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NEW METHODS AND REAGENTS IN ORGANIC SYNTHESIS. 10.[1]
TRIMETHYLSILYLDIAZOMETHANE(TMSCHN$_2$).
A NEW, STABLE, AND SAFE REAGENT FOR THE HOMOLOGATION OF KETONES

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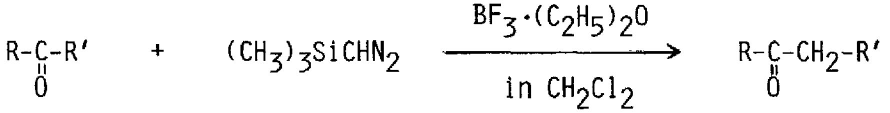
Homologation of ketones can be achieved with trimethylsilyldiazomethane(TMSCHN$_2$) which is a stable and safe substitute for hazardous diazomethane.

Reaction of diazomethane[2] with ketones is a well-known method for chain or ring homologations.[2,3,4] However, diazomethane, though very useful in organic synthesis, is notorious as a highly toxic and explosive gas and it should be manipulated with great care.[5]

In our previous paper of the series,[6] we proposed the use of trimethylsilyldiazomethane(TMSCHN$_2$)[7,8] as a stable and safe substitute for very hazardous diazomethane in the Arndt-Eistert synthesis, a method for the homologation of carboxylic acids. We now wish to report that TMSCHN$_2$ can be also used for the homologation of ketones in place of diazomethane. We have found that TMSCHN$_2$ easily reacts with various ketones in the presence of boron trifluoride etherate in methylene chloride solution to give homologated ketones:



$$\underset{\displaystyle O}{\overset{\|}{\text{R-C-R}'}} \quad + \quad (CH_3)_3SiCHN_2 \xrightarrow[\text{in } CH_2Cl_2]{BF_3\cdot(C_2H_5)_2O} \underset{\displaystyle O}{\overset{\|}{\text{R-C-CH}_2\text{-R}'}}$$

A typical experimental procedure for the new homologation is as follows: To a stirred mixture of 4-tert-butylcyclohexanone(162 mg, 1 mM)[9] and boron trifluoride etherate(0.19 ml, 1.5 mM) in methylene chloride(10 ml) was added TMSCHN$_2$ (1.5 mM)[10] in methylene chloride(10 ml) at -13° during 20 min. The mixture was stirred at -10° for 2 hr, and poured into ice-water. After the separation of the methylene chloride layer, the water layer was extracted with chloroform. The combined organic layer was washed with saturated aqueous sodium chloride, and dried over magnesium sulfate. Evaporation of the solvent gave a colorless oil

(260 mg), which was purified by a column chromatography(Merck silica gel 60, 18 g) with ethyl acetate-hexane(1:20) to give 4-tert-butylcycloheptanone[11] (117 mg, 70 %) as a colorless oil.

The scope of the new homologation procedure is shown in Table. The reaction proceeds below 0° during 1-4 hr, and much more efficient homologation has been realized with $TMSCHN_2$ than diazomethane. Boron trifluoride etherate seems to be essential to conduct the reaction. Methylene chloride may be replaced with diethyl ether, in which, however, the reaction proceeds more slowly.

Various alicyclic ketones smoothly undergo the homologation reaction to furnish ring-enlarged ketones. Reaction of 2-undecanone with diazomethane has been reported[12] to give 1,2-epoxy-2-methylundecane only,[3] but the homologation with $TMSCHN_2$ affords a mixture of 2- and 3-dodecanones in almost equal amounts. Even if the epoxide is once formed with $TMSCHN_2$, boron trifluoride etherate will transform the epoxide to the homologated ketones. Although benzophenone has been described[13] as "unreactive toward diazomethane", $TMSCHN_2$ reacts with benzophenone to yield deoxybenzoin though in low yield. In the homologation of 2-methylcyclohexanone, deoxybenzoin, and methyl dihydrojasmonate, the insertion of methylene group occurs predominantly at the less hindered side, as shown in Table.

Homologation of fluorenone(1) with $TMSCHN_2$ is worthy of comment. The reaction product initially formed from fluorenone(1) will be the trimethylsilyl ketone(2), which will be rearranged to give the trimethylsilylether(3) of 9-phenanthrol. The ether(3) resists hydrolysis moderately, and refluxing in the presence of water for 1 hr is necessary to convert the ether(3) to 9-phenanthrol (4) after the usual reaction procedure in methylene chloride. 9-Methoxyphenanthrene is also formed though in only 4 % yield.

