Studies on Heterocyclic Amidines: Synthesis of new Azaindene Derivatives

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Several new pyrazolo[1,5-a]pyrimidines and pyrazolo[5,1-c]-1,2,4-triazine derivatives were synthesised from 3(5)-aminopyrazoles **1a, b** as starting components.

Studie von Heterocyclischen Amidinen: Synthese von Neuen Azainden-Derivaten

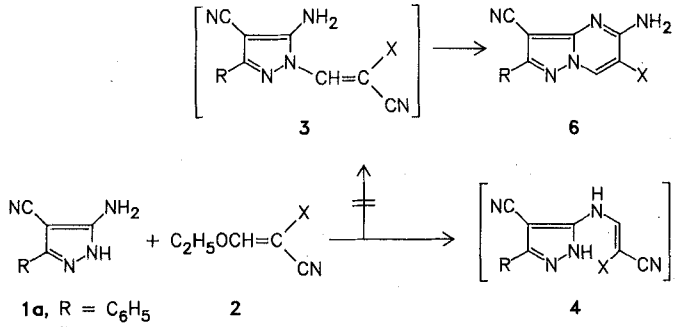
Einige neue Pyrazolo[1,5-a]pyrimidine und Pyrazolo[5,1-c]-1,2,4-triazin-Derivate wurden aus 3(5)-Aminopyrazolen **1a, b** hergestellt.

Interest in the chemistry of condensed pyrazoles has recently been revived[1]. Several biological activities have been established for pyrazoles fused to six-membered rings[2,3]. Among these activities is the reported antischistosomal activity of certain substituted pyrazolo[1,5-a]pyrimidines. As Schistosomiasis is a national problem in our country (Egypt) we have developed a program aiming to synthesis new pyrazolo[1,5-a]pyrimidines as well as their aza derivatives for evaluating their antischistosomal activity. In the present article we describe results of our work directed to the synthesis of azaindenecarbonitriles.

Thus, it has been found that 5-amino-3-phenylpyrazol-4-carbonitrile **(1a)**, prepared following our synthetic approach[4], reacts with ethyl 2-cyano-3-ethoxyacrylate **(2a)** to yield a product via ethanol elimination.

Several isomeric structures seemed possible for this product (cf. structures **3–6**). Acyclic structures **3** and **4** were eliminated based on IR-spectra which revealed only one cyano band. Structure 5 was preferred over the possible isomere **6** based on the ^{1}H-NMR-spectrum, which revealed amino protons at $\delta = 9.0$ ppm. If this product was the isomere **6**, the amino signal at $\delta = 4$–6 ppm should have been observed. Deshielding of pyrazolopyrimidin-7-amine protons by ring nitrogen anisotropy has been previously observed[5].

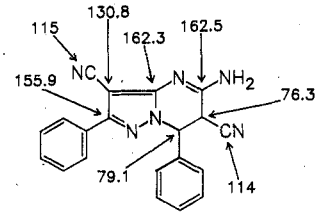
Similarly, compounds **1a, b** reacted with **2b** to yield the pyrazolo-[1,5-a]pyrimidine derivatives **5b, c.**



2, 5	R	X
a	C_6H_5	$CO_2C_2H_5$
b	C_6H_5	CN
c	H	CN

Attempts to add **1b** to **2a** under the same conditions were unsuccessful. The reactants were recovered almost unchanged.

Compound **1a** reacts with benzylidenemalononitrile **7a** to yield a product $C_{20}H_{14}N_6$ ($M^{+\cdot}$ at m/z = 338). Again two isomeric structures (**8** and **9**) were considered. Although it was previously assumed that α, β-unsaturated nitriles react with 3(5)-aminopyrazoles via initial attack of ring nitrogen at the electron deficient carbon in the α, β-unsaturated system[6], a sequence that would lead to **8**, a confirmatory structure elucidation seemed mandatory as *Soto* et al.[7] have assumed formation of 7-aminopyrazolo[1,5-a]pyrimidines from the reaction of 4-benzyl-3,5-diaminopyrazole with **7a** based on similarity to the reported behaviour of 3(5)-aminopyrazoles with α, β-unsaturated nitriles. It seems that they meant by this statement reaction of 3(5)-aminopyrazoles with **2a, b** as cyanoethylation of aminopyrazoles has been established by us to occur via attack of the ring nitrogen at the α, β-unsaturated moiety[8,9]. Spectral data established the 5-aminopyrazolo[1,5-a]pyrimidine structure **8** for the reaction product: ^{13}C-NMR revealed signals for *two* sp^3 carbons at = 76.3 and 79.1 ppm. If the reaction product was **9** only *one* sp^3 carbon would appear.



