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α,β-Unsaturated Nitriles in Heterocyclic Synthesis: Synthesis of Some New Pyrazolo[1,5—a]pyrimidine Derivatives

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3-Antipyrinyl-5-aminopyrazole (**1**) reacted with acrylonitrile to afford 5-amino-1-β-cyanoethyl-3-antipyrinylpyrazole (**2**). Compound **2** could also be obtained from the reaction of β-cyanoethylhydrazine (**3**) and compound **4**. **2** was readily cyclized into 2-antipyrinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-5-one (**5**) by acetic-hydrochloric acid. **5** could be also obtained from the reaction of **1** and methyl acrylate. The reaction of **1** and cinnamonitrile derivatives **7a–e** resulted in the formation of pyrazolo[1,5-a]pyrimidine derivatives **9**, **11** and **12**.

(Keywords: Cinnamonitriles; Cyanoethylations; Heterocycles)

α,β-Ungesättigte Nitrile in der Heterocyclen-Synthese: Synthese einiger neuer Pyrazolo[1,5—a]pyrimidin-Derivate

3-Antipyrinyl-5-aminopyrazol (**1**) reagierte mit Acrylnitril zu 5-Amino-1-β-cyanoethyl-3-antipyrinylpyrazol (**2**). **2** konnte ebenfalls aus der Reaktion von β-Cyanethylhydrazin (**3**) und Verbindung **4** erhalten werden. **2** wurde mittels Essigsäure-Salzsäure glatt zu 2-Antipyrinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]-pyrimidin-5-on (**5**) cyclisiert. **5** konnte auch aus der Reaktion von **1** mit Methylacrylat erhalten werden. Die Reaktion von **1** mit Zimtsäurenitrilderivaten **7a–e** ergab die Pyrazolo[1,5-a]pyrimidin-Derivate **9**, **11** und **12**.

Introduction

Interest in the synthesis of pyrazolo[1,5-a]pyrimidines has recently been revieved, as antischistosomal activity has been observed for derivatives of this ring system[1] making these fused azoles excellent candidates as potential drugs for schistosomiasis. Schistosomiasis is one of the most difficult diseases to treat and a national problem in this

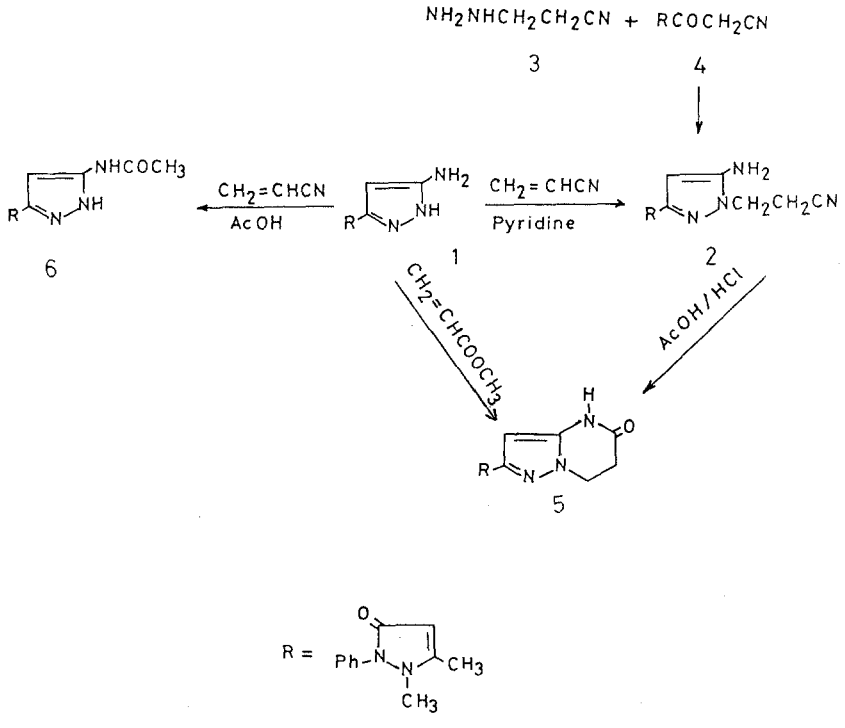
country[2–4] (Egypt). Consequently, we have resumed our interest in synthesis of pyrazolo[1,5-a]pyrimidines and defining the scope and limitation of our newly developed procedures[5,6]. In the following paper we report on the utility of α,β-unsaturated nitriles for the synthesis of pyrazolo[1,5-a]pyrimidines.

