New Methods and Reagents in Organic Synthesis; 73.[1] Trimethylsilyldiazomethane: A Convenient Reagent for the Conversion of Aliphatic Aldehydes to the Homologous Methyl Ketones

Toyohiko Aoyama,* Takayuki Shioiri*

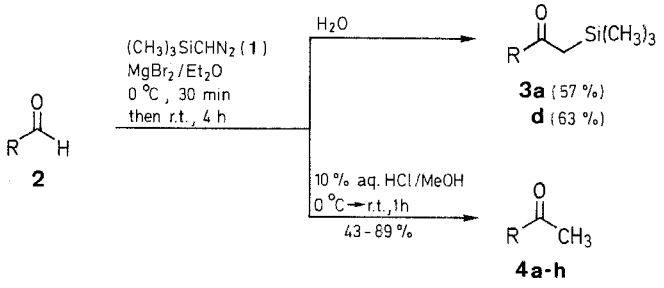
Faculty of Pharmaceutical Sciences, Nagoya City University, Tanabe-dori, Mizuho-ku, Nagoya 467, Japan

Trimethylsilyldiazomethane reacts smoothly with aliphatic aldehydes in the presence of magnesium bromide (1.5 equiv) to give homologous methyl ketones after direct treatment with 10% hydrochloric acid/methanol (1:1).

The conversion of aldehydes to the homologous methyl ketones has been carried out generally by a three-step procedure involving the methylation of masked aldehydes such as 1,3-dithianes or cyanohydrin trimethylsilyl ethers,[2] by the homologation of aldehydes with hazardous diazomethane,[3] or by the oxidation of secondary alcohols prepared from aldehydes and methylmagnesium halide.

We have already reported that trimethylsilyldiazomethane (**1**), which is quite useful as a reagent for introducing a C_1-unit,[4] smoothly reacts with aromatic aldehydes in the presence of triethylamine in methanolic solution to give homologous compounds.[5] Unfortunately, this reaction is of limited preparative value, since the products depend on the reaction solvent and on the substituents on the benzene ring. Here we report a simple, one-pot conversion of aliphatic aldehydes to homologous methyl ketones using **1**.

Aldehydes **2** smoothly react with **1** in the presence of magnesium bromide to give 2-oxoalkylsilanes **3**, which are treated with 10% hydrochloric acid/methanol (1:1) to give methyl ketones **4** in good yields.[6] 2-oxoalkylsilanes **3** can be isolated, if desired, by quenching the reaction with water instead of 10% hydrochloric acid/methanol.



The results are summarized in the Table. Magnesium bromide seems to be the additive of choice, though magnesium chloride or lithium bromide[7] can be used. Various aliphatic aldehydes including primary, secondary, and tertiary ones smoothly react with **1** to give **4**. 4-Oxoaldehyde **2h** also reacts with **1** to give 2,5-undecadione **(4h)** in moderate yield.

The present method, using commercially available trimethylsilyldiazomethane (**1**), is simple to conduct and provides a convenient one-pot conversion of aliphatic aldehydes to homologous methyl ketones. A further advantage of the method is that the method can also be used for the preparation of synthetically useful 2-oxoalkylsilanes.[8]

$MgBr_2$ was prepared from 1,2-dibromoethane (2.82 g, 15 mmol) and Mg turnings (486 mg, 20 mmol) in anhydrous Et_2O (8 mL) and was used as 1 M solution in Et_2O/benzene (ca. 1:1) by dilution with benzene. 4-Oxodecanal **(2h)** was prepared according to the literature[9] from heptanoyl chloride and 2-(2-bromoethyl)-1,3-dioxane.

Table. 2-Oxoalkylsilanes **3** and Methyl Ketones **4** Prepared.

Aldehyde No	R	Product[a]	Yield (%)	bp (°C)/torr[b] or mp (°C) (solvent)	Molecular Formula[c] or Lit. Data
2a	n-C_9H_{19}	**3a**	57	95–100/0.4	$C_{14}H_{30}OSi$ (242.5)
2a	n-C_9H_{19}	**4a**	71	110–115/21	109–110/11[11]
2b	$C_6H_5CH_2CH_2$	**4b**	73	120–125/20	118/14[12]
2c	$CH_2{=}CH(CH_2)_8$	**4c**	78	125–130/18	120/15[13]
2d	4-t-$C_4H_9C_6H_4CH_2CH(CH_3)$	**3d**	63	80–85/0.01	$C_{18}H_{30}OSi$ (290.5)
2d	4-t-$C_4H_9C_6H_4CH_2CH(CH_3)$	**4d**	74	100–105/0.75	$C_{15}H_{22}O$ (218.3)
2e	$CH_3(CH_2)_3CH(C_2H_5)$	**4e**[d]	67	86–87 (C_6H_6/hexane)	86[14]
2f	c-C_6H_{11}	**4f**[e]	72	136–138 (EtOH/H_2O)	140[15]
2g	t-C_4H_9	**4g**[e]	89	123.5–124.5 (EtOH)	126[16]
2h	n-$C_6H_{13}COCH_2CH_2$	**4h**	43	31–32	33–34[17]

