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Preparation of Nitriles by the Modification of Mitsunobu-Wilk Procedure III Carbon Elongation of Hydroxy Esters

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PREPARATION OF NITRILES BY THE MODIFICATION OF MITSUNOBU-WILK PROCEDURE III CARBON ELONGATION OF HYDROXY ESTERS.

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ABSTRACT: An efficient one-step procedure for the conversion of hydroxy esters into the corresponding nitrile esters using triphenylphosphine (PPh_3)-diethyl azodicarboxylate (DEAD) in the presence of acetone cyanohydrin is described.

Recently, we have described a simple, mild procedure for the conversion of olefinic[1] and β-acetylenic[2] alcohols into the corresponding nitriles, which are important methods in elongation of the chain by one carbon[3]. The resulting unsaturated nitriles are useful synthetic intermediates for the synthesis of biologically active compounds[3, 4]. The direct transformation of esters containing terminal or non-terminal hydroxy group, into the corresponding nitrile ester had

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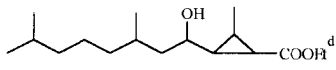
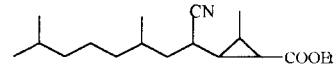
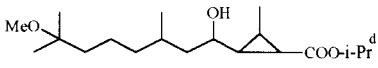
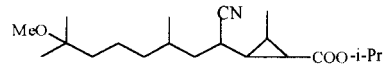
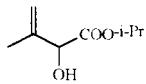
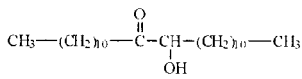
Table: Conversion of Alcohols to Nitriles

Entry	Substrate	Product	Yield (%)[a]
1	$HO-(CH_2)_8-COOMe$[b]	$NC-(CH_2)_8-COOMe$	70
2	$HO-(CH_2)_{10}-COOMe$[c]	$NC-(CH_2)_{10}-COOMe$	75
3			55
4			48
5		NO REACTION/ DECOMP.	
6	$CH_3-CH(OH)-COOH$	NO REACTION/ DECOMP.	
7		NO REACTION/ DECOMP.	
8	$CH_3-C(CH_3)(NH_2)-CH_2OH$	NO REACTION/ DECOMP.	

[a] Yields refer to isolated, chromatographically homogeneous materials.

[b] Lit. [6]; [c] Lit. [7]; [d] Lit. [8].

not been achieved by Wilk procedure[5]. Our attempts for cyanization of methyl-1-hydroxydecanoate (Table; entry 2) according to the procedure of Mitsunobu-Wilk, adding subsequently DEAD and acetone cyanohydrin to a solution of PPh_3 and alcohol, gave only poor result (20% yield).

This paper describes the application of our modification with a change of reaction condition for the conversion of alcohols carrying ester function into the corresponding nitriles. Addition of DEAD to a cold solution of PPh_3, was

followed by the addition of alcohol, and then the resulting mixture was stirred under cooling for 30 min. Acetone cyanohydrin was then added and the resulting mixture was stirred at low temperature for 6 hr, and then at r.t. Usual workup afforded the corresponding nitrile in good or acceptable yields (Table; entries 1-3).

However, no nitrile products were observed in the reactions of sterically hindered α-hydroxy ester and α-hydroxy acid (Table; entries 5 and 6).We also failed to perform the carbon elongation with amino alcohol and α-hydroxy ketone (Table; entries 7 and 8). In these cases, the starting compounds decomposed during the above reaction conditions.

In summary, under modified conditions described above, hydroxy esters can be converted conveniently into the corresponding nitriles by Mitsunobu-Wilk method.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were recorded with a Varian WXR-400 instrument at 400 and 100 MHz: internal standard TMS. The following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). Gas chromatographic analysis were conducted on Hewlett-Packard 5890 instrument equipped with a flame -ionisation detector and employing Hp-1(Methyl Silicone Gum): (5m x 0.53 mm x 2.65 μm thickness).

General Procedure:

To a stirred solution of triphenylphosphine (1.0 g; 3.8 mmol) in dry ether (10 ml) was added dropwise diethyl azodicarboxylate (0.66 g; 3.8 mmol) at - 20 °C, under nitrogen. The resulting mixture was stirred for 20 min. under cooling, and then the alcohol (2.5 mmol) was added dropwise at - 20 °C. After stirring for 30

min at this temperature, a solution of acetone cyanohydrin (0.32 g; 3.75 mmol) in dry ether (5 ml) was added slowly and the mixture was stirred at this temp. for 6 hr. The reaction mixture was allowed to warm to r.t. and stirred overnight. The white precipitate was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (hexane - acetone 10:0.5) to afford pure nitrile (Table).

