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Novel 1,3-diol monoethers by a triple tandem aldolization/etherification/Meerwein–Ponndorf–Verley reduction of aliphatic aldehydes

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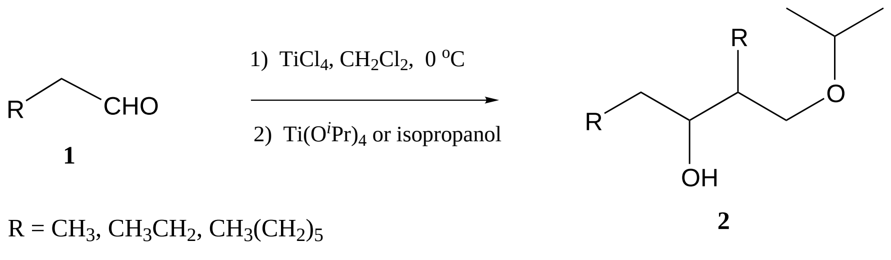
Abstract—A one-pot reaction of aliphatic aldehydes with $TiCl_4$ and $Ti(O^iPr)_4$ or isopropanol in CH_2Cl_2 produces dimeric 3-hydroxyethers in moderate yield. © 2001 Elsevier Science Ltd. All rights reserved.

Titanium(IV) reagents are presently widely used as mild Lewis acid, ligand exchange or transmetallation reagents in synthetic chemistry,[1] and have proved very useful as catalysts in the aldol reaction. In most cases the titanium(IV) reagents are used for preparing various preformed enolates. We report here that simple aliphatic aldehydes **1**, when treated with $TiCl_4$ and $Ti(O^iPr)_4$ or isopropanol in CH_2Cl_2, give the dimeric diol monoethers **2** (Scheme 1) in an unprecedented triple tandem aldolization/etherification/Meerwein–Ponndorf–Verley reduction sequence (Scheme 2).

The isolated yields are only moderate and the diastereoselectivities likewise (Table 1), but we find in our reactions none of the 1,3-diols recently reported[2] in reactions of aldehydes under very similar conditions. Instead, particularly at above zero temperatures, aldol condensation products (enals) appear as predominant products. In place of $Ti(O^iPr)_4$, isopropanol itself can be used as long as $TiCl_4$ is present. Preliminary experiments, to be reported shortly in full detail, also show that the reaction is quite general so that other alcohols, including primary ones, may be used. Also α-branched aldehydes give the corresponding 3-hydroxyether products. We assume that the *anti* diastereomer would be the major one due to its more stable six-membered transition state structure. Also, the NMR studies of the corresponding 1,3-diols support this presumption.[3]

It is known that $TiCl_4/Ti(O^iPr)_4$ mixtures quickly equilibrate at 0°C.[1b] We envisage that the mechanism of the triple tandem reaction comprises (i) a Ti(IV) species induced aldol addition; (ii) addition of isopropanol, and (iii) an intramolecular Meerwein–Ponndorf–Verley oxidation/reduction hydride exchange via a six-membered transition state (Scheme 2). In keeping with this, acetone was identified as a byproduct in the reaction mixture.



Scheme 1.

Keywords: 3-hydroxyethers; $TiCl_4$; aldol reaction; Meerwein–Ponndorf–Verley reaction.

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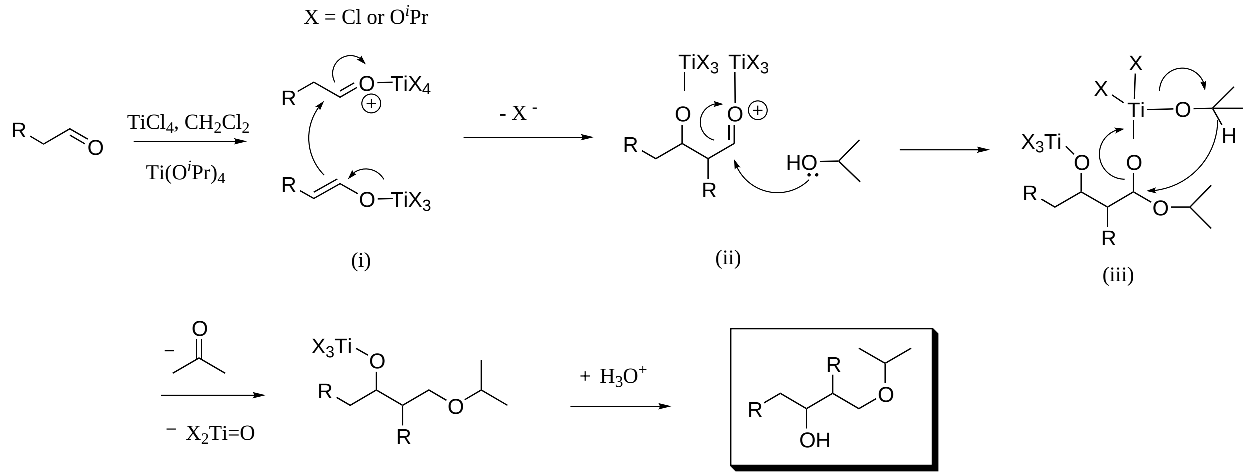


Scheme 2.

