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CYCLOCONDENSATION OF 3-ARYL-2-CYANO-2-BUTENOIC ACID ESTERS WITH SCHIFF BASES

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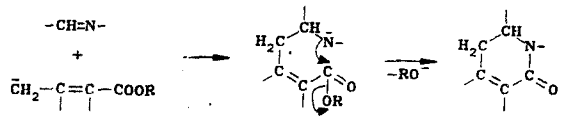
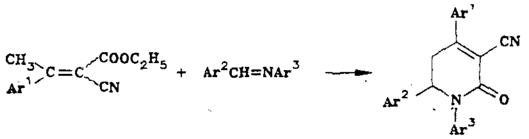
The condensation of ethyl 3-aryl-2-cyano-2-butenoates with benzylideneanilines in the presence of aluminum chloride affords 1,4,6-triaryl-2-oxo-1,2,5,6-tetrahydropyridine-2-carbonitriles; the reaction with hydrobenzamide gives N-unsubstituted tetrahydropyridine.

The first attempts to use the reaction of Schiff bases with CH-acid compounds in the synthesis of six-membered nitrogen-containing heterocycles showed that it is possible to obtain compounds of the tetrahydropyridine [1] and dihydroisoquinolinone [2, 3] series. This simple reaction was the basis of the synthesis of several alkaloids and their analogs [4]. At the same time, the formation of cyclic compounds from γ-carbanions of 2-butenoic acid esters [5, 6] suggested that it is possible to obtain pyridine derivatives according to the scheme



As far as we know, cyclocondensation of this type has not been described in the literature.

Attempts to carry out such cyclocondensation with a basic catalyst (sodium hydride in tetrahydrofuran or lithium amide in liquid ammonia) were unsuccessful. Therefore, we decided to use anhydrous aluminum chloride, catalyzing the reaction of Schiff bases with arylacetic acid esters to β-anilinopropionic acids [7].



Ia,f,g IIa-e IIIa-g

I—III a $Ar^1=Ar^2=Ar^3=C_6H_5$, b $Ar^1=Ar^3=C_6H_5$, $Ar^2=4\text{-}CH_3OC_6H_4$, c $Ar^1=Ar^3=C_6H_5$, $Ar^2=4\text{-}ClC_6H_4$, d $Ar^1=Ar^2=C_6H_5$, $Ar^3=4\text{-}CH_3OC_6H_4$, e $Ar^1=Ar^2=C_6H_5$, $Ar^3=4\text{-}ClC_6H_4$, f $Ar^1=4\text{-}CH_3C_6H_4$, $Ar^2=Ar^3=C_6H_5$, g $Ar^1=4\text{-}ClC_6H_4$, $Ar^2=Ar^3=C_6H_5$

It was found that in the presence of aluminum chloride at 20°C, ethyl 3-aryl-2-cyanobutenoates I reacted with benzylideneaniline and substituted benzylideneanilines II, forming in comparatively good yields (48-62%) the expected 1,4,6-triaryl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitriles (III). Ethyl 3-aryl-2-butenoates not containing a cyano group in the α-position did not react with Schiff bases under these conditions, but the reaction of ethyl 3-phenyl-2-cyano-2-butenoate (Ia) with hydrobenzamide IV occurred in 20% yield only with heating.

The composition and structure of all the synthesized compounds were confirmed by data of elemental analysis and spectroscopy (Tables 1 and 2). For compound V, it was determined that during preparation it was partially dehydrogenated to nitrile VI, identical to the one described in [8] with respect to melting point and spectral data. The two substances were separated by preparative thin-layer chromatography.

