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Studies with Polyfunctionally Substituted Heterocycles: New Synthesis of Pyrido[5′,4′:2,3][1,3,4]oxadiazolo[3,2-a]pyridine; Pyridazine; 1,3,4-Oxadiazole; and Pyrazolo[1,5-a]Pyrimidine Derivatives

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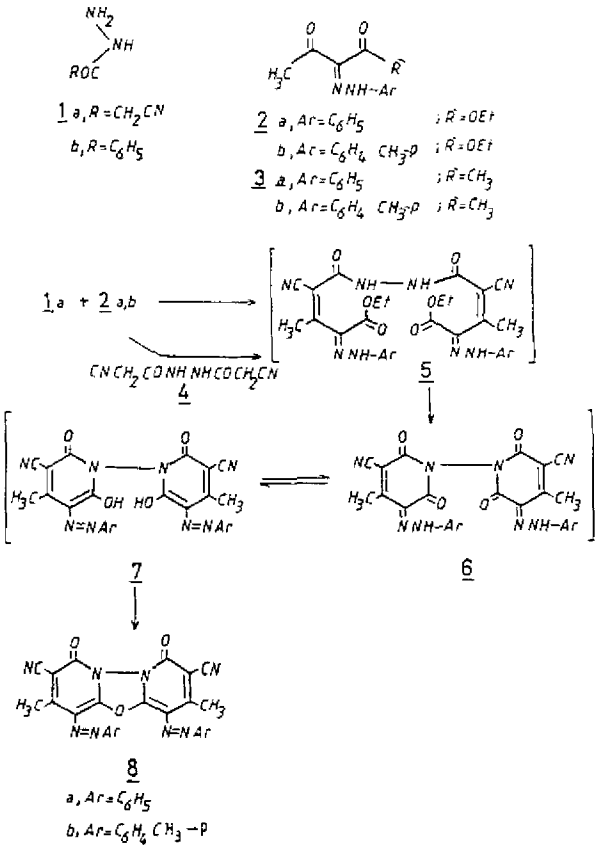
Cyanoacetohydrazide **1a** reacts with 2-arylhydrazoketons **2a,b** and **3a,b** in refluxing ethanol to yield pyrido[5′,4′:2,3][1,3,4]oxadiazolo[3,2-a]pyridine and pyridazine derivatives; in the absence of solvent pyrazolo[1,5-a]pyrimidine derivatives were obtained. The reaction of **2a,b** and **3a,b** with benzoylhydrazine afforded 1,3,4-oxadiazole and pyrazole derivatives.

INTRODUCTION

Polyfunctionally substituted condensed heterocycles are biologically interesting compounds, and their chemistry has received considerable recent interest.[1,3] In previous work part of our group have developed a new synthetic approach to polyfunctionally substituted bicyclic heteroaromatic compounds which are required as potential biodegradable agrochemicals via reacting ethyl 3-amino-3-ethoxy-2-propenoate with benzoylhydrazine.[4,5] In conjunction with this work we report results of our investigation on the behavior of cyanoacetohydrazide and benzoylhdrazine toward 2-arylhydrazoketones. It has been found that ethyl 2-phenylhydrazo-3-oxobutyrate **2a** reacts with cyanoacetohydrazide **1a** in refluxing ethanol in the presence of catalytic amounts of piperidine affording, unexpectedly, a product of molecular formula corresponding to $C_{26}H_{16}N_8O_3$, (M^+ 488). Structure **8a** was assigned for the reaction product based on analytical and spectral data. The IR spectra showed characteristic absorption bands at 1670 and 2220 cm^{-1} due to the carbonyl and cyano groups, respectively. The ^1H NMR spectra exhibited in addition to the aromatic proton region (δ = 7.40-8.11), only one signal at (δ = 2.32) corresponding to the two methyl groups. Moreover, ^{13}C NMR revealed all expected signals characteristic for compound **8a**.