Table 1. 3-Hydroxyethers produced in TiCl$_4$ induced reaction with alkanals

Entry	R	Reagent	RT (days)	Ds ratio A:B[a]	Yield (%)[b]
1	CH_3	Ti(O^{i}Pr)$_4$	1	56:44	52
2	CH_3	Isopropanol	1	64:36	32
3	CH_3CH_2	Ti(O^{i}Pr)$_4$	1	53:47	63
4	CH_3CH_2	Isopropanol	1	61:39	41
5	$CH_3(CH_2)_5$	Ti(O^{i}Pr)$_4$	4	62:38	58
6	$CH_3(CH_2)_5$	Isopropanol	2	57:43	56

[a] Determined by GC and ^{1}H NMR.

[b] Isolated yield.

1. Experimental

^{1}H NMR spectra (400 MHz) were recorded with a Bruker AMX 400 and ^{13}C NMR spectra at 125 MHz using TMS as internal standard. ESI mass spectra were recorded on a PE Biosystems Mariner™ ESI-TOF mass spectrometer. CI mass spectrum was recorded on a JEOL JMS SX102 mass spectrometer operating at 70 eV. Reactions were monitored with an Orion Analytica Micromat HRGC 412 using a PE-VAX column (30 m, ∅ 0.32 mm, 0.5 μm). All reactions were carried out under an argon atmosphere and in dried glassware. All reagents and solvents were dried and distilled prior to use.

1.1. General method

TiCl$_4$ (0.01 mol) was added slowly to the aldehyde (0.02 mol) in dry CH$_2$Cl$_2$ (20 ml) at −20°C. The resulting bright yellow mixture was stirred for a further 0.5 h at this temperature and Ti(O^{i}Pr)$_4$ (0.005 mol) or an alcohol (0.02 mol) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm slowly to +5°C and stirred overnight at this temperature. The reaction mixture was quenched with water and extracted with diethyl ether (3×30 ml). The combined organic layers were washed with brine until neutral, dried over MgSO$_4$ and concentrated in vacuo leaving a yellow liquid. The 3-hydroxyether was purified by flash chromatography using hexane:EtOAc (80:20) as eluent.

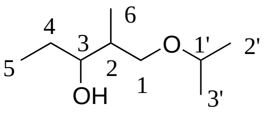
1.2. 1-(1-Methylethoxy)-2-methyl-3-pentanol

The product is a mixture of two diastereomers A:B (56:44) (Scheme 3). The diastereomer ratio is determined by NMR and GC. To avoid confusion all protons of both diastereomers are informed as integer.

^{1}H NMR (CDCl$_3$) ppm: δ 0.87 (3H, d, $J=7.0$ Hz, H$_A$-6), 0.91 (3H, d, $J=7.1$ Hz, H$_B$-6), 0.96 (3H, t, $J=7.4$ Hz, H$_B$-5), 0.97 (3H, t, $J=7.4$ Hz, H$_A$-5), 1.14–1.17 (6H, m, H$_B$-2′+H$_B$-3′), 1.15–1.18 (6H, m, H$_A$-2′+H$_A$-3′), 1.37–1.55 (3H, m, H$_{A',B,B'}$-4), 1.54–1.64 (1H, dqd, $J=3.6$ Hz, $J=7.6$ Hz, $J=13.8$ Hz, H$_A$-4), 1.73–1.88 (2H, m, H$_{A+B}$-2), 3.01 (2H, br s, A+B-O**H**), 3.38 (1H, dd, $J=7.9$ Hz, $J=9.1$ Hz, C$_{A'}$-1), 3.42 (1H, td, $J=3.6$ Hz, $J=7.6$ Hz, H$_A$-3), 3.47 (1H, dd, $J=5.9$ Hz, $J=8.9$ Hz, H$_{B'}$-1), 3.51 (1H, dd, $J=4.3$ Hz, $J=8.8$ Hz, H$_B$-1), 3.53 (1H, septet, $J=6.1$ Hz, H$_B$-1′), 3.57 (1H, septet, $J=6.1$ Hz, H$_A$-1′), 3.58 (1H, dd, $J=4.1$ Hz, $J=9.1$ Hz, H$_A$-1), 3.64 (1H, ddd, $J=2.4$ Hz, $J=5.0$ Hz, H$_B$-3).

