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Reactions with Heterocyclic Amidines, VII:

Synthesis of Some New Pyrazolo[1,5—c]-1,2,4-triazines, Pyrazolo[1,5—a]-1,3,5-triazines and Pyrazolo[1,5—a]pyrimidines

Mohamed Hilmy Elnagdi*, Ezzat M. Zayed, M. A. Elsayed Khalifa, and **Said A. Ghozlan**

Department of Chemistry, Faculty of Science, Cairo University, Giza, A.R. Egypt

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Diazotised 5-amino-3-methyl-4-phenylpyrazole (**1**) reacted with active methylene reagents and with β-naphthol to yield the pyrazolo[1,5—c)-1,2,4-triazine derivatives **2a—e** and **5**. Compound **1** reacted with benzoyl isothiocyanate and with phenyl isothiocyanate to yield the corresponding pyrazol-5-yl-thiourea derivatives **6a, b**. **5a** was converted into the thiourea derivative **8** by the action of acids or alkalies. A synthesis of 2-methyl-3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5—a]-pyrimidin-5-one from the reaction of α-phenyl-acetoactonitrile (3-oxo-2-phenyl-butyric nitrile) and β-cyanoethylhydrazine is reported.

(Keywords: Cyanoethylation; Heterocyclic compounds)

Reaktionen mit heterocyclischen Amidinen, VII: Synthese einiger neuer Pyrazolo[1,5—c]-1,2,4-triazine, Pyrazolo[1,5—a]-1,3,5-triazine und Pyrazolo[1,5—a]pyrimidine

Diazotiertes 5-Amino-3-methyl-4-phenylpyrazol (**1**) reagiert mit einer aktiven Methylenkomponente und β-Naphthol zu den Pyrazolo[1,5—c]-1,2,4-triazin-Derivaten **2a—e** und **5**. **1** ergibt mit Benzoylisothiocyanat und Phenylisothiocyanat die entsprechenden Pyrazol-5-yl-thioharnstoffe **6a, b**. **5a** wurde mittels Säure oder Base in das Thioharnstoffderivat **8** umgewandelt. Es wird über eine Synthese von 2-Methyl-3-phenyl-4,5,6,7-tetrahydropyrazolo[1,5—a]-pyrimidin-5-on aus α-Phenylacetoacetonitril (3-Oxo-2-phenyl-butyronitril) und β-Cyanoethylhydrazin berichtet.

Interest in the synthesis of fused pyrazoles has recently been revived[1–4]. The reported antipyritic[5], analgesic[6], *CAMP* phosphodiasterase inhibitory action[7–9] and *CNS* activity[10,11] of certain

