Studies on Condensed Pyrazoles
A New Route for Synthesis of Pyrazolo[4,3-c]pyrazoles

Mohamed Hilmy Elnagdi[a,*], Ahmed Hafez Hussien Elghandour[a], Kamal Usef Sadek[b], and Mahmoud Mohamed Mahfouz Ramiz[c]

Chemistry Department, Faculty of Science, Cairo University, and Minia University, A.R. Egypt[a,b]
Faculty of Electronic Engineering, Menoufia University Menouf, A.R. Egypt[c]

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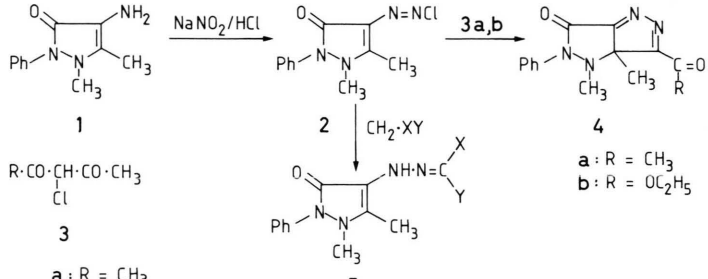
A novel synthesis of pyrazolo[4,3-c]pyrazoles *via* 1,5-dipolar cyclization of products of coupling of 2,3-dimethyl-1-phenyl-5-oxo-3-pyrazolin-4-diazonium chloride with active methylene reagents is reported.

Interest in the chemistry of condensed pyrazoles has recently been revived [1–3]. The interesting biological activities of condensed pyrazoles [4] may be due to this revival of interest. In the last decade we have been involved in a program directed for developing new approaches for the synthesis of polyfunctionally substituted condensed pyrazoles utilizing inexpensive and readily obtainable starting materials [5,6]. In conjunction to this work we report here a new route for the synthesis of pyrazolo[4,3-c]pyrazoles. Synthetic approaches to this ring system are rather limited and generally require not readily accessible starting materials [7]. Claimed synthesis of these derivatives *via* cyclization of 4-acylpyrazol-5-one phenylhydrazones proved to be incorrect [8]. Some time ago we reported that refluxing of the product of coupling of 2,3-dimethyl-1-phenyl-5-oxo-3-pyrazolin-4-diazonium chloride (formed by diazotization of **1** in presence of hydrochloric acid) **2** with α-chloroacetylacetone **3a** and ethyl α-chloroacetylacetate **3b** affords the pyrazolo[4,3-c]pyrazoles (**4a, b**) [9]. We became interested thus, to see if this approach to pyrazolo[4,3-c]pyrazoles can be extended to constitute a new general route to derivatives of this ring system.

Compound **2** couples with active methylene reagents to yield the hydrazones **5a–g.** Compounds **5e, f** have been previously reported [10]. The hydrazone structure **5** was prefered for these products over the possible azo form based on UV spectra which are characteristic for arylhydrazones [11].

When **5a, b** were refluxed in ethanol in presence of concentrated hydrochloric acid, products **8a, b** were obtained *via* a 1,5-dipolar cyclization [9] that yields



* Reprint requests to Prof. Dr. M. H. Elnagdi.

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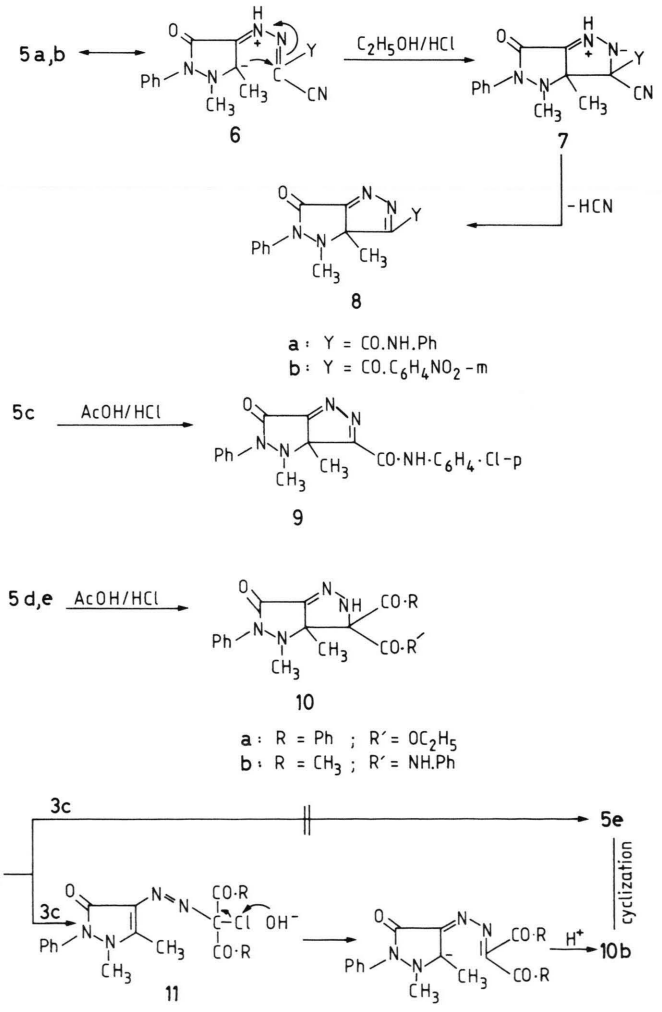
at first **7a,b** *via* dipolar form **6.** These then loose hydrogen cyanide to yield the more stable **8a,b.**