^{13}C NMR (CDCl$_3$) ppm: δ 9.4 (q, C$_A$-6), 10.6 (q, C$_B$-6), 10.7 (q, C$_B$-5), 13.9 (q, C$_A$-5), 21.8 (q, C$_{A+B}$-2′ or C$_{A+B}$-3′), 21.9 (q, C$_A$-2′ or C$_A$-3′), 22.0 (q, C$_B$-2′ or C$_B$-3′), 26.7 (t, C$_B$-4), 27.7 (t, C$_A$-4), 37.3 (d, C$_B$-2), 37.7 (d, C$_A$-2), 72.1 (d, C$_B$-1′), 72.3 (d, C$_A$-1′), 73.0 (t, C$_B$-1), 73.5 (t, C$_A$-1), 76.2 (d, C$_B$-3), 77.9 (d, C$_A$-3).

MS ESI: 183 (100, [M+Na]$^+$), 161 (13, [M+H]$^+$), 143 (2, [M+H–H$_2$O]$^+$).



Scheme 3.

1.3. 1-(1-Methylethoxy)-2-ethyl-3-hexanol

^{1}H NMR ($CDCl_3$) ppm: δ 0.92–0.95 (6H, m, H-6+H-8), 1.15–1.17 (6H, m, H-2′+H-3′), 1.32–1.38 (2H, m), 1.40–1.57 (4H, m), 1.59–1.66 (1H, m), 3.33 (1H, br s, **OH**), 3.45–3.63 (3H, m), 3.69–3.76 (1H, m).

^{13}C NMR ($CDCl_3$) ppm: δ 11.7 (q, C_A-8), 12.3 (q, C_B-8), 14.16 (q, C_B-6), 14.18 (q, C_A-6), 18.5 (t, C_B-7), 19.0 (t, C_A-5), 19.6 (t, C_B-5), 21.83 (q, C_{A+B}-2′ or C_{A+B}-3′), 21.86 (t, C_A-7), 21.97 (q, C_A-2′ or C_A-3′), 22.0 (q, C_B-2′ or C_B-3′), 35.4 (t, C_B-4), 38.0 (t, C_A-4), 44.4 (d, C_A-2), 44.9 (d, C_B-2), 69.5 (t, C_A-1), 70.2 (t, C_B-1), 72.2 (d, C_B-1′), 72.3 (d, C_A-1′), 74.3 (d, C_A-3), 74.7 (d, C_B-3).

MS ESI: 227 (6, $[M+K]^+$), 211 (100, $[M+Na]^+$), 189 (4, $[M+H]^+$), 171 (3, $[M+H-H_2O]^+$), 129 (5, $[M+H-OCHMe_2]^+$), 111 (5, $[M+H-OCHMe_2-H_2O]^+$).

1.4. 1-(1-Methylethoxy)-2-hexyl-3-decanol

^{1}H NMR ($CDCl_3$) ppm: δ 0.87–0.89 (6H, m, H-10+H-16), 1.14–1.16 (6H, m, H-2′+H-3′), 1.22–1.34 (18H, m), 1.36–1.51 (4H, m), 1.67–1.77 (1H, m), 3.31–3.75 (5H, m).

^{13}C NMR ($CDCl_3$) ppm: δ 14.06 (q, A+B), 14.07 (q, A+B), 21.9 (q, C_{A+B}-2′ or C_{A+B}-3′), 22.0 (q, C_B-2′ or C_B-3′), 22.02 (q, C_A-2′ or C_A-3′), 22.62 (t, A+B), 21.65 (t, A+B), 25.6 (t, A), 25.9 (t, B), 26.5 (t, A), 27.3 (t, B), 29.0 (t, A+B), 29.30 (t, A), 29.32 (t, B), 29.5 (t, A), 29.6 (t, B), 29.74 (t, A), 29.77 (t, B), 31.75 (t, A), 31.79 (t, B), 31.8 (t, A+B), 33.2 (t, C_A-4), 35.7 (t, C_B-4), 42.8 (d, C_B-2), 43.0 (d, C_A-2), 70.0 (t, C_B-1), 70.7 (t, C_A-1), 72.27 (d, C_A-1′), 72.33 (d, C_B-1′), 74.9 (d, C_B-3), 75.2 (d, C_A-3).

MS ESI: 339 (28, $[M+K]^+$), 323 (68, $[M+Na]^+$), 301 (100, $[M+H]^+$), 283 (25, $[M+H-H_2O]^+$).

MS CI: 301 (5, $[M+H]^+$), 282 (42, $[M-H_2O]$), 240 (72, $[M-OCHMe_2]$), 222 (20, $[M-OCHMe_2-H_2O]$), 201 (100, $[M-(CH_2)_6CH_3]$).

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