151-127 aromatic Carbons

Moreover, the amino function of the product appeared at $\delta = 4$ ppm. If the product was the 7-aminoisomer **9** this signal should have appeared at lower field as a result of ring nitrogen anisotropic effect. Moreover, the two protons at C-6 and C-7 appeared as two douplets at $\delta = 2.7$ and 2.9 ppm. It this product was **9** one would expect only one proton signal at such field strengths.

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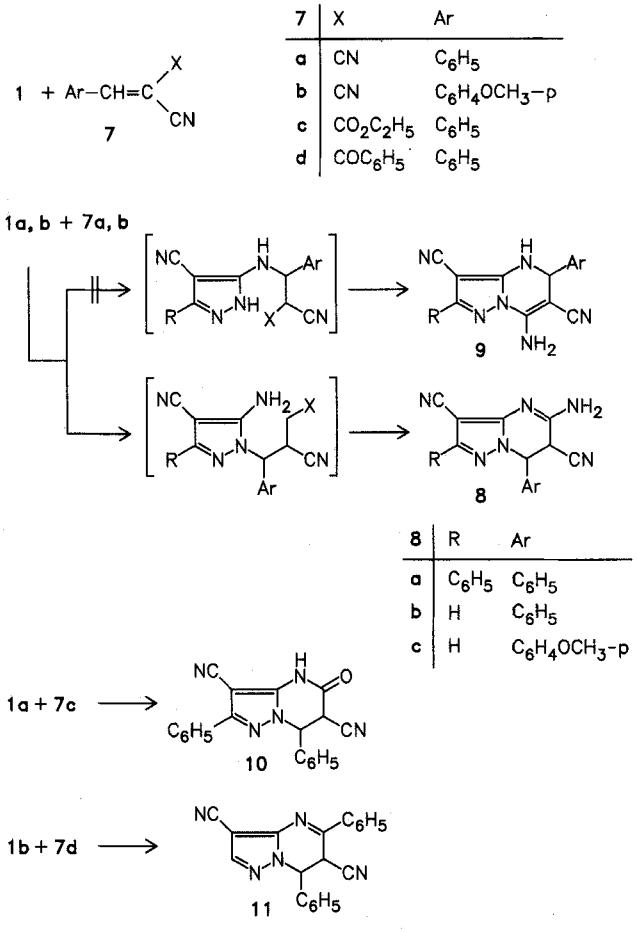
Similarly **1b** reacts with (arylmethylene)malononitriles **7a, b** to yield 1:1 adducts. The 5-aminopyrazolo[1,5-a]pyrimidines **8b, c** were formulated for the reaction products based on analytical and spectral data.

In contrast, **1a** condensed with **7c** to yield a product with concomitant ethanol elimination. The ^{13}C-NMR-spectrum confirmed the pyrazolo[1,5-a]pyrimidine structure **10** as it reveales two sp^3 carbons at $\delta = 65.6$ and 73.8 ppm.

Similarly, **1b** reacted with **7d** to yield **11** through condensation by water elimination.

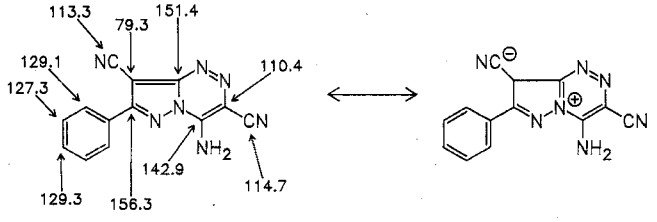


7	X	Ar
a	CN	C_6H_5
b	CN	$C_6H_4OCH_3$-p
c	$CO_2C_2H_5$	C_6H_5
d	COC_6H_5	C_6H_5

8	R	Ar
a	C_6H_5	C_6H_5
b	H	C_6H_5
c	H	$C_6H_4OCH_3$-p

Compounds, **1a, b** reacted with dimethyl acetylenedicarboxylate **(12)** to yield pyrazolo[1,5-a]pyrimidines **13a, b** respectively.