Compound **5c** cyclized to give **9** on refluxing in acetic acid, hydrochloric acid mixture. In contrast to this, compound **5d** only isomerized on treatment with AcOH/HCl to form **10a.**

Aryl diazonium salts have been reported to couple with α-chloroketones **3a,b** to yield hydrazonyl halides [12]. In earlier work [9], we reported that the reaction of **2** with **3a,b** affords a coupling product which when boiled in ethanolic hydrochloric acid affords **4a,b** *via* assumed intermediacy of the hydrazonyl halides **11a,b.** The latter (**11**) were not, however, characterized.

It has been found now that **3c** couples with **2** to yield th product **10b** instead of **5e.** Compound **10b** proved different from **5e,** prepared *via* coupling **2** with acetoacetanilide. Structure **10b** was confirmed by cyclizing **5e.** The formation of **10b** from **2** and **3c** is assumed to proceed *via* **11.** The products of coupling of **2** with **3a,b,** unexpectedly were found to be **5f,g,** identical with authentic speciments prepared by coupling of **2** with acetylacetone and ethyl acetoacetate respectively. The elimination of halogen in this reaction is the first reported halogen elimination in the Japp-Klingeman reaction.

Compounds **5f,g** afforded **4a,b** on refluxing in acetic acid in the presence of concentrated hydro-



chloric acid. Compound **5e** did not cyclize under our reaction condition.

Experimental

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP 1100 spectrophotometer. ^{1}H NMR spectra on a Varian EM-390 spectrometer (90 MHz) using TMS as internal standard. Microanalytical data were obtained from the Microanalytical Data Unit at Cairo University.

Compounds **5a–g:** – *General procedure*

A solution of 2.5 g of **2** (0.01 mol) in water (20 ml) was added to a cold solution of the active methylene reagent (0.01 mol) in ethanol (100 ml) and sodium acetate (0.9 g; 0.012 mol) with stirring. The reaction mixture was kept at 0 °C for 3 h. The precipitated product was filtered off, washed with water and recrystallized.

Compounds **8a, b:**

A solution of 3.4 g of **5a** or 4.0 g of **5b** (0.01 mol) in ethanol (50 ml) was treated with 10 ml of concentrated HCl (37.5%). The reaction mixture was refluxed for 3 h. The solvent was removed *in vacuo* and the remaining solid product was treated with water and left to stand. The product, so formed, was collected by filtration and recrystallized.

Compounds **9, 10a, b:**

A suspension of 4.2 g of **5c,** 4.0 g of **5d,** or 3.9 g of **5e** (0.01 mol) in AcOH (50 ml) was treated with 10 ml of concentrated HCl (37.5%), and the reaction mixture refluxed for 3 h. The solvent was removed *in vacuo* and the remaining solid product was treated with water. The product, so formed, was collected by filtration and recrystallized.

Table I. List of the new compounds.

Compound	Yield [%]	m.p [°C] (solvent)	Molecular formula	Elementary analysis [%]	C	H	N	Cl
5a	65	160 (ethanol)	$C_{20}H_{18}N_6O_2$ (347.4)	Calcd	64.15	4.84	22.44	
				Found	64.52	4.56	22.81	
5b	60	> 300 (ethanol)	$C_{20}H_{16}N_6O_4$ (404.4)	Calcd	59.40	3.98	20.78	
				Found	59.73	3.98	21.02	
5c	70	220 (ethanol)	$C_{21}H_{20}N_5O_3Cl$ (425.9)	Calcd	59.22	4.73	16.44	8.32
				Found	59.60	4.95	16.15	8.01
5d	60	133 (ethanol-dioxan)	$C_{22}H_{22}N_4O_4$ (406.4)	Calcd	65.01	5.45	13.78	
				Found	65.22	5.73	13.95	
5e	60	224 (dioxan)	$C_{21}H_{21}N_5O_3$ (391.4)	Calcd	64.43	5.40	17.89	
				Found	64.72	5.71	18.23	
5f	55	166 (ethanol)	$C_{16}H_{18}N_4O_3$ (314.3)	Calcd	61.13	5.77	17.82	
				Found	61.49	6.02	18.17	
5g	65	160 (ethanol-DMF)	$C_{17}H_{20}N_4O_4$ (344.4)	Calcd	59.29	5.85	16.27	
				Found	59.61	6.10	16.62	
8a	55	94 (ethanol)	$C_{19}H_{17}N_5O_2$ (347.4)	Calcd	65.96	4.93	20.16	
				Found	65.62	5.31	20.35	
8b	50	170 (ethanol)	$C_{19}H_{16}N_6O_4$ (392.4)	Calcd	58.15	4.11	21.41	
				Found	58.42	4.42	21.75	
9	60	100 (ethanol)	$C_{19}H_{16}N_5O_2Cl$ (381.8)	Calcd	59.76	4.22	18.34	9.28
				Found	60.02	4.53	18.70	9.55
10a	65	110 (methanol)	$C_{22}H_{22}N_4O_4$ (406.4)	Calcd	65.01	5.45	13.78	
				Found	65.22	5.73	13.95	
10b	60	190 (ethanol)	$C_{21}H_{21}N_5O_3$ (391.4)	Calcd	64.44	5.41	17.89	
				Found	64.70	5.75	17.69	

