Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 6047–6049

TETRAHEDRON
LETTERS

The Mukaiyama–Michael addition of a β,β-dimethyl substituted silyl ketene acetal to α,β-unsaturated ketones using tetra-*n*-butylammonium bibenzoate as a nucleophilic catalyst

Rudhramyna Gnaneshwar, Prakash P. Wadgaonkar and Swaminathan Sivaram*

Division of Polymer Chemistry, National Chemical Laboratory, Pune 411008, India

Received 29 April 2003; revised 6 June 2003; accepted 13 June 2003

Abstract—The Michael addition of a β,β-dimethyl substituted silyl ketene acetal [$Me_2C{=}C(OMe)OSiMe_3$] to α,β-unsaturated ketones, namely, 2-cyclopentenone, 2-cyclohexenone, 3-methyl-2-cyclohexenone, isophorone, methyl vinyl ketone and mesityl oxide occurs smoothly in the presence of the nucleophilic catalyst, tetra-*n*-butyl ammonium bibenzoate (TBABB) in THF giving the corresponding 1,4-adducts in excellent yields.

The conjugate addition of *O*-silylated ketene acetals to α,β-unsaturated ketones (the Mukaiyama–Michael reaction) is a well documented and important method for carbon–carbon bond formation.[1,2] The utility of the reaction has been demonstrated by numerous applications in organic synthesis.[3,4] The reaction has been performed at high temperatures[5] or high pressures.[6] However, a strong Lewis acid is normally used to catalyze the reaction under moderate conditions. Typical Lewis acids reported to be useful are $TiCl_4$, $TiCl_4$/$Ti(i\text{-}PrO)_4$,[7] $SnCl_4$,[8] SmI_2,[9] and lanthanum triflates.[10] Cobalt–bis-dicarbollide[11] [$LiCo\ (B_9C_2H_{11})_2$], $Mg(ClO_4)_2$[12] and $LiClO_4$ in diethyl ether have also been reported[13] as useful catalysts for this reaction. Uncatalyzed Mukaiyama–Michael reactions (solvent assisted reaction) have also been reported in highly polar solvents such as acetonitrile,[14] nitromethane[2] and in DMSO.[15]

In 1984, Rajan Babu reported[2] the successful Mukaiyama–Michael reaction of trimethyl-silyl ketene acetals with α,β-unsaturated ketones catalyzed by tris-(dimethylamino) sulfonium difluorotrimethyl siliconate (TASF). Under these conditions silylated 1,4-adducts could be isolated. TASF also catalyzes the polymerization of α,β-unsaturated esters (methyl methacrylate) initiated by the trimethylsilyl ketene acetal. Subsequently, it was reported[16,17] that this reaction (termed 'group-transfer polymerization') can also be catalyzed by tetra-*n*-butylammonium bibenzoate (TBABB), a 2:1 complex of benzoic acid and tetra-*n*-butylammonium hydroxide, which functions as a weak Lewis base.[18]

We now report that TBABB is also a useful catalyst for Mukaiyama–Michael reactions of the β,β-dimethyl-substituted silyl ketene acetal **2** [$Me_2C{=}C(OMe)OSiMe_3$] with α,β-unsaturated ketones. Compared to the hygroscopic TASF, the use of TBABB offers several advantages. It is easy to prepare[17,18] from readily available starting materials, is crystalline, non-hygroscopic, and soluble in THF and it can be stored and handled with much greater ease. In addition, the reaction can be conveniently carried out at room temperature or above using only 0.1 mol% of TBABB catalyst. In contrast, TASF is reported to require low temperatures (–78°C).[2]

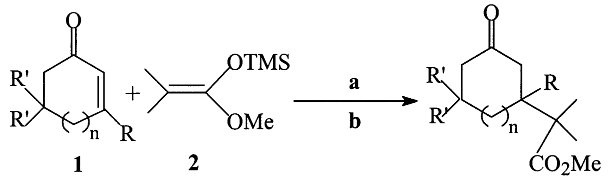
General procedure for the Michael addition

A clean and flame dried 50 mL round bottom flask was charged with 2.46×10^{-3} mmol of the TBABB catalyst (0.1 mol% based on the silyl ketene acetal **2**). Dry THF (10 mL) was transferred at room temperature using a cannula. The β,β-dimethyl-substituted silyl ketene acetal **2** (1.1 equiv.) was then added and stirred for 5 min. Subsequently 2.46 mmol of the α,β-unsaturated ketone was added under nitrogen and the reaction continued either at room temperature or under reflux. No attempt was made to isolate the silyl enol ether intermediates.

Keywords: Mukaiyama–Michael reactions; conjugate addition; 1,4-addition; δ-ketoester; *O*-silylated ketene acetal; α,β-unsaturated ketones.