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TABLE 1. Physicochemical Characteristics of Pyridine-3-carbonitriles IIIa-g and V

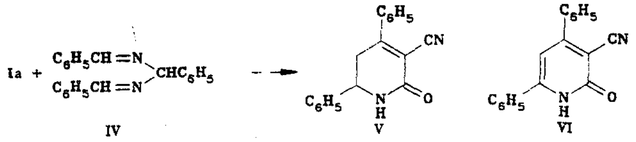
Compound	mp,* °C	Found, %			Empirical formula	Calculated, %			Yield, %
		C	H	N		C	H	N	
IIIa	200—202	82,1	5,4	7,8	$C_{24}H_{18}N_2O$	82,3	5,2	7,8	62
IIIb	198—200	78,9	5,6	7,4	$C_{25}H_{20}N_2O_2$	78,9	5,3	7,4	62
IIIc	226—228	74,9	4,7	7,1	$C_{24}H_{17}ClN_2O$	74,9	4,5	7,3	48
IIId	210—212	79,2	5,4	7,4	$C_{25}H_{20}N_2O_2$	78,9	5,3	7,4	55
IIIe	182—184	75,3	4,6	7,2	$C_{24}H_{17}ClN_2O$	74,9	4,5	7,3	50
IIIf	204—210†	82,1	5,7	7,5	$C_{25}H_{20}N_2O$	82,4	5,5	7,7	55
IIIg	227—235†	74,8	4,5	7,6	$C_{24}H_{17}ClN_2O$	74,9	4,5	7,3	55
V	188—190	78,8	5,5	10,3	$C_{18}N_{14}N_2O$	78,8	5,1	10.2	20

*Solvent for crystallization: IIIa-c, e, ethyl acetate; IIIf, g, ethyl acetate—benzene; V, ethanol. Compound IIId was purified by chromatography on a column with Kieselgel 40-Merck 0.063-0.200 mm (substance-sorbent ratio 1:50) in chloroform.

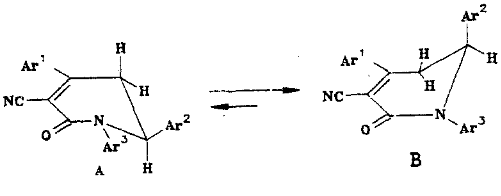
†The mp range could not be narrowed by recrystallizing the compound from different solvents.

TABLE 2. Spectral Characteristics of Compounds IIIa-g

Compound	Proton NMR spectrum, δ, ppm (J, Hz)	IR spectrum, ν, cm^{-1}
IIIa	3,05 (1H, d.d, J_{gem}=18,0, J_{56}=3,8, 5-H); 3,53 (1H, d.d J_{56}=6,8, 5-H); 5,0 (1H, m, 6-H); 6,8—7,2 (15H, m, Ar)	2230, 1665
IIIb	3,05 (1H, d.d, J_{gem}=19,1; J_{56}=4,1, 5-H); 3,4 (1H, m, J_{56}=6,5, 5-H); 3,55 (3H, s CH_3O); 5,0 (1H, m, 6-H); 6,6—7,2 (14H, m, Ar)	2230, 1665
IIIc	3,00 (1H, d.d., J_{gem}=18,9, J_{56}=3,9, 5-H); 3,49 (1H, d.d, J_{56}=6,8, 5-H); 4,8 (1H, m., 6-H); 6,6—7,2 (14H, m, Ar)	2220, 1665
IIId	3,15 (1H, d.d, J_{gem}=18,8, J_{56}=3,8, 5-H); 3,59 (3H, s, CH_3O); 3,6 (1H, m, J_{56}=6,8, 5-H); 5,0 (1H, m, 6-H); 6,6—7,2 (14H, m, Ar)	2230, 1670
IIIe	3,05 (1H, d.d., J_{gem}=18,5, J_{56}=4,2, 5-H); 3,50 (1H, d.d, J_{56}=6,8, 5-H); 4,8 (1H, m, 6-H); 6,6—7,2 (14H, m, Ar)	2230, 1665
IIIf	2,01 (3H, s CH_3); 3,05 (1H, d.d J_{gem}=18,8, J_{56}=3,8, 5-H); 3,52 (1H, d.d, J_{56}=6,8, 5-H); 4,8 (1H, m, 6-H); 6,6—7,2 (14H, m, Ar)	2220, 1665
IIIg	3,01 (1H, d.d, J_{gem}=18,0, J_{56}=3,8, 5-H); 3,53 (1H, d.d. J_{56}=7,1, 5-H); 5,0 (1H, m, 6-H); 6,6—7,2 (14H, m, Ar)	2220, 1670



