Alkyl-Oxygen Cleavage of α, β-Unsaturated Esters with Secondary Amines

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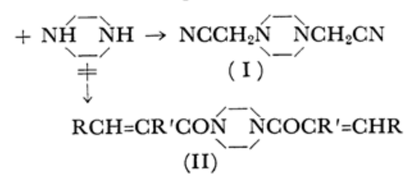
The bimolecular alkyl-oxygen cleavage of esters by amines has recently been reported.[1,2] We have found another example of alkyl-oxygen cleavage in the reaction of α, β-unsaturated esters with secondary amines.

An attempt to synthesize α, β-unsaturated amides by the reaction of α, β-unsaturated esters with amines usually failed because of the formation of a Michael adduct. But some activated esters, *e. g.* cyanomethyl and *p*-nitrophenyl esters, which are usually used in a peptide synthesis,[3] of α, β-unsaturated acids react with primary amines to give amides in fairly good yields.[4] Although we attempted to synthesize α, β-unsaturated amides by the reaction of activated cyanomethyl esters of α, β-unsaturated acids, *e. g.* cyanomethyl acrylate, methacrylate and crotonate, with piperazine, we obtained unexpectedly only 1, 4-bis(cyanomethyl)piperazine (I) resulting from the alkyl-oxygen cleavage; amides (II) were not detected.



(I)

(II)

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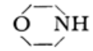
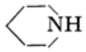
[1] H. E. Zaugg, P. E. Helgren and A. D. Schaefer, *J. Org. Chem.*, **28**, 2617 (1963).

[2] L. Weintraub and R. Terrell, *ibid.*, **30**, 2470 (1965).

[3] R. Schwyzer, B. Iselin and M. Feuer, *Helv. Chim. Acta*, **38**, 69 (1955).

[4] R. Harada and H. Kondo, unpublished results; Cyanomethyl methacrylate reacted with hydrazine hydrate to give hydrazide in a fairly good yield.

TABLE 1. REACTIONS OF CYANOMETHYL METHACRYLATE WITH SECONDARY AMINES

Amine	pK_a of amine[a]	Yield, %	
		Amide	Cyanomethyl amine
	8.36	0	21[b),**]
Me_2NH aq.[c]	10.87	0	68[d),*]
Et_2NH	10.98	0	55[e),*]
Et_2NH aq.[c]	10.98	0	72[e),*]
n-Pr_2NH	11.00	0	11[f),**]
	11.22	0	96[g),**]
n-Bu_2NH	11.25	0	60[h),**]

a) M. Kotake, "The Constants of Organic Compounds," The Asakura Publishing Co., Ltd., Tokyo, Japan (1963), p. 585.

b) Mp 58°C. Found: C, 57.01; H, 8.02; N, 22.34%. Calcd for $C_6H_{10}N_2O$: C, 57.11; H, 7.99; N, 22.21%. The unchanged cyanomethyl ester was recovered (42%).

c) 40% Aqueous solution.

d) HCl salt, mp 146°C. Found: C, 39.73; H, 7.51; N, 23.31; Cl, 29.25%. Calcd for $C_4H_9N_2Cl$: C, 39.84; H, 7.52; N, 23.23; Cl, 29.40%.

e) HCl salt, mp 186°C (lit.[5] mp 186°C).

f) Picrate, mp 108°C. Found: C, 45.50; H, 5.26; N, 18.91%. Calcd for $C_{14}H_{19}N_5O_7$: C, 45.53; H, 5.19; N, 18.96%. The unchanged cyanomethyl ester was recovered (70%). The poor yield of cyanomethyl amine may be attributed to the hindered nature of di-n-propylamine.

g) Mp 29°C, bp 59°C/0.1 mmHg.

h) Bp 78°C/0.3 mmHg. Found: C, 71.81; H, 12.01; N, 16.48%. Calcd for $C_{10}H_{20}N_2$: C, 71.37; H, 11.98; N, 16.65%.

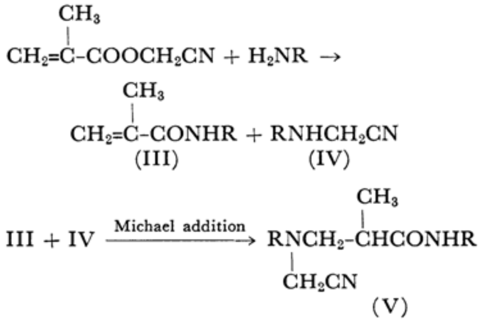
* The reaction mixture was treated by the method A.

