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Abstract

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ON THE INTERACTION OF β-CYANOVINYL KETONES WITH SECONDARY AMINES

In a recently published paper we reported (^{1}) the synthesis of previously unknown derivatives of acrylonitrile—β-cyanovinyl ketones. The preliminary results already obtained in studying the interaction of these compounds with nucleophilic reagents demonstrate the high electrophilic activity of their double bond. Many of them add amines, phenols, acetoacetic and malonic esters.* It is interesting to note that the group determining the orientation of addition, of the two competing groups $> C = O$ and $-C \equiv N$, is the carbonyl group, and that addition proceeds in the direction opposite to that occurring in reactions of cyanoethylation with acrylonitrile:

$$CH_2 = CHCN + HX \to XCH_2CH_2CN,$$

$$RCOCH = CHCN + HX \to RCOCH_2CH(CN)X.$$

This makes possible quite different synthetic applications when β-cyanovinyl ketones (β-acylacrylonitriles) are used. In the present article we describe the reactions of β-cyanovinyl ketones with secondary amines. Aromatic and aliphatic β-cyanovinyl ketones show an interesting difference. Aryl-β-cyanovinyl ketones give products of addition of amines (even in the presence of a large excess of amine) at the double bond. We have obtained products of addition of diethylamine, piperidine, and morpholine to several aryl-β-cyanovinyl ketones:

$$ArCOCH = CHCN + HNR_2 \to ArCOCH_2CH(CN)NR_2,$$

where

$$\begin{aligned} &Ar = C_6H_5,\ HNR_2 = NH(C_2H_5)_2,\ NHC_5H_{10},\ NHC_4H_8O,\\ &Ar = n\text{-}BrC_6H_4,\ n\text{-}NO_2C_6H_4,\ HNR_2 = NHC_4H_8O. \end{aligned}$$

The resulting addition products are readily crystallizing substances which, however, change on prolonged storage, which affects the analysis. Under the action of alkali these products of addition of amines to aryl-β-cyanovinyl ketones split off hydrocyanic acid and give aryl-β-aminovinyl ketones, which can be obtained from aryl-β-chlorovinyl ketones. Consequently, the addition products are nitriles of α-amino-α-ketocarboxylic acids. Thus, on treatment of the nitrile of α-(N-piperidyl)-β-benzoylpropionic acid with the calculated amount of alcoholic alkali, phenyl-β-(N-piperidyl)-β-vinyl ketone is formed, identical with that obtained by counter-synthesis from phenyl-β-chlorovinyl ketone and piperidine:

$$C_6H_5COCH_2CH(CN)N\langle C_5H_{10} \xrightarrow{\text{NaOH}} C_6H_5COCH=CH-N\langle C_5H_{10}.$$

* This material will be published later.

When concentrated hydrochloric acid acts on the nitrile of α-(N-piperidyl)-β-benzoylpropionic acid, hydrolysis takes place with formation of the corresponding acid, which we isolated in the form of a stable hydrochloride. By the action of ethylene oxide on this hydrochloride, α-(N-piperidyl)-β-benzoylpropionic acid was obtained, identical with that obtained by counter-synthesis from β-benzoylacrylic acid and piperidine (2).

$$C_6H_5COCH_2CH(CN)-N\langle(CH_2)_5 \xrightarrow{\text{HCl}} C_6H_5COCH_2CH(COOH)-N\langle(CH_2)_5 \cdot HCl$$

In carrying out the hydrolysis of the nitrile of α-(N-morpholyl)-β-benzoylacrylic acid under the same conditions, the amide of the corresponding acid was obtained.

It should be noted that the chemistry of β-aroylacrylic acids, although known for a very long time, has developed only weakly. The question of the structure of the products of addition of ammonia and amines to benzoylacrylic acid long remained unresolved. Some considered them to be α-amino- (2–4), others β-amino-γ-ketocarboxylic acids (5,6). Recently Cromwell and co-workers showed, although by a rather complicated route, that they are α-amino-γ-ketocarboxylic acids (2). Our method of proof is very simple and may be used subsequently to establish the structure of other products of addition across the double bond of β-cyanovinyl ketones and β-acylacrylic acids.

Methyl-β-cyanovinyl ketone behaves differently under analogous conditions. With diethylamine and piperidine it exchanges the CN group for an amino group and gives the corresponding methyl-β-diethylamino- and methyl-β-piperidylvinyl ketones, identical with the products of interaction of methyl-β-chlorovinyl ketone with these same amines (7):

$$CH_3COCH=CHCN + HNR_2 \rightarrow CH_3COCH=CHNR_2,$$

where $HNR_2 = (C_2H_5)_2NH,\ NHC_5H_{10}$.

With hydrazine, similarly to methyl-β-chlorovinyl ketone, methyl-β-cyanovinyl ketone gives 3-methylpyrazole ([8]). Thus, in this case the CN group exhibits pseudo-halogen properties. This should be compared with the manifestation of pseudo-halogen properties by the CN group of pyruvic acid nitrile ([9]), which is related to methyl-β-cyanovinyl ketone by vinylogy. At the same time, the results described naturally lead to the supposition that, in the exchange of the CN group, in the first stage addition of the amine to the double bond occurs and then hydrocyanic acid is eliminated. A final judgment on the mechanism of the CN-group substitution reaction requires special investigation.

Experimental Part

1. Preparation of nitriles of α-amino-β-aroylpropionic acid. To a solution of 0.1 mole of aryl-β-cyanovinyl ketone in a minimum amount of benzene, 0.2 mole of amine was added with cooling by water. In the case of diethylamine, strong cooling is used. The reaction proceeds very rapidly, with heating. The crystals that separated were filtered off and washed on the filter with petroleum ether. On evaporation of the mother liquor, an additional small amount of nitrile of α-amino-β-aroylpropionic acid was obtained. The synthesis data are summarized in Table 1.

