A Practical Preparation of 2-Hydroxymethyl-2-cyclopenten-1-one by Morita–Baylis–Hillman Reaction

Hisanaka Ito,* Yosuke Takenaka, Shouhei Fukunishi, Kazuo Iguchi*

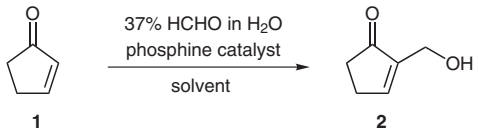
School of Life Science, Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan
Fax +81(426)767282; E-mail: itohisa@ls.toyaku.ac.jp; E-mail: onocerin@ls.toyaku.ac.jp

Received 9 May 2005; revised 15 June 2005

Abstract: Tributylphosphine or dimethylphenylphosphine (1–5 mol%) catalyzed the Morita–Baylis–Hillman reaction of 2-cyclopenten-1-one (**1**) with 1.2 equivalents of formalin proceeded nicely to give 2-hydroxymethyl-2-cyclopenten-1-one (**2**) within a short period and in an excellent yield. The efficiency of the reaction (yield and time) was strongly dependent on the solvent and the best result was obtained in the case of an aqueous MeOH–$CHCl_3$ solvent system.

Key words: addition reactions, carbocycles, catalysis, enones, phosphorus

2-Hydroxymethyl-2-cyclopenten-1-one (**2**) is a useful building block for the synthesis of naturally occurring and biologically active compounds which contain a polyfunctionalized cyclopentane ring in the structure.[1] One of the most common synthetic methods for compound **2** was reported by Smith et al.[2] This procedure requires 4 steps for the synthesis of compound **2** from commercially available 2-cyclopenten-1-one (**1**). As a part of our program focused on the synthesis of marine prostanoids containing a cyclopentane ring[3] the development of a practical and efficient preparative method for 2-hydroxymethyl-2-cyclopenten-1-one (**2**) was required (Scheme 1).



Scheme 1

The Morita–Baylis–Hillman reaction is one of the most useful reactions for the construction of α-methylene-β-hydroxycarbonyl compounds through the addition of an unsaturated carbonyl group to aldehyde in the presence of a catalytic amount of tertiary amine or trialkylphosphine.[4] Although this reaction has been applied to the construction of many building blocks with the aim of synthesizing natural and/or biologically active compounds, there are some problems (yield and/or reaction time). Recently, a number of modified reaction conditions have been reported to improve the yield and long reaction time. Many bases have been employed for the acceleration of the reaction; however a hindered tertiary amine like 1,4-diazabicyclo[2.2.2]octane (DABCO) has been most commonly used. Among them, tributylphosphine has been focused on as the catalyst because of its high reactivity and neutral property.[5]

The direct approach for the synthesis of compound **2** through Morita–Baylis–Hillman reaction has been examined by several groups.[6] Although compound **2** was obtained in satisfactory yield, these reaction conditions require a long reaction time, excess of formalin, and/or exact stoichiometric amount of catalyst. In the case of imidazole-catalyzed reaction, 17 days were required to obtain compound **2** in 86% yield.[6b] Very recently, the *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine-catalyzed preparative method of compound **2** was reported, but 50 mol% of catalyst, 5 equivalents of formalin and long reaction time (72 h) were required to obtain the satisfactory yield (56%).[6c] Uskokovic et al. reported the tributylphosphine-catalyzed Morita–Baylis–Hillman reaction of 2-cyclopenten-1-one (**1**) with formalin for the synthesis of vitamin D_3 metabolites in 1996, but the reaction conditions and yield of compound **2** were not mentioned.[1d] Now we report herein a practical preparative method for compound **2** by phosphine-catalyzed Morita–Baylis–Hillman reaction.

The results are shown in Table 1. At first, tributylphosphine was used as a catalyst. The reaction proceeded in THF or dioxane at room temperature in the presence of 10 mol% of catalyst to give compound **2** in 60% and 58% yields, respectively (entries 1 and 2). In both cases, the reaction did not complete within 55 hours and a significant amount of dimer of **1** was also obtained. The reaction was dramatically accelerated by the use of MeOH as solvent and was completed within 30 minutes along with a small amount of by-products (entry 3). In the case of $CHCl_3$–water biphasic system, the reaction was shown to be faster than that in THF and dioxane and compound **2** was obtained in 81% yield (entry 4). Therefore, a MeOH–$CHCl_3$ solvent system was examined. In the presence of 10 mol% of tributylphosphine, the adduct **2** was obtained in 97% yield (entry 5). The reaction was complete within 30 minutes and almost no by-product was observed. A decreased amount of catalyst could be used in this solvent system and use of 5 mol% of catalyst was enough for the reaction and compound **2** was obtained within 2.5 hours in 96% yield (entry 7). Other phosphine catalysts were also examined. Dimethylphenylphosphine also worked nicely and