** The reaction mixture was treated by the method B.

The reactions of cyanomethyl methacrylate, a representative of α, β-unsaturated esters, with other secondary amines were examined under the same reaction conditions. The results given in Table 1 show that in all cases the corresponding cyanomethyl amines were the only products and that their yields were approximately proportional to the basicities of the starting amines, except for highly hindered amines. These results may be explained as follows: 1) The attack by amines at the acyl carbon atom was suppressed by the conjugation of the carbonyl group with the double bond.

2) Secondary amines are known to have a stronger tendency toward alkyl-oxygen cleavage than primary amines.[1,2]

For comparison, reactions of cyanomethyl esters of saturated acids with secondary amines and those of cyanomethyl methacrylate with primary amines were examined. These results, given in Tables 2 and 3, respectively, show that in both cases the corresponding amide (III) and cyanomethyl amines (IV) were formed. In the latter reactions, a third product, the Michael adduct (V), also was formed according to the mechanism shown below.

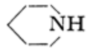
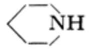


$$CH_2{=}\overset{CH_3}{\overset{|}{C}}\text{-}COOCH_2CN + H_2NR \rightarrow \underset{(III)}{CH_2{=}\overset{CH_3}{\overset{|}{C}}\text{-}CONHR} + \underset{(IV)}{RNHCH_2CN}$$

$$III + IV \xrightarrow{\text{Michael addition}} \underset{(V)}{RNCH_2\text{-}\overset{CH_3}{\overset{|}{C}}HCONHR \atop {\overset{|}{CH_2CN}}}$$

$R = C_6H_5CH_2$, $C_6H_{11}CH_2$ and C_6H_{11}

TABLE 2. REACTIONS OF SATURATED CYANOMETHYL ESTERS WITH SECONDARY AMINES

Cyanomethyl ester	Amine	pK_a of amine[a]	Yield, %	
			Amide	Cyanomethyl amine
$(CH_3)_2CHCOOCH_2CN$		8.36	85[b]	43
$(CH_3)_2CHCOOCH_2CN$		11.22	51[c]	70
$(CH_3)_2CHCH_2COOCH_2CN$		11.22	55[d]	73

a) M. Kotake, "The Constants of Organic Compounds," The Asakura Publishing Co., Ltd. Tokyo (1963), p. 585.

b) Bp 84°C/1 mmHg. Found: C, 60.98; H, 9.46; N, 8.89%. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91%.

c) Bp 57—59°C/0.1 mmHg. Found: C, 69.47; H, 11.00; N, 8.97%. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02%.

d) Bp 74°C/0.2 mmHg. Found: C, 70.71; H, 11.21; N, 8.52%; mol wt (ethanol), 170.16. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.32; N, 8.23%; mol wt, 169.26.

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[5] E. Knoevenagel and E. Mercklin, *Ber.*, **37**, 4089 (1904).

Table 3. Reactions of cyanomethyl methacrylate with primary amines

Amine	pK_a of amine[a]	Yield, %		
		Amide	Cyano-methyl amine	Michael adduct
$C_6H_5CH_2NH_2$	9.3	43	29	36
$C_6H_{11}CH_2NH_2$	10.45	26	25	51[b]
$C_6H_{11}NH_2$	11.54	18	13	45[c]

a) These values were measured by potentiometric titration at 22°C in aqueous solution.

b) Mp 97°C. Found: C, 71.71; H, 10.69; N, 12.47%. Calcd for $C_{20}H_{35}N_3O$: C, 72.02; H, 10.58; N, 12.60%.

c) Mp 75°C. Found: C, 70.49; H, 10.11; N, 14.05%. Calcd for $C_{18}H_{31}N_3O$: C, 70.77; H, 10.23; N, 13.76%.

In Tables 2 and 3, the total yields of products exceed theoretical values based on the starting esters. These facts are explained by assuming that part of cyanomethyl amines may be formed by the alkyl-oxygen cleavage, but rest of them may be formed by the reaction of the starting amines with cyanomethanol,[6] which is the intermediate resulting from the acyl-oxygen cleavage.

On the other hand, amides are formed only by the acyl-oxygen cleavage, because the reaction of free methacrylic acid with amines does not give amides under these reaction conditions.

Experimental

Cyanomethyl Esters. The esters were prepared according to the procedure of Schwayzer.[3] The following procedure is typical.