* Corresponding author. Tel.: +91-20-5893030; fax: +91-20-5893355; e-mail: sivaram@ems.ncl.res.in

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0040-4039(03)01511-9



1 2 3(a-d)

n = 0, R= H, R'= H, **1a**
n = 1, R= H, R'= H, **1b**
n = 1, R= CH_3, R'= H, **1c**
n = 1, R= CH_3, R'= CH_3, **1d**

Scheme 1. *Reagents and conditions*: (a) catalyst, TBABB (0.1 mol% of **2**), THF (b) THF: 1N HCl = 20:1, 0°C, 0.5 h.

The reaction mixture was quenched with 1N HCl and stirred at 0°C for 0.5 h, the water separated, and the product extracted into ethyl acetate and dried over Na_2SO_4.

After concentration of the organic layer, column chromatography (60–120 mesh silica gel, EtOAc/*n*-hexane as eluent) afforded δ-ketoesters **3a–d** and **5a–b** (Schemes 1 and 2) in high yields (Table 1).

The products **3a–d** and **5a–b** were analyzed by FT-IR, ^1H and ^{13}C NMR spectroscopy.[19] The diastereotopic CH_3's resolved into two peaks of equal intensity in the ^1H NMR spectrum of adducts **3a**, **3b** and **3d**. Also, the diastereotopic methyls in **3b** and **3d** could be distinguished in the ^{13}C NMR spectrum; however, they could not be distinguished in the case of **3a** and **3c**. All compounds gave satisfactory elemental analyses.

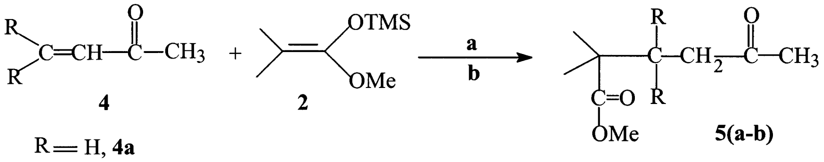
No reaction occurred between the enones and the β,β-dimethyl-substituted silyl ketene acetal **2** in the absence of TBABB catalyst in THF at room temperature. β,β-Dimethyl-substituted silyl ketene acetal **2** which is a hindered ketene acetal, in the presence of TBABB generates a very potent carbon nucleophile which in reactivity is equivalent to an ester enolate. The addition to α,β-unsaturated ketones occurs efficiently in an exclusive 1,4 fashion to give the δ-ketoesters in excellent yields.

Simple Michael acceptors, such as, 2-cyclopentenone (**1a**), 2-cyclohexenone (**1b**) and methyl vinyl ketone (**4a**) react smoothly, even at room temperature. Methyl vinyl ketone, the simplest α-enone, which is an acid sensitive substrate, gave the 1,4-adduct **5a** in quantitative yield without competing polymerization (entry 5, Table 1) using the TBABB catalyst in THF. The reaction was exothermic and was complete in 10 min at room temperature. More hindered α,β-unsaturated ketones (3-methyl-2-cyclohexenone (**1c**), isophorone (**1d**) and mesityl oxide (**4b**)) require heating at reflux for the reaction to proceed to completion.

In conclusion, we have found that Michael addition of a β,β-dimethyl-substituted silyl ketene acetal [$Me_2C{=}C(OMe)OSiMe_3$] to α,β-unsaturated ketones occurs smoothly in the presence of the weak nucleophilic catalyst TBABB in THF. The corresponding δ-ketoesters were formed in excellent yields. The high efficiency of the TBABB catalyzed conjugate addition of β,β-dimethyl-substituted silyl ketene acetal to α,β-unsaturated ketones should find considerable use in organic synthesis.

Acknowledgements

R.G. thanks CSIR New Delhi for a Senior Research Fellowship.



4 2 5(a-b)

R= H, **4a**
R= CH_3, **4b**

Scheme 2. *Reagents and conditions*: (a) catalyst, TBABB (0.1 mol% of **2**), THF (b) THF: 1N HCl = 20:1, 0°C, 0.5 h.

Table 1. Reaction of α,β-unsaturated ketones[a] with silyl ketene acetal **2**

Entry	α,β-Unsaturated ketone	Reaction temperature (°C)	Reaction time (min)	Isolated yield[b] (%)
1	**1a**	25	10	94 (**3a**)
2	**1b**	25	10	95 (**3b**)
3	**1c**	65	300	88 (**3c**)
4	**1d**	65	900	85 (**3d**)
5	**4a**	25	10	96 (**5a**)
6	**4b**	65	180	87 (**5b**)

[a] α,β-unsaturated ketone: 2.46 mmol, **2**: 2.46 mmol, TBABB: 2.46×10^{-3} mmol, THF: 10 mL.

