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A NEW PROCEDURE FOR α-ALKOXYALKYLATION OF α,β-UNSATURATED KETONES[1]

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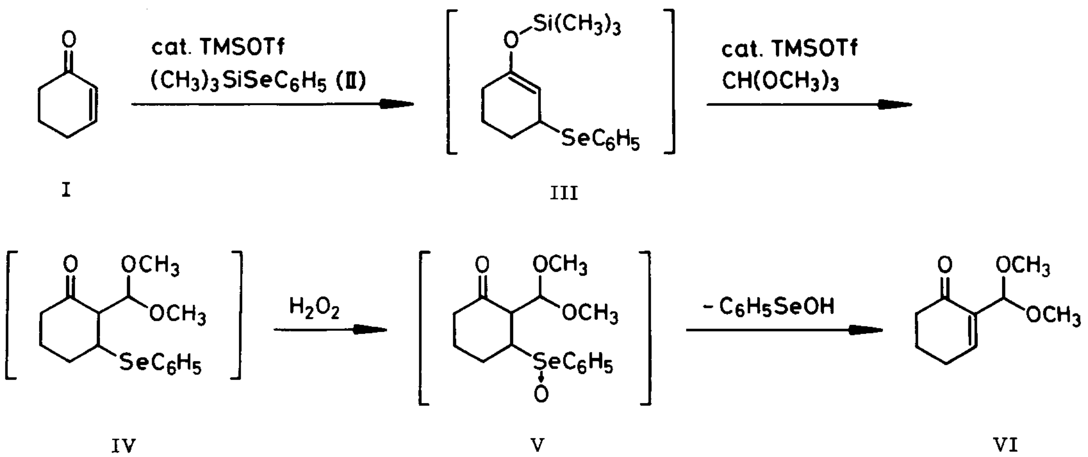
Summary: A one-pot procedure for α-alkoxyalkylation of α,β-unsaturated ketones has been devised, which by combination with the organocopper conjugate addition reaction provides a new tool for vicinal carba-condensation of enones.

Introduction of an organic group to the sp^2-hybridized α position of α,β-unsaturated ketones is an important operation, but this problem has not come to a satisfactory solution.[2] Disclosed herein is a new process for incorporation of an alkoxyalkyl or dialkoxyalkyl group with enone substrates.

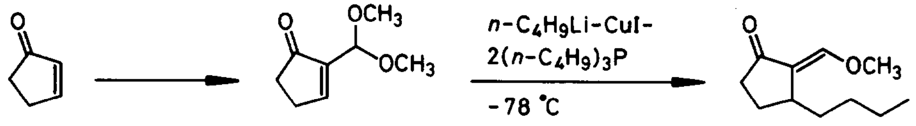
The present method is based on the efficiency of the conjugate addition of a phenyl silyl selenide to α,β-unsaturated ketones[3] and the aldol-type reaction of enol silyl ethers and acetals or ortho esters[4] (both are catalyzed by trimethylsilyl trifluoromethanesulfonate (TMSOTf)) and the propensity of selenoxides to undergo ready β-elimination.[5] The transformation is illustrated by dimethoxymethylation of 2-cyclohexenone (I) (Scheme I). Reaction of I with phenyl trimethylsilyl

Scheme I

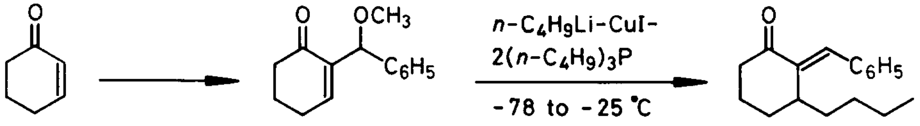


selenide (II) in the presence of a catalytic amount of TMSOTf in dichloromethane generates the positionally defined enol silyl ether III, which in turn is condensed with methyl orthoformate to afford the vicinally functionalized ketone IV. Exposure of IV to hydrogen peroxide gives the desired dimethoxymethylated product VI by way of the selenoxide V. This overall conversion can be accomplished in one pot without isolation of the intermediates III—V. Some examples of the alkoxyalkylation procedure are given in Table I.

This method, when coupled with the recently developed organocopper conjugate addition reaction,[6] provides a versatile tool for regiospecific, vicinal carba-condensation[7] with α ,β -unsaturated ketones. The present recipe is characterized by the initial carbon-carbon bond formation at the α (not β) position of enones which avoids formation of α', β -condensation products.[8] Preparations of VII and VIII are the typical examples.



VII, 60%[9]



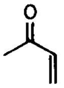
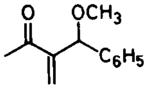
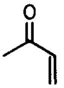
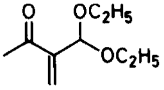
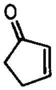
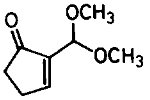
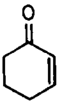
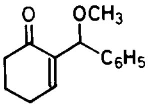
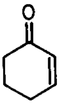
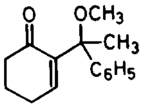
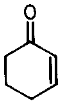
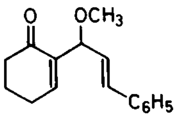
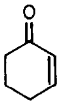
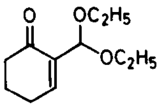
VIII, 89%

The following experimental procedures are illustrative.

