J. Org. Chem. **1994**, 59, 4725−4726

Organoaluminum-Promoted Homologation of Ketones with Diazoalkanes

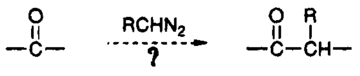
Keiji Maruoka, Arnel B. Concepcion, and Hisashi Yamamoto*

School of Engineering, Nagoya University, Chikusa, Nagoya 464-01, Japan

Received February 9, 1994®

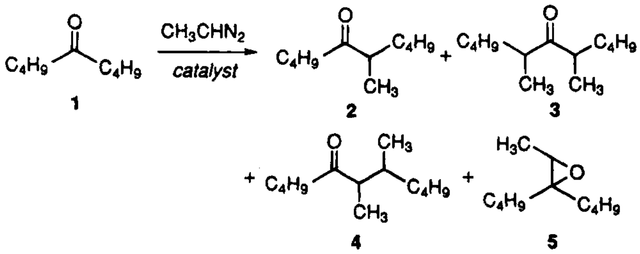
Summary: Organoaluminum-promoted single homologation of aliphatic and aromatic ketones with diazoalkanes has been described, and among various organoaluminum reagents, especially bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) is found to be highly effective for the selective homologation of various ketones.

The single carbon homologation of aliphatic and aromatic ketones is a frequently encountered synthetic objective. The most effective technique is obviously the direct insertion of an alkylidene unit from diazoalkane.[1] This reaction, however, has severe experimental limitations, the most serious of which include the low reactivity, multiple homologation, and oxirane formation. The rate of the homologation reaction can be somewhat accelerated by the use of protic solvents such as alcohols and water, which are not generally applicable to less reactive ketones.[2,3] Protic acids and Lewis acids usually decompose diazoalkanes.[4–6] In this context, we have been interested for some time in the possibility that certain bulky, oxygenophilic organoaluminum reagents might be highly effective for the single homologation of ketones with diazoalkane because of their carbonyl activation ability which does not affect the interaction of diazoalkane. In this paper, we wish to report our preliminary results from this study.



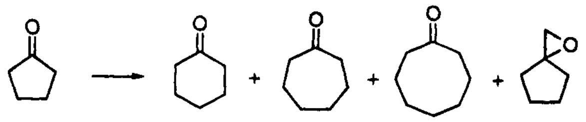
$$-\overset{O}{\overset{\|}{C}}- \xrightarrow[?]{RCHN_2} -\overset{O}{\overset{\|}{C}}-\overset{R}{\overset{|}{C}}H-$$

First, we examined the reaction of 5-nonanone (**1**) with diazoethane in the presence of various activation catalysts, which gave homologation products **2**−**4** and epoxide **5**. The previously known catalysts such as alcohols and lithium chloride are totally ineffective for the less reactive 5-nonanone substrate.[1a] A common Lewis acid, $BF_3{\cdot}OEt_2$, afforded only trace amounts of the homologation products.[5] However, trialkylaluminum gave quite satisfactory results in chemical yield and product selectivity. This is rather surprising since organoaluminums are reported to react easily with diazoalkanes to give insertion products with the evolution of nitrogen.[7]



Me_3Al, CH_2Cl_2, -78 °C, 1 h : 52% (92 : 0 : 0 : 8)
Me_3Al, CH_2Cl_2, 0 °C, 1 h : 60% (91 : 1 : 0 : 8)
i-Bu_3Al, CH_2Cl_2, -78 °C, 1 h : 65% (92 : 1 : 0 : 7)
Et_2AlCl, CH_2Cl_2, -78 °C, 1 h : 74% (63 : 30 : 7 : 0)
BF_3OEt_2, ether, -20~0 °C : 2%

The homologation of cyclopentanone with diazoalkanes results in formation of undesired cycloheptanones at the expense of the intermediary cyclohexanone. This is because the reactivity of cyclic ketones is in the order of cyclohexanone > cyclopentanone > cycloheptanone.[2] The organoaluminum-promoted single homologation of cyclopentanone has been effected with (trimethylsilyl)diazomethane,[6] where the single-homologated cyclohexanone is successfully trapped as its trimethylsilyl enol ether.[8]



Me_3Al/Me_3SiCHN_2, -20~0 °C : 68% (96 : 2 : 0 : 2)
BF_3OEt_2/Me_3SiCHN_2, -20 °C : 35% (64 : 23 : 10 : 3)

In the homologation of 4-*tert*-butylcyclohexanone with Me_3Al/diazoethane, the isomeric ratio of *trans*- and *cis*-5-*tert*-butyl-2-methylcycloheptanone is ~3:2. Since 5-substituted 2-methylcycloheptanones constitute an important framework for the synthesis of guaiazulene ses-

---

® Abstract published in *Advance ACS Abstracts,* August 1, 1994.