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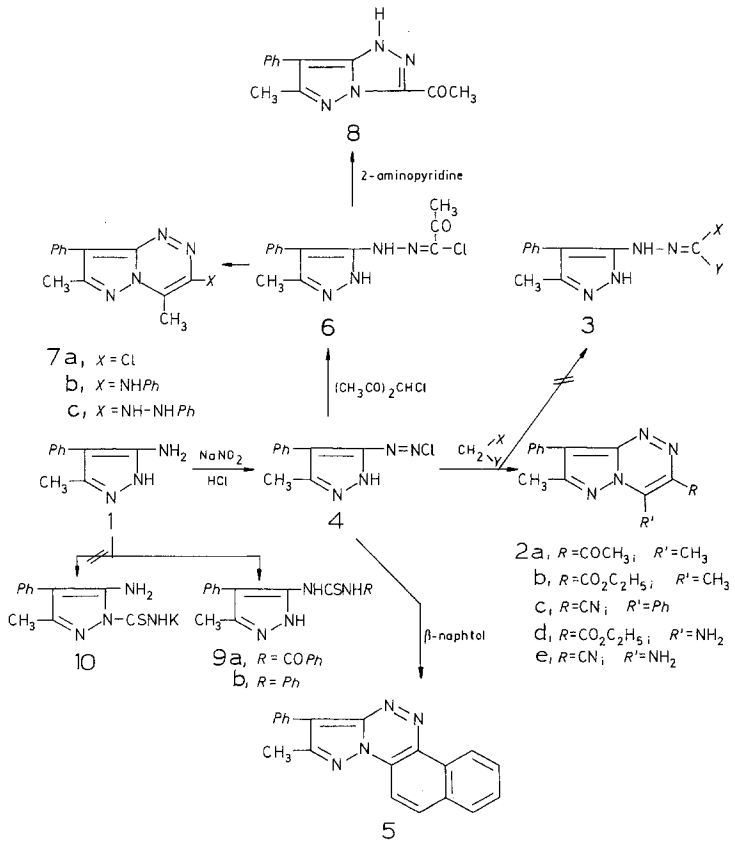
3-substituted pyrazolo[1,5—a]pyrimidines as well as its azo analogues has promoted this interest. In spite of the enormous number of reported derivatives of these ring systems to our knowledge 3-aryl-pyrazolo[1,5—a]-pyrimidines and analogous aryl derivatives of the azo analogues pyrazolo[1,5—c]-1,2,4-triazines and pyrazolo[1,5—a]-1,3,5-triazines have not yet been reported. As a part of our programe dealing with the synthesis and biological evaluation of fused pyrazole derivatives[12] we reported the results of our attempted synthesis of these derivatives from 5-amino-3-methyl-4-phenylpyrazole (**1**) utilising procedures similar to those developed recently by us[12–21] for the synthesis of other pyrazolo[1,5—c]-1,2,4-triazines, pyrazolo[1,5—c]-1,2,4-triazines, pyrazolo[1,5—a]-1,3,5-triazines and pyrazolo[1,5—a]-pyrimidines. It has been found that diazotation of **1** in the presence of concentrated hydrochloric acid affords in solution a product which reacted with active methylene derivatives namely acetylacetone, ethyl acetoacetates benzoylacetonitrile, ethyl cyanoacetate and malono-

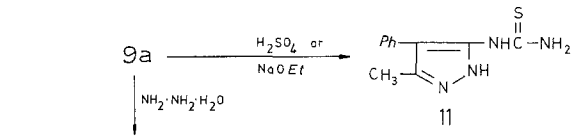


nitrile to yield the pyrazolo[1,5—c]-1,2,4-triazine derivatives **2 a—e**, respectively. The direct formation of cyclic products from the reaction of diazotised **1** with acetylacetone and with ethyl acetoacetate is in accordance with the previously reported direct formation of pyrazolo[1,5—c]-1,2,4-triazines on treatment of diazotised 5-aminopyrazoles with both reagents[13,14]. However, in previous reports hydrazone derivatives (cf. **3**) which were readily cyclised into pyrazolo[1,5—c]-1,2,4-triazines were reported to be formed from reaction of diazotised 5-aminopyrazoles with benzoylacetonitrile, ethyl cyanoacetate and malonitrile[13,14]. Assuming that the previously suggested mechanism for these reactions is the one operating here, it may be assumed that the reacting species in the present work is the diazobetain **4**[14].

Diazotised **1** reacted with β-naphthol to yield the pyrazolo[1,5—c]-1,2,4-triazine derivative **5** via a cyclocondensation reaction which took place under the coupling reaction conditions. This is similar to the previously reported behaviour of diazotised aminopyrazoles with β-naphthol[15].

In contrast to the observed direct formation of pyrazolo[1,5—c]-1,2,4-triazines on treating diazotised **1** with active methylene reagents and with β-naphthol, diazotised **1** coupled with α-chloroacetylacetone to yield the hydrazonyl chloride derivative **6**. **6** could be readily cyclised into a variety of pyrazolo[1,5—c]-1,2,4-triazines and pyrazolo[1,5—c]-1,2,4-triazoles. Thus, when an ethanolic solution of **6** was refluxed for one hour, it was quantitatively converted into the pyrazolo[1,5—c]-1,2,4-triazine derivative **7**. The pyrazolo[1,5—c]-1,2,4-triazine derivatives **7 b, c** could also be obtained on treatment of **6** with aniline and phenylhydrazine, respectively. On the other hand, compound **6** was cyclised into the pyrazolo[1,5—c]-1,2,4-triazole derivative **8** on refluxing in ethanol in the presence of piperidine or 2-aminopyridine.

