JOC*Note*

One-Step Conversion of Alcohols into Nitriles with Simultaneous Two-Carbon Chain Elongation. (Cyanomethyl)trimethylphosphonium Iodide as a Reagent with a Dual Mode of Action

Florencio Zaragoza

Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Måløv, Denmark

flo@novonordisk.com

Received March 19, 2002

Abstract: Treatment of alcohols with an excess of (cyanomethyl)trimethylphosphonium iodide leads, after aqueous hydrolysis, to the clean formation of nitriles with two more carbon atoms than present in the original alcohol. Benzylic, allylic, and aliphatic alcohols without β-branching (RCH_2CH_2OH) have been converted to nitriles with success. The required phosphonium iodide is simple to prepare and can be stored for a long time at room temperature.

We recently reported the use of (cyanomethyl)trialkylphosphonium iodides as mediators of the intermolecular alkylation of amines[1] and thiols[2] with aliphatic alcohols. These reactions presumably proceed via initial conversion of the alcohol into an alkyl iodide, which then alkylates the amine or the thiol. Because only water-soluble and volatile byproducts are formed, these reactions yield crude products of high purity, and are therefore well suited for parallel solution-phase chemistry.

While investigating the reactions of alcohols with an excess of (cyanomethyl)trimethylphosphonium iodide in the absence of additional nucleophiles, with the aim of preparing alkyl iodides and thereby substantiate our mechanistic proposal, the formation of C-alkylated (cyanomethyl)phosphonium salts **7** was observed (Scheme 1).[3] These phosphonium salts were unstable toward aqueous base, and when water was added to the reaction mixture and heating was continued, these phosphonium salts underwent dealkylation to yield nitriles **8**. A possible mechanism for this reaction is sketched in Scheme 1.

This new reaction turned out to be applicable to benzylic, allylic, and aliphatic alcohols without β-branching (RCH_2CH_2OH, Table 1). It represents a practical alternative to known, multistep procedures, in which the alcohol first has to be converted into an alkyl halide or sulfonate, which is then treated with lithiated acetonitrile[4,5] or with a synthetic equivalent thereof.[6]

SCHEME 1. Possible Mechanism for the Phosphonium Salt-Mediated Formation of Nitriles 8 from Alcohols 2

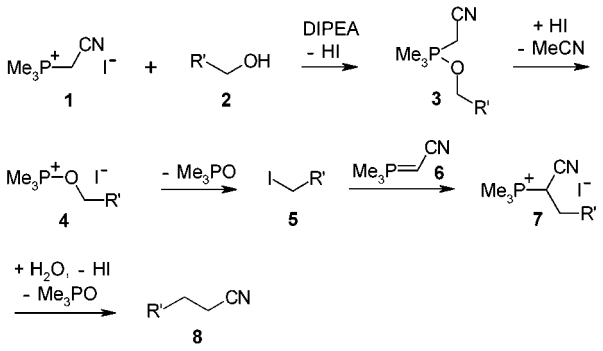
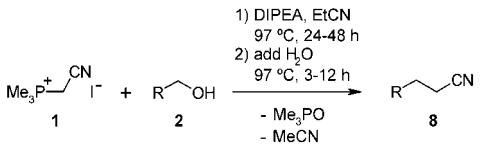
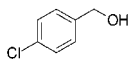
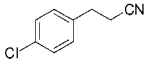
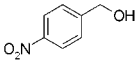
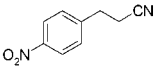
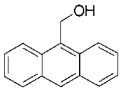
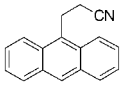
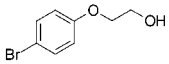
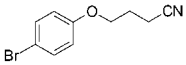
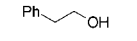
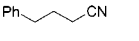
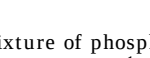
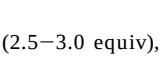


TABLE 1. Phosphonium Iodide-Mediated Conversion of Alcohols into Nitriles[a]



Entry	Alcohol 2	Time[b]	Nitrile 8	Yield[c]
a		24 h / 4 h		79%
b		23 h / 2 h		52%
c		20 h / 1 h		71%
d		25 h / 14 h		52%
e		24 h / 4 h		53%
f		26 h / 16 h		35%
g		24 h / 15 h		74%

[a] A mixture of phosphonium salt **1** (2.5−3.0 equiv), alcohol **2** (1.0 equiv, 0.5 mol L^{-1}), propionitrile, and diisopropylethylamine (DIPEA, 3.0−3.5 equiv) was stirred at 97 °C for 20−26 h. Water (6 equiv) was then added, and stirring at 97 °C was continued for 1−16 h. [b] Reaction times (alkylation/hydrolysis). [c] Yields of purified products. Products **8a**, **8d**, **8f**, and **8g** were purified by bulb-to-bulb distillation; products **8b**, **8c**, and **8e** were purified by column chromatography.

