Reaction of Ethyl Arylidenecyanoacetates with Hydrazine Derivatives

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Summary: Several new polysubstituted pyrimidine and pyrazole derivatives were synthesized *via* reaction of ethyl arylidenecyanoacetates with different hydrazine derivatives.

Introduction

α,β-unsaturated nitriles have been utilized for the synthesis of a variety of mono- and polyheterocyclic derivatives [1-3]. As a continuation of previous work from our laboratory [4,5] aimed at developing new efficient procedures for the synthesis of polysubstituted heterocycles, this work deals with the synthesis of polysubstituted pyrimidine and pyrazole derivatives using ethyl arylidenecyanoacetates as starting material.

Results and Discussion

Compound (**1a-c**) (Scheme 1) reacted with semi carbazide hydrochloride in ethanol and in the presence of sodium acetate to give 3-amino-5-arylidene-4-imino-pyrimidine-2,6-diones (**IIIa-c**). The isolated products were assumed to be formed by condensation of (**Ia-c**) with semicarbazide *via* loss of ethanol to give the acyclic intermediates (**IIa-c**) which readily cyclized under the reaction conditions. Structures (**IIIa-c**) were established on the basis of IR and ^{1}H-NMR spectra (c.f. Table 2).

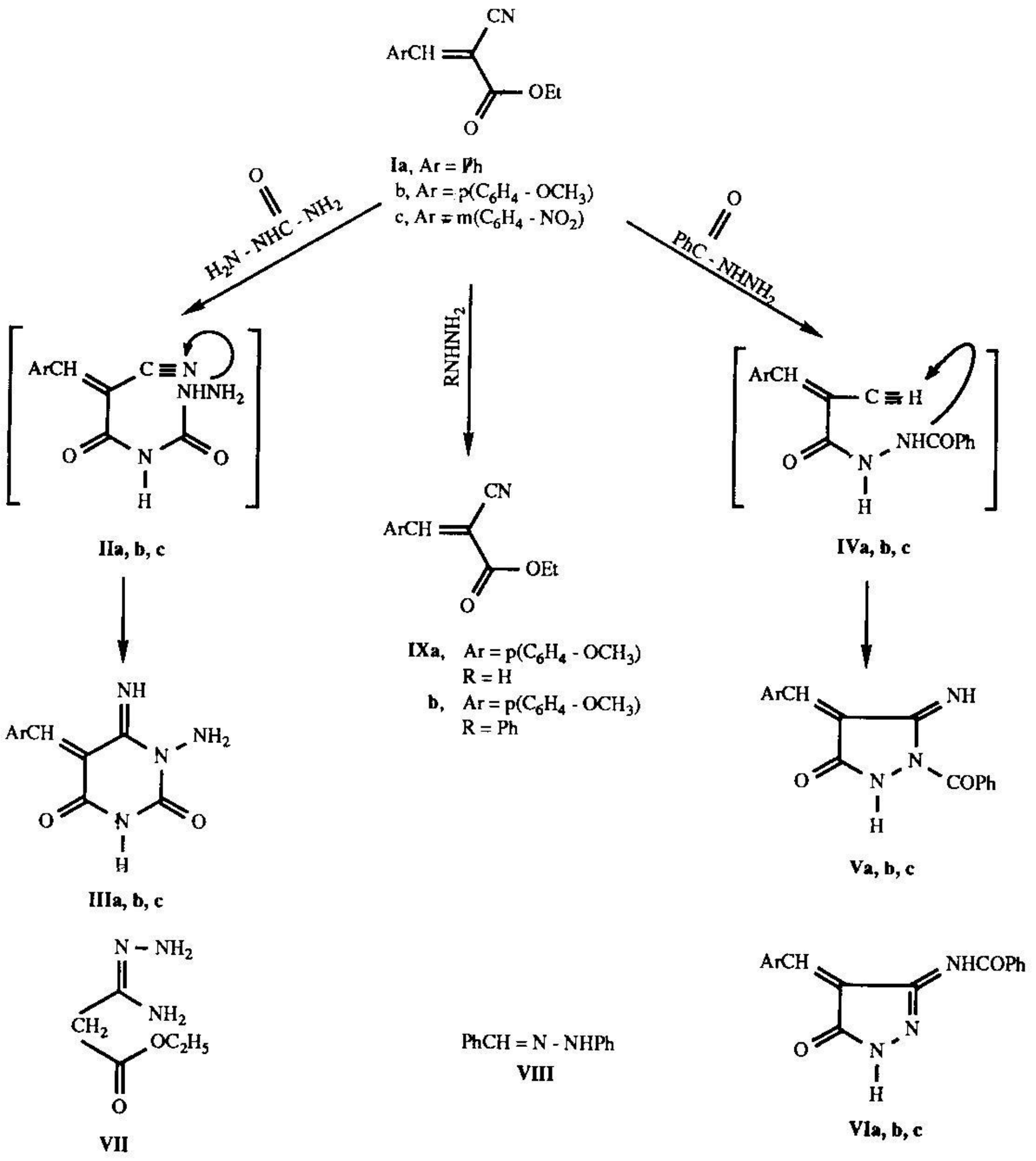
4-Arylidene-3-benzanilidopyrazole-5-one derivative (**VIa-c**) were obtained upon refluxing the chalcones (**1a-c**) with benzoylhydrazine in dioxane. Compounds (**VIa-c**) were suggested to be formed *via* condensation of (**Ia-c**) with benzoylhydrazine to form the nonisolable (**IVa-c**), which cyclized to (**Va-c**) *via* addition to the cyano functions of (**IVa-c**). Compounds (**Va-c**) readily undergo rearrangement under the reaction conditions to (**VIa-c**). Such rearrangement of a similar compounds was previously observed [6]. The assigned structures were confirmed *via* inspection of the spectral data (c.f. Table 2).