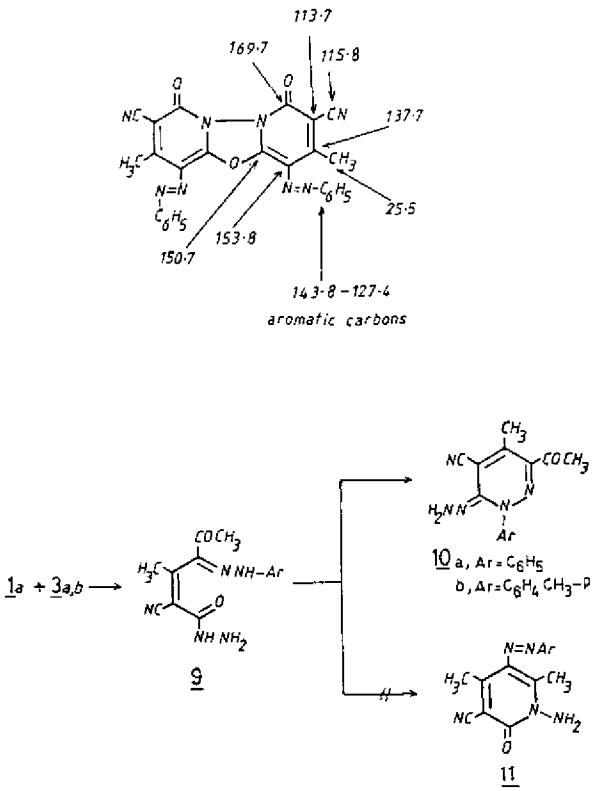
A possible mechanism for the formation of **8a** is depicted in Scheme I. Under reaction conditions cyanoacetohydrazide can be dimerized to **4**. Formation of such a dimer has been observed before 6. This dimer then condenses with two molecules of **2a** to yield **5**. The elimination of two ethanol molecules from this adduct may provide **6**. Losing water leads to the tricyclic final product **8**. In order to elucidate the mechanism of formation of **8** the dimer **4** was synthesized and allowed to react with **2a**. The result was very clear, and we obtained **8** quantitatively. The reaction of **1a** with **3a** under the same reaction conditions afforded a product with molecular formula $C_{14}H_{13}N_5O$ and (M^+ 267). Two isomeric structures **10** and **11**, were suggested, structure **10** was assigned for the reaction product based on ^1H NMR which revealed two methyl signals at δ = 2.65 and 2.80. If

Scheme I



this product was the isomer **11**, the two methyl group signals should be observed between δ = 2.20, and 2.40, the formation of the pyridazine derivative **10** is assumed to proceed via the reaction sequence shown in Scheme II.

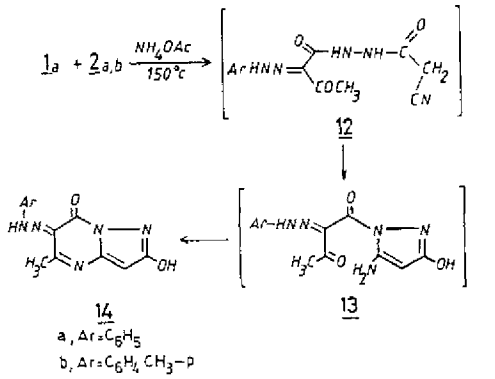
Scheme II



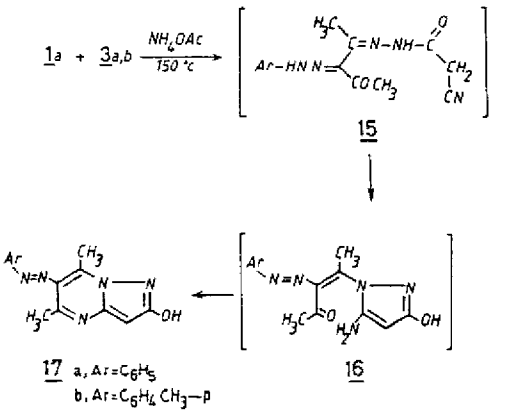
When **1a** was heated with **2a** at 150 °C for 10 min in the presence of ammonium acetate a product with molecular formula $C_{13}H_{11}N_5O_2$ and (M^+ 269) was yielded. No cyano absorption band was exhibited in its IR spectra. The ^1H NMR spectra clearly indicated all skeletal protons expected in the aromatic region (δ = 7.43-8.54), one singlet at δ = 2.20 corresponding to a methyl group and one singlet at 6.42 due to the pyrazole 1H. Structure **14** was assigned for this product based on spectral data and supported by elemental analysis. Formation of **14** is believed to proceed via the intermediacy of monocyanoacetohydrazone derivative **12**, which then double cyclizes to the final isolable product **14** (Scheme III). Similarly, **1a** was heated with **3a** to afford **17** through the intermediacy of **15** and **16**. The compound exists as an enolate form based on the IR and ^1H NMR spectra.

Compound **1b** reacted also with **2a** both in refluxing ethanol catalyzed with piperidine and fusion in the presence of ammonium acetate, in each case a product of condensation and subsequent elimination of ethanol was obtained (M^+ 306). Two isomeric structures, **18** and **19** seemed possible for the reaction products. Structure **18** was established for the product obtained in refluxing ethanol based on ^1H NMR spectra, which revealed in addition to the aromatic protons region, one singlet at (δ = 2.83). IR spectra also exhibit only one absorption band at 1710 cm^{-1}. These data can only be intelligibly interpreted for **18**. On the other hand structure **19** was assigned for the other product based on spectral data. Its ^1H NMR revealed a singlet at (δ = 2.00). IR spectra showed two absorption bands at 1695, and 1655 cm^{-1} corresponding to the two carbonyl groups.