[1] (a) Gutsche, C. D. *Org. React.* **1954**, *8*, 364. (b) Gutsche, C. D.; Redmore, D. *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968. (c) Cowell, G. W.; Ledwith, A. *Q. Rev. Chem. Soc.* **1970**, *24*, 119. (d) McMurry, J. E.; Coppolino, A. P. *J. Org. Chem.* **1973**, *38*, 2821. (e) Krief, A.; Dumont, W.; Laboureur, J. L. *Tetrahedron Lett.* **1988**, *29*, 3265. (f) Satoh, T.; Itoh, N.; Gengyo, K.; Yamakawa, K. *Ibid.* **1992**, *33*, 7543.

[2] The reactivity of two series of ketones studied under controlled conditions is in the order of Cl_3COCH_3 > CH_3COCH_3 > $C_6H_5COCH_3$ and cyclohexanone > cyclopentanone > cycloheptanone > cyclooctanone. See ref 1a.

[3] The homologation of cyclohexanones, which are easily susceptible toward nucleophilic attack, can be executed with diazoethane in EtOH/ether solvents. See: Marshall, J. A.; Partridge, J. J. *J. Org. Chem.* **1968**, *33*, 4090. For the ring expansion of norcamphor with diazoethane in MeOH, see: McKinney, M. A.; Patel, P. P. *J. Org. Chem.* **1973**, *38*, 4064.

[4] For example, zinc chloride, aluminum alkoxide, boron alkoxide, and antimonous acid are reported to decompose diazomethane rapidly. See: (a) Caronna, G.; Sansone, B. *Atti X^O Congr. Intern. Chim.* **1939**, *3*, 77. (b) Meerwein, H. *Angew. Chem.* **1948**, *60*, 78. (c) Buckley, G. D.; Ray, N. H. *J. Chem. Soc.* **1952**, 3701.

[5] Electronically stabilized diazoacetic esters are combined with Lewis acids such as $BF_3{\cdot}OEt_2$, $SbCl_5$, and triethyloxonium fluoroborate. See: (a) Muller, E.; Bauer, M. *Liebigs Ann. Chem.* **1962**, *654*, 92. (b) Eistert, B.; Haupter, F.; Schank, K. *Ibid.* **1963**, *665*, 55. (c) Tai, W. T.; Warnhoff, E. W. *Can. J. Chem.* **1964**, *42*, 1333. (d) DoMinh, T.; Strausz, O. P.; Gunnina, H. E. *Tetrahedron Lett.* **1968**, 5237. (e) Mock, W. L.; Hartman, M. E. *J. Am. Chem. Soc.* **1970**, *92*, 5767. (f) Ledon, H.; Linstrumelle, G.; Julia, S. *Tetrahedron* **1973**, *29*, 3609. (g) Liu, H. J.; Majumdar, S. P. *Synth. Commun.* **1975**, *5*, 125. (e) Liu, H. J. *J. Org. Chem.* **1975**, *40*, 2252. (h) Mock, W. L.; Hartman, M. E. *Ibid.* **1977**, *42*, 459. (i) Baldwin, S. W.; Landmesser, N. G. *Synth. Commun.* **1978**, *8*, 413.

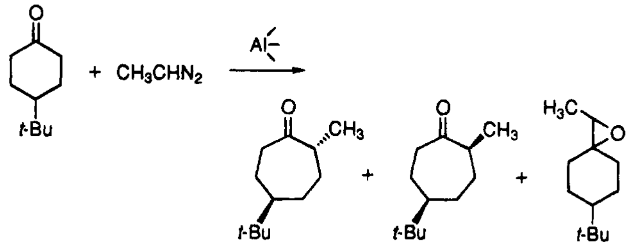
[6] The sterically hindered and electronically stabilized (trimethylsilyl)diazomethane can be successfully utilized for the homologation of ketones in the presence of $BF_3{\cdot}OEt_2$. See: Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, *21*, 4619.

[7] (a) Hoberg, H. *Ann. Chem.* **1962**, *656*, 1. (b) Hoberg, H. *Ibid.* **1966**, *695*, 1. (c) Hoberg, H. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 513. (d) Hoberg, H.; Ziegler, E. *Ibid.* **1967**, *6*, 452. (e) Hoberg, H. *Ann. Chem.* **1967**, *703*, 1.

[8] By a nonacidic workup, the trimethylsilyl enol ether of cyclohexanone can be isolated in good yields.

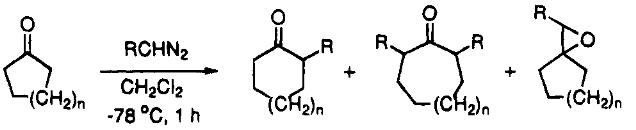
0022-3263/94/1959-4725$04.50/0

quiterpenes,[9] we continued our search for more superior organoaluminum catalysts for stereoselective ring expansion of 4-*tert*-butylcyclohexanone with diazoethane. Exceptionally bulky methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) has been found to be highly effective for this transformation.[10] Noteworthy is the fact that diazoethane should be added to the organoaluminum–ketone complex, and attempted reaction of ketone with a mixture of diazoalkane and organoaluminum at −78 °C gave none of the homologation products.