It was reported [7] that one of the routes for the formation of the pyrazole derivatives was the reaction of arylidene ω-cyanoacetophenone with hydrazines. In this part of the paper, the behaviour of (**1a-c**) towards hydrazines was investigated. Thus, (**Ia**) reacted with hydrazine hydrate to form (**VII**). Compound (**VII**) was obtained through cleavage of the benzylidene group of (**Ia**) and addition of hydrazine hydrate to the cyano function to form the aminohydrazone (**VII**). Compound (**Ia**) also reacted with phenylhydrazine to give benzylidene phenylhydrazone (**VIII**) as the only isolable product (m.p. and mixed m.p. [8]). The scission of the double bond in the arylidene derivative (**Ia**) was similar to that previously reported for the arylidene derivatives of 3-oxoalkane nitriles [9]. Similarly the hydrazone (**VIIIb**) and the phenylhydrazone (**VIIIc**) derivatives were obtained upon reaction of (**Ic**) with hydrazine and phenylhydrazine respectively. The products (**VIIIb,c**) were found to be identical with the authentic samples obtained from reaction of *m*-nitrobenzaldehyde with either hydrazine or phenylhydrazine respectively.

Table 1: The newly synthesized compounds

Compound	M.P. [°C] (Solvent)	Yield [%]	Molecular formula (molecular mass)	Analysis C	H	Calcd./Found N
(**IIIa**)	216	70	$C_{11}H_{10}N_4O_2$	57.4	4.3	24.3
	(E)		(230)	57.5	4.3	24.5
(**IIIb**)	208	73	$C_{12}H_{12}N_4O_2$	59.0	4.9	23.0
	(E)		(244)	58.9	4.7	23.1
(**IIIc**)	240	70	$C_{11}H_9N_5O_4$	48.0	3.3	25.5
	(D)		(275)	48.2	3.0	25.2
(**VIa**)	210	73	$C_{17}H_{13}N_3O_2$	70.1	4.5	14.4
	(E)		(291)	69.9	4.5	14.4
(**VIb**)	152	75	$C_{18}H_{15}N_3O_2$	70.8	4.9	13.8
	(M)		(305)	70.5	5.0	13.7
(**VIc**)	173	75	$C_{17}H_{12}N_4O_4$	60.7	3.6	16.7
	(E)		(336)	60.5	3.6	16.8
(**VII**)	180	60	$C_5H_{11}N_3O_2$	41.4	7.6	29.0
	(E)		(145)	41.3	7.5	29.0
(**IXa**)	202	50	$C_{11}H_{11}N_3O_2$	60.8	5.1	19.4
	(E)		(217)	61.0	5.2	19.3
(**IXb**)	109	52	$C_{17}H_{15}N_3O_2$	69.6	5.1	14.3
	(M)		(293)	69.7	5.3	14.0

E = ethanol; M = methanol; D = dioxane.



