Synthesis of α,β-Unsaturated Carboxylic Hydrazides

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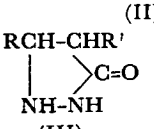
Carboxylic hydrazides are usually prepared by the reaction of carboxylic esters with hydrazine hydrate.[1] However, when this general method is applied to the synthesis of α,β-unsaturated carboxylic hydrazides, the main product is not simple carboxylic hydrazide, but pyrazolidone (III) resulting from the Michael addition.[2]

$$RCH{=}CR'COOR'' + NH_2NH_2 \rightarrow$$

(I)

$$[NH_2NHCHR\cdot CHR'COOR''] \rightarrow$$

(II)



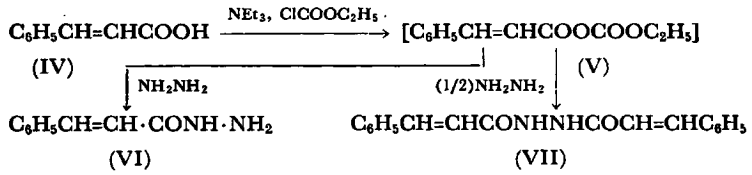
(III)

Therefore, pyrazolidones obtained by this method have often been believed to be carboxylic hydrazides. Godtfredsen[3] has, however, shown

1) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, New York (1953), p. 569.

2) C. Gansser, *Helv. Chim. Acta*, **36**, 1423 (1963); F. H. Stodla, *J. Org. Chem.*, **13**, 757 (1948); T. Lieser, *Chem. Ber.*, **84**, 4 (1951); P. Ruggli, *Helv. Chim. Acta*, **24**, 899 (1941).

3) W. Q. Godtfredsen and S. Vangedal, *Acta Chem. Scand.*, **9**, 1498 (1955).



that the cinnamohydrazide synthesized by Muckermann[4] was not the hydrazide, but in fact 5-phenyl-3-pyrazolidone, he synthesized real cinnamohydrazide (VI) by the reaction of cinnamic ethoxyformic anhydride (V) with hydrazine hydrate.

Several papers have appeared reporting the synthesis of acrylo-,[5] methacrylo-[6] and crotonohydrazide[4] by the reaction of the corresponding esters with hydrazine hydrate. The structures of these hydrazides have seemed doubtful, however, so we attempted the synthesis of real hydrazides.

To accelerate the attack of hydrazine on the carbonyl carbon instead of on the α,β-double bond, the activated esters, which are usually used for the synthesis of peptides, seemed to be useful. We wish to report on the synthesis of α,β-unsaturated carboxylic hydrazides (X) by the reaction of activated esters (IX) with hydrazine hydrate.

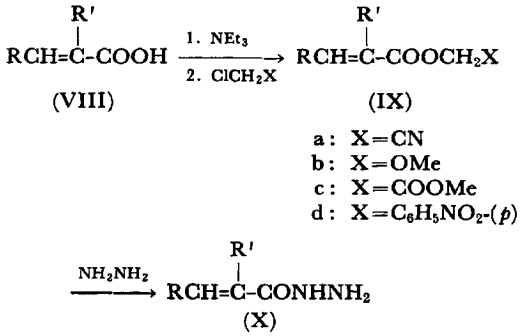
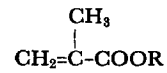


TABLE 1.* THE REACTION OF HYDRAZINE HYDRATE WITH METHACRYLATE



R	Yield of product (%)	
	Methacrylohydrazide	4-Methyl-3-pyrazolidone
$-CH_2CN$	83	0
$-CH_2OCH_3$	33	0
$-CH_2COOC_2H_5$	7	0
$-CH_2C_6H_4NO_2$-(p)	0	35

* The solvent was chloroform.

The reaction of hydrazine hydrate with several activated esters (IX) of methacrylic acid have been examined; the results are shown in Table 1.

Of these activated esters, cyanomethyl methacrylate gave the best results. The reaction was influenced by the solvents; when chloroform or methylene chloride was used as the solvent, methacrylohydrazide was obtained in 83% or 69% yield, respectively. In ethanol, however, 17% *N,N'*-dimethacroyl hydrazine, 28% 4-methyl-3-pyrazolidone, and no hydrazide were obtained.

In chloroform, cyanomethyl cinnamate gave 82% hydrazide, but under the same reaction conditions cyanomethyl acrylate and crotonate gave no hydrazides, but only 11% and 27% pyrazolidones, respectively.

For the sake of comparison with the activated ester methods, the mixed acid anhydride methods have been tried; in the case of methacrylic ethoxyformic anhydride, 72% hydrazide and 11% *N,N'*-dimethacroyl hydrazine were formed.

