, H-3), 7.26 (m, 1H, H-7),7.47 (m, 1H, H-8), 7.70 (d, 1H, *J* = 9Hz, H-9), 8.23 (d, 1H, *J* = 8 Hz, H-2), 8.40 (d, 1H, *J* = 9 Hz, H-6), Anal. Calcd for $C_{10}H_8N_4$ (184.20): C, 65.21; H, 4.38; N, 30.42. Found: C, 65.35; H, 4.33; N, 30.32 %.

3-(4-Chlorophenylazo)pyrimido[1,2-a]benzimidazol-4-amine (**15b**): A mixture of (**3a**) (0.02 mole) with 2-aminobenzimidazole **13** (0.02 mole) was refluxed in pyridine (25 ml) for 3 h. The reaction mixture was then poured into water (100ml) and concentrated HCl (10ml) and boiled for 5 min. The solid that formed was collected by filtration and crystallised from ethanol/DMF as yellow crystals (82%), m.p. 315 °C. IR (KBr): ν_{max}/cm^{-1} 3117, 3062 (NH_2). MS: *m/z* 322 (M^+ 100%). Anal. Calcd for $C_{16}H_{11}ClN_6$ (322.76): C, 59.54; H, 3.44; N, 26.04. Found: C, 59.61; H, 3.42; N, 25.88 %.

General procedure for the preparation of pyrazolo[5,1-c][1,2,4]triazine-3-carbonitriles (**19a–c**): Aqueous sodium nitrite (0.7 g in 5 ml H_2O) was added to a cold (0 °C) stirred solution of the aminopyrazole (10 mmol) in concentrated HCl (5 ml). The resulting pyrazolediazonium salt solution was then added to a cold solution of enaminonitrile (**1d–g**) in ethanol (50 ml) containing sodium acetate (3 g). The mixture was stirred at room temperature for 1 h and the solid product was collected by filtration and crystallised from ethanol**.**

7-Methyl-8-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carbonitrile (**19a**): Red crystals (79%), m.p. 224 °C. IR (KBr): ν_{max}/cm^{-1} 3445 (over tone and combination bands), 2234 (CN). MS: *m/z* 235 (M^+). ^{1}H NMR (DMSO-d_6): δ 2.87 (s, 3H, CH_3), 7.27–7.82 (m, 5H, Ar–H), 8.83 (s, 1H, triazine-H). Anal. Calcd for $C_{13}H_9N_5$ (235.27): C, 66,37; H, 3.86; N, 29.77. Found: C, 66.34; H, 3.79; N, 29.65 %.

7-Methyl-8-(phenylazo)pyrazolo[5,1-c][1,2,4]triazine-3-carbonitrile (**19b**): Yellow crystals (78%), m.p. 218 °C. IR (KBr): ν_{max}/cm^{-1}: 3328 (over tone and combination bands), 2228 (CN). MS: *m/z* 263 (M^+). ^{1}H NMR (DMSO-d_6): δ 2.23 (s, 3H, CH_3), 7.41 (m, 5H, Ar–H), 7.93 (s, 1H, triazine-H). Anal. Calcd for $C_{13}H_9N_7$ (263.26): C, 59.31; H, 3.45; N, 37.24. Found: C, 59.26; H, 3.33; N, 37.36 %.

7-Amino-8-(phenylazo)pyrazolo[5,1-c][1,2,4]triazine-3-carbonitrile (**19c**): Yellow crystals (73%), m.p. 218 °C. IR (KBr): ν_{max}/cm^{-1} 3320, 3220, 3100 (NH_2), 2220 (CN), MS: *m/z* 264 (M^+). Anal. Calcd for $C_{12}H_8N_8$ (264.25): C, 54.54; H, 3.05; N, 42.40. Found: C, 54.48; H, 2.98; N, 42.34 %.

2-Amino-4-phenyl-4H-pyran-3,5-dicarbonitrile (**21**): The enamine **1d** (10 mmol) and benzylidenemalononitrile (**20**) (10 mmol) were refluxed in ethanol (20 ml) containing piperidine (2 drops) for 3 h. The reaction mixture was then poured into cold water. The solid that separated was collected by filtration and crystallised from ethanol. Compound **21** was obtained as yellow crystals (54%), m.p. 198–200 °C. IR (KBr): ν_{max}/cm^{-1}: 3429 (broad NH_2), 2247, 2178 (2 CN). MS: *m/z* 223 (M^+). ^{1}H NMR (DMSO-d_6): δ 3.44 (br, 2H, NH_2), 3.69 (s, 1H, pyran-H4), 6.62 (s, 1H, pyran-H6), 7.26–7.65 (m, 5H, Ar–H). Anal. Calcd for $C_{13}H_9N_3O$ (223.24): C, 69.95; H, 4.06; N, 18.82. Found: C, 69.80; H, 3.92; N, 19.10 %.