On the other hand, (Ib) reacted with either hydrazine hydrate or phenylhydrazine to give (IXa) and (IXb) respectively. Compound (IXa,b) were formed *via* condensation of the chalcone (Ib) with the hydrazines *via* loss of ethanol. It can be presumed that the presence of *p*-methoxy group in the arylidene derivative (Ib) promotes the conjugative effect which reduces the probability of the fission of the arylidene group. Trials to isolate identifiable products upon reaction of (Ic) with hydrazine hydrate or phenylhydrazine under a variety of conditions were unsuccessful.

Experimental

All melting points are uncorrected. IR spectra were determined on Perkin Elmer 1430 Spectrophotometer. ^{1}H-NMR were recorded on a Varian A 60 using DMSO as solvent. TMS was used as internal standard and chemical shifts are expressed in ppm.

Table 2: IR and ^{1}H-NMR data

Compound	IR [cm^{-1}] (selected bands)	^{1}H-NMR (ppm)
(IIIa)	3500 (NH), 3340, 3200 (NH$_2$) 1700 (CO), 1600 (CO).	6.55 (*s*, 2H, NH$_2$); 7.3-7.8 (m, 6H, C$_6$H$_5$ and arylidene CH); 7.9 (s, 1H, NH); 10.5 (*s*, 1H, NH).
(IIIb)	3460 (NH), 3300, 3200 (NH$_2$), 1690 (CO), 1650 (CO).	
(IIIc)	3500 (NH), 3340, 3260 (NH$_2$) 1690 (CO), 1650 (CO).	7.25 (s, 2H, NH$_2$); 7.65- 8.25 (m, 5H, CH$_4$ and arylidene CH); 8.6 (s, 1H, NH); 10.6 (s, 1H, NH).
(VIa)	3240, 3100 (NH), 1700 (CO), 1660 (CO).	7.3-7.9 (m, 11H, 2C$_6$H$_5$ and arylidene CH); 8.4 (s, 1H, NH); 11.6 (s, 1H, NH).
(VIb)	3340 (NH), 3500 (NH), 1700 (CO), 1650 (CO).	3.85 (s, 3H, CH$_3$); 7.1-7.95 (m, 10 H, C$_6$H$_5$).
(VIc)	3340 (NH), 3200 (NH), 1700 (CO), 1650 (CO).	
(VII)	3400, 3200 (NH$_2$), 1650 (ester CO)	
(IXa)	3210 (NH), 3100 (NH), 2225(CNH), 1670 (CO).	
(IXb)	3310 (NH), 3200 (NH), 2200 (CN), 1660 (CO)	

Table 3: Reaction conditions

Hydrazine derivatives	Reaction time	Reaction medium
Semicarbazide hydrochloride	4 hrs	Ethanol
Benzoyl hydrazine	6 hrs	Dioxane
Hydrazine hydrate or phenylhydrazine	5 hrs	Neat (at 100°C0 or in either Ethanol, Dioxane, or Acetic acid

Analytical data were performed by the analytical data unit at Cairo University.

Reaction of ethyl arylidenecyanoacetates (**IIIa-c**) *with hydrazine derivatives (general procedure)*

To a solution of the appropriate ethyl arylidene cyanoacetates (**Ia-c**) (0.01 mole) in the suitable solvent (30 ml) was added the appropriate hydrazine derivative (0.01 mole), in case of semicarbazide hydrochloride sodium acetate (1 g) was added. The reaction mixture was refluxed for the appropriate time and then evaporated *in vacuo* (c.f. Table 3). To the obtained solid water was added, filtered and crystallized from the suitable solvent. The products were identified as (**IIIa-c, VIIIa-c**) and (**IXa,b**) respectively (c.f. Tables 1 and 2).

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