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214. Pyrimidine Derivatives and Related Compounds II: Synthesis of some Derivatives of Pyrimido[1,2:2',3']pyrazolo- [1,5-*a*]pyrimidines, a New Ring System

by **Mohamed Helmi Elnagdi, Mohamed Mohamed Mohamed Sallam,
and Mohamed Ajmal Mohamed Ilias**

Department of Chemistry, Faculty of Science, Cairo University, Giza, Egypt

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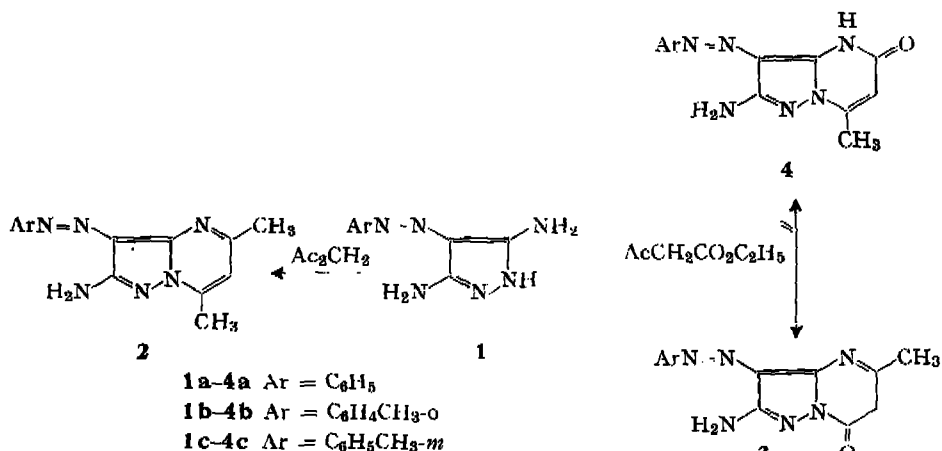
Summary. 3,5-Diamino-4-phenylazo-pyrazoles (**1a–1c**) react with acetylacetone and with ethyl acetoacetate to yield the corresponding pyrazolo[1,5-*a*]pyrimidine derivatives **2a–2c** and **3a–3c**, respectively.

Whereas **1a–1c** add readily to methyl acrylate yielding the 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine derivatives **5a–5c**, **1a–1c** add to methylacrylonitrile or methyl methacrylate only under drastic conditions to yield **5d–5f**. The pyrimido[1,2:2',3']pyrazolo[1,5-*a*]pyrimidine derivatives **10a–10c** are prepared by the action of acrylonitrile on **2a–2c**. Compounds **10a–10c** are readily converted into the corresponding oxo derivatives **12a–12c** on treatment with acetic acid-hydrochloric acid mixture.