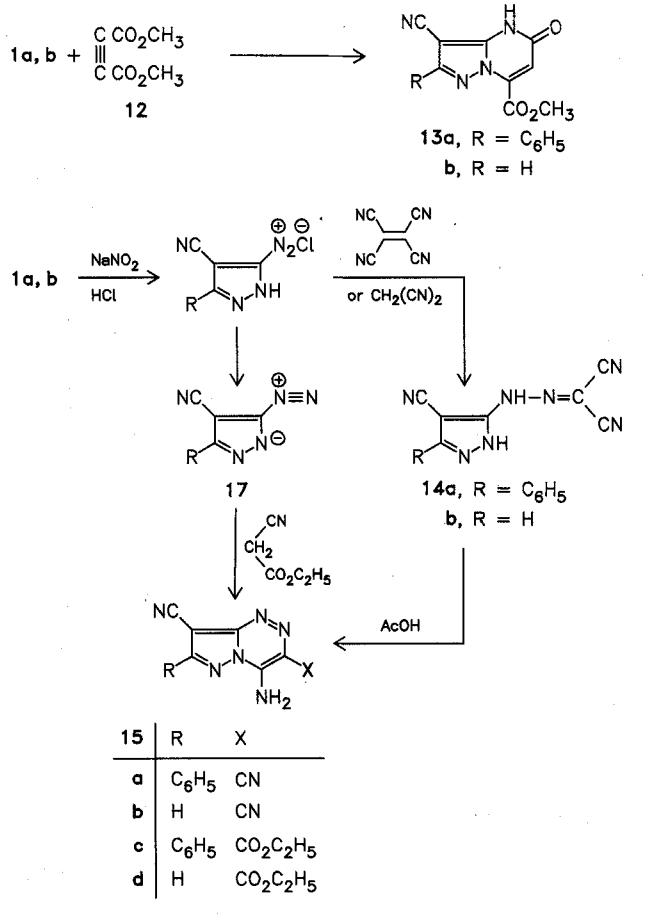
Diazotisation of aminopyrazoles leads to the corresponding diazonium salts that can be converted into diazobetaines on basification[10]. These diazobetaines have been reported to add electron rich and electron poor olefins as well as phosphorous ylides and isocyanates to yield mainly pyrazolo[5,1-c]-1,2,4-triazines[11, 12]. To prepare pyrazolo[5,1-c]-1,2,4-triazincarbonitriles we investigated the reaction of diazotised **1a, b** with electron poor olefins: diazotised **1a** reacted with tetracyanoethylene in aqueous basic medium to yield a product of condensation by mesoxalonitrile elimination. This product was found identical with the product of coupling diazotised **1a** with malononitrile and was considered to be either the hydrazone **14a** or the pyrazolo[5,1-c]-1,2,4-triazine **15a**. The pyrazolo[5,1-c]-1,2,4-triazine structure **15** was established based on its stability under conditions reported to effect cyclisation of pyrazol-5-ylhydrazones of similar structure[13]. For example, **15a** was recovered unreacted on reflux in acetic acid. In addition IR- and ^{1}H-NMR-spectra of the product revealed the presence of an amino function. Although the acyclic **14a** hydrazone could be obtained in crude state, trials to obtain a pure sample were unsuccessful and the cyclic product **15** was the only obtainable product. The ^{13}C-NMR-spectrum of the reaction product revealed C-8 at $\delta = 79.2$ ppm. Shielding of this C-atom can be interpreted by assuming that **15** exists as the zwitter ion **16** (Scheme 3).



Diazotised **1b** reacted with tetracyanoethylene to yield the hydrazone **14b**. This product was identical with the product of coupling diazotised **1b** with malononitrile. This product could be cyclised into pyrazolo[5,1-c]-1,2,4-triazine **15b** on reflux in acetic acid.

Similarly, diazotised **1a** reacts with benzylidenemalononitrile **(7a)** to yield **14a** which cyclises to the pyrazolo[5,1-c]-1,2,4-triazine **15a** on attempted purification.

In contrast, the diazobetaine **17** (R = H) was isolated from the reaction of diazotised **1b** with **7a**.