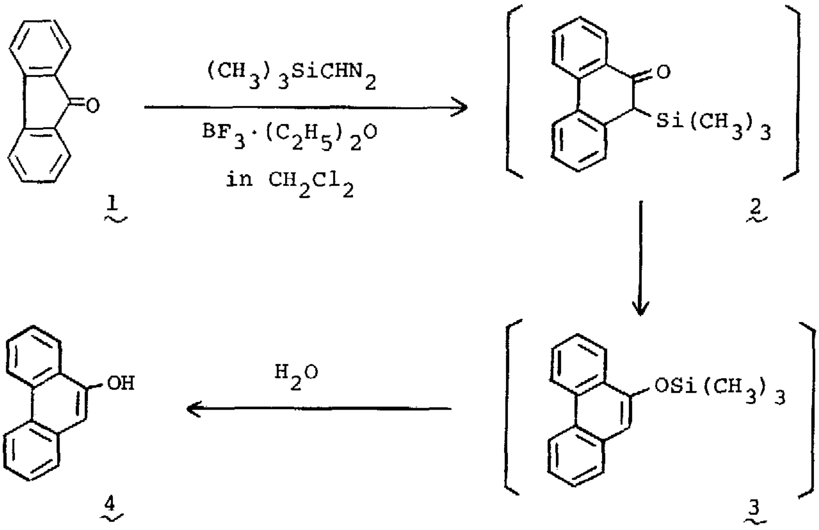


Table. Homologation of Ketones with TMSCHN$_2$[a]

Ketone	Reaction Conditions Temp.	Time, hr	Product	Yield,[b] %
Cyclohexanone	-45 ~ -40°	1.5	Cycloheptanone Cyclooctanone	57[c] (33~36)[14] 5[c]
4-tert-Butylcyclohexanone	-13 ~ -10°	2.3	4-tert-Butylcycloheptanone	70 (55)[15]
2-Methylcyclohexanone	-15°	4	2-Methylcycloheptanone	69 (10)[d,16]
Cyclododecanone	-10°	2	Cyclotridecanone	72[e]
2-Undecanone	-10°	2.5[f]	2-Dodecanone[g] 3-Dodecanone	25 24
Benzophenone	-5°	2.5	Deoxybenzoin[g]	27[h]
Deoxybenzoin	-15°	1	Dihydrochalcone	74
Fluorenone	-15 ~ -10°	3	9-Phenanthrol[g] 9-Methoxyphenanthrene	80 (5)[17] 4 (30)
Methyl dihydrojasmonate[i]	-13 ~ 0°	2.3	3-Methoxycarbonylmethyl-2-pentylcyclohexanone	19

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[a] All the reactions were carried out as in the typical experimental procedure

[b] Yields by the reported procedure using diazomethane are in parentheses.

[c] Determined by gas chromatography.

[d] 3-Methylcycloheptanone and 1,1-epoxymethylene-2-methylcyclohexane were also obtained in 7 and 26 % yields, respectively.

[e] As its 2,4-dinitrophenylhydrazone.

[f] Diethyl ether was used as solvent.

[g] See the text.

[h] Determined by NMR analysis.

[i] Kindly donated by Dr. K. Miki of Takasago Perfumery Co. Ltd., to whom the authors' thanks are due.

Homologation of ketones[18] with $TMSCHN_2$ smoothly proceeds under mild conditions with much higher efficiency than that with diazomethane and can be conducted without any anxiety against explosion. Thus, stable and safe $TMSCHN_2$ can replace hazardous diazomethane and should find wide use in organic synthesis.

References and Notes

1 Part 9, Y. Hamada, K. Ando, and T. Shioiri, Synthesis, submitted.

2 For a review on diazomethane, see J.S. Pizey, "Synthetic Reagents", Vol. II, Ellis Horwood Ltd., Chichester, 1974, Chapter 2.

3 The formation of epoxides sometimes occurs according to substrates and reaction conditions.[2,4]

4 For a review, see C.D. Gutsche, Org. Reactions, **8**, 364(1954).

5 For a caution against the handling of diazomethane, see J.A. Moore and D.E. Reed, Org. Syntheses, Col. Vol. 5, 352(1973).

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8 For a recent improved procedure for the preparation of $TMSCHN_2$, see T.J. Barton and S.K. Hoekman, Synth. React. Inorg. Metal-Org. Chem., **9**, 297(1979); C. A., **91**, 140899d(1979).

9 95 % Purity.

10 $TMSCHN_2$ was prepared by the Seyferth's method,[7] which we slightly modified. The actual reagent used has been a mixture of $TMSCHN_2$ and hexamethyldisiloxane (7:3), the latter of which has no influence on the reaction.

11 All the products were identified by IR and NMR spectral measurements as well as elemental analysis.

12 Reference 4, p. 369 and p. 410.

13 Reference 4, p. 379 and p. 410.

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18 Preliminary experiments on the reaction of aldehydes with $TMSCHN_2$ under similar reaction conditions to the homologation of ketones afforded a complicated mixture.

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