Results and Discussion

Similar to previous reports[5,7], 5-aminopyrazole (**1**) reacted with acrylonitrile in pyridine to yield a 1 : 1 aduct for which structure **2** was suggested. Structure **2** was established for this product by its synthesis from β-cyanoethylhydrazine (**3**) and 4-cyanoacetylantipyrine (**4**).

Compound **2** readily cyclized into the tetrahydropyrazolo[1,5-a]-pyrimidine derivative **5** via treatment with acetic-hydrochloric acid mixture. The same product could be directly obtained by reacting **1** with methyl acrylate (Scheme 1).

Scheme 1



In contrast to a previous report[8] cyanoethylation of **1** in acetic acid afforded – instead of the anticipated pyrazolo[1,5-a]pyrimidine derivative[8] – the 5-acetylaminopyrazole derivative **6** as the only isolable product. Compound **6** could be directly obtained from the reaction of **1** with acetic acid (Scheme 1).

Recently[9] it has been shown that cinnamonitrile derivatives react readily with oxo- and aminodiazoles to yield fused azole derivatives. We have been interested to extend reactions of this type to a general approach for the synthesis of diazolopyrimidines. It has been found that **1** reacts with the cinnamonitrile derivatives **7a–c** to yield products, for which structures **8**, **9** seemed possible (Scheme 2). Although structure **8** seems more likely than **9** based on analogy to the behaviour of **1** towards acrylonitrile[5], the ^{1}H-NMR spectrum indicates clearly that the reaction product is rather **9** than **8**. This is indicated by the aromatic protons, including pyrazole H-4, at δ 7.3–7.7 ppm (see Exp.). If this product were **8** the two *ortho* protons of the phenyl group at position 7 should appear separately at lower field (ca. δ 8–9 ppm)[10].

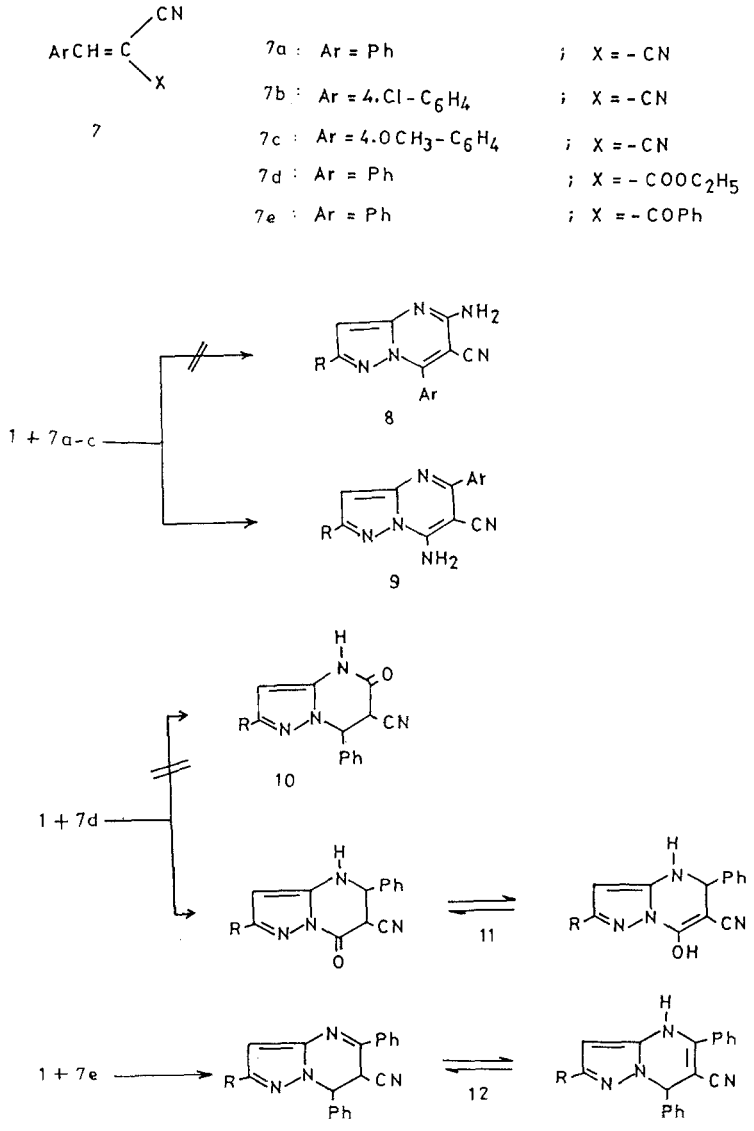
It is interesting to note that the pyrazole H-4 proton is deshielded by about 1 ppm as compared to that in compounds **2** and **5**. This can be readily understood since in both (**2** and **5**) charge separated resonance forms may contribute to the actual state of the molecule. This phenomenon has been previously discussed in details[11,12]. In compound **9** such separated charge resonance forms cannot contribute. The formation of **9** from the reaction of **1** and **7a–c** is assumed to proceed via addition of the exocyclic amino group to the double bond in **7** and cyclization via addition of ring nitrogen to the cyano group. The resulting product is then oxidized to the final isolable reaction product by another molecule of arylidenemalonitrile. Oxidation of dihydroazines by arylidenemalononitrile has recently been observed[13]. Although the ring nitrogen is the most nucleophilic center in the molecule, it is also the most hindered one and additions to the cinnamonitrile derivattives seem to be totally determined by steric considerations. Predominance of products resulting from steric considerations has been previously observed in reaction of enaminonitriles with aminopyrazoles[14].