15	R	X
a	C_6H_5	CN
b	H	CN
c	C_6H_5	$CO_2C_2H_5$
d	H	$CO_2C_2H_5$

In contrast to the behaviour of diazotised **1a, b** toward malononitrile the pyrazolo[5,1-c]-1,2,4-triazines **15c, d** were directly obtained from the reaction of diazotised **1a, b** with ethyl cyanoacetate. Again **15b** could be obtained from the reaction of diazotised **1a** with **7c**. Attempts at coupling of diazotised **1b** with **7c** were unsuccessful.

Experimental Part

Melting points are uncorrected. – IR spectra (KBr): Pye Unicam SP-1100 and Shimadzu 408 spectrophotometers. – ^{1}H-NMR spectra: [D_6] DMSO, Varian EM 390 (90 MHz), TMS as int. standard, chemical shifts: δ values. – ^{13}C-NMR spectra: Bruker WP 200, chemical shifts: δ-values. Mass spectra: MS 30 (AEI) 70 EV. – Microanalytical data: Microanalytical Data Unit at Cairo University.

Condensation of **1a, b** *with* **2a, b,** *General procedure*

A solution of **1a** or **b** (0.01 mol) and the appropriate **2a, b** (0.01 mol) in ethanol (50 ml) was heated with triethylamine (0.01 mol) under reflux for 1 h then evaporated in vacuo. The solid product, so formed, was collected and crystallised from the proper solvent.

Ethyl 7-amino-3-cyano-2-phenylpyrazolo[1,5-a]pyrimidine-6-carboxylate **(5a)**

Pale yellow crystals from ethanol; m.p. 250 °C. – IR: ν̃ = 3410; 3370; 3250 cm^{-1} (NH_2): 2200 (CN); 1710 (ester CO). – ^{1}H-NMR: δ = 1.3 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.6–8.1 (m, 5H, C_6H_5), 8.6 (s, 1H, pyrimidine 5-H), 9.0 (br. s, 2H, NH_2). – $C_{16}H_{13}N_5O_2$ (307.3) Calcd. C 62.5 H 4.3 N 22.8 Found C 62.7 H 4.2 N 22.6.

7-Amino-2-phenylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile **(5b)**

Yellow crystals from ethanol-dioxane; yield 70 %; m.p. 200 °C. – IR: ν̃ = 3350 cm^{-1} (NH_2); 2190; 2200 (CN); 1670 (C=N). – ^{1}H-NMR: δ = 7.6–8.2 (m, 5H, C_6H_5), 8.6 (s, 1H, pyrimidine 5-H), 9.3 (s, 2H, NH_2). – $C_{14}H_8N_6$ (260.3). Calcd. C 64.6 H 3.1 N 32.3 Found C 64.5 H 3.1 N 32.3.

7-Aminopyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile **(5c)**

Yellow crystals from ethanol; yield 60 %; m.p. > 250 °C. – IR: ν̃ = 3250; 3100 cm^{-1} (NH_2); 2190; 2200 (CN); 1670 (C=N). – $C_8H_4N_6$ (184.2) Calcd. C 52.2 H 2.2 N 45.6 Found C 52.3 H 2.2 N 45.6.

Reaction of **1a, b** *with (arylmethylene)malononitriles* **7a–d** *General procedure*

A solution of **1a** or **b** (0.01 mol) and the appropriate **7a–d** (0.01 mol) in pyridine (50 ml) was heated under reflux for 4 h. The solvent was then evaporated in vacuo and the reamining solid product was collected and crystallised from the proper solvent.

5-Amino-6,7-dihydro-2,7-diphenylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile **(8a)**

Yellow crystals from ethanol-dioxane; yield 76 %; m.p. > 250 °C. – IR: ν̃ 3320 cm^{-1} (NH_2); 2190; 2200 (CN); 1650 (C=N). – ^{1}H-NMR: δ = 2.7; 2.9 (2 d, pyrimidine 6,7-H), 4.0 (s, 2H, NH_2), 7.2–8.3 (m, 10 H, 2 C_6H_5). – $C_{20}H_{14}N_6$ (338.4) Calcd. C 71.0 H 4.2 N 24.8 Found C 71.0 H 4.3 N 24.7. Mol. mass 338 (MS).

5-Amino-6,7-dihydro-7-phenylpyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile **(8b)**

Colourlees crystals from ethanol; yield 60 %; m.p. > 250 °C. – IR: ν̃ = 3150; 3300 cm^{-1} (NH_2); 2190; 2200 (CN); 1660 (C=N). – ^{1}H-NMR: δ = 2.8; 2.0 (2 d, pyrimidine 6,7-H), 4.2 (s, 2H, NH_2), 7.2–7.9 (m, 5H, C_6H_5), 9.0 (s, 1H, pyrazole 2-H). – $C_{14}H_{10}N_6$ (262.3) Calcd. C 64.1 H 3.9 N 32.0 Found C 64.0 H 4.0 N 32.3.

