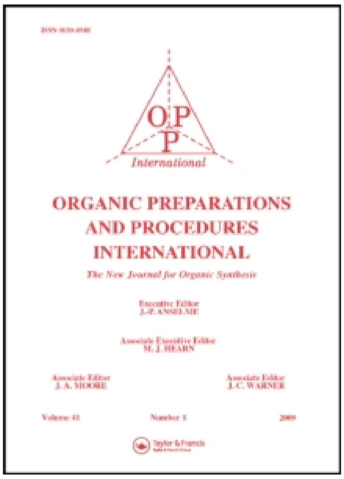

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# A FACILE SYNTHESIS OF ACYL-PROTECTED FORMALDEHYDE CYANOHYDRINS

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## OPPI BRIEFS

# A FACILE SYNTHESIS OF ACYL-PROTECTED FORMALDEHYDE CYANOHYDRINS

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In the course of several ongoing studies, several acyl-protected formaldehyde cyanohydrins were required. The only general literature procedure for the synthesis of compounds of this type involves the reaction of glycolonitrile with a variety of acid chlorides.[1] The drawbacks of this method are that it requires freshly prepared glycolonitrile, and gives only modest yields (48-74%). We describe herein a simpler method, involving the reaction of carboxylate anions with chloroacetonitrile. The only previous mention of an approach similar to this involved the cyanomethylation of N-protected amino acids.[2] However, this less desirable procedure required the use of chloroacetonitrile as the reaction solvent in order to achieve satisfactory yields. In addition, our procedure affords material of purity suitable for most uses upon simple elution through Florisil.

$$RCO_2H + ClCH_2CN \xrightarrow[DMSO]{Na_2CO_3} RCO_2CH_2CN$$

## EXPERIMENTAL SECTION

Proton NMR spectra were determined at 300 mHz on a General Electric GN-300 Omega NMR spectrometer. Infrared spectra were obtained on a Perkin Elmer 1600 FTIR spectrometer. Combustion analyses were carried out by Atlantic Microlab Inc., Norcross, GA 30091.

General Procedure.- Chloroacetonitrile (0.38 g, 5 mmol), anhydrous $Na_2CO_3$ (1.06 g, 10 mmol) and 7.5 mmol of the desired carboxylic acid were dissolved in 10 mL of dimethyl sulfoxide. The reaction mixture was heated to 80° overnight under $N_2$ or Ar with stirring. After cooling to room temperature, the mixture was diluted with an equal volume of EtOAc, and was washed repeatedly with water, once with brine, dried over $MgSO_4$, filtered, and solvents were removed by rotary evaporation. The crude product was eluted through a 1-in pad of Florisil with ether to remove the small amount of colored polar material. The ether was subsequently removed by rotary evaporation to afford products, pure by NMR and homogeneous by thin-layer chromatography on silica gel with 9:1 hexane:EtOAc.

TABLE. Yields, IR and $^1$H NMR of $RCO_2CH_2CN$

| | R | Yield (%) | IR (C=O, cm-1) | Proton NMR (δ) |
|---|---|---|---|---|
| 1 | $C_6H_5$- | 97 | 1725<br>(lit.[1] 1730) | 7.2-8.15 (m,5), 4.95 (s,2)[ lit.[1] 7.25-8.2 (m,5), 4.96 (s,2)] |
| 2 | 1-$C_{10}H_7$- | 96 | 1722 | 8.95 (d,1), 8.3 (d of d,1), 8.1 (d,1), 7.9 (d,1), 7.5-7.7 (m,3), 5.05 (s,2) |
| 3 | 3-MeO-4-EtO-$C_6H_3CH_2$- | 60 | 1750 | 6.78-6.84 (m,3), 4.7 (s,2), 4.1 q,2), 3.9 (s,3), 3.7 (s,2), 1.45 (t,3) |
| 4 | $CH_3(CH_2)_9CH_2$- | 97 | 1758 | 4.7 (s,2), 2.35 (t,2), 1.6 (m,2), 1.25 (m,16), 0.85 (t,3) |
| 5 | 2-$CNCH_2OC_6H_4$- | 86 | 1715 | 7.9 (d of d,1), 7.6 (m,1), 7.2 (m,2), 4.93 (s,2), 4.88 (s,2) |

1-Naphthoyloxyacetonitrile (2), recrystallized from hexane to give white crystals, mp. 61.5-62.5°.

Anal. Calcd. for $C_{13}H_9NO_2$: C, 73.92; H, 4.29. Found: C, 73.99; H, 4.31

Cyanomethyl(4-ethoxy-3-methoxyphenyl)acetate (3), purified by medium pressure liquid chromatography with 9:1 hexane-EtOAc to give a colorless liquid.

Anal. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07. Found: C, 62.61; H, 6.07

Lauroyloxyacetonitrile (4), purified by medium pressure liquid chromatography with 19:1 hexane-EtOAc to give a colorless liquid.

Anal. Calcd. for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53. Found: C, 70.46; H, 10.55

2-Cyanomethoxybenzoylacetonitrile (5)[3], recrystallized from hexane to give white crystals, mp. 44-46°.

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.08; H, 3.73. Found: C, 61.18; H, 3.70

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2. (a) R. Schwyzer, B. Iselin and M. Feurer, Helv. Chim. Acta., 38, 69 (1955). (b) B. Iselin, M. Feurer and R. Schwyzer, ibid., 38, 1508 (1955). (c) R. Schwyzer, B. Iselin, W. Rittel and P. Sieber, ibid., 39, 872 (1956).

3. Due to the fact that there were two nucleophilic sites in salicylic acid, the amounts of chloroacetonitrile and $Na_2CO_3$ were doubled, to 10 mmol and 20 mmol, respectively. Attempts at selective cyanomethylation of either the acid or phenol were not successful, as only **5** was obtained when the usual quantities of reagents were used. The synthesis of aryl-protected formaldehyde cyanohydrins upon reaction of phenol with chloroacetonitrile under basic conditions has been noted: G. H. Sidhu, G. Thyagarajan and M. Mazharuddin, Indian J. Chem., 2, 170 (1964).