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# CONDENSATION OF ENOL SILYL ETHERS AND DIALKOXYMETHANES CATALYZED BY TRIMETHYLSILYL TRIFLUOROMETHANESULFONATE. REGIOSPECIFIC SYNTHESIS OF α-ALKOXYMETHYL KETONES[1]

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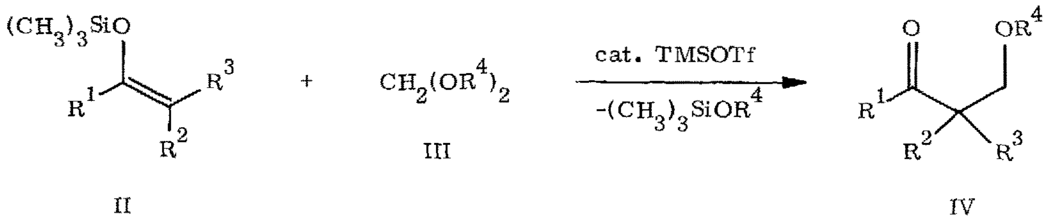
Summary: A facile, regiospecific entry to α-alkoxymethyl ketones is described.

Recently we found an efficient, erythro-selective aldol type condensation of enol silyl ethers and acetals catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf, I).[2] Unfortunately, however, the original procedure for this reaction could not utilize simple dialkoxymethanes as acetal substrates.[3] Described herein is a modified recipe which allows facile synthesis of mono-α-alkoxymethyl ketones.



The condensation of enol silyl ethers (II) and dialkoxymethanes (III) was conducted in dichloromethane containing catalytic amounts (5—10 mol %) of I and a sterically hindered nitrogen base such as 2,6-di-t-butylpyridine (V) or dicyclohexylmethylamine (VI). The typical procedure is illustrated by the preparation of 2-benzyloxymethylcyclopentanone. 1-Trimethylsiloxycyclopentene (501 mg, 3.1 mmol) and V (63 mg, 0.33 mmol) were dissolved in dry dichloromethane (7 mL) under argon atmosphere. To this was added 0.15 M dichloromethane solution of I (2.2 mL, 0.33 mmol) at 12 °C. The mixture was stirred at this temperature for 10 h and quenched by addition of saturated aqueous $NaHCO_3$ solution (5 mL). Extractive work-up with dichloromethane (10 mL x 3) followed by column chromatography on silica gel (15 g, 3:1 petroleum ether/ether mixture as eluant) afforded the desired benzyloxymethyl ketones as an oil (480 mg, 76% yield), bp 140 °C (bath temp) at 0.3 mmHg.[4]

Table I. Condensation of Enol Silyl Ethers and Dialkoxymethanes in Dichloromethane

| enol silyl ether, II | | | | conditions | | | | % yield |
|---|---|---|---|---|---|---|---|---|
| $R^1$ | $R^2$ | $R^3$ | dialkoxymethane, III | I, mol % | base[a] | temp, °C | time, h | of IV[b] |
| $(CH_2)_3$ | | H | $CH_2(OCH_2C_6H_5)_2$ | 10 | V | 12 | 10 | 76 |
| $(CH_2)_3$ | | H | $CH_2(OCH_2C_6H_5)_2$ | 10 | VI | 12 | 100 | 65 |
| $(CH_2)_4$ | | H | $CH_2(OCH_2C_6H_5)_2$ | 10 | V | 18 | 12 | 87 |
| $(CH_2)_4$ | | H | $CH_2(OCH_3)_2$ | 5 | V | 16 | 10 | 48[c] |
| $CH_3CH(CH_2)_3$ | | H[d] | $CH_2(OCH_2C_6H_5)_2$ | 10 | V | 14 | 12 | 78[e] |
| $C_6H_5$ | H | H | $CH_2(OCH_2C_6H_5)_2$ | 7 | V | 17 | 12 | 92 |
| $C_6H_5$ | H | $CH_3$ | $CH_2(OCH_2C_6H_5)_2$ | 7 | V | 18 | 12 | 77 |

[a] Ratio of I to base was 1:1. [b] Isolated yield. All products were identified by IR and $^1H$ NMR spectra as well as elemental analysis. [c] Cyclohexanone dimethyl acetal was obtained in 20% yield. [d] 6-Methyl-1-trimethylsiloxycyclohexene. [e] A mixture of cis and trans isomers.

Some examples are given in Table I. Thus this procedure offers a method for the controlled, regiospecific introduction of a single alkoxymethyl substituent to the α position of ketones.[5] Benzyl protective group in the products is readily removed by catalytic hydrogenolysis. For instance, when a mixture of 2-benzyloxymethylcyclopentanone and 5% Pd/C catalyst in 15:1 ethanol/acetic acid was stirred at 18 °C for 10 h under atmospheric pressure of hydrogen, 2-hydroxymethylcyclopentanone was obtained in 97% yield. Hydroxymethyl and alkoxymethyl ketones are masked forms of α-methylene ketones, well-known useful synthetic intermediates.[5a, 6]

## REFERENCES AND NOTES

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4. IR (neat) 1738 $cm^{-1}$ (C=O); NMR ($CCl_4$) $\delta$ 1.6–2.5 (m, 7, CH and $CH_2$), 3.58 (d, 2, $J$ = 3.5 Hz, $C_6H_5CH_2OC\underline{H}_2$), 4.43 (s, 2, $C_6H_5C\underline{H}_2$), 7.23 (s, 5, $C_6H_5$).
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