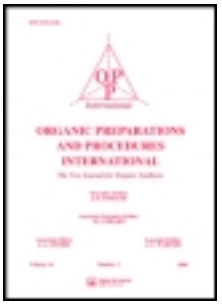

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A NOVEL METHOD OF SYNTHESIS OF ALKYL α-CYANOACRYLOYL GLYCOLATES

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A NOVEL METHOD OF SYNTHESIS OF ALKYL α-CYANOACRYLOYL GLYCOLATES

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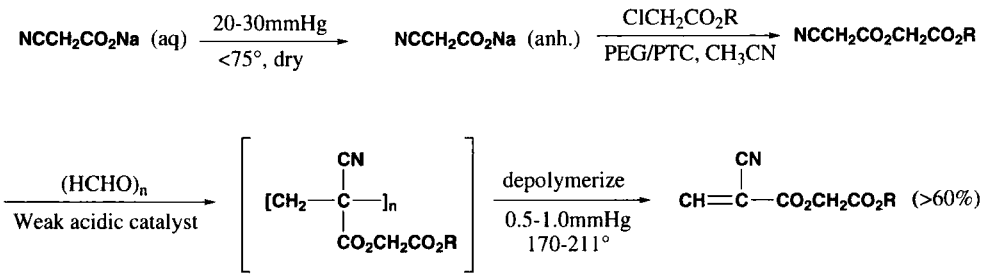
Alkyl α-cyanoacryloyl glycolates which can be used as an "ideal" soft tissue adhesive hemostatic agent, have been synthesized by Jaffe,[1] Hirakawa,[2] Aronovich[3] and Cainelli.[4] However, these methods are far from useful because the starting materials are expensive and the overall yields are low (24-46%). We now report a novel procedure for the synthesis of the alkyl α-cyanoacryloyl glycolates as illustrated below.



R = Me, Et, *i*-Pr, *i*-Bu, *i*-Am

Because the monomer polymerizes readily at room temperature, the condensation of formaldehyde with alkyl α-cyanoacetyl glycolates is best carried out under weakly acidic conditions. The lower molecular weight of the polymers and the narrower molecular weight distribution, led to smooth depolymerization on distillation to give higher yields of monomers of excellent purity.

TABLE 1. Yields, Physical Constants and ^{1}H NMR Data of Alkyl α-Cyanoacetyl Glycolates (**1**)

R	bp. (°C /mmHg)	Yield(%)	^{1}H NMR Data δ (ppm)
CH_3	106-110/1.0	81.5	3.75 (s, 3H,-CH_3), 4. 64 (s, 2H, -$COOCH_2CO$-), 3.90 ($NCCH_2CO$-)
C_2H_5	108-112/1.0	83.2	1.25 (t, 3H, -$CH_2\underline{CH_3}$), 4.20 (m, 2H, -$\underline{CH_2}CH_3$), 4. 62 (s, 2H, -$COOCH_2CO$-),3.58 (s, 2H, $NCCH_2$-)
i-C_3H_7	109-113/1.0	82.1	1.25 [d, 6H,-CH ($\underline{CH_3})_2$], 4.10 [m, 1H,-$\underline{CH}(CH_3)_2$], 4. 60 (s, 2H,-$COOCH_2CO$-), 3.50 (s, 2H, $NCCH_2$-)
i-C_4H_9	111-115/1.0	85.7	0.85 [d, 6H,-CH($\underline{CH_3})_2$], 2.05 [m, 1H,-$\underline{CH}(CH_3)_2$], 3. 85 (d, 2H,-$\underline{CH_2}CH(CH_3)_2$], 4.60 (s, 2H, -$COOCH_2CO$-), 3.51 (s, 2H, $NCCH_2$-)
i-C_5H_{11}	113-116/1.0	87.1	0.90 [m, 6H,-CH($\underline{CH_3})_2$], 1.45 [m, 1H, -$CH_2\underline{CH}(CH_3)_2$], 1.90 (m, 2H,-$CH_2\underline{CH_2}CH(CH_3)_2$], 4.0 (m, 2H, -$O\underline{CH_2}CH_2$-), 4.50 (s, 2H, -$COOCH_2CO$-), 3.40 (s, 2H, $NCCH_2$-)

EXPERIMENTAL SECTION

All boiling points are uncorrected. ^{1}H NMR spectra were recorded as CCl_4, solutions on a Varian EM-360 (60MHz) spectrometer, using TMS as internal standard. Alkyl chloracetates were synthesized from chloracetic acid with the appropriate alcohol; sodium cyanoacetate was prepared by the reaction of sodium cyanide and chloracetic acid.