It has been previously reported that the nature of the reaction product of 5-aminopyrazoles with isothiocyanic acid esters depends on the reaction conditions and the nature of substituents on the pyrazole ring[16]. Now it has



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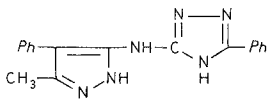

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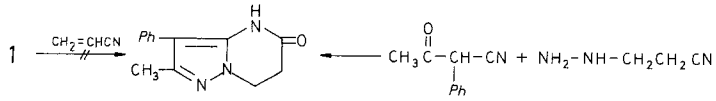
been found that **1** reacts with benzoyl isothiocyanate and with phenyl isothiocyanate to yield a 1:1 adduct. Two structures seemed possible for this adduct (cf. **9** and **10**). Structure **9** was considered most likely for the adducts based on the stability of the reaction products of **1** and isothiocyanates under conditions reported to effect decomposition of *N*-thiocarbamoylpyrazoles[17]. Attempts to effect cyclization of **9a** by the action of concentrated sulphuric acid or by ethanolic sodium hydroxide under conditions previously utilised to effect cyclization of 2-pyrazol-5-yl-3-arylthiourea has resulted in the decomposition of **9a** into the pyrazol-5-ylthiourea derivative **11**.

Similar to the recently reported behaviour of 1-pyrazol-5-yl-3-arylthioureas[18], **6a** reacted with hydrazine hydrate to yield the pyrazol-5-yl-1,2,4-triazole derivate **12**.

Cyanoethylation of 5-aminopyrazoles has been previously shown to afford 5-amino-1-β-cyanoethylpyrazole derivatives which could be readily cyclised into 4,5,6,7-tetrahydropyrazolo[1,5—a]pyrimidine derivatives[19,21]. However, attempts to utilise a similar procedure for the synthesis of the tetrahydropyrazolo[1,5—a]pyrimidine derivative **13** was obscured by the inability to effect cyanoethylation of **1** under a variety of experimental conditions. Consequently an alternate route utilising the reaction of β-cyanoethylhydrazine (**14**) and α-phenylacetoacetonitrile (**15**) was attempted. Again **12** was recovered almost unaffected after reflux with **11** in ethanol. However, when **15** was treated with **14** in refluxing acetic acid utilising previously reported procedure for condensation of benzoylacetonitrile and **14**, the pyrazolo[1,5—a]pyrimidine derivative **13** was obtained with excellent yield.



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The results obtained in the present work demonstrates the scope and limititions for the utility of our previously reported procedures for the synthesis of fused pyrazoles. Moreover several new pyrazole derivatives of interesting potential biological acitvity have been synthesised.

Experimental

All melting points are uncorrected. IR spectra were recorded on a pye-unicam SP 1000 spectrophotometer.

2-Methyl-3-phenyl-6,7-disubstitutedpyrazolo[1,5—c]-1,2,4-triazines (**1a—e**)

A solution of diazotised **1** (prepared from 0.1 mol of **1** and the appropriate quantities of concentrated hydrochloric acid and sodium nitrite as has been

described by us for the preparation of 3-phenylpyrazole diazonium chloride)[12] was added to a solution of the active methylene reagent (0.1 mol) in ethanol (150 ml) and sodium acetate (13.0 g). The reaction mixture was stirred at room temperature for 2 h and the solid product, so formed, was collected by filtration and crystallised from the proper solvent. The obtained pyrazolo[1,5—c]-1,2,4-triazines **2a—e** are listed in Table 1.