High concentrations of reactants and long reaction times (24−48 h) were generally required to attain good yields. Because the conversion of alcohols into iodides with reagent **1** is complete in less than 1 h under the currently used conditions,[1] the long reaction times are probably required because of the slow C-alkylation of the cyanomethylphosphorane **6**. When the alkylation[3] and the hydrolysis were complete, a simple aqueous extrac-

(1) Zaragoza, F.; Stephensen, H. *J. Org. Chem.* **2001**, *66*, 2518−2521.
(2) Zaragoza, F *Tetrahedron* **2001**, *57*, 5451−5454.
(3) The alkylated phosphonium salts **7** were isolated by aqueous workup under acidic conditions and identified by HPLC-MS and ^{1}H NMR. The title reaction can be monitored by hydrolysis of small samples with aqueous hydrochloric acid (1 M), extraction with ethyl acetate, concentration of the organic layer, and determination of the ratio **5**/**7** by ^{1}H NMR.
(4) Jansen, F. J. H. M.; Lugtenburg, J. *Eur. J. Org. Chem.* **2000**, 829−836.
(5) Inaba, S.; Rieke, R. D. *Synthesis* **1984**, 842−844.
(6) Hunter, D. A.; Perry, R. A. *Synthesis* **1977**, 37−39.

10.1021/jo025731r CCC: $22.00 © 2002 American Chemical Society
Published on Web 05/11/2002

tion yielded crude products of high purity, as judged by ^{1}H NMR, and small amounts of colored, polar byproducts could be easily removed by filtration through a pad of silica or by bulb-to-bulb distillation. With secondary alcohols the reaction did not proceed at all, and with β-branched alcohols (R_2CHCH_2OH) or when the alkylation was interrupted too early, mixtures of the desired nitriles **8** and alkyl iodides **5** were obtained.

The results given in Table 1 indicate that the phosphonium salt **1** is a valuable reagent for the conversion of alcohols into nitriles with simultaneous chain elongation by two carbon atoms. This salt thereby mediates two types of reaction: the halogenation and the chain extension of the alcohol. Phosphonium iodide **1** is easy to prepare and nonhygroscopic[1] and can be kept at room temperature without decomposition. The reactions of this salt with alcohols are easy to perform and significantly less tedious than alternative, multistep protocols, and yield crude products of high purity.

Experimental Section

General Procedure for the Preparation of Nitriles. Octanenitrile (8g). To a mixture of 1-hexanol (204 mg, 2.00 mmol) and (cyanomethyl)trimethylphosphonium iodide[1] (**1**, 1.24 g, 5.10 mmol) were added propionitrile (4.0 mL) and DIPEA (1.10 mL, 6.32 mmol), and the mixture was stirred at 97 °C for 24 h. Water (0.20 mL, 11.1 mmol) was added (strong bubbling), and stirring at 97 °C was continued for 15 h. Water (25 mL) and concentrated hydrochloric acid (1.0 mL, 12 mmol) were added, and the mixture was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed once with brine, dried with magnesium sulfate, and concentrated. The residue was purified by bulb-to-bulb distillation (10 mbar), to yield 185 mg (74%) of the title compound as an oil, 98% pure by GC. The ^{1}H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectra of this product and an authentic sample were identical.

3-(4-Chlorophenyl)propionitrile (8a). Oil. The ^{1}H NMR spectrum of this product was identical to the reported one.[5] ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 31.3, 119.1, 129.4, 130.1, 133.6, 136.8. Anal. Calcd for C_9H_8ClN (165.62): C, 65.27; H, 4.87; N, 8.46. Found: C, 64.84; H, 4.96; N, 8.77.

3-(4-Nitrophenyl)propionitrile (8b). Yellow crystals, mp 82.5−83.5 °C (lit. 79 °C[7]). The ^{1}H and ^{13}C NMR spectra of this product were identical to the reported ones.[7] Anal. Calcd for $C_9H_8N_2O_2$ (176.18): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.45; H, 4.50; N, 15.87.

3-Anthracen-9-ylpropionitrile (8c). Orange crystals, mp 148.5−149.5 °C (lit. 143−145 °C[8]). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.79 (t, J = 7 Hz, 2H), 4.03 (t, J = 7 Hz, 2H), 7.50 (m, 2H), 7.58 (m, 2H), 8.04 (br d, J = 8 Hz, 2H), 8.19 (br d, J = 8 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 23.7, 119.2, 123.0, 125.1, 126.5, 127.4, 129.4, 129.6, 131.5. Anal. Calcd for $C_{17}H_{13}N$ (231.30): C, 88.28; H, 5.67; N, 6.06. Found: C, 88.04; H, 5.72; N, 5.97.

5-Methyl-4-hexenenitrile (8d). Oil, 93% pure by GC. The ^{1}H NMR spectrum of this product was identical to the reported one.[4] ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 17.8, 24.1, 25.7, 119.7, 120.2, 135.6.

4-(4-Bromophenoxy)butyronitrile (8e). Oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (quint, J = 7 Hz, 2H), 2.58 (t, J = 7 Hz, 2H), 4.04 (t, J = 7 Hz, 2H), 6.78 (m, 2H), 7.39 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 25.8, 66.0, 113.9, 116.7, 119.4, 132.8, 157.9; IR 2943, 2880, 2248, 1591. Anal. Calcd for $C_{10}H_{10}BrNO$ (240.10): C, 50.03; H, 4.20; N, 5.83. Found: C, 50.06; H, 4.20; N, 5.92.

4-Phenylbutyronitrile (8f). Oil, 98% pure by GC. The ^{1}H NMR (300 MHz) and ^{13}C NMR (100 MHz) spectra of this product and an authentic sample were identical.

Acknowledgment. I thank Otto Larsson, Henrik Stephensen, and Flemming Gundertofte for technical assistance.

JO025731R

(7) Strazzolini, P.; Giumanini, A. G.; Runcio, A.; Scuccato, M. *J. Org. Chem.* **1998**, *63*, 952−958.

(8) Rhodes, R. A.; Boykin, D. W. *Synth. Commun.* **1988**, *18*, 681−688.