[b] The purity of the δ-ketoesters (≥98%) was checked by GLC and TLC.

References

1. (a) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron* **1991**, *47*, 9773–9782; (b) Huffman, J. W.; Potnis, S. M.; Satish, A. V. *J. Org. Chem.* **1985**, *50*, 4266–4270; (c) Otera, J.; Wakahara, Y.; Kamei, H.; Sato, T.; Nozaki, H.; Fukuzumi, S. *Tetrahedron Lett.* **1991**, *32*, 2405–2408.
2. Rajan Babu, T. V. *J. Org. Chem.* **1984**, *49*, 2083–2089 and references cited therein.
3. Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665–4668.
4. Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, 4943–4946.
5. (a) Kita, Y.; Segawa, J.; Haruta, J.; Fujii, T.; Tamura, Y. *Tetrahedron Lett.* **1980**, *21*, 3779–3782; (b) Danishefsky, S.; Vaughan, K.; Gadwood, R.; Tsuzuki, K. J. *J. Am. Chem. Soc.* **1981**, *103*, 4136–4141; (c) Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* **1986**, 1817–1818; (d) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H.; Kamei, H.; Fukuzumi, S. *Tetrahedron Lett.* **1991**, *21*, 2405–2408.
6. (a) Matsumoto, K. *Angew. Chem.*, *Int. Ed. Eng.* **1980**, *19*, 1013–1014; (b) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943–4946; (c) Matsumoto, K.; Uchida, T. *Chem. Lett.* **1981**, 1673–1676.
7. Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163–164.
8. (a) Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *J. Am. Chem. Soc.* **1991**, *113*, 4028–4030; (b) Fujita, Y.; Fukuzumi, S.; Otera, J. *Tetrahedron Lett.* **1997**, *38*, 2117–2120.
9. Weghe, P.; Collin, J. *Tetrahedron Lett.* **1993**, *34*, 3881–3884.
10. (a) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Tetrahedron Lett.* **1992**, *33*, 6815–6818; (b) Kobayashi, S.; Hachiya, I.; Takahori, T.; Araki, M.; Ishitani, H. *Synlett* **1993**, 472–474; (c) Kobayashi, S.; Horibe *J. Am. Chem. Soc.* **1994**, *116*, 9805–9806; (d) Kobayashi, S.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3590–3596; (e) Kobayashi, S.; Hachiya, I.; Araki, M. *J. Org. Chem.* **1994**, *59*, 3758–3759; (f) Kawada, A.; Mitamura, S.; Kobayashi, S. *Chem. Commun.* **1996**, 183–184.
11. Grieco, P. A.; Dubay, W. J.; Todd, L. J. *J. Org. Chem.* **1994**, *59*, 6898–6899.
12. Fukuzumi, S.; Okamoto, T.; Yasui, K.; Suenobu, T.; Itoh, S.; Otera, J. *Chem. Lett.* **1997**, 667–668.
13. (a) Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595–4596; (b) Forman, M. A.; Dailey, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 2761–2762; (c) Ipaktschi, J.; Heydari, A. *Angew. Chem.*, *Int. Ed. Engl.* **1992**, *31*, 313–314; (d) Grieco, P. A.; Collins, J. L.; Henry, Jr. *Tetrahedron Lett.* **1992**, *33*, 4735–4738; (e) Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665–4668; (f) Reetz, M. T.; Raguse, B.; Marth, C. F.; Hugel, H. M.; Bach, T.; Fox, D. N. A. *Tetrahedron Lett.* **1993**, *34*, 1119–1122.
14. (a) Kita, Y.; Segawa, J.; Haruta, J.; Fujii, T.; Tamura, Y. *Tetrahedron Lett.* **1980**, *21*, 3779–3782; (b) Kita, Y.; Segawa, J.; Haruta, J.; Yasuda, H.; Tamura, Y. *J. Chem. Soc.*, *Perkin Trans. 1* **1982**, 1099–1104; (c) Bunce, R. A.; Schlecht, M. F.; Dauben, W. G.; Heathcock, C. H. *Tetrahedron Lett.* **1983**, *24*, 4943–4946; (d) Berl, V.; Helmchen, G.; Preston, S. *Tetrahedron Lett.* **1994**, *35*, 233–236.