According to the literature data for six-membered nitrogen-containing compounds whose molecules, like compounds IIIa-g and V, contain a conjugated system of an unsaturated amide of a carboxylic acid, the preferred conformation is "envelope" type with the $C_{(6)}$ atom out of the plane containing the remaining five atoms. In the proton NMR spectra of compounds IIIa-g, the signals of the 5-H and 6-H protons form an ABX spin system with vicinal constants J = 6.5-7.1 and J = 3.8-4.2 Hz, which do not make it possible to determine accurately the equilibrium position between conformers A and B. A probable reason for the destabilization of conformation A is steric interaction between pseudoequatorial substituent Ar^2 and Ar^3 at the nitrogen atom, which decreases when the substituent at $C_{(6)}$ moves into the pseudoaxial position (B).



A simplified proton NMR spectrum of A_2X type was observed for N-unsubstituted pyridine-3-carbonitrile V (Ar^3 = H): a triplet for the 6-H proton and a doublet for the two 5-H protons. This pseudoequivalence of the 5-H protons can be explained by fast interconversion of the conformers A $\rightleftarrows$ B.

EXPERIMENTAL

The melting points of the analytically pure substances were determined on a Boëtius heating table with a microscope and were not corrected. The purity of the compounds was monitored by thin-layer chromatography on Silufol UV-254 plates in the hexane—acetone—benzene system, 8:4:3. The IR spectra were recorded on a Specord-71 IR Zeiss instrument for 1% chloroform solutions. The proton NMR spectra were recorded on a Joel PS-100 spectrometer in CF_3COOH, and the internal standard was TMS.

Starting ethyl 3-aryl-2-cyano-2-butenoates Ia, f, and g were synthesized by the procedure of [9].

1,4,6-Triaryl-2-oxo-1,2,5,6-tetrahydropyridine-3-carbonitriles (IIIa-g). To a solution of 5 mmoles of ethyl 2-butenoate I and 10 mmoles of the corresponding Schiff base II in 2 ml of benzene, 1.35 g (10 mmoles) of anhydrous aluminum chloride was added in small portions. The reaction mixture was kept at 20°C for 24 h. After the addition of water and acidification with dilute (1:4) hydrochloric acid, 2-3 ml of chloroform was added, and the emulsion was stirred for 30 min. The chloroform layer was separated, the aqueous layer was extracted with chloroform, and the extracts were combined and dried with sodium sulfate. After removal of the solvent, the residue was treated with 2-3 ml of ethanol, and the crystallized product was filtered and purified by recrystallization or column chromatography (see Tables 1 and 2).

2-Oxo-4,6-diphenyl-1,2,5,6-tetrahydropyridine-3-carbonitrile (V). This compound was obtained similarly from 1.07 g (5 mmoles) of compound Ia, 1.48 g (5 mmoles) of hydrobenzamide IV, and 0.7 g (5 mmoles) of aluminum chloride, but with heating of the reaction mixture to 70°C for 1 h. After removal of the solvent, the residue was treated with 50 ml of ether, and after 24 h the solidified mass was filtered and purified by preparative chromatography on Kieselgel 60 F-254-Merck plates (25 × 25 × 2 mm) in a chloroform—ethyl acetate mixture, 85:15 (development in UV light at 254 nm). We obtained 0.28 g (20%) of compound V, mp 188-190°C (from ethanol). IR spectrum ($CHCl_3$): 3200 (NH), 2220 (CN), 1675 cm^{-1} (CO). Proton NMR spectrum (CF_3COOH): 2.89 (2H, d, J_{56} = 8.3 Hz, CH_2); 4.59 (1H, t, 6-H); 6.8-7.2 ppm (10H, multiplet, Ar).

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