Table II. IR and ^{1}H NMR data of the new compounds.

Compound	IR [cm^{-1}]	^{1}H NMR [ppm]
5a	3300–2900 (NH); 2250 (CN); 1675 (CO); 1630 (C=N)	2.4 (s, 3H, CH_3); 3.8 (s, 3H, N–CH_3); 7.0–7.7 (m, 10H$_{arom.}$); 11.3 (s, br, 1H, NH); 14.2 (s, 1H, NH)
5b	3600–3000 (NH); 2220 (CN); 1650 (CO); 1600 (C=N)	2.4 (s, 3H, CH_3); 3.2 (s, 3H, N–CH_3); 7.1–7.9 (m, 9H$_{arom.}$); 8.6 (s, br, 1H, NH)
5c	3400–2900 (NH); 1650 (CO); 1620 (C=N)	2.4 (s, 3H, CH_3); 2.5 (s, 3H, CH_3CO); 3.2 (s, 3H, N–CH_3); 7.3–7.7 (m, 9H$_{arom.}$); 11.3 (s, 1H, NH); 14.2 (s, 1H, NH)
5d	3600–2950 (NH); 1650 (CO); 1600 (C=N)	1.2 (t, 3H, CH_3); 2.1 (s, 3H, CH_3); 3.0 (s, 3H, N–CH_3); 4.2 (q, 2H, CH_2); 7.1–7.8 (m, 10H$_{arom.}$); 11.8 (s, br, 1H, NH)
5e	3400–2900 (NH); 1650 (CO); 1600 (C=N)	2.3 (s, 3H, CH_3); 2.5 (s, 3H, CH_3CO); 3.1 (s, 3H, N–CH_3); 7.1–7.6 (m, 10H$_{arom.}$); 8.0 (s, 1H, NH); 8.1 (s, 1H, NH)
5f	3200–2900 (NH); 1670 (CO); 1620 (C=N)	2.4 (s, 3H, CH_3); 2.5 (s, 3H, CH_3CO); 3.2 (s, 3H, N–CH_3); 7.2–7.6 (m, 5H$_{arom.}$); 14 (s, br, 1H, NH)
5g	3350–2900 (NH); 1660 (CO); 1630 (C=N)	1.2 (t, 3H, CH_3); 2.2 (s, 3H, CH_3); 3.2 (s, 3H, CH_3CO); 3.3 (s, 3H, N–CH_3); 4.2 (q, 2H, CH_2); 7.2–7.6 (m, 5H$_{arom.}$); 14.2 (s, br, 1H, NH)
8a	3280, 3220, 3180 (NH); 1680 (CO); 1600 (C=N)	2.4 (s, 3H, CH_3); 3.6 (s, 3H, N–CH_3); 7.0–7.9 (m, 10H$_{arom.}$); 11.0 (s, br, 1H, NH)
8b	3480, 3420, 3180 (NH); 1680 (CO); 1600 (C=N)	2.5 (s, 3H, CH_3); 2.7 (s, 3H, N–CH_3); 7.3–7.7 (m, 9H$_{arom.}$)
9	3340–3220 (NH); 1680 (CO); 1610 (C=N)	2.5 (s, 3H, CH_3); 2.8 (s, 3H, N–CH_3); 7.2–7.6 (m, 9H$_{arom.}$); 8.2 (s, 1H, NH)
10a	3350–3200 (NH); 1700 (CO); 1685 (CO); 1620 (C=N)	1.3 (t, 3H, CH_3); 2.2 (s, 3H, CH_3); 3.0 (s, 3H, N–CH_3); 4.2 (q, 2H, CH_2); 7.1–7.7 (m, 10H$_{arom.}$); 11.4 (s, br, 1H, NH)
10b	3100–3000 (NH); 1680 (CO); 1600 (C=C)	2.4 (s, 3H, CH_3); 2.5 (s, 3H, CH_3CO); 3.1 (s, 3H, N–CH_3); 7.0–7.8 (m, 10H$_{arom.}$); 11.5 (s, br, 1H, NH); 14.7 (s, br, 1H, NH)

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