[a] All products had IR and ^{1}H-NMR spectra consistent with the assigned structures.
[b] Kugelrohr apparatus.
[c] Satisfactory microanalyses obtained: C ±0.3, H ±0.4.
[d] Isolated as the semicarbazone due to the volatility of the ketone.
[e] Isolated as the 2,4-dinitrophenylhydrazone due to the volatility of the ketone.

Methyl Ketones (4a–d, h); General Procedure:
To a solution of aldehyde **2** (1 mmol) and the 1 M $MgBr_2$ solution described above (1.5 mL, 1.5 mmol) in anhydrous Et_2O (10 mL), a 1.8 M solution of trimethylsilyldiazomethane **(1)** in hexane[10] (0.67 mL, 1.2 mmol) is added dropwise at 0 °C. The mixture is stirred at 0 °C for 30 min, then at room temperature for 4 h. MeOH (1 mL) and 10% aq. HCl (1 mL) are added to the mixture at 0 °C, followed by stirring at room temperature for 1 h. After dilution with Et_2O/hexane (1:1, 100 mL), the mixture is washed with water (50 mL) and the organic phase dried ($MgSO_4$). The solvent is concentrated *in vacuo*, and the residue is purified by column chromatography on silica gel using hexane/EtOAc (40:1 for **4a**, 15:1 for **4b**, and 20:1 for **4c–d**) or CH_2Cl_2/EtOAc (150:1 for **4h**) as eluent (see Table).

4-(4-tert-Butylphenyl)-3-methyl-2-butanone **(4d)**:
IR (neat): $\nu = 1720\ cm^{-1}$ (C=O).

^{1}H-NMR ($CDCl_3$): $\delta = 1.07$ (d, 3 H, $J = 7$ Hz, $CHCH_3$); 1.27 (s, 9 H, *t*-C_4H_9); 2.06 (s, 3 H, $COCH_3$); 2.30–3.16 (m, 3 H, CH_2CH); 7.03 and 7.30 (A_2B_2, 4 H, $J = 9$ Hz, H_{arom}).

3-Ethyl-2-heptanone Semicarbazone **(4e)**:
The reaction is carried out as described above. After stirring at room temperature for 4 h, the reaction mixture is concentrated *in vacuo*. MeOH (2 mL) and 10% aq. HCl (0.1 mL) are added to the residue at 0 °C, and the mixture is stirred at room temperature for 1.5 h. Semicarbazide hydrochloride (123 mg, 1.1 mmol) and water (2 mL) are added to the mixture at room temperature. The mixture is neutralized by addition of NaOAc and stirred at 60 °C for 10 min, then at room temperature for 14 h. MeOH is removed *in vacuo*, and the residue is extracted with CH_2Cl_2 (2 × 50 mL). The combined organic phase is washed with water (50 mL), and dried ($MgSO_4$). The solvent is evaporated, and the residue is purified by preparative TLC on silica gel using CH_2Cl_2/EtOH (20:1) as eluent.

Cyclohexyl Methyl Ketone 2,4-Dinitrophenylhydrazone **(4f)**:
The reaction is carried out as described in the general procedure. After stirring at room temperature for 4 h, the reaction mixture is concentrated *in vacuo*. A solution of 2,4-dinitrophenylhydrazine (218 mg, 1.1 mmol) in 10% aq. HCl (5 mL) and MeOH (5 mL) is added to the residue at 0 °C, and the mixture is stirred at room temperature for 1 h. The resulting precipitates are collected by filtration and washed with water (10 mL), MeOH/water (1:1; 2 mL), and dried *in vacuo*.

3,3-Dimethyl-2-butanone 2,4-Dinitrophenylhydrazone **(4g)**:
The reaction and work up are carried out as described for the preparation of **4f**.

1-Trimethylsilyl-2-undecanone (3a):
To a solution of decanal (**2a**; 156 mg, 1 mmol) and the 1 M $MgBr_2$ solution described above (1.5 mL, 1.5 mmol) in anhydrous Et_2O (10 mL), 1.8 M trimethylsilyldiazomethane **(1)** in hexane[10] (0.67 mL, 1.2 mmol) is added dropwise at 0 °C. The mixture is stirred at 0 °C for 30 min, then at room temperature for 4 h. The mixture is treated with water (10 mL) and extracted with Et_2O/hexane (1:1, 100 mL). The organic layer is washed with water (50 mL) and dried ($MgSO_4$). The solvent is evaporated, and the residue is purified by distillation under reduced pressure (see Table).