2-Oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carbonitrile (**22**): A mixture of enamine (**1d**), benzaldehyde and urea (0.01 mole) of each was refluxed for 3 h in acetic acid (15 ml) containing hydrochloric acid (3 ml). The whole was then poured into water, and the solid that separated was collected by filtration and crystallised from ethanol. Compound **22** formed yellow crystals (58%), m.p. 260 °C. IR (KBr) ν_{max}/cm^{-1}: 3297, 3211 (NH), 2219 (CN), 1685 (CO). MS: *m/z* 198 (M^+). ^{1}H NMR (DMSO-d_6): δ 5.10 (d, 1H, pyrimidne-H4), 7.20 (d, 1H, NH), 7.25–7.40 (m, 5H, Ar–H), 7.75 (d, 1H, pyrimidine–H6), 9.45 (d, 1H, NH). ^{13}C NMR (DMSO-d_6): δ 55.2, 83.7 (CH pyrimidine), 118.2 (CN), 126.5, 128.3, 128.8, 139.7 (CH aromatic), 142.6 (CH pyrimidine), 150.4 (CO). Anal. Calcd for $C_{11}H_9N_3O$ (199.21): C, 66.32; H, 4.55; N, 21.09. Found: C, 66.04; H, 4.22; N, 20.84 %.

One of the authors (H. Gaber) is greatly indebted to the World Laboratory for granting a research fellowship, and to Prof. E.B. Pedersen, Nucleic Acid Center, Department of Chemistry, University of Southern Denmark, Odense M, Denmark, for hospitality and NMR facilities.

Received: 6 April 2004; accepted 15 September 2004
Paper 04/2452

References

1 A.A. Elassar and A.A. El-khair, *Tetrahedron*, 2003, **59**, 8463.
2 P. Langer, *Angew. Chem. Int. Ed*., 2000, **39**, 3049.
3 K.M. Davis and B.K. Carpenter, *J. Org. Chem***.**, 1996, **61**, 4617.
4 B. Stanovnik, *J. Heterocycl. Chem*., 1999, **36**, 1581.
5 S. Patai, Ed, *The Chemistry of Enamines*, J. Wiley and Sons, New York, 1994.
6 A. Winter and N. Risch, *Synlett*, 2003, 1.
7 K.M. Al-Zaydi, E.A. Hafiz and M.H. Elnagdi, *J. Chem. Res. (S)*, 2000, 154, 510.
8 F. Al-Omran, M.M.A. Khalik, A.A. El-Khair and M.H. Elnagdi, *Synthesis*, 1997, 91.
9 M.M.A. Khalik, and M.H. Elnagdi, *Synthetic Commun.*, 2002, **32**, 159.
10 F. Al-Omran, N. Al-Awadi, A.A. El-Khair and M.H. Elnagdi, *Org. Prep. Proc. Int.*, 1997, **29**, 285.
11 A. Al-Anezi, B. Al-Saleh and M.H. Elnagdi, *J. Chem. Res. (S)*, 1997, 116.
12 F.M.A. El-Taweel and M.H. Elnagdi, *J. Heterocyclic Chem*., 2001, **38**, 981.
13 B. Al-Saleh, N. Al-Awadi, M.M. Abdel-khalik, and M.H. Elnagdi, *J. Chem. Res (S)*, 2000, **16**, 201.
14 S. Al-Mousawi, M.M. Abdel-khalik, E. John and M.H. Elnagdi, *J. Heterocyclic Chem.*, 2003, **40**, 689.
15 B. Al-Saleh, M.M. Abdel-khalik, O.A. Salah and M.H. Elnagdi, *Heteroatom Chem.*, 2002, **13**, 141.
16 F. Scotti and E.J. Frazza, *J. Org. Chem*., 1964, **29**, 1800.
17 E.C. Leonard, *Vinyl and Diene Monomers*, p. 22. Wiley-Interscience, New York 1970.
18 G. Rudolf and H. Urich, *Angew. Chem.*, 1981, **93**, 297.
19 H. Wamhoff, J. Dzenis and K. Hirota, *Adv. Heterocycl. Chem*., 1992, **55**, 129.
20 L. Rene; J. Poncent and G. Auzou, *Synthesis*, 1986, 419.
21 B. Al-Saleh, M. Al-Apasery and M.H. Elnagdi, *J. Chem. Res*., 2004, in press.
22 B. Al-Saleh, M.M. Abdel-khalik, A.M. Eltoukhy and M.H. Elnagdi, *J. Heterocyclic Chem.*, 2002, **39**, 1035.
23 A.A. Hassanien, S.A.S. Ghozlan and M.H. Elnagdi, *J. Heterocyclic Chem.*, 2003, **40**, 225.

24 M. H. Elnagdi, N.H. Taha, F. A. Abdel-All, R.M. Abdel-Moteleb and F.F. Mahmoud, *Collection Czech. Chem. Commun*. 1989, **54**, 1982.
25 M.H. Elnagdi, N.H Taha, F.A. Abdell-All, R.M. Abdel-Moteleb and F.F. Mahmoud, *Collection Czech. Chem. Commun.*, 1989, **54**, 1982
26 K. Makino, H.S. Kim and Y. Kurasawa, *J. Heterocyclic Chem.*, 1998, **35**, 489 and references therein.
27 H. Behhbehani, M.A. Kalik and M.H. Elnagdi, *Org. Prep. Proced. Int.*, 1999, 551.
28 K.M. Al-Zaydi, R.M. Borik and M.H. Elnagdi, *Molecules*, 2003, **8**, 910.
29 M.H. Elnagdi, M.R.H. Elmoghayer and K.U. Sadek, *Adv. Heterocyclic Chem*. 1990, **48**, 223.
30 J.A. Ciller, N. Martin, C. Seoane and J.L. Soto, *J. Chem. Soc., Perkin Trans.* 1985, *1*, 2581.