2-Methoxyphenylmethyl-2-cyclohexenone. To a solution of TMSOTf (44.4 mg, 0.2 mmol) in dry dichloromethane (20 mL) were successively added the silyl selenide II (2.29 g, 10 mmol) and 2-cyclohexenone (I) (0.96 g, 10 mmol) at -78 °C under argon atmosphere. After the mixture was stirred at -78 °C for 30 min, benzaldehyde dimethyl acetal (1.52 g, 10 mmol) was added at this temperature. Then the mixture was warmed to -25 °C and kept for 40 min. Pyridine (50 mg) and 30% hydrogen peroxide (3 mL) were added to the mixture at this temperature. When this mixture was warmed slowly to 15 °C, vigorous exothermic reaction took place. After the solvent reflux ceased, the mixture was quenched with water and subjected to extractive workup with dichloromethane (20 mL x 3). Chromatography of the crude product on a silica gel column (50 g, 15:1 benzene/ethyl acetate mixture as eluant) gave 2-methoxyphenylmethyl-2-cyclohexenone (1.63 g, 75% yield) as a colorless oil.

2-Benzylidene-3-butylcyclohexanone. To a suspension of copper(I) iodide (701 mg, 3.68 mmol) in dry ether (60 mL) was added tributylphosphine (1.83 mL, 7.36 mmol). After the mixture was stirred for 10 min at room temperature, the resulting solution was cooled to -78 °C. To this was added butyllithium in hexane (2.24 mL, 3.68 mmol) and the mixture was stirred for 30 min. Then a solution of 2-methoxyphenylmethyl-2-cyclohexenone (796 mg, 3.68 mmol) in dry ether (15 mL) was

Table I. α-Alkoxy- or Dialkoxyalkylation of α, β-Unsaturated Ketones[a]

entry	enone	trapping acetal or ortho ester	product	% yield[b]
1		$C_6H_5CH(OCH_3)_2$		57
2		$CH(OC_2H_5)_3$		53
3		$CH(OCH_3)_3$		58
4		$C_6H_5CH(OCH_3)_2$		75
5		$C_6H_5C(CH_3)(OCH_3)_2$		30
6		$C_6H_5CH{=}CHCH(OCH_3)_2$		83
7		$CH(OC_2H_5)_3$		76

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[a] Unless otherwise stated, the reaction was carried out in dichloromethane under argon atmosphere. Usually, reaction of phenyl trimethylsilyl selenide and an enone (1:1 mol ratio) was conducted in the presence of a catalytic amount (2—2.5 mol %) of TMSOTf at -78 °C for 30 min. Reaction of the resulting enol silyl ether and an acetal or ortho ester was performed at -50 to -20 °C for 0.5 to 1 h. Subsequent removal of the phenylseleno group was done by oxidation (30% H_2O_2, 0 °C) followed by heating of the system (15—40 °C). All new compounds gave consistent spectral characteristics and correct elemental analysis.

[b] Isolated yield after silica gel column chromatography.

added at -78 °C under vigorous stirring. After the mixture was stood at -78 °C for 1 h, it was warmed up to -25 °C over a period of 3.5 h and quenched by addition of saturated ammonium chloride solution (50 mL) with vigorous shaking at -25 °C. The combined ethereal extracts were dried over magnesium sulfate and evaporated. The residue was chromatographed on silica gel (100 g, 50:1 benzene/ethyl acetate mixture) to give 2-benzylidene-3-butylcyclohexanone (796 mg, 89% yield) as a colorless oil.

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2. Some solutions have been advanced in literature. (a) G. Stork and G. Birnbaum, *Tetrahedron Lett.*, 313 (1961); G. Stork and J. Benaim, *J. Am. Chem. Soc.*, **93**, 5938 (1971); T. Mukaiyama, K. Inomata, and M. Muraki, *Ibid.*, **95**, 967 (1973); E. J. Corey and D. Enders, *Tetrahedron Lett.*, 11 (1976); S. J. Branca and A. B. Smith, III, *J. Am. Chem. Soc.*, **100**, 7767 (1978); D. J. Ager and I. Fleming, *J. Chem. Soc., Chem. Commun.*, 177 (1978); T. Shono, Y. Matsumura, S. Kashimura, and K. Hatanaka, *J. Am. Chem. Soc.*, **101**, 4752 (1979); E. J. Corey and H. L. Pearce, *Ibid.*, **101**,5841 (1979); A. Itoh, S. Ozawa, K. Oshima, and H. Nozaki, *Tetrahedron Lett.*, **21**, 361 (1980). (b) Review: D. Caine, "Carbon-Carbon Bond Formation" R. L. Augustine, Ed., Marcel Dekker, New York, 1979, Vol. 1, pp 300—309.
3. For the related conjugate additions to α,β-unsaturated ketones see: R. D. Miller and D. R. McKean, *Tetrahedron Lett.*, 2305 (1979); M. R. Detty, *Ibid.*, 4189 (1979).
4. S. Murata, M. Suzuki, and R. Noyori, *J. Am. Chem. Soc.*, **102**, 3248 (1980).
5. For recent reviews see: D. L. J. Clive, *Tetrahedron*, **34**, 1049 (1978); H. J. Reich, *Acc. Chem. Res.*, **12**, 22 (1979).
6. M. Suzuki, T. Suzuki, T. Kawagishi, and R. Noyori, *Tetrahedron Lett.*, **21**, 1247 (1980).
7. This term was suggested by Professor B. M. Trost for such type of transformations.
8. In certain cases, enolates formed by conjugate addition to enones equilibrate quite readily. See Chapter 1 and 2 in the review.[2b]
9. In addition, 3-butyl-2-dimethoxymethylcyclopentanone was obtained in 35% yield.

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