The methacrylohydrazide obtained above has a mp of 86—88°C and ν_{max}^{KBr} 3325, 3200, 1663, 1612, 1550, 890 cm^{-1}, and it is different from Shvaika's methacrylohydrazide (bp 140°C/11 mmHg,[6] ν_{max} 3300, 1670 cm^{-1}).

Several attempts to isolate acrylohydrazide prepared by the mixed acid anhydride method were unsuccessful because of its high polymerizability. The fairly-pure acrylohydrazide (yield 30%) isolated by silica-gel column chromatography was a viscous oil (ν_{max} 3250, 1660, 1610, 1545, 990, 910 cm^{-1}) and gave acrylic benzylidenehydrazide by the reaction with benzaldehyde.

The crotonohydrazide synthesized above has a mp of 87—89°C and ν_{max}^{KBr} 3300, 1664, 1615, 1550, 895 cm^{-1}, it is different from Muckerman's crotonohydrazide (bp 120°C/4 mmHg).[4]

The acrylo-, methacrylo-, and crotonohydrazide obtained above absorbed one mole of hydrogen and gave propiono-, isobutyro-, and *n*-butylohydrazide, respectively.

Experimental

Activated Esters of Methacrylic Acid. *a) Cyanomethyl Ester.* The ester was prepared according to the general procedure of Schwyzer.[7] Triethylammonium methacrylate (14.3 g) was reacted with chloroacetonitrile (6.8 g) in ethyl acetate. Yield, 73.2%; bp 48—49°C/2 mmHg.

4) E. Muckermann, *J. Pract. Chem.*, (2) **83**, 513 (1911); *Ber.*, **42**, 3449 (1909).
5) C. S. Rondestvedt, *J. Am. Chem. Soc.*, **77**, 6532 (1955).
6) O. P. Shvaika and Yu. I. Makarenks, *Zh. Obshch. Khim.*, **33**, 1233 (1963).
7) R. Schwyzer and B. Iselin, *Helv. Chim. Acta*, **38**, 69 (1955).

Found: C, 57.34; H, 5.87; N, 11.14%. Calcd for $C_6H_7O_2N$: C, 57.59; H, 5.64; N, 11.20%.

b) Ethoxycarbonylmethyl Ester. The ester was prepared from methacrylic acid, triethylamine, and ethyl chloroacetate according to the general method.[7] Yield, 59%; bp 67—68°C/0.8 mmHg.

Found: C, 55.67; H, 6.39%. Calcd for $C_9H_{12}O_4$: C, 55.80; H, 7.03%.

c) Methoxymethyl Ester. The ester was prepared from the acid, triethylamine, and chloromethyl methyl ether.[7] Yield, 62%; bp 70—71°C/40 mmHg.

Found: C, 55.65; H, 7.63%. Calcd for $C_6H_{10}O_3$: C, 55.40; H, 7.69%.

d) p-Nitrobenzyl Ester. The ester was prepared from the acid, triethylamine, and *p*-nitrobenzyl chloride.[8] Yield, 55%; mp. 82—84°C.

Found: C, 59.69; H, 4.97; N, 6.22%. Calcd for $C_{11}H_{11}O_4N$: C, 59.71; H, 5.01; N, 6.33%.

Methacrylohydrazide. *a) A Typical Activated-ester Method.* To a solution cyanomethyl methacrylate (3.75 g) in chloroform (100 cc), 80% hydrazine hydrate (3.0 g) was added. The solution was stirred for 2 hr at room temperature and then refluxed for 1 hr. After drying, the solvent was removed. The crystallization of the residue from ethanol-ether (1 : 1) gave colorless needles. Yield, 83%; mp 86—88°C.

Found: C, 47.85; H, 8.01; N, 27.95%. Calcd for $C_4H_8ON_2$: C, 47.98; H, 8.05; N, 27.98%.

Methacrylic benzylidenehydrazide was prepared according to the general method; mp 155—156°C, ν_{max}^{KBr} 3200, 1660, 1620, 1600, 1555 cm^{-1}.

Found: C, 69.86; H, 6.45; N, 14.82%. Calcd for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88%.

Methacrylohydrazide in ethanol absorbed 1 mol of hydrogen at room temperature with a Raney nickel catalyst and afforded crystals (mp 103—104°C), just like the authentic isobutyrohydrazide.

