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TRIETHYLSILANE AS HYDRIDE DONOR IN ETHER FORMATION FROM CARBONYL COMPOUNDS

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Abstract Triethylsilane is a convenient hydride source in the conversion of ketones or aldehydes to ethers under mild neutral conditions.

Ether synthesis under mild acid-free conditions from carbonyl compounds has been studied by Olah and co-workers[1], who used trimethylsilyl cation as coupling catalyst and trialkylsilanes as hydride donor.

They concluded that use of triethylsilane in the catalytic cycle produces disiloxanes which would be more difficult to remove than the more volatile side-products from trimethylsilane. Solutions of trimethylsilane gas must however be prepared and stored at low temperature, and the gas is not widely available from commercial sources. We therefore assessed the use of triethylsilane, with trimethylsilyl iodide as catalyst, where the product ethers are solids or high-boiling liquids.

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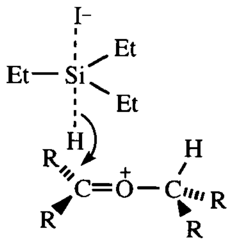
We have found these reaction conditions to be generally successful for the following structural combinations: coupling of two moles of an aldehyde, a methyl ketone or a cyclic ketone (Reaction 1); and coupling of an aldehyde, methyl ketone or cyclic ketone with an alkoxy silane (Reaction 2).

No reaction could be detected for open-chain ketones where both R groups were larger than methyl. There can be high stereoselectivity in these reactions resulting from substitution on the α-carbons of the reactants which controls preferential approach of the trialkyl silane hydride donor (see Scheme of reaction mechanism for hydride addition). Apparently at least one of the ketone α-carbons must be unsubstituted for any hydride transfer to take place.

In cyclic ketones, α-substitution and ring conformation also influence the reaction, reducing rates after production of the alkoxy silyl ether[2]. This may become the main product if triethyl silyl groups or higher alkyl silyl groups are present in both catalyst and hydride donor.

$$R^1R^2C{=}O \xrightarrow{Et_3SiH} R^1R^2CH\text{-}O\text{-}CHR^1R^2 \qquad (1)$$

$$R^1R^2C{=}O \;+\; Si(CH_3)_3\text{-}O\text{-}CHR^3R^4 \longrightarrow R^1R^2CH\text{-}O\text{-}CHR^3R^4 \qquad (2)$$



Scheme of hydride addition

Table

Reaction	R^1	R^2	R^3, R^4	Yield%[a]
1	2-naphthyl	H	-	60
1	4-carboxybutyl	CH_3	-	15[b]
2	2-naphthyl	H	cyclohexyl	25
2	4-carboxybutyl	CH_3	cyclohexyl	10[b]
2	---------- cyclohexyl ----------		cyclohexyl	75

[a]Unoptimised. [b]Stereoisomer ratios not determined. Stereoselectivity is expected[1,2].

In spite of these steric limitations, the combination of trimethyl silyl iodide as catalyst generated from hexamethyldisilane, and triethyl silane as hydride donor, is clearly convenient for the synthesis of many ethers. Yields for the examples given (Table) compare favourably even with those for known one-step preparations, such as the yield of 25% for preparation of bis(2-naphthylmethyl) ether from 2-naphthylmethanol[3]. Use of strong acid catalysts, or the need to introduce a leaving group before a final reaction probably under basic conditions, is avoided. Conditions for the method are compatible with a number of functional groups such as ester, amide, acid, acid chloride and nitrile.

EXPERIMENTAL

Typical reaction conditions are given for preparation of an alkoxytrimethyl silane[5], and for reactions (1) and (2).

Cyclohexyloxytrimethylsilane. A solution of cyclohexanol (5 ml, 48 mmol) and chlorotrimethyl silane (9.25 ml, 72 mmol) in dry ether was cooled to 0° under an atmosphere of nitrogen, and triethylamine (10ml, 72 mmol) was added slowly. The reaction mixture was stirred at room temperature for 16 h. Triethylamine hydrochloride was filtered off and volatiles removed under vacuum to obtain product (2.8g, 65%), b.p. 142-145°, which was used without further purification.