IR (neat): $\nu = 1695$ (C=O), 1250, 860 cm^{-1} [$Si(CH_3)_3$].

^{1}H-NMR ($CDCl_3$): $\delta = 0.12$ [s, 9 H, $Si(CH_3)_3$]; 0.87–1.73 [m, 17 H, $(CH_2)_7CH_3$]; 2.18 (s, 2 H, $COCH_2Si$); 2.33 (t, 2 H, $J = 7$ Hz, $COCH_2$).

4-(4-*tert*-Butylphenyl)-3-methyl-1-trimethylsilyl-2-butanone (3d):
Prepared from 3-(4-*tert*-butylphenyl)-2-methylpropanal (**2d**; 306 mg, 1.5 mmol), 1.8 M trimethylsilyldiazomethane (**1**) in hexane[10] (1 mL, 1.8 mmol), and 1 M $MgBr_2$ described above (2.3 mL, 2.3 mmol) as described for the preparation of **3a** (see Table).

IR (neat): $\nu = 1695$ (C=O), 1260, 860 cm^{-1} [$Si(CH_3)_3$].

^{1}H-NMR ($CDCl_3$): $\delta = 0.00$ [s, 9 H, $Si(CH_3)_3$]; 1.04 (d, 3 H, $J = 7$ Hz, $CHCH_3$); 1.28 (s, 9 H, *t*-C_4H_9); 2.08, 2.22 (AB, 2 H, $J = 11$ Hz, $COCH_2Si$); 2.32–3.10 (m, 3 H, CH_2CH); 7.06, 7.28 (A_2B_2, 4 H, $J = 8$ Hz, H_{arom}).

Received: 8 July 1987; revised: 13 October 1987

(1) For Part 72, see: Ando, A., Shioiri, T. *J. Chem. Soc. Chem. Commun.*, **1987**, 1620.
(2) Seebach, D. *Angew. Chem.* **1979**, *18*, 259; *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 239.
(3) Gutsche, C.D. *Org. React.* **1954**, *8*, 364.
(4) Aoyama, T., Shioiri, T. *Tetrahedron Lett.* **1986**, *27*, 2005.
For a review, see: Shioiri, T., Aoyama, T. *J. Synth. Org. Chem. Jpn.* **1986**, *44*, 149.
(5) Hashimoto, N., Aoyama, T., Shioiri, T. *Heterocycles* **1981**, *15*, 975.
(6) Aromatic aldehydes also undergo the homologation under the same reaction conditions, but a mixture of homologous compounds is formed. For example, the reaction of benzaldehyde with **1** gave acetophenone 2,4-dinitrophenylhydrazone (34%) and phenylacetaldehyde 2,4-dinitrophenylhydrazone (33%) when the reaction was carried out as described for the preparation of **4f**.
(7) Lithium bromide has been reported to promote the homologation of aldehydes with aryldiazomethanes; see:
Loeschorn, C.A., Nakajima, M., Anselme, J.-P. *Bull. Soc. Chim. Belg.* **1981**, *90*, 985.
Loeschorn, C.A., Nakajima, M., McCloskey, P.J., Anselme, J.-P. *J. Org. Chem.* **1983**, *48*, 4407.
(8) Colvin, E.W. *Silicon in Organic Synthesis*, Butterworths, London, 1981, Chapters 12 and 17.
Weber, W.P. *Silicon Reagents for Organic Synthesis*, Springer-Verlag, Berlin, 1983, Chapter 16.
(9) Stowell, J.C. *J. Org. Chem.* **1976**, *41*, 560.
(10) Mori, S., Sakai, I., Aoyama, T., Shioiri, T. *Chem. Pharm. Bull.* **1982**, *30*, 3380.
(11) Grunanger, P., Grieco, D. *Gazz. Chim. Ital.* **1958**, *88*, 296.
(12) Clark, C.M., Johnson, J.D.A. *J. Chem. Soc.* **1962**, 126.
(13) Sörensen, N.A., Mehlum, J. *Acta Chem. Scand.* **1948**, *2*, 146.
(14) Arucs, C.L., Smyth, D.G. *J. Chem. Soc.* **1955**, 34.
(15) Lecomte, J., Gault, H. *C. R. Acad. Sci.* **1954**, *238*, 2538.
(16) Hickinbottom, W.J., Hogg, D.R., Peters, D., Wood, D.G.M. *J Chem. Soc.* **1954**, 4400.
(17) Rosini, G., Ballini, R., Sorrenti, P. *Tetrahedron* **1983**, *39*, 4127.