Reaction of diazotised **1** *with β-naphthol*

β-Naphthol was treated with diazotised **1** under the experimental conditions described above. The obtained pyrazolo[1,5—c]-1,2,4-triazine derivative **5** was purified by crystallization and is listed in Table 1.

Reaction of diazotised **1** *with α-chloroacetylacetone*

A solution of diazotised **1** (prepared from 0.1 mol of **1**) was added to a solution of 0.1 mol of α-chloroacetylacetone in ethanol (100 ml) and sodium acetate (3.5 g). The reaction mixture was stirred for 2 h at room temperature and the resulting solid product was collected by filtration and crystallised from ethanol.

Compound **6** formed yellow crystals; m.p. 162°; yield 70%. IR: 1,620 cm^{-1} (C=N), 1,675 cm^{-1} (acetyl CO).

$C_{13}H_{13}ON_4Cl$. Found: C 56.2, H 4.8, Cl 13.0%.
Calcd: C 56.4, H 4.7, Cl 12.8%.

Table 1. *List of the pyrazolo[1,5—c]-1,2,4-triazines* **2a—e** *and* **5**

Compd.	M.p.°	Yield %	Mol. Formula*	IR (selected bands)
2a	122	80	$C_{15}H_{14}ON_4$	1,700 cm^{-1} (acetyl CO)
2b	154	60	$C_{16}H_{16}O_2N_4$	1,750 cm^{-1} (ester CO)
2c	222	75	$C_{19}H_{13}N_5$	2,220 cm^{-1} (CN)
2d	184	60	$C_{15}H_{15}O_2N_5$	3,450, 3,350 cm^{-1} (ν NH_2); 1,700 cm^{-1} (ester CO) and 1,630, 1,620 cm^{-1} (δ NH_2)
2e	275	80	$C_{13}H_{10}N_6$	3,360, 3,220, 3,180 (ν NH), 2,225 (CN) and 1,650 (δ NH_2)
5	198	60	$C_{20}H_{14}N_4$	no absorption above 1,600 cm^{-1} except at 3,000 cm^{-1} for CH_3

* The C, H, N analysis agreed in all cases well with the postulated structures.

6-Chloro-2,7-dimethyl-3-phenylpyrazolo[1,5—c]-1,2,4-triazine (**7a**)

A solution of **6** (2.0 g) in ethanol 50 ml was refluxed for 1 h. The solvent was then removed by evaporation. The remaining solid product was triturated with water and collected by filtration.

Compound **7 a** formed orange crystals; m.p. 112°; yield 90%.

$C_{13}H_{11}N_4Cl$. Found: C 60.4, H 4.3%.
Calcd: C 60.3, H 4.3%.

2,7-Dimethyl-6-substituted amino-3-phenylpyrazolo[1,5—c]-1,2,4-triazines (**7 c**)

A suspension of **6** (0.01 mol) in ethanol (30 ml) was treated with aniline and or phenylhydrazine (0.012 mol). The reaction mixture was refluxed for 4 h and then evaporated in vacuo. The remaining product was triturated with water and the resulting solid was collected by filtration and crystallised from ethanol.

Compound **7 b** formed orange crystals 202; yield 80%.

$C_{19}H_{17}N_5$. Found: C 72.2, H 5.3, N 22.0%.
Calcd: C 72.4, H 5.4, N 22.2%.

Compound **7 c** formed orange crystals; m.p. 162°; yield 85%.

$C_{19}H_{18}N_6$. Found: C 69.1, H 5.5, N 25.1%.
Calcd: C 69.1, H 5.5, N 25.5%.

6-Acetyl-2-methyl-3-phenylpyrazolo[1,5—c]-1,2,4-triazole (**8**)

A suspension of **6** (2.0 g) in ethanol (30 ml) was treated with 2-aminopyridine (1.0 g). The reaction mixture was refluxed for 2 h then evaporated in vacuo. The remaining product was triturated with water. The resulting solid product was collected by filtration and crystallised from acetic acid.

Compound **8** formed brown crystals; m.p. 242; yield 80%. IR: 1,680 cm^{-1} (CO).