When the reaction was carried out in ethanol, *N,N'*-dimethacroylhydrazine (yield, 17%; mp 136—137°C, ν_{max}^{KBr} 3250, 1665, 1615, 1560, 890 cm^{-1}, Found: C, 57.05; H, 7.61; N, 16.71%. Calcd for $C_6H_8O_2N_2$: C, 57.13; H, 7.19; N, 16.17%.) and 4-methyl-3-pyrazolidone (yield, 28%; 115°C/4 mmHg, ν_{max} 3300, 1670 cm^{-1}) were obtained after the reaction products had been purified by sillica-gel column chromatography.

b) Mixed Acid Anhydride Method. The hydrazide was synthesized according to the general procedure of Godtfredsen.[3] The mixed acid anhydride prepared from potassium methacrylate (13.8 g), pyridine (0.2 g), and ethyl chloroformate (12.0 g) in chloroform (100 cc) was added rapidly to a stirred, ice-cooled suspension of 80% hydrazine hydrate (10.0 g) in chloroform (100 cc). After standing at 0°C overnight, the solution was filtered. The filtrate was washed with a saturated sodium bicarbonate solution, and then dried. The solvent was removed, and the residue recrystallized from benzene. Yield, 72%; mp 86—88°C, which was identical with that of the product of Method a).

8) B. Iselin and R. Schwyzer, *ibid.*, **40**, 373 (1957).

Acrylohydrazide. *a) Mixed Acid Anhydride Method.* The mixed acid anhydride prepared from potassium acrylate (20.0 g), pyridine (0.5 g), and ethyl chloroformate (22.6 g) in methylene chloride (200 cc) was added to a stirred, ice-cooled suspension of 80% hydrazine hydrate (18.0 g) in methylene chloride (150 cc). After stirring for 30 min at 0°C, potassium chloride was filtered off. The filtrate was kept at 0°C overnight, and dried, and then the solvent was removed. The oily residue was purified by silica-gel column chromatography. From the chloroform-methanol (5%) eluted fractions, a colorless, viscous oil was obtained. Yield, 30%; ν_{max}^{KBr} 3250, 1670, 1620, 1550, 980 cm^{-1}.

Acrylic benzylidenehydrazide was prepared by the general method: Yield, 78%; mp 131—132°C.

Found: C, 68.68; H, 5.90; N, 16.27%. Calcd for $C_{10}H_{10}ON_2$: C, 68.95; H, 5.79; N, 16.08%.

Acrylohydrazide in ethanol absorbed 1 mol of hydrogen at room temperature with a Raney nickel catalyst; the product (mp 38—40°C) was identical with the authentic propionohydrazide.

b) Activated-ester Method. Cyanomethyl acrylate was prepared according to the general method. Yield, 71%; bp 66—68°C/6.5 mmHg.

Found: C, 54.22; H, 4.59; N, 12.55%. Calcd for $C_5H_5O_2N$: C, 54.05; H, 4.54; N, 12.61%.

80% Hydrazine hydrate (4.5 g) was added to a solution of the cyanomethyl ester (3.3 g) in chloroform (100 cc), and the solution was stirred for 2 hr at room temperature. After drying, the solvent was removed *in vacuo*.

The residue was purified by silica-gel chromatography. From the chloroform-methanol (5%) eluted fractions, an oily product (0.24 g, yield, 9.3%) was obtained, its IR spectrum (ν_{max}) 3300, 1670 cm^{-1}) was identical with that of the 3-pyrazolidone derivative.

Crotonohydrazide. Crotonohydrazide was prepared according to the general procedure of Godtfredsen.[3] Yield, 48%; mp 86—89°C, ν_{max}^{KBr} 3300, 1665, 1620, 1530, 960 cm^{-1}.

Found: C, 48.07; H, 8.02; N, 27.90%. Calcd for $C_4H_8ON_2$: C, 47.98; H, 8.05; N, 27.98%. The crotonic benzylidenehydrazide was prepared by the general method. Yield, 58%; mp 165—166°C.

Found: C, 69.91; H, 6.41; N, 14.83%. Calcd for $C_{11}H_{12}ON_2$: C, 70.18; H, 6.43; N, 14.88%.

Crotonohydrazide in ethanol absorbed 1 mol of hydrogen at room temperature in the presence of a Raney nickel catalyst. The product (mp 41—43°C) was identical with the authentic butyrohydrazide.

Cinnamohydrazide. Cyanomethyl cinnamate was prepared by the same procedure as cyanomethyl methacrylate. Yield, 79.0%; mp 62—63°C.

Found: C, 70.47; H, 4.86; N, 7.57%. Calcd for $C_{11}H_9O_2N$: C, 70.58; H, 4.85; N, 7.48%.

The reaction of cyanomethyl cinnamate with 80% hydrazine hydrate gave 82% of cinnamohydrazide, mp 116—117°C, which was identical with Godtfredsen's cinnamohydrazide (mp 117—117.5°C).[3]