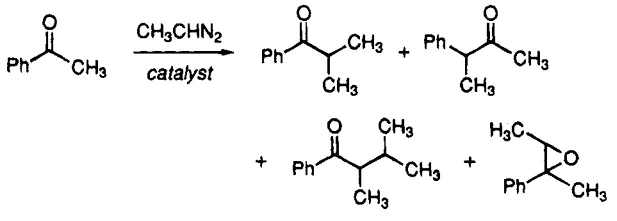


20% EtOH/ether	91%	(43 : 43 : 14)
Me_3Al, CH_2Cl_2	81%	(54 : 32 : 14)
i-Bu_3Al, CH_2Cl_2	85%	(67 : 20 : 13)[11]
DAD, CH_2Cl_2	84%	(80 : 10 : 10)
MAD, CH_2Cl_2	87%	(94 : 3 : 3)

Since a variety of diazoalkanes including functionalized ones are readily accessible from the corresponding amines in three-step sequences,[12,13] the present technique has a broad applicability in selective organic synthesis. For example, use of diazopropene permits α-vinylation of cyclic ketones with ring enlargement, hitherto difficult by other chemical transformations.[14] Organoaluminum-promoted insertion of long-chain diazoalkane appears feasible. Another characteristic feature is the reaction of acetophenone, where three methods showed totally different selectivity and where MAD has proved to be effective for the regioselective single homologation.

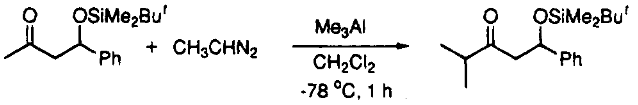


(n = 2; R = vinyl)	Me_3Al, $CH_2{=}CHCHN_2$	51%	(100 : 0 : 0)
(n = 4, R = Me)	MAD, CH_3CHN_2	56%	(100 : 0 : 0)
	Me_3Al, CH_3CHN_2	60%	(98 : 1 : 1)
(n = 4, R = pentyl)	Me_3Al, $CH_3(CH_2)_4CHN_2$	88%	(100 : 0 : 0)

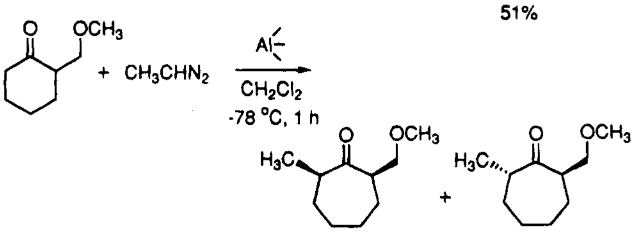


MAD, CH_2Cl_2, -78 °C	85%	(80 : 0 : 3 : 17)
Me_3Al, CH_2Cl_2, -78 °C	83%	(36 : 0 : 40 : 24)
MeOH/ether, 0 °C	18%	(57 : 43 : 0 : 0)

This methodology is successfully applied to the regio- and stereocontrolled homologation of aldol derivatives with diazoalkanes as illustrated below.



51%



Me_3Al	69%	(38 : 62)
MAD	71%	(98 : 2)

Supplementary Material Available: Typical experimental procedures and spectral data of products are available (5 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

---

(9) (a) Marshall, J. A.; Partridge, J. J. *Tetrahedron Lett.* **1966**, 2545. (b) Marshall, J. A.; Partridge, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 1090. (c) Marshall, J. A.; Partridge, J. J. *Tetrahedron* **1969**, *25*, 2159.

(10) MAD and DAD (dimethylaluminum 2,6-di-*tert*-butyl-4-methylphenoxide) can be prepared by treatment of MeAl in hexane with 2 and 1 equiv of 2,6-di-*tert*-butyl-4-methylphenol, respectively, in CH_2Cl_2 at room temperature for 1 h. For details, see: Maruoka, K.; Itoh, T.; Sakurai, M.; Nonoshita, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588.

(11) The epoxide was transformed to 1-(4-*tert*-butyl-1-cyclohexenyl)ethanol via the *i*-Bu_3Al-catalyzed rearrangement under the reaction conditions.

(12) Brewbaker, J. L.; Hart, H. *J. Am. Chem. Soc.* **1969**, *91*, 711.

(13) Diazopropene and diazohexane were prepared as follows:

$$RCH_2NH_2 \xrightarrow{a} RCH_2NHCO_2Et \xrightarrow{b} RCH_2N(NO)CO_2Et \xrightarrow{c} RCHN_2$$

(52~68% overall yield)

(a) $ClCO_2Et$, *aq.* NaOH, ether; (b) $NaNO_2$, Ac_2O, AcOH; (c) NaOMe, MeOH, ether.

(14) For an alternative vinylative homologation, see: Kim, S.; Lee, S. *Tetrahedron Lett.* **1991**, *32*, 6575.