5-Amino-6,7-dihydro-7-(4-methoxyphenyl)pyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile **(8c)**

Brown crystals from methanol-water; yield 60 %; m.p. > 250 °C. – IR ν̃ = 3350; 3200 cm^{-1} (NH_2); 2190; 2200 (CN). – ^{1}H-NMR: δ = 2.7; 2.9 (2 d, pyrimidine 6,7-H), 3.9 (s, 3H, OCH_3), 4.2 (s, 2H, NH_2), 7.2–7.9 (m, 4H, C_6H_4), 9.0 (s, 1H, pyrazole 2-H). – $C_{15}H_{12}N_6O$ (292.3) Calcd. C 61.6 H 4.1 N 28.7 Found C 61.4 H 4.2 N 28.5.

2,7-Diphenyl-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidine-3,6-dicarbonitrile **(10)**

Pale buff crystals from ethanol-dioxane; yield 65 %; m.p. > 250 °C. – IR: ν̃ = 2190; 2200 cm^{-1} (CN), 1670 (C=N). – ^{1}H-NMR: δ = 2.7; 2.9 (2 d, pyrimidine 6,7-H), 7.2–8.0 (m, 10 H, 2C_6H_5). – $C_{20}H_{13}N_5O$ (339.4) Calcd. C 71.0 H 4.2 N 24.8 Found C 71.0 H 4.3 N 24.5. – Mol. mass 339 (MS).

6,7-Dihydro-5,7-diphenylpyrazolo[1,5-a]pyrimidines-3,6-dicarbonitrile **(11)**

Yellow crystals from DMF-methanol; yield 65 %; m.p. > 250 °C. – IR: ν̃ = 2190; 2200 cm^{-1} (CN); 1620 (C = N). – ^{1}H-NMR: δ = 2.6; 2.9 (2 d, pyrimidine 6,7-H), 7.0–8.2 (m, 10 H, 2 C_6H_5), 9.0 (s, 1H, pyrazole 2-H). – $C_{20}H_{13}N_5$ (323.4) Calcd. C 74.3 H 4.1 N 21.7 Found C 74.5 H 4.2 N 21.5.

Reaction of **1a, b** *with methyl acetylenedicarboxylate* **(12)** *General procedure*

An equimolecular amount (0.01 mol) of **1a** or **b** and methyl acetylenedicarboxylate were treated with a catalytic amount of pyridine (1 ml) at room temp. for 1 h, then triturated with ethanol. The solid product, so formed, was collected and crystallised from the proper solvent.

Methyl 3-cyano-5,6-dihydro-5-oxo-2-phenylpyrazolo[1,5-a]pyrimidine-7-carboxylate **(13a)**

Yellow crystals from ethanol; yield 60 %; m.p. > 250 °C. – IR: ν̃ = 2200 cm^{-1} (CN), 1710 (C=O); 1640 (C=N). – ^{1}H-NMR: δ = 4.0 (s, 3H, OCH_3), 7.2–7.9 (m, 5H, C_6H_5), 8.3 (s, 1H, NH). – $C_{15}H_{10}N_4O_3$ (294.3) Calcd. C 61.2 H 2.7 N 19.0 Found C 61.0 H 2.7 N 19.0.

Methyl 3-cyano-5,6-dihydro-5-oxopyrazolo[1,5-a]pmidine-7-carboxylate **(13b)**

Yellow crystals from ethanol-water; yield 62 %; m.p. 108 °C. – IR: ν̃ = 3350 cm^{-1} (NH); 2200 (CN); 1740 (br., ester and ring C=O); 1640 (C=N). – $C_9H_6N_4O_3$ (218.2) Calcd. C 49.6 H 2.8 N 25.6 Found C 50.0 H 2.8 N 25.5.

Coupling diazotised **1a, b** *with active methylene reagents, tetracyanoethylene and (arylmethylene) malononitriles General procedure*

A solution of diazotised **1a** or **b**[10] (0.01 mol) was added to a solution of the appropriate active methylene reagent, tetracyanoethylene or the (arylmethylene)malononitriles **(7a, b)** (0.01 mol) in ethanol (50 ml) in the presence of sodium acetate (5 g). The solid product formed on standing was collected and crystallised from the proper solvent.