9-Cyanononanoic acid methyl ester[9]**.** GC: Rt= 6.3 min.

^{1}H-NMR($CDCl_3$): 1.25-1.5 (m, 8H, $4CH_2$), 1.55-1.7 (m, 4H, $2CH_2$), 2.29 (t, 2H, J= 6Hz, CH_2), 2.32 (t, 2H, J= 6Hz, CH_2), 3.66 (s, 3H, CH_3).

^{13}C-NMR($CDCl_3$): 17.10 (C-9), 24.90 (C-3), 25.33 (C-8), 28.72 (C-4), 29.09 (C-5); 29.22 (C-6), 29.23 (C-7), 34.04 (C-2), 52.10 (CH_3), 119.84 (C-N), 174.28 (CO).

11-Cyanoundecanoic acid methyl ester[10]**.** GC: Rt= 8.016 min.

^{1}H-NMR($CDCl_3$): 1.25-1.5 (m, 12H, $6CH_2$), 1.55-1.7 (m, 4H, $2CH_2$), 2.30 (t, 2H, J= 6Hz, CH_2), 2.34 (t, 2H, J= 6Hz, CH_2), 3.67 (s, 3H, CH_3).

^{13}C-NMR($CDCl_3$): 17.12 (C-11), 24.92 (C-3), 25.37 (C-10), 28.65 (C-4), 28.73 (C-5), 29.09 (C-6), 29.18 (C-7), 29.22 (C-8), 29.27 (C-9), 34.08 (C-2), 52.15 (CH_3), 119.84 (C-N), 174.28 (CO).

2-(1-Cyano-3,7-dimethyloctyl)-3-methylcyclopropanecarboxylic acid ethyl ester. GC: Rt= 9.4 min.

^{1}H-NMR($CDCl_3$): 0.83 (d, 3H, J= 7Hz, CH_3), 0.93 (t, 3H, J= 6Hz, CH_3), 1.05-1.9 (m, 13H, $4CH_2$, 5CH), 1.12 (s, 6H, $2CH_3$), 1.24 (d, 3H, J= 7Hz, CH_3), 3.20 (m, H, CHCN), 4.07 (m, 2H, $COOCH_2$).

^{13}C-NMR($CDCl_3$): 11.3 (C-3-CH_3), 13.8 (OCH_2-$\underline{CH_3}$), 15.8 (C-8'), 17.9 (C-8'-CH_3), 19.9 (C-1'), 19.95 (C-3'-CH_3), 22.7 (C-6'), 24.5 (C-7'), 25.6 (C-5'), 25.7 (C-1), 27.9 (C-3'), 30.2 (C-3'CH_3), 35.8 (C-2), 36.21 (C-4'), 51.7 (C-2'), 63.5 (O-CH_2), 119.6 (C-N), 169.8 (CO).

2-(1-Cyano-3,7-dimethyl-7-methoxyoctyl)-3-methylcyclopropanecarboxylic acid isopropyl ester. GC: Rt= 11.3 min.

^{1}H-NMR($CDCl_3$): 0.83 (d, 3H, J= 7Hz, $3CH_3$), 1.05-1.9 (m, 12H, $4CH_2$, 4CH), 1.12 (s, 6H, $2CH_3$), 1.21 (d, 6H, J= 6Hz, CH), 1.24 (d, 3H, J= 7Hz, CH_3), 3.15 (m, H, CHCN), 3.16 (s, 3H, CH_3O), 4.98 (t, 1H, J= 6Hz, COOCH).

^{13}C-NMR($CDCl_3$): 11.3 (C-3, CH_3), 15.8 (C-8'), 17.9 (C-7'-CH_3), 19.9 (C-1'), 19.95 (C-3'-CH_3), 22.2-22.5 [CH-($\underline{CH_3}$)$_2$], 22.7 (C-6'), 24.5 (C-7'), 25.6 (C-5'), 25.7 (C-3), 27.9 (C-1), 30.2 (C-3'-CH_3), 35.8 (C-2), 36.21 (C-4'), 51.7 (C-2), 95.2 (O-CH), 119.5 (C-N), 169.8 (CO).

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