In contrast to the behaviour of **1** towards **7a–c**, compound **1** reacted with **7d** to yield a product resulting from addition of **1** to ethyl benzylidenecyanoacetate and ethanol elimination (Scheme 2). Although it seems quite difficult to exclude structure **10** completely for this product, structure **11** seemed to be more likely based on the IR spectrum which revealed a ring CO group at 1 700 cm^{-1}. For structure **10** the ring CO group should be observed at lower frequency.

In addition, compound **1** reacted with **7e** to yield 2-antipyrinyl-6-

cyano-5,7-diphenyl-6,7-dihydropyrazolo[1,5-a]pyrimidine (**12**) in good yield (Scheme 2). The structure of **12** followed from correct analytical and spectral data.

Scheme 2



Experimental

Melting points were determined with a Thomas Hoover melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained with a Varian A-60 spectrometer with *TMS* as internal standard and chemical shifts are expressed as δ parts per million with *DMSO-d_6* as solvent. The infrared spectra were determined utilizing pressed KBr disks, with a Beckman IR spectrometer. Satisfactory analytical data ($\pm$ 0.3% in agreement with the molecular formulas given) were performed by the microanalytical Unit at Cairo University.

5-Amino-1-β-cyanoethyl-3-antipyrinylpyrazole (**2**)

From **1** and acrylonitrile: A solution of **1** (2.0 g) in pyridine (40 ml) and water (10 ml) was treated with acrylonitrile (1.0 ml) and the reaction mixture was refluxed for 4 h. The solvent was removed *in vacuo* and the residue was dissolved in hot 50% aqueous ethanol. The solid product obtained on standing was collected by filtration and crystallization from ethanol. Compound **2** formed yellow crystals; m. p. 238 °C; yield 55%; $C_{17}H_{18}N_6O$ (322).

From β-cyanoethylhydrazine and 4-cyanoacetylantipyrine: A suspension of 4-cyanoacetylantipyrine (10 gm) in *Et*OH (100 ml) was treated with 7 ml of β-cyanoethylhydrazine. The reaction mixture was refluxed for 3 h. The solvent was then removed on a water bath and the remaining solid filtered and identified as **2** (m.p. and mixed m.p.); yield 62%.

2-Antipyrinyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-5-one (**5**)

From **2** and acetic acid-hydrochloric acid mixture: A suspension of **2** (2.0 g) in *Ac*OH (30 ml) was treated with 5 ml of concentrated HCl (37.5%). The reaction mixture was refluxed for 2 h. The solvent was removed *in vacuo* and the remaining solid product was treated with little water and left to stand. The product so formed was collected by filtration and crystallized from ethanol. Compound **5** formed colourless crystals; m.p. 285 °C; yield 52%; $C_{17}H_{17}N_5O_2$ (323).

From 1 and methyl acrylate: A solution of **2** (2.0 g) in pyridine (40 ml) and water (10 ml) was treated with methyl acrylate (1.0 ml) and the mixture was refluxed for 4 h. The solvent was then removed *in vacuo* and the remaining residue was dissolved in hot ethanol. The solid product obtained on cooling was collected by filtration and recrystallized from ethanol and identified (m.p. and mixed m.p.) as **5**, yield 75%.

5-Acetylamino-3-antipyrinylpyrazole (**6**)

A solution of **1** (2.0 g) in acetic acid (40 ml) was treated with acrylonitrile (1.0 ml) and the reaction mixture was refluxed for 4 h. The solvent was removed *in vacuo* and the remaining residue was dissolved in hot 50% aqueous ethanol. The solid product obtained on standing was collected by filtration and crystallized from an alcohol–chloroform mixture. Compound **6** formed colourless crystals; m. p. 296 °C; yield 82%; $C_{16}H_{17}N_5O_2$ (311).