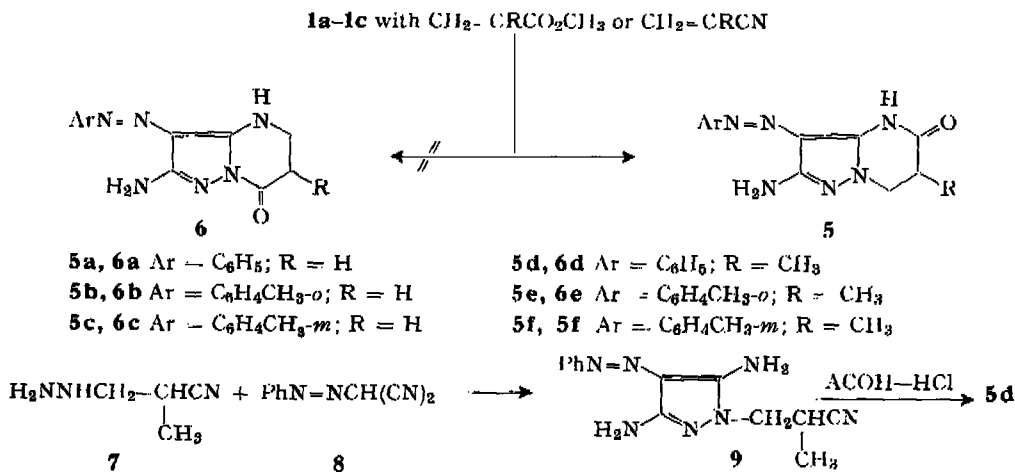
Earlier work in this laboratory directed for the synthesis of fused pyrimidines with bridgehead nitrogen [1] [2] stimulated an investigation of a possible route for the synthesis of substituted pyrimido[1,2:2',3']pyrazolo[1,5-*a*]pyrimidines, derivatives of a novel ring system. *Ried et al.* [3] have reported that 3-unsubstituted-2-aminopyrazolo[1,5-*a*]pyrimidines react with β -bifunctional reagents to yield pyrido[3,4:3',4']-pyrazolo[1,5-*a*]pyrimidines. It seemed to us that 3-substituted-2-aminopyrazolo[1,5-*a*]pyrimidines may react with bifunctional reagents to yield derivatives of the required ring system. Literature survey indicated that 3-substituted-2-aminopyrazolo[1,5-*a*]pyrimidines have been prepared *via* a multistage inefficient synthesis [4] and only through pyrazolo[1,5-*a*]pyrimidine intermediates. In the present paper we report a convenient synthesis of a variety of 3-arylazo-2-aminopyrazolo[1,5-*a*]pyrimidine derivatives from the readily obtainable 3,5-diamino-4-arylazopyrazoles **1a–1c** and on the utility of these pyrazolo[1,5-*a*]pyrimidines for the synthesis of a variety of arylazopyrimido[1,2:2',3']pyrazolo[1,5-*a*]pyrimidine derivatives. In this manner, the 2-amino-3-arylazo-5,7-dimethylpyrazolo[1,5-*a*]pyrimidine derivatives **2a–2c** were prepared by the action of acetylacetone on **1a–1c** in refluxing acetic acid. The structure of the products was supported by analytical and IR. data.

When the compounds **1a–1c** were treated with ethyl acetoacetate in refluxing acetic acid, the pyrazolo[1,5-*a*]pyrimidine derivatives **3a–3c** or possible isomeric **4a–4c** were obtained in high yields. Structure **3** was preferred on the basis of IR.

spectra which revealed pyrimidine ring $>\text{CO}$ absorption at $\sim 1710\text{ cm}^{-1}$ almost with no shift from that reported [1] [2] for pyrimidine ring $>\text{CO}$ absorption of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine. If these pyrazolo[1,5-*a*]pyrimidines had formula 4, they would exhibit a large downshift in the frequency of the ring $>\text{CO}$, due to the conjugation of the $>\text{CO}$ with $-\text{C}-\text{C}$. This conclusion is also based on the reported behaviour of 5-aminopyrazoles toward the action of β -ketoesters [5].