4-Cyanopyrazol-5-ylhydrazonomesoxalonitrile **(14b)**

Yellow crystals from acetone; yield 72 %; m.p. 240 °C. – IR: ν̃ = 3050 cm^{-1} (NH); 2200 (CN); 1640 (C=N). – $C_7H_3N_7$ (185.2) Calcd. C 45.4 H 1.6 N 53.0 Found C 45.7 H 1.8 N 53.0.

4-Amino-7-phenylpyrazolo[5,1-c][1,2,4]triazine-3,8-dicarbonitrile **(15a)**

Brown crystals from DMF-ethanol; yield 77 %; m.p. > 250 °C. – IR: $\tilde{\nu}$ = 3400; 3120 cm^{-1} (NH_2); 2190; 2200 (CN); 1660 (C=N). – ^{1}H-NMR: δ 7.6–8.2 (m, 5H, C_6H_5), 9.9 (s, 2H, NH_2). – $C_{13}H_7N_7$ (261.3) Calcd. C 59.8 H 2.8 N 37.5 Found C 59.7 H 3.0 N 37.3.

Ethyl 4-amino-8-cyano-7-phenylpyrazolo[5,1-c][1,2,4]triazine-3-carboxylate **(15c)**

Buff crystals from ethanol-dioxane; yield 77 %; m.p. > 250 °C. – IR: $\tilde{\nu}$ = 3410; 3310; 3270 cm^{-1} (NH_2); 2220 (CN); 1690 (C=O). – ^{1}H-NMR: δ = 1.3 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.6–8.2 (m, 5H, C_6H_5), 9.9 (s, 2H, NH_2). – $C_{13}H_7N_7$ (261.3) Calcd. C 59.8 H 2.8 N 37.5 Found C 59.7 H 3.0 N 37.3.

Ethyl 4-amino-8-cyano-7-phenylpyrazolo[5,1-c]]1,2,4]triazine-3-carboxylate **(15c)**

Buff crystals from ethanol-dioxane; yield 77 %; m.p. > 250 °C. – IR: $\tilde{\nu}$ = 3410; 3310; 3270 cm^{-1} (NH_2); 2220 (CN); 1690 (C=O). – ^{1}H-NMR: δ = 1.3 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.6–8.2 (m, 5H, C_6H_5), 9.4 (s, br., 2H, NH_2). – $C_{15}H_{12}N_6O_2$ (308.3) Calcd. C 58.4 H 3.9 N 27.3 Found C 58.4 H 3.8 N 27.2. – Mol. mass 308 (MS).

Ethyl 4-amino-8-cyanopyrazolo[5,1-c][1,2,4]triazine-3-caroboxylate **(15d)**

Yellow crystals from ethanol; yield 82 %; m.p. > 250 °C. – IR: $\tilde{\nu}$ = 3370; 3050 cm^{-1} (NH_2), 2210 (CN), 1730 (ester C=O). – ^{1}H-NMR δ = 1.3 (t, 3H, CH_3), 4.4 (q, 2H, CH_2), 8.9 (s, 1H, pyrazole 7-H), 9.6 (s, br., 2H, NH_2). – $C_9H_8N_6O_2$ (232.2) Calcd. C 46.6 H 3.5 N 36.2 Found C 46.6 H 3.6 N 36.4.

Cyclisation of the hydrazone **14b**

A solution of **14b** (2 g) in acetic acid (30 ml) was heated under reflux for 30 min, then it was evaporated in vacuo. The reamining solid product was triturated with water, collected and crystallised from ethanol:

4-Aminopyrazolo[5,1-c][1,2,4]triazine-3,8-dicarbonitrile **(15b)**

Yellow crystals; yield 80 %; m.p. > 250 °C. – IR: $\tilde{\nu}$ = 3250; 3100 cm^{-1} (NH_2); 2200 (CN); 1650 (C=N). – ^{1}H-NMR: δ = 8.9 (s, 1H, pyrazole 7-H), 9.9 (s, br., 2H, NH_2). – $C_7H_{13}N_7$ (185.2). Calcd. C 45.4 H 1.6 N 53.0 Found C 45.5 H 1.7 N 53.20.

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