2. Preparation of phenyl-β-(N-piperidyl)-vinyl ketone from the nitrile of α-(N-piperidyl)-β-benzoylpropionic acid. 1 g of the nitrile of α-(N-piperidyl)-β-benzoylpropionic acid was shaken for 2 h with 0.2 g of sodium hydroxide in 10 ml of absolute alcohol. A precipitate of sodium cyanide separates. To the reaction mixture

Table 1

$ArCOCH_2C(CN)(NR_2)$

No.	Ar	$-NR_2$	m.p., °C	Yield, %	C found	C calc.	H found	H calc.	N found	N calc.	Br found	Br calc.
1	C_6H_5	$-N(C_2H_5)_2$	79–81 (from petr. ether)	62	72.92	73.00	8.05	7.87				
2	C_6H_5	piperidino	135 (from alcohol)	95	74.29	74.38	7.63	7.43	11.45	11.57		

No.	Ar	$-NR_2$	m.p., °C	Yield, %	C found	C calc.	H found	H calc.	N found	N calc.	Br found	Br calc.
3	C_6H_5	morpholino	130–132 (from alcohol)	93	68.71	68.85	6.46	6.55	11.50	11.47		
4	*p*-BrC_6H_4	morpholino	155–156 from alcohol	83.5	51.91	52.01	4.73	4.64	8.72	8.66	24.79	24.76
5	*p*-$NO_2C_6H_4$	morpholino	150–153 from acetone	81.3	58.36	58.13	5.28	5.19	14.80	14.53		

anhydrous ether was added to remove the unreacted starting material. The precipitate was filtered off. The filtrate was diluted with 70 ml of water and extracted with ether. After drying over sodium sulfate, the ether was evaporated. The yield of phenyl-β-(N-piperidyl)-vinyl ketone was 0.75 g (85.2% of theory), m.p. 86–89° (from alcohol and petroleum ether). A mixed sample with an authentic specimen obtained from phenyl-β-chlorovinyl ketone and piperidine by Kochetkov' s method (7) showed no depression of the melting point.

Found, %:	C 78.28;	H 7.82
$C_{14}H_{17}ON$. Calculated, %:	C 78.13;	H 7.90

3. Hydrolysis of the nitrile of α-(N-piperidyl)-β-benzoylpropionic acid.

3 g of the nitrile was dissolved in 25 ml of concentrated hydrochloric acid. Vigorous heating was observed; after 30–40 min a precipitate separated, which dissolved again on standing. A red solution was formed. After 24 hours the reaction mixture was evaporated to a volume of ~ 10 ml. The crystals that separated were filtered off and washed on the filter with concentrated hydrochloric acid and with a small amount of cold alcohol. The yield of the hydrochloride of α-(N-piperidyl)-β-benzoylpropionic acid was 3 g (81% of theory), m.p. 140–143° (from methanol).

Found, %:	C 60.54;	H 6.75;	N 4.97
$C_{15}H_{20}O_3NCl$. Calculated, %:	C 60.50;	H 6.77;	N 4.70

α-(N-Piperidyl)-β-benzoylpropionic acid was obtained from the hydrochloride by treatment with ethylene oxide, m.p. 166—167.5° with decomposition (from alcohol). A mixed sample with a specimen obtained from β-benzoylacrylic acid and piperidine (^{2}) showed no depression of the melting point.

4. Hydrolysis of the nitrile of α-(N-morpholyl)-β-benzoylpropionic acid.

The hydrolysis was carried out under the same conditions. The yield of the hydrochloride of the amide of α-(N-morpholyl)-β-benzoylpropionic acid was 80% of theory, m.p. 148—150° with decomposition (from methanol).

Found, %:	C 56.23;	H 6.54;	N 9.63;	Cl 11.75
$C_{14}H_{19}O_3N_2Cl$. Calculated, %:	C 56.29;	H 6.36;	N 9.38;	Cl 11.89

5. Reaction of methyl-β-cyanovinyl ketone with diethylamine.

To a solution of 3.4 g of methyl-β-cyanovinyl ketone in 20 ml of absolute ether, 3 g of diethylamine was added. Heating was observed.

After 30 min, the ether was distilled off and the residue was distilled under vacuum. Yield of methyl-β-diethylaminovinyl ketone: 4 g (74% of theory), b.p. 133°/12 mm, n_D^{20} 1.5370. Picrate: m.p. 114-116°. Literature data: b.p. 125°/6 mm, n_D^{20} 1.5378; picrate: m.p. 115-116° (7).

6. **Reaction of methyl-β-cyanovinyl ketone with piperidine.** In an analogous manner, methyl-β-(N-piperidyl)vinyl ketone was obtained by the reaction of 4 g of methyl-β-cyanovinyl ketone and 4 g of piperidine. B.p. 156°/7 mm, n_D^{20} 1.5718. Picrate: m.p. 121-122°. Literature data: b.p. 154-155°/7 mm, n_D^{20} 1.5730; picrate m.p. 122-123° (7).
7. **Reaction of methyl-β-cyanovinyl ketone with hydrazine.** In the reaction of 4 g of methyl-β-cyanovinyl ketone with 5 ml of hydrazine hydrate in 10 ml of ether, according to the procedure described for the synthesis of 3-methylpyrazole from methyl-β-chlorovinyl ketone (8), 3-methylpyrazole was obtained. Yield 0.5 g, b.p. 205-206°/756 mm, n_D^{21} 1.4960. Picrate: m.p. 142-143°. Literature data: b.p. 204-206°/755 mm, n_D^{14} 1.4935. Picrate: m.p. 141-141.5° (8).

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Note: Figure translations are in progress. See original paper for figures.