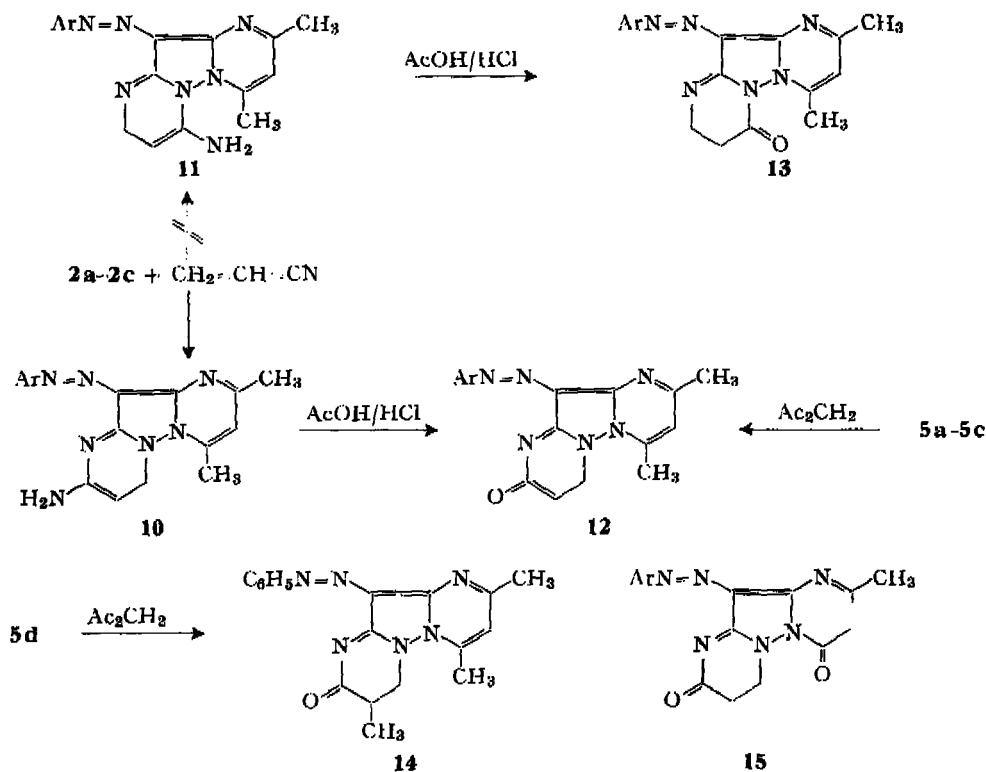
In a previous paper [1] it has been shown that **1a** reacts with methyl acrylate in refluxing pyridine to yield 2-amino-3-phenylazo-5-oxo-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidine (**5a**). Now, we have found that **1b** and **1c** react similarly to afford the pyrazolo[1,5-*a*]pyrimidine derivatives **5b**, **5c**, respectively. Under similar conditions **1a-1c** did not add to methylacrylonitrile or methyl methacrylates. But, when **1a-1c** were refluxed for a long period with either of the reagents in pyridine and in the presence of a catalytic amount of potassium hydroxide, the reaction products seemed to have either structure **5** or the possible isomeric **6**. Structure **5** was established for these products by synthesis of **5d** via the action of β -cyanopropylhydrazine (**7**) on phenylazomalononitrile (**8**) and cyclization of the resulting 3,5-diamino-1- β -cyanopropyl-4-aryloxy-pyrazole (**9**).



The pyrazolo[1,5-*a*]pyrimidine derivatives **2a-2c** reacted with acrylonitrile to yield products the analytical data for which indicated addition of one molecule of either of the reagents. The IR. spectra of these products presented an absorption band for only one amino group. Two structures seemed possible for these products, *i.e.* **10** and **11**. When these products were boiled with acetic acid-hydrochloric acid mixture for a short period, the corresponding oxo derivatives **12** or possible isomeric **13** were obtained. These derivatives were found identical with products obtained by the action of acetylacetone on the pyrazolo[1,5-*a*]pyrimidine derivatives **5a-5c**, thus establishing structure **10** for the reaction products of **2a-2c** with acrylonitrile and structure **12** for their hydrolysis products.

Attempts to add methylacrylonitrile or methyl methacrylate to **2a-2c** were unsuccessful. However, the pyrimido[1,2:2',3']pyrazolo[1,5-*a*]pyrimidine derivative **14** could be prepared by action of acetylacetone on the tetrahydropyrazolo[1,5-*a*]pyrimidine derivative **5d** in aqueous pyridine in presence of a catalytic amount of potassium hydroxide. Analytical and IR. data for the product are in good agreement with the proposed structure.

Compounds **5a-5c** reacted with ethyl acetoacetate to yield products for which structure **15** is proposed on the basis of analytical and IR. data, and analogy to the well established behaviour of 5-aminopyrazoles toward the action of β -ketoesters. However, we were not able to synthesise compounds **15a-15c** by action of acrylo-



10a, 12a, 15a Ar = C₆H₅

10b, 12b, 15b Ar = C₆H₄CH₃-*o*

10c, 12c, 15c Ar = C₆H₄CH₃-*m*

nitrile on **3a–3c**, since the cyanoethylation of these compounds afforded polycyanoethylated products for which no complete structure could be deduced.

Experimental

The m.p.s. are uncorrected. IR. Spectra were recorded in KBr on a Perkin-Elmer 337 spectrophotometer.