Bis-(2-naphthylmethyl) ether. To a reaction flask equipped with a nitrogen inlet and rubber septum was added a solution of hexamethyldisilane (1 ml, 0.55 mmol) and iodine (0.17 g, 0.75 mmol) in dry dichloromethane (10 ml). Triethylsilane (0.2 ml, 1.3 mmol) was added under an atmosphere of nitrogen. The resulting solution was stirred at 0° for 10 min and then a solution of 2-naphthaldehyde (1 g, 6.4 mmol) in dry dichloromethane (10 ml) was added. The reaction solution was stirred for a further 30 min at 0°, then allowed to come to room temperature and stirred for 2.5 h. Solvent was removed under vacuum and the crude product was recrystallised from methanol; yield 0.96 g (60%), m.p. 120-122° (Lit.[3,4] 122-123°), m/z 298 (M^+). ^1H NMR: δ 7.83 (m, 8H, H-4, H-4', H-5, H-5', H-7, H-7', H-8, H-8'), 7.48 (m, 6H, H-1, H-1', H-3, H-3', H-6, H-6'), 4.75 (s, 4H, CH_2OCH_2).

Bis-(6-carboxy-2-hexyl) ether. Reaction (1), using 6-oxo-heptanoic acid; after reaction, the solution was extracted with aqueous sodium hydroxide (0.1M), the extract was neutralised with hydrochloric acid (0.1 M), and the product extracted into dichloromethane. Evaporation of solvent gave pure product; yield 15%, m.p. 42-45°, m/z 274 (M^+). ^1H NMR: δ 2.3 (m, 4H, H-6), 2.95 (d, J=9 Hz, 6H, CH_3), 1.65 (m, 6H, H-2, H-5), 1.2 (m, 8H, H-3, H-4).

Cyclohexyl 2-naphthylmethyl ether. To a reaction flask equipped with a nitrogen inlet and rubber septum was added a solution of hexamethyldisilane (0.8

ml, 0.4 mmol) and iodine (0.1 g, 0.44 mmol) in dry dichloromethane (10 ml). The solution was cooled to 0° under an atmosphere of nitrogen, and stirred for 10 min before addition of cyclohexyloxytrimethylsilane (0.7 g, 3.9 mmol) and 2-naphthaldehyde (0.6 g, 1.9 mmol) in dry dichloromethane (10 ml), followed by triethylsilane (1.25 ml, 7.9 mmol). Stirring was continued for 30 min at 0°, and for a further 2.5h at room temperature. The reaction solution was washed with saturated aqueous $Na_2S_2O_3$ (10ml, twice), then water (10 ml, twice), and dried with anhydrous magnesium sulphate. The crude product was purified by chromatography on silica, with diethyl ether as eluant; yield 0.2 g (25%), m.p. 112-116°. Anal. Calc. for $C_{17}H_{20}O$: C, 84.94; H, 8.33%. Found: C, 83.78; H, 8.60%. ^1H NMR: δ 7.8 (m, 3H, aromatic protons), 7.4 (s, 2H, $ArCH_2$), 3.4 (m, 1H, cyclohexyl H-1), 1.97 (m, 2H, cyclohexyl H-2a, H-6a), 1.76 (m, 2H, cyclohexyl H-2b, H-6b), 1.3 (m, 6H, cyclohexyl H-3, H-4, H-5).

6-Carboxy-2-hexyl cyclohexyl ether. Reaction (2) using 6-carboxy-2-hexanone; the solution after reaction was extracted with aqueous sodium hydroxide (0.1M). Acidification of the extract with hydrochloric acid (0.1M), and final extraction with dichloromethane, gave product (10%), m.p. 39-41°. Anal. Calc. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59%. Found: C, 67.94; H, 10.49%. ^1H NMR: δ 2.33 (t, J=7.4Hz, 2H, H-6), 1.85 (m, 2H, H-3), 1.5 (m, 12H, H-2, cyclohexyl protons), 1.2 (m, 4H, H-4, H-5), 1.12 (t, 3H, H-1).

Dicyclohexyl ether. Reaction (2) using cyclohexanone; the solution after reaction was washed with 10% $Na_2S_2O_3$ (10ml, 4 times), then water (10 ml, 4 times) and dried with anhydrous magnesium sulphate before evaporation of solvent under vacuum to obtain pure product (75%), m.p. 120-122° (Lit.[1] m.p., 122-123°). Anal. Calc. for $C_{12}H_{22}O$: C, 79.06; H, 12.16%. Found: C, 78.87; H, 11.96%. ^1H

NMR: δ 2.89 (m, 2H, H-1), 1.89 (m, 4H, H-2a, H-2a', H-6a, H-6a'), 1.73 (m, 4H, H-2b, H-2b', H-6b, H-6b'), 1.53 (m, 4H, H-4), 1.24 (m, 8H, H-3, H-5).

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