Methacrylic acid (51.7 g, 0.6 mol), triethylamine (60.7 g, 0.6 mol) and hydroquinone (0.05 g) were disolved in 100 m*l* of ethyl acetate. Chloroacetonitrile (51.3 g, 0.6 mol) was added dropwisely to the solution, which was refluxed for 3 hr. The reaction mixture was stood for overnight and then formed triethylamine hydrochloride was filtered off. Evapolation of the solvent and distillation gave 57.0 g of crude cyanomethyl methacrylate, bp 87—91°C/20 mmHg, which was redistilled at 83°C/11 mmHg, 48.8 g, 65% yield, infrared ν_{max} 2950, 1735, 1635, 1150, 910, 810 cm^{-1}.

Found: C, 57.57; H, 5.39; N, 11.21%; mol wt, 123. Calcd for $C_6H_7NO_2$: C, 57.59; H, 5.64; N, 11.20%; mol wt, 125.12.

1, 4-Bis(cyanomethyl)piperazine. A mixture of cyanomethyl acrylate (1.11 g, 0.01 mol), piperazine hexahydrate (1.94 g, 0.01 mol), hydroquinone (0.01 g) and ethyl acetate (10 m*l*) was heated at 70°C for 3 hr. After cooling to a room temperature, 50 m*l* of ethyl acetate was added, the organic layer was separated, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was recrystallized from ethyl acetate to afford 1, 4-bis(cyanomethyl)piperazine: 0.799 g, 82.7% yield, mp 159°C, infrared ν_{max}^{KBr} 2925, 2880, 2220, 865, 795 cm^{-1}.

Found: C, 58.60; H, 7.41; N, 33.91%. Calcd for $C_8H_{12}N_4$: C, 58.51; H, 7.31; N, 34.12%.

Cyanomethyl methacrylate and cyanomethyl crotonate were worked up as above and afforded 1, 4-bis(cyanomethyl)piperazine: 69.4% and 57.8% yield, respectively.

Reaction of Cyanomethyl Methacrylate with Secondary Amines. A mixture of cyanomethyl methacrylate (2.5 g, 0.02 mol) and a secondary amine (0.04 mol) was heated at 70°C for 3 hr. The reaction mixture was treated by one of the following methods.

Method A. Water (25 m*l*) was added to the reaction mixture, which was then extracted twice with 25 m*l* of ether. The extracts were combined and dried over anhydrous sodium sulfate. Into the ether solution dry hydrogen chloride was bubbled, and cyanomethyl amine hydrochloride was crystallized out. It was filtered, recrystallized from methanol-chloroform (1 : 1).

The aqueous layer was neutralized with dilute hydrochloric acid and extracted with 10 m*l* of ether three times. The extract was dried over magnesium sulfate. Ether was removed under reduced pressure to afford free methacrylic acid.

Method B. Cyanomethyl amines were isolated by distillation.

Reaction of Cyanomethyl Esters of Saturated Acids with Secondary Amines. The following procedure is typical. A mixture of cyanomethyl isobutyrate (0.02 mol) and morpholine (0.04 mol) was heated at 70°C for 3 hr. To the reaction mixture 50 m*l* of chloroform was added and the organic layer was separated, washed with 25 m*l* of water, and dried over anhydrous sodium sulfate. After removal of the solvent, the products were isolated by distillation.

Reaction of Cyanomethyl Methacrylate with Primary Amines. A mixture of cyanomethyl methacrylate (0.02 mol) and benzylamine (0.04 mol) was heated at 70°C for 3 hr. After cooling, 50 m*l* of chloroform was added to the reaction mixture. The chloroform layer was separated, washed with 25 m*l* of water and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and from the residue a solid was filtered off. Recrystallization from chloroform-ether (1 : 1) afforded a Michael adduct, $C_6H_5CH_2N(CH_2CN)CH_2CH(CH_3)CONHCH_2C_6H_5$, mp 103.3°C.

Found: C, 74.72; H, 7.21; N, 12.97%; mol wt, 315. Calcd for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07%; mol wt, 321.41.

The filtrate was treated by silica-gel chloromatography with chloroform-methanol (9 : 1) and two fractions obtained were distilled to give *N*-(cyanomethyl)benzylamine, bp 105°C/0.1 mmHg, Found: C, 73.55; H, 7.01; N, 19.03%. Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16%, and the corresponding amide, bp 120°C/0.1 mmHg, Found: C, 74.97; H, 7.45; N, 8.24%. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99%. respectively.

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[6] J. V. Braun, *ibid.*, **40**, 3933 (1907).