TABLE 2. Yields, Physical Constants and ^{1}H NMR Data of Alkyl α-Cyanoacryloyl Glycolates (**2**)

R	bp. (°C /mmHg)	Yield(%)	^{1}H NMR Data δ (ppm)
CH_3	108-112/1.0	66.9	3.66 (s, 3H,-CH_3), 4.64 (s, 2H,-CH_2CO-) 6.66 (s, 1H, olefinic H), 7.01 (s, lH, olefinic H)
C_2H_5	110-114/1.0	83.3	1.25 (t, 3H,-CH_2CH_3), 4.20 (m, 2H, -CH_2CH_3), 4.62 (s, 2H, -$COOCH_2$CO-) 6.66 (s, 1H, orefinic H), 0.01 (s, 1H, orefinic H)
i-C_3H_7	112-116/1.0	68.9	1. 25 [d, 6H,-CH($\underline{CH_3}$)$_2$], 4.06 [m, 1H, -$\underline{CH}$(CH_3)$_2$], 4.60 (s, 2H, -$COOCH_2$CO-), 6.60 (s, 1H, orefinic H),7.01 (s, 1H, olefinic H)
i-C_4H_9	115-120/1.0	78.0	0. 92 [d, 6H,-CH($\underline{CH_3}$)$_2$], 1.97 [m, 1H, -$\underline{CH}$(CH_3)$_2$], 3.70 (d, 2H, -$\underline{CH_2}$CH(CH_3)$_2$] 6.60 (s, 2H, olefinic H),6.95 (s, 1H, olefinic H)
i-C_5H_{11}	118-123/1.0	65.6	0.90 [m, 6H, -CH($\underline{CH_3}$)$_2$], 1. 50 [m, 1H, -$\underline{CH}$(CH_3)$_2$], 1. 96 (m, 2H, -$CH_2\underline{CH_2}$CH(CH_3)$_2$], 4.02 (t, 2H, -O$\underline{CH_2}CH_2$-), 6.50 (s, 1H. orefinic H), 6.90 (s, 2H, olefinic H)

Alkyl Cyanoacetyl Glycotates (1).- Sodium cyanoacetic acid (0.5mol), alkyl chloracetate (1mol), polyethylene glycol-400 (0.1mol), sodium bromide (0.15mol) and acetonitrile (80mL) were added to a 500mL three-necked flask fitted with a mechanical stirrer and a reflux condenser. The mixture was stirred for 6 hours at 80°. After cooling to room temperature, sodium chloride was removed by filtration and the mixture was washed with water until neutral. The mixture was dried and acetonitrile and excess alkyl chloracetate was distilled. Finally, the mixture was fractionated under reduced pressure(1.0-2.0mmHg, 100-130°) to give pure alkyl α-cyanoacetyl glycolates whose purity was checked by ^{1}H NMR spectroscopy.

Alkyl α-Cyanoacryloyl Glycolates (2).- To a mixture of 0.08mol of the alkyl acyanoacetyl glycolate, 0.5mL of catalyst (piperidine-acetic acid-hydrochloric acid 1: 1.5: 1 v/v), 40mL of cyclohexane in a 250mL 3-necked flask fitted with a mechanical stirrer, a reflux condenser and a Dean-Stark trap, was added a mixture of 3g (0.1mol) of paraformaldehyde and 0.02mol of alkyl α-cyanoacetyl glycolates dropwise over a period of 1 h. Then 20mL of tricresyl phosphate was added and mixture was heated of reflux for 1 h. After 1.8mL of water had collected into the trap, it was replaced with oven-dried short-path distillation apparatus with a sulfur dioxide bleed. The mixture was then cooled to 70-80° and 1.5g of P_2O_5 and 0.15g of 2,6-di-(*tert*-butyl)*p*-cresol were added to the flask; cyclohexane was distilled, after which the oligomer was cracked under sulfur dioxide atmosphere into a chilled receiver

containing a small amount of 2,6-di-(*tert*-butyl)*p*-cresol at 170-211°/0.5-1.0mmHg to give the pure monomer. The purity of monomer was greater than 95%.

TABLE 3. Elemental Analysis of Alkyl α-Cyanoacryloyl Glycolate

	Calcd(Found)		
R	C	H	N
i-C_3H_7	54.82 (55.06)	5.62 (5.75)	7.10 (7.15)
i-C_4H_9	56.87 (57.11)	6.20 (6.28)	6.63 (6.89)
i-C_5H_{11}	58.67 (58.68)	6.71 (6.78)	6.21 (6.08)

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