15. Genisson, Y.; Gorrichon, L. *Tetrahedron Lett.* **2000**, *41*, 4881–4884.
16. Dicker, I. B.; Cohen, G. M.; Farnham, W. B.; Hertler, W. R.; Laganis, E. D.; Sogah, D. Y. *Macromolecules* **1990**, *23*, 4034–4041.
17. Brittain, W. J. *J. Am. Chem. Soc.* **1988**, *110*, 7440–7444.
18. Puranik, V. G.; Tavale, S. S.; Iyer, V. S.; Sehra, J. C.; Sivaram, S. *J. Chem. Soc.*, *Perkin Trans. 2* **1993**, 1517–1520.
19. Spectroscopic data of δ-ketoester: **3a**: light yellow liquid, FT-IR (neat); $\nu_{\max}$ 1732, 1699 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$); δ 1.11 (2s, separated by 3 Hz, 6H); 1.49–2.55 (m, 7H); 3.59 (s, 3H); ^{13} C NMR (50 MHz, CDCl$_3$); δ 22.49 (2C), 24.29, 38.63, 40.28, 43.70, 44.95, 51.56, 177.02, 217.71; Anal. calcd for $C_{10}H_{16}O_3$ (184.23); C, 65.19; H, 8.75. Found: C, 65.07; H, 8.98. **3b**: light yellow liquid, FT-IR (neat); $\nu_{\max}$ 1734, 1716 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$); δ 1.19 (2s, separated by 3.9 Hz, 6H); 1.40–2.95 (m, 9H); 3.60 (s, 3H); ^{13} C NMR (50 MHz, CDCl$_3$); δ 20.84, 21.09, 24.10, 25.35, 40.13, 42.26, 44.25, 44.91, 50.72, 176.21, 209.80. Anal. calcd for $C_{11}H_{18}O_3$ (198.26); C, 66.64; H, 9.15. Found C, 66.76; H, 9.27. **3c**: light yellow liquid, FT-IR (neat) $\nu_{\max}$ 1734, 1712 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$); δ 0.85 (s, 3H); 1.14 (s, 6H); 1.64 (m, 2H); 1.73 (m, 1H); 1.92 (m, 1H); 2.14 (d, J=13.5 Hz, 1H); 2.17 (dd, J=7.1, 13.1 Hz, 1H); 2.28 (m, 1H); 2.48 (d, J=13.5 Hz, 1H); 3.60 (s, 3H); ^{13} C NMR (125 MHz, CDCl$_3$); δ 19.11, 20.80 (2C), 21.50, 30.83, 36.86, 40.57, 42.45, 48.81, 51.34, 176.69, 211.90; Anal. calcd for $C_{12}H_{20}O_3$ (212.28); C, 67.89; H, 9.49. Found C, 67.98; H, 9.60. **3d**: light yellow liquid, FT-IR (neat) $\nu_{\max}$ 1736, 1670 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$); δ 0.90 (2s, separated by 2.2 Hz, 6H); 0.94 (s, 3H); 1.15 (2s, separated by 5.2 Hz, 6H); 1.49 (d, J=14.3 Hz, 1H); 1.69 (d, J=14.3 Hz, 1H); 2.11 (d, J=14.7 Hz, 2H); 2.15 (d, J=13.5 Hz, 1H); 2.64 (d, J=13.9 Hz, 1H); 3.65 (s, 3H); ^{13} C NMR (125 MHz, CDCl$_3$); δ 20.68, 20.74, 22.95, 28.95, 34.31 (2C), 41.97, 44.11, 47.40, 49.86, 51.21, 52.91, 176.67, 212.02. Anal. calcd for $C_{14}H_{24}O_3$ (240.34); C, 69.96; H, 10.06. Found C, 70.0; H, 10.14. **5a**: light yellow liquid, FT-IR (neat) $\nu_{\max}$ 1738, 1726 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$); δ 1.07 (s, 6H); 1.69 (t, J=8.1 Hz, 2H); 2.04 (s, 3H); 2.31 (t, J=8.0 Hz, 2H); 3.56 (s, 3H); ^{13} C NMR (50 MHz, CDCl$_3$); δ 24.84 (2C), 29.55, 33.70, 39.14, 41.31, 51.45, 177.50, 207.64. Anal. calcd for $C_9H_{16}O_3$ (172.22); C, 62.76; H, 9.36. Found C, 62.36; H, 9.34. **5b**: light yellow liquid, FT-IR (neat) $\nu_{\max}$ 1734, 1723 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$); δ 0.98 (s, 6H); 1.08 (s, 6H); 2.08 (s, 3H); 2.42 (s, 2H); 3.59 (s, 3H); ^{13} C NMR (50 MHz, CDCl$_3$); δ 21.02 (2C), 22.05 (2C), 32.85, 38.04, 48.88, 49.32, 51.34, 177.13, 208.92. Anal. calcd for $C_{11}H_{20}O_3$ (200.27); C, 65.96; H, 10.06. Found C, 65.69; H, 9.97.