2-Amino-3-arylazo-5,7-dimethyl-pyrazolo[1,5-a]pyrimidines (2a–2c) (Table 1). To a solution of each of **1a–1c** (0.1 mol) in acetic acid (100 ml) acetylacetone (0.1 mol) was added. The mixture was refluxed for 12 h and evaporated *in vacuo*. The residue was diluted with water and rendered basic by addition of ammonia. The resulting precipitate was filtered off and crystallized from ethanol.

2-Amino-3-arylazo-7-oxo-4,5-dihydropyrazolo[1,5-a]pyrimidines (3a–3c) (Table 1). To a suspension of each of **1a–1c** (0.1 mol) in acetic acid (100 ml) ethyl acetoacetate (0.1 mol) was added. The mixture was refluxed for 10 h and then treated as described above (crystallization from acetic instead of ethanol).

2-Amino-3-arylazo-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-5-ones (5b, 5c) (Table 1). These were prepared using procedure described in [1] for the synthesis of **5a**.

2-Amino-3-arylazo-6-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrimidin-5-ones (5d–5f) (Table 1). – (a) A solution of each of **1a–1c** (0.1 mol) in pyridine (80 ml) and water (20 ml) was treated with one ml of 40% potassium hydroxide solution then with methylacrylonitrile or methyl methacrylate (0.12 mol). After refluxing for 15 h the mixture was evaporated *in vacuo*, the residue was triturated with water, boiled for a short period with acetic acid and then left to stand. The

Table 1. Pyrazolo[1,5-a]pyrimidine derivatives **2a–2c**, **3a–3c**, **5b–5f**

Compound	m.p. °C	IR. cm ⁻¹ , selected bands	Formula	Analysis, %		
				Calc. Found	C	H N
2a	232	3415, 3280 (NH ₂ vibration); 1620 (NH ₂ deformation)	C ₁₄ H ₁₄ N ₆	63.14 62.90	5.30 5.52	31.56 31.51
2b	238	3410, 3290 (NH ₂ vibration); 1625 (NH ₂ deformation)	C ₁₅ H ₁₆ N ₆	64.27 64.20	5.75 5.81	29.98 30.00
2c	216	3410, 3290 (NH ₂ vibration); 1620 (NH ₂ deformation)	C ₁₅ H ₁₆ N ₆	64.27 64.11	5.75 5.76	29.98 30.02
3a	260	3360, 3280, 3200 (NH ₂ and NH); 1715 (ring CO); 1630 (NH ₂ deformation)	C ₁₃ H ₁₂ N ₆ O	58.20 58.30	4.51 4.61	31.33 31.00
3b	260		C ₁₄ H ₁₄ N ₆ O	59.56 59.66	5.00 4.80	29.77 30.00
3c	270		C ₁₄ H ₁₄ N ₆ O	59.56 59.86	5.00 4.90	29.77 29.50
5b	206	3400, 3325, 3280–3240 (NH ₂ vibrations); 2250 (CN); 1620 (NH ₂ deformation)	C ₁₃ H ₁₄ N ₆ O	57.76 58.00	5.22 5.00	31.10 31.00
5c	300	3400, 3325, 3280, 3240 (NH ₂ vibration); 2250 (CN); 1620 (NH ₂ deformation)	C ₁₃ H ₁₄ N ₆ O	57.76 57.70	5.22 5.31	31.10 31.10
5d	240	3440, 3300, 3270 (NH ₂ vibration); 1700 (ring CO); 1625 (NH ₂ deformation)	C ₁₃ H ₁₄ N ₆ O	57.76 57.51	5.22 5.40	31.10 30.90
5e	220		C ₁₄ H ₁₆ N ₆ O	59.14 59.22	5.67 5.81	29.56 29.46
5f	192		C ₁₄ H ₁₆ N ₆ O	59.14 59.15	5.67 5.40	29.56 29.30

solid product obtained was filtered off and crystallized from ethanol. **9** formed yellow crystals; m.p. 126. – IR.: 3390, 3320, 3280, 3250 cm^{-1} (NH_2 vibrations), 2250 cm^{-1} (CN) and 1620 cm^{-1} (NH_2 deformation).