Reaction of **1** *with* **7a–c**. *General Procedure*

A suspension of (0.01 mol) of **1** and (0.014 mol) of **9** in ethanol (30 ml) was refluxed with piperidine (1 ml) until the reaction was complete (tlc control) (time ranges from 15 min to 10 h cf. Table 1). The solvent was then evaporated *in vacuo*

and the remaining product was triturated with a little water and then acidified with concentrated hydrochloric acid. The resulting solid products, listed in Table 1, were collected by filteration and crystallized from the proper solvents.

Table 1. *Data for the 7-amino-2-antipyrinyl-5-aryl-6-cyanopyrazolo[1,5-a]-pyrimidines* **9a–c**, *2-antipyrinyl-6-cyano-5-phenyl-4,5,6,7-tetrahydropyrazolo-[1,5-a]pyrimidin-7-one* (**11**), *and 2-antipyrinyl-6-cyano-5,7-diphenyl-6,7-dihydro-pyrazolo[1,5-a]pyrimidine* (**12**)

Compd.	Reac. time (min)	Cryst. Solv.	M. P. °C	Yield %	Mol. Form.
9a	60	*Et*OH	298	48	$C_{24}H_{21}N_7O$
9b	150	*DMF*	> *300*	42	$C_{24}H_{20}ClN_7O$
9c	150	*DMF*	> 300	45	$C_{25}H_{23}N_7O_2$
11	360	$CHCl_3$	> 300	72	$C_{24}H_{20}N_6O_2$
12	15	*Et*OH	282	89	$C_{30}H_{22}N_6O$

IR (γ/cm^{-1}) *and NMR* (δ/ppm) *of the newly synthesised compounds*

2: IR: 3 300 – 3 150 (NH_2), 2 225 (C≡N), 1 660 – 1 620 (antipyrinyl CO and C=C) and 1 595 (C=N). NMR: 2.5 (s, 3 H, CH_3), 3.2 (s, 3 H, N—CH_3), 3.25 – 3.5 (m, 4 H, 2 CH_2), 6.45 (s, 1 H, pyrazole H-4), 7.45–7.75 (m, 7 H, C_6H_5 and NH_2).

5: IR: 3 200–3 050 (NH, 2 920–2 895 (2 CH_2), 1 700 (azolyl CO) and 1 650–1 620 (antipyrinyl CO and C=C). NMR: 2.65 (s, 3 H, CH_3), 2.85 (t, 2 H, CH_2), 3.15 (s, 3 H, N-CH_3), 4.25 (t, 2 H, CH_2), 6.25 (s, 1 H, pyrazole H-4), 7.3–7.6 (m, 5 H, C_6H_5), 10.7 (s, br, 1 H, NH).

6: IR: 3 400–3 300, 3 200 (NH), 1 700 (CO amide) and 1 650–1 615 (antipyrinyl CO and C=C). NMR: 2 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 3.2 (s, 3 H, N—CH_3), 6.65 (s, 1 H, pyrazole H-4), 7.4–7.7 (m, 5 H, C_6H_5), 10.5 and 12.2 (two s, br, 2 NH).

9a: IR: 3 420, 3 180 (NH_2), 2 218 (C≡N), 1 650–1 600 (antipyrinyl CO and NH_2). NMR: 2.0 (s, 3 H, CH_3), 3.2 (s, 3 H, N—CH_3), 7.3–7.7 (m, 13 H, 2 × C_6H_5, NH_2 and pyrazole H-4).

9b: IR: 3 300, 3 200 (NH_2), 2 200 (C≡N) and 1 625 (antipyrinyl CO). NMR: Insufficiently soluble in commonly used NMR solvents.

9c: IR: 3 380, 3 340, 3 200 (NH_2), 2 180 (C≡N), 1 650 (antipyrinyl CO) and 1 620 (C=C). NMR: Insufficiently soluble in commonly used NMR solvents.

11: IR: 3 480, 3 380 (OH and NH), 2 180 (C≡N), 1 700 (CO), 1 640 (antipyrinyl CO). NMR: 2.4 (s, 3 H, CH_3), 3.25 (s, 3 H, N—CH_3), 2.8 (d, 1 H, CH), 4.8 (d, 1 H, CH), 6.1 (s, br 1 H, exchangeable with D_2O), 6.8–7.6 (m, 11 H, 2 × C_6H_5 and pyrazole H-4).

12: IR: 3 280 (NH), 2 190 (C≡N), 1 650–1 630 (antipyrinyl CO and C=C). NMR: 1.8 (s, 3 H, CH_3), 3.45 (s, 3 H, N—CH_3), 5.0 (s, 1 H, CH), 6.9–7.6 (m, 16 H, 3 × C_6H_5, pyrazole H-4) and 9.9 (s, 1 H, NH).

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