Scheme III

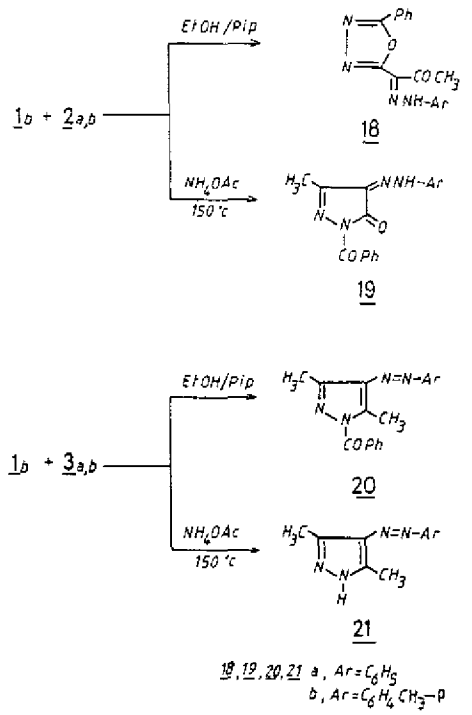


Scheme IV



When 2-arylhydrazoketone derivative **3a** was subjected to the previous refluxing and fusion reaction conditions with **1b**, two products were obtained, **20** and **21**, in good yields. According to their mass spectra the molecular weights were found to be $C_{18}H_{16}N_4O$ (M^+ 304), and $C_{11}H_{12}N_4$ (M^+ 200), respectively. The IR spectra resembled each other. The absorption band assigned for the amino group was absent in the spectra of **20** and **21**. This fact sug-

Scheme V



gested that this group of the reagent paricipated in the reaction. These spectral data and their analytical data confirm that **20** and **21** are N-benzoylarylazopyrazole and arylazopyrazole derivatives, respectively.

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a pye-Unicam SP-1100 spectrophotometer ^{1}H NMR spectra were measured on a Varian EM-390 spectrometer with DMSO and $CHCl_3$ as solvents and TMS, as internal standard. ^{13}C spectra were taken on a Bruker Model WP-80 (internal standard: TMS).

Reaction of 2-arylhydrazoketones 2a,b and 3a,b with 1a or 1b

Method 1

A suspension of an equimolar amounts (0.01) of **2a,b**; **3a,b** and the appropriate amount of **1a** or **1b** (0.01 mol) in ethanol was refluxed with piperidine (catalytic amounts) until a precipitate was formed (or until the reaction was complete, tlc control) time range from 3-6 hrs, the resulted solid product formed was collected by filtration and crystallized from the proper solvent (cf. Table 1).

Table 1. Analytical and Physical Data of New Compounds

Compd.	M.P°C (solvent)	Yield %	Formula (M.W)	Calculated/Found % C	% H	% N
8a	200	80	$C_{26}H_{16}N_8O_3$	63.93	3.30	22.94
	ethanol		(488.47)	63.71	3.45	22.85
8b	220	78	$C_{28}H_{20}N_8O_3$	65.11	3.90	21.69
	ethanol		(516.52)	65.35	3.86	21.54
10a	270-1	75	$C_{14}H_{13}N_5O$	62.91	4.90	26.20
	ethanol		(267.29)	63.02	4.76	26.12
10b	285-6	70	$C_{15}H_{15}N_5O$	64.04	5.38	24.90
	dioxane		(281.32)	64.27	5.09	24.69
14a	>300	73	$C_{13}H_{11}N_5O_2$	59.99	4.12	26.01
	DMF		(269.27)	60.21	3.93	25.86
14b	>300	70	$C_{14}H_{13}N_5O_2$	59.36	4.63	24.72
	dioxane		(283.29)	59.48	4.49	24.64
17a	>300	65	$C_{14}H_{13}N_5O$	62.91	4.90	26.20
	ethanol		(276.29)	62.73	4.66	26.12
17b	>300	60	$C_{15}H_{16}N_5O$	64.04	5.38	24.90
	ethanol		(281.32)	64.24	5.19	24.59
18a	220	80	$C_{17}H_{14}N_4O_2$	66.66	4.61	18.29
	ethanol		(306.33)	66.45	4.72	17.97
18b	205-7	80	$C_{18}H_{16}N_4O_2$	67.49	5.04	17.49
	dioxane		(320.35)	67.33	4.96	17.15
19a	230	76	$C_{17}H_{14}N_4O_2$	66.66	4.61	18.29
	dioxane		(306.33)	66.45	4.72	17.97
19b	200-1	65	$C_{18}H_{16}N_4O_2$	67.49	5.04	17.49
	dioxane		(320.35)	67.11	5.13	17.85
20a	257-8	80	$C_{18}H_{16}N_4O$	71.04	5.30	18.41
	ethanol		(304.35)	70.85	5.11	18.29
20b	215	75	$C_{19}H_{18}N_4O$	71.68	5.70	17.60
	dioxane		(318.38)	71.32	5.53	17.85
21a	155-7	80	$C_{11}H_{12}N_4$	65.98	6.04	27.98
	ethanol		(200.25)	65.75	5.91	27.69
21b	170	80	$C_{12}H_{14}N_4$	67.27	6.59	26.15
	ethanol		(214.27)	67.11	6.43	26.21