$\text{C}_{13}\text{H}_{15}\text{N}_7$ Calc. C 57.99 H 5.61 N 36.47% Found C 58.11 H 5.76 N 36.40%

(b) *Cyclization of 9 by action of AcOH-HCl mixture.* To a suspension of compound **9** (5.0 g) in acetic acid (80 ml) concentrated hydrochloric acid (5 ml) was added. The mixture was refluxed for 3 h and then evaporated *in vacuo*. The residue was triturated with ethanol and the resulting solid was filtered off, crystallized (yield 76%), and identified as **5a** by m.p. and mixed m.p.

7-Amino-5-arylaazo-1,3-dimethylpyrimido[1,2:2',3']pyrazolo[1,5-a]pyrimidines (10a-10c) (Table 2). To a suspension of each of **2a-2c** (0.1 mol) in pyridine (100 ml) and water (20 ml), acry-

Table 2. *Pyrimido[1,2:2',3']pyrazolo[1,5-a]pyrimidine derivatives*

Com- pound	m. p. °C	IR. cm^{-1} , selected bands	Formula	Analysis, %			
				Calc. Found	C	H	N
10a	220	3415, 3380 (NH_2 vibration); 1620 (NH_2 deformation)	$\text{C}_{17}\text{H}_{17}\text{N}_7$	63.93 63.70	5.37 5.32	30.70 30.61	
10b	255		$\text{C}_{18}\text{H}_{19}\text{N}_7$	64.84 65.00	5.74 5.61	29.41 29.30	
10c	234		$\text{C}_{18}\text{H}_{19}\text{N}_7$	64.84 64.66	5.74 5.87	29.41 29.58	
12a	291	1635 (ring CO); 1605 (C–N)	$\text{C}_{17}\text{H}_{16}\text{N}_6\text{O}$	63.73 63.50	5.04 4.89	26.24 26.22	
12b	206		$\text{C}_{18}\text{H}_{18}\text{N}_6\text{O}$	64.65 64.41	5.43 5.33	25.14 25.31	
12c	310		$\text{C}_{18}\text{H}_{18}\text{N}_6\text{O}$	64.65 64.65	5.43 5.40	25.14 25.00	
14	300	1680 (ring CO); 1610 (C–N)	$\text{C}_{18}\text{H}_{18}\text{N}_6\text{O}$	64.65 64.31	5.43 5.21	25.14 25.25	
15a	220	3320 (NH vibration); 1720, 1700 (ring CO groups); 1610 (C=N)	$\text{C}_{18}\text{H}_{14}\text{N}_6\text{O}_2$	59.62 59.68	4.38 4.57	26.07 26.30	
15b	212		$\text{C}_{17}\text{H}_{16}\text{N}_6\text{O}_2$	60.77 60.68	4.80 4.62	24.99 25.00	
15c	218		$\text{C}_{17}\text{H}_{16}\text{N}_6\text{O}_2$	60.77 60.80	4.80 5.00	24.99 24.86	

onitrile (0.15 mol) and one drop of 40% potassium hydroxide solution were added. The mixture was refluxed for 10 h and then evaporated *in vacuo*. The residue was triturated with water, filtered off and crystallized from ethanol.

5-Arylaazo-1,3-dimethyl-7,8-dihydro-7-oxo-pyrimido[1,2:2',3']pyrazolo[1,5-a]pyrimidines (12a-b) (12c) (Table 2). – (a) *From compounds 10a-10c and AcOH-HCl mixture.* The procedure described for the cyclization **9** into **5a** was adopted. Crystallization of the reaction products from ethanol yielded brownish-yellow crystals.

(b) *From 5a-5c and acetylacetone.* To a solution of each of **5a-5c** (0.1 mol) in acetic acid (100 ml) acetylacetone (0.12 mol) was added. After refluxing for 10 h the mixture was evaporated *in vacuo*. The residue was triturated with water. The resulting solid was filtered off and identified by m.p. and mixed m.p. as **12a-12c**.

