UTILIZATION OF ACETONE CYANOHYDRIN IN THE REISSERT REACTION

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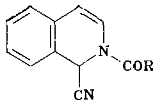
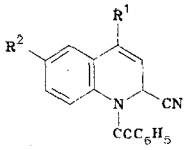
A modification of the Reissert reaction based on the utilization of acetone cyanohydrin instead of potassium cyanide is proposed.

Isoquinoline derivative I and quinoline derivative II, which are so-called Reissert compounds, are valuable synthones [1-3]. Their preparation is based on the Reissert reaction, in the classical variant of which an emulsion of isoquinoline (or quinoline) in an aqueous solution of an alkali metal cyanide is treated with an acyl halide. The known modifications of this reaction reduce to carrying out of the process under anhydrous conditions with replacement of the alkali metal cyanide by hydrocyanic acid, trimethylsilyl cyanide, or silver cyanide [3]. Good results are obtained when the reaction is carried out in a methylene chloride—water system [1, 3]; interphase catalysis is sometimes used in this case to increase the yields [3].

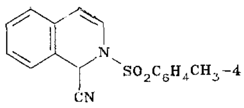
We have studied the reaction of isoquinoline, quinoline, and 4-methyl-6-methoxyquinoline with various acyl chlorides or p-toluenesulfonyl chloride in the presence of acetone cyanohydrin and potassium carbonate. The reaction was carried out in both an aqueous medium (method A) and in a water—methylene chloride system in the absence (method B) or in the presence of an interphase catalyst (method C). Benzyltriethylammonium chloride was used as the catalyst. To obtain the Reissert compounds we used benzoyl chloride, which is most often used for this purpose, as well as cyclohexyl- and 1-cyclohexenylcarbonyl chlorides and ethyl chloroformate.



Ia-d



IIa,b



III

I a $R=C_6H_5$, b $R=$cyclohexyl, c $R=$1-cyclohexenyl, d $R-OC_2H_5$; II a $R^1=R^2=H$, b $R^1=CH_3$, $R^2=OCH_3$

The "classical" isoquinoline (quinoline)—acyl chloride—cyanide ratio (1:2:3) was used in the reaction. The results obtained are presented in Table 1, from which it is apparent that the described compounds (Ia, d, IIa, and III) were obtained in yields close to those described in the literature. The utilization of potassium hydroxide instead of potassium carbonate leads to a decrease in the yield (in the preparation of Ia). The synthesis of Ib,c was of interest, since they are starting compounds for the preparation of the effective anthelmintic praziquantel (Embay 8440) [4]. It is apparent from Table 1 that the yields of these substances differ by more than an order of magnitude. The low yield of Ib is in agreement with the literature data, which indicate that highly active alkanoyl chlorides are not effective in the Reissert reaction [5]. The Ic that we obtained has a melting point that differs from the melting point described in [4]; however, its structure was confirmed by the results of elementary analysis and IR and PMR spectroscopy.

Thus we have proposed a new convenient modification of the Reissert reaction.

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TABLE 1. Characteristics of the Reissert Compounds

Compound	Method of synthesis	mp, °C	IR spectrum, cm^{-1}	Yield, %	Literature data		
					mp, °C	yield, %	source
Ia	A	124—125	1662 (C=O), 1633 (C=C)	54	124—125	58—77	[6]
	A[a]			34			
	B			60		69	[7]
	C			69			
Ib	B	126—127[b]	1675 (C=O), 1640 (C=C)	5			
	C			10			
Ic	B	161—162[c]	1670 (C=O), 1630 (C=O)[d]	73	148		[4]
	C			75			
Id	C	84—85	1715 (C=O), 1645 (C=C)	68	85—85,5	65	[8]
IIa	A	152—154[e]	1640 (C=O)	59	154—155	75	[9]
IIb	B	133—135[f]	1665 (C=O)	66			
III	C	100—102	1625 (C=C), 1370 (SO), 1175 (SO)	67	1100—102	65	[8]

[a] Potassium hydroxide was used as the base. [b] Found: C 76.7; H 6.5; N 10.9%. $C_{17}H_{18}N_2O$. Calculated: C 76.7; H 6.8; N 10.5%. [c] Found: C 77.5; H 6.1; N 10.8%. $C_{17}H_{16}N_2O$. Calculated: C 77.3; H 6.1; N 10.6%. [d] PMR spectrum: 7.02-7.35 (4H, m, aromatic protons), 6.77 (1H, d, J = 7 Hz, 3-H), 6.36 (1H, s, 1-H), 6.08-6.21 (1H, m, 2-H), 5.96 (1H, d, J = 7.5 Hz, 4-H), 2.25-2.51 (4H, m, 3'-H, 6'-H), and 1.78-2.19 ppm (4H, m, 4'-H, 5'-H). [e] This substance was recrystallized from ethyl acetate. [f] Found: C 74.6; H 5.0; N 9.3%. $C_{19}H_{16}N_2O_2$. Calculated: C 75.0; H 5.3; N 9.2%.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-20 spectrometer. The PMR spectrum of a solution in $CDCl_3$ was obtained with a Tesla BS-467 spectrometer (60 MHz) with hexamethyldisiloxane as the internal standard.

Reissert Compounds Ia-d, IIa,b, and III. A 0.2-mole sample of isoquinoline, quinoline, or 4-methyl-6-methoxyquinoline and 0.6 mole of acetone cyanohydrin were added to a solution of 0.6 mole of K_2CO_3 in 250 ml of water, and the mixture was stirred for 30 min. A 0.4-mole sample of the acyl chloride was added gradually in the course of 2 h, after which the mixture was stirred for another 2 h and extracted with methylene chloride. The organic extract was washed successively with 5% HCl, water, 5% $NaHCO_3$, and water and dried with Na_2SO_4. The solvent was removed by distillation, a small amount of alcohol was added to the residue, and the resulting precipitate was removed by filtration, washed with alcohol, and dried.

B) A solution of 0.4 mole of the acyl chloride in 100 ml of anhydrous methylene chloride was added gradually in the course of 2 h to a mixture of 0.2 mole of isoquinoline, quinoline, or 4-methyl-6-methoxyquinoline, 0.6 mole of acetone cyanohydrin, 0.6 mole of K_2CO_3, 200 ml of water, and 200 ml of methylene chloride, after which the mixture was stirred for another 2 h and diluted with water. The organic layer was separated, and the aqueous layer was extracted with methylene chloride. The extracts were combined and worked up as in method A.

C) This method was similar to method B, except that 5-10% benzyltriethylammonium chloride was introduced into the reaction mixture.

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