$C_{13}H_{12}ON_4$. Found: C 64.9, H 5.2%.
Calcd: C 65.5, H 5.0%.

1-Benzoyl-3-(3-methyl-4-phenylpyrazol-5-yl)thiourea (**9 a**)

To a benzoyl isothiocyanate solution in acetone (prepared from 0.12 g of NH_4SCN and 0.1 mol of benzoyl chloride)[13] compound **1** was added. The reaction mixture was refluxed for 3 h and then evaporated. The remaining product was then triturated with water and the so formed solid product was collected by filtration.

Compound **9 a** formed pale yellow crystals from methanol—water mixture; m.p. 198–200°; yield 90%. IR: 3,420, 3,340 and 3,200 (ν NH) and 1,680 cm^{-1} (benzoyl CO).

$C_{18}H_{16}ON_4S$. Found: C 64.0, H 5.0, N 17.1, S 9.4%.
Calcd: C 64.2, H 4.7, N 16.6, S 9.5%.

1-Phenyl-3-(3-methyl-4-phenylpyrazol-5-yl)thiourea (**9 b**)

A solution of **1** (0.01 mol) in pyridine (50 ml) was treated with phenyl isothiocyanate (0.01 mol). The reaction mixture was refluxed for 6 h and then evaporated in vacuo. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised.

Compound **9 b** formed pale yellow crystals from ethanol; m.p. 182°; yield 80%.

$C_{17}H_{16}N_4S$. Found: C 66.3, H 5.2, S 10.4%.
Calcd: C 66.2, H 5.1, S 10.3%.

1-(3-Methyl-4-phenylpyrazol-5-yl)thiourea (**11**)

(a) *From* **9a** *and sulphuric acid*:

A mixture of **6a** (2.0 g) and concentrated sulphuric acid (1.5 ml) was left over night at room temperature then poured onto cold water and neutralised by the addition of ammonia. The solid product, so formed, was collected by filtration and crystallised from methanol.

Compound **11** formed colourless crystals; m.p. 192°; yield 60%.

$C_{11}H_{12}N_4S$. Found: C 56.8, H 5.2, S 14.2%.
Calcd: C 56.9, H 5.2, S 13.8%.

(b) *From* **9a** *and ethanolic sodium ethoxide*:

A solution of **9a** (2.0 g) in ethanol (30.0 ml) was treated with sodium hydroxide (0.5 g). The reaction mixture was refluxed for 3 h and then poured onto cold water. The solid product, so formed, was collected by filtration, crystallised and identified (m.p. and mixed m.p.) as **11**. Yield 80%.

5-(3-Phenyl-1,2,4-triazol-5-yl)amino-3-methyl-4-phenylpyrazole (**12**)

A solution of **9a** (2.0 g) in ethanol (50 ml) was treated with hydrazine hydrate (1.0 ml; 98%). The reaction mixture was refluxed for 6 h then evaporated in vacuo. The remaining product was triturated with water and the resulting solid product was collected by filtration and crystallised from benzene.

Compound **12** formed white crystals; m.p. 185°; yield 70%.

$C_{18}H_{16}N_6$. Found: C 67.9, H 5.0, N 24.0%.
Calcd: C 68.3, H 5.1, N 23.6%.

3-Methyl-4-phenyl-5-oxo-4,5,6,7-tetrahydroxypyrazolo[1,5—a]-pyrimidine (**13**)

A solution of **15** (0.01 mol) in acetic acid (30 ml) was treated with **14** (0.01 mol). The reaction mixture was refluxed for 7 h and then evaporated with water and the resulting solid product was collected by filtration and crystallised from methanol.

Compound **13** formed colourless crystals; m.p. 180°; yield 70%. IR: 3,220 cm^{-1} (NH), 2,940, 2,890 cm^{-1} (CH_2) and 1,700 cm^{-1} (ring CO).

$C_{13}H_{13}ON_3$. Found: C 68.5, H 5.7%.
Calcd: C 68.7, H 5.7%.

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