5-Phenylazo-7,8-dihydro-1,3,8-trimethyl-pyrimido[1,2:2',3']pyrazolo[1,5-a]pyrimidine (14) (Table 2). Was synthesised by reaction of acetylacetone with compound **5d** under the conditions described above for the synthesis of **12a-12c** by reaction of **5a-5c** with acetylacetone.

5-Arylaazo-1,7-dioxo-1,2,7,8-tetrahydropyrimido[1,2:2',3']pyrazolo[1,5-a]pyrimidines (15a-15c) (Table 2). A mixture of each of **5a-5c** (0.1 mol) and ethyl acetoacetate (0.15 mol) was heated at 170° (bath temperature) for 5 h, then dissolved in ethanol, and left to stand. The resulting solid was filtered off and crystallized from ethanol.

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215. Intramolekulare Cycloadditionen in der Reihe der Binaphthyle¹⁾

von **Yushin Nakamura, Roger Hollenstein, Janos Zsindely und Hans Schmid**

Organisch-chemisches Institut der Universität Zürich

Rämistrasse 76, 8001 Zürich

und **Willi E. Oberhänsli**

Forschungsabteilung der F. Hoffmann-La Roche & Co. AG, Basel

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Intramolecular cycloadditions of binaphthyl compounds. *Summary.* Three new bridged ketones, **7**, **8** and **9**, have been isolated in 44%, 3% and 19% yields respectively (Scheme 2) by heating 2,2'-bis-allyloxy-1,1'-binaphthyl (**5**) at 215° for 16 hours. These compounds could be epimerized about C(16) by bases, and in particular **9** yielded the new epimer **10**. The structures of the alcohols obtained by reduction of the keto group are also given (Scheme 2). The constitution of all compounds was derived from spectroscopic data, chiefly from their ¹H-NMR. spectra (tab. 2, 3 and fig. 1). The assignments were based on the observed long-range coupling constant between H(*endo*)-C(16) and H(*endo*)-C(5) in **7** and **10** and on the analysis of chemical shifts and coupling constants in both the ketones and their derivatives. Moreover, the structures of the compounds investigated have been proved by x-ray analysis of ketone **8** (chap. 3, fig. 2). The thermal conversion of binaphthylether **5** to the bridged ketones proceeds via an intramolecular *Diels-Alder* reaction, followed by *Claisen* rearrangement (Scheme 8). On heating, the bis-β-methylallyl ether **20** yielded the ketone **21** and a small amount of the ether **23** (Schemes 5 and 7). Ether **23** and binaphthyl monoallyl ether **26** were converted thermally to the bridged ketones **31** (Scheme 7) and **27** (Scheme 6) respectively. In addition, **26** underwent an intramolecular *ene*-reaction to give the spiroketone **28** (Schemes 6 and 9). The structures of these compounds were also established, mainly by analysis of their ¹H-NMR. spectra.

1. Thermische Reaktionen von 2,2'-Bis-allyloxy-1,1'-binaphthyl (**5**).

Während Allyl-(1-allylnaphth-2-yl)-äther (**1**) und Allyl-(1-methylnaphth-2-yl)-äther (**3**) beim Erhitzen auf 200° mit den entsprechenden Benzo-cyclohexa-2,4-dienonen **2** bzw. **4** im thermischen Gleichgewicht stehen (Schema 1) und Propargyl-(1-alkylnaphth-2-yl)-äther bei Temperaturen von 185–200° eine *Claisen*-Umlagerung (mit Folgereaktionen) eingehen [4], wurde 2,2'-Bis-allyloxy-1,1'-binaphthyl (**5**) beim Erhitzen bis 185° nicht verändert. Auch bei höheren Reaktionstemperaturen wurde nicht das erwartete Bis-benzocyclohexadienon **6** erhalten (Schema 1).

16-Stdg. Erhitzen von **5** in Mesitylen auf 215° lieferte drei Produkte **7**, **8** und **9** (44%, 3% bzw. 19% Ausbeute) (Schema 2), die chromatographisch getrennt werden

¹⁾ Teilweise vorgetragen an der Herbstversammlung der Schweizerischen Chemischen Gesellschaft am 20.10.1973 in Lugano [1].