Method 2

Equimolar amounts (0.01 mol) of **2a,b** and **3a,b** and the appropriate amount of **1a** or **1b** (0.01 mol) in presence of a small amount of ammonium acetate were heated in an oil bath for about 15-20 min. at 150-160 °C. The reaction mixture was allowed to cool and was triturated with ethanol. The resulted solid product formed was collected by filtration and crystallized from the proper solvent (cf. Table 1).

Table 2. IR and ^{1}H NMR Data of Newly Synthesized Compounds

Compound	^{1}H NMR (DMSO-d_6) ppm	IR cm^{-1}
8a	2.32 (s, 6H, 2CH_3); 7.40-8.11 (m, 10H, aromatic protons)	2930 (CH_3); 2220 (CN); 1670 (CO); 1620 (N=N)
8b	2.18 (s, 6H, 2CH_3); 2.35 (s, 6H, 2CH_3); 7.50-8.22 (m, 8H, aromatic protons)	2990 (CH_3); 2220 (CN); 1665 (CO); 1630 (N=N)
10a	2.65 (s, 3H, CH_3); 2.80 (s, 3H, $COCH_3$); 7.50-8.01 (m, 5H, aromatic protons); 8.56 (br, 2H, NH_2)	3500-3200 (NH_2); 2220 (CN); 1715 (CO); 1630 (C=N)
10b	2.12 (s, 3H, CH_3); 2.66 (s, 3H, CH_3); 8.2 (s, 3H, $COCH_3$); 7.65-8.22 (m, 4H, aromatic protons); 8.66 (br, 2H, NH_2)	4440-3200 (NH_2); 2220 (CN); 1723 (CO); 1640 (C=N)
14a	2.20 (s, 3H, CH_3); 6.42 (s, 1H, ptrazole); 7.43-8.54 (m, 5H, aromatic protons); 9.45 (s, 1H, OH)	3340-3325 (NH, OH); 1660 (CO)
14b	Insoluble in available NMR solvents	3345-3350 (NH, OH); 1665 (CO)
17a	2.11 (s, 3H, CH_3); 2.22 (s, 3H, CH_3); 6.53 (s, 1H, pyrazole) 7.43-8.54 (m, 5H, aromatic protons); 9.22 (s, 1H, OH)	3465-3330 (OH); 1630 (N=N)
17b	2.11 (s, 3H, CH_3); 2.34 (s, 3H, CH_3); 2.45 (s, 3H, CH_3); 6.71 (s, 1H, pyrazole); 7.90-8.54 (m, 4H, aromatic protons)	3370-3320 (OH); 1632 (N=N)
18a	2.83 (s, 3H, $COCH_3$); 6.96-7.52 (m, 10H, aromatic protons); 7.92 (br, 1H, NH)	3300 (NH); 1710 (CO)
18b	2.17 (s, 3H, CH_3); 2.80 (s, 3H, $COCH_3$); 7.09-8.01 (m, 9H, aroprotons); 8.34 (br, 1H, NH)	3350 (NH); 1715 (CO)
19a	2.00 (s, 3H, CH_3); 7.50-8.11 (m, 11H, aromatic and, NH protons)	3200-3051 (NH); 1695, 1655 (CO); 1632 (C=N)
19b	1.82 (s, 3H, CH_3); 2.11 (s, 3H, CH_3); 7.65-8.31 (m, 11H, aromatic and NH protons)	3220-3142 (NH); 1700, 1650 (CO); 1632 (C=N)
20a	1.90 (s, 3H, CH_3); 2.11 (s, 3H, CH_3); 7.55-8.60 (m, 10H, aromatic protons)	1675 (CO); 1625 (N=N)
21a	1.95 (s, 3H, CH_3); 2.15 (s, 3H, CH_3); 2.25 (s, 3H, CH_3); 7.69-8.75 (m, 6H, aromatic and NH protons)	3220-3050 (NH); 1630 (N=N)

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Key Words

Pyrido[5′,4′:2,3][1,3,4]oxadiazolo[3,2-a]pyridine; 1,3,4-Oxadiazole.

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