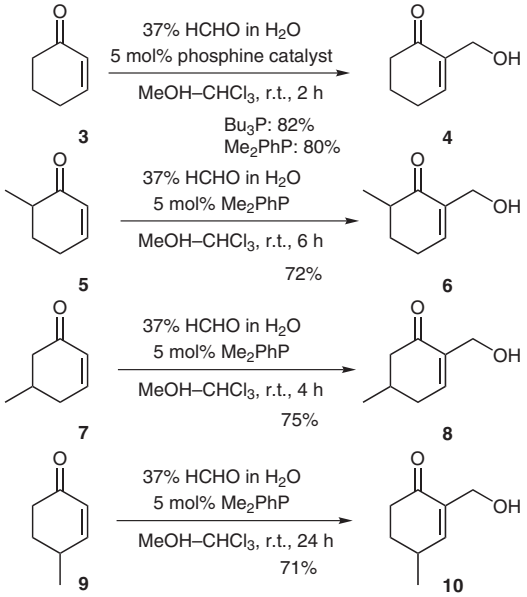
SYNTHESIS 2005, No. 18, pp 3035–3038
Advanced online publication: 06.10.2005
DOI: 10.1055/s-2005-916030; Art ID: F08005SS

the product **2** was obtained in 97% yield within one hour (entry 12). This case also showed the best result by the use of the MeOH–$CHCl_3$ solvent system. The amount of catalyst could be decreased to 1 mol% (entry 13). Although the reaction proceeded to give compound **2**, the reaction rate was significantly slower in the case of methyldiphenylphosphine as a catalyst (entries 14 and 15). In all cases, the use of 1.2 equivalents of formalin was enough to give compound **2** in a satisfactory yield.

Table 1 Preparation of **2** by Phosphine-Catalyzed Morita–Baylis–Hillman Reaction

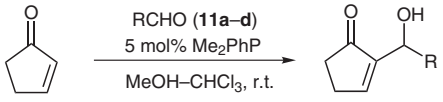
Entry	Catalyst[a]	Solvent[b]	Temp (°C)	Time (h)	Yield (%)[c]
1	Bu_3P (10)	THF	r.t.	55	60
2	Bu_3P (10)	dioxane	r.t.	55	58
3	Bu_3P (10)	MeOH	r.t.	0.5	74
4	Bu_3P (10)	$CHCl_3$	r.t.	2	81
5	Bu_3P (10)	MeOH–$CHCl_3$	r.t.	0.5	97
6	Bu_3P (5)	MeOH–$CHCl_3$	r.t.	0.5	88
7	Bu_3P (5)	MeOH–$CHCl_3$	r.t.	2.5	96
8	Bu_3P (5)	MeOH–$CHCl_3$	0	2.5	89
9	Me_2PhP (5)	MeOH	r.t.	0.5	84
10	Me_2PhP (5)	$CHCl_3$	r.t.	24	20
11	Me_2PhP (5)	MeOH–$CHCl_3$	0	3	97
12	Me_2PhP (5)	MeOH–$CHCl_3$	r.t.	1	97
13	Me_2PhP (1)	MeOH–$CHCl_3$	r.t.	24	80
14	$MePh_2P$ (10)	MeOH–$CHCl_3$	0	24	90
15	$MePh_2P$ (5)	MeOH–$CHCl_3$	r.t.	21	67

[a] Numbers in parentheses are the mol% of the catalyst.
[b] All solvent systems contained water derived from 37% formalin.
[c] Isolated yield.



Scheme 2

Table 2 Morita–Baylis–Hillman Reaction of 2-Cyclopenten-1-one (**2**) with Various Aldehydes



1

12a (R = phenyl)
12b (R = 2-phenylethyl)
12c (R = cyclohexyl)
12d (R = 2-furanyl)

Entry	Aldehyde	Time (h)	Yield (%)
1	benzaldehyde (**11a**)	24	76
2	3-phenylpropionaldehyde (**11b**)	23	98
3	cyclohexanecarboxaldehyde (**11c**)	22	70
4	furfural (**11d**)	21	76

2-Hydroxymethyl-2-cyclohexen-1-one (**4**) is also a useful building block for the synthesis of biologically active compounds. The approaches for the synthesis of compound **4** by Morita–Baylis–Hillman reaction have been reported.[7] Morita–Baylis–Hillman reactions of 2-cyclohexen-1-one (**3**) and related compounds (**5**, **7**, and **9**) with formalin were also examined by employing our developed conditions and hydroxymethylated compounds were obtained in good yields (Scheme 2).

We also examined the Morita–Baylis–Hillman reaction of 2-cyclopenten-1-one with various aldehydes under the above-mentioned conditions, which were optimized for the preparation of **2**. The results are shown in Table 2.

Melting points were measured on a Yazawa YB-1 apparatus. ^1H and ^{13}C NMR spectra were measured on a Bruker AV-300 (^1H; 300 MHz, ^{13}C; 75 MHz) and the chemical shifts are given in ppm using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^1H NMR and $CDCl_3$ (77.0 ppm) for ^{13}C NMR as an internal standard, respectively. IR spectra were taken with a Perkin-Elmer PARAGON 1000 FT-IR and only noteworthy absorptions are listed. Mass spectra were measured on a Micromass LCT. Materials and solvents were obtained from commercial suppliers and were used without further purification. Methyl substituted 2-cyclohexen-1-one derivatives were prepared according to the literature procedure.[8] The reactions were carried out under an Ar atmosphere. Column chromatography was performed on silica gel 60 (70–230 mesh).

2-Hydroxymethyl-2-cyclopenten-1-one (2); Typical Procedure

To a solution of 2-cyclopenten-1-one (**1**; 100 mg, 1.22 mmol) in $CHCl_3$ (1.5 mL) and MeOH (1 mL) was added 37% formaldehyde in water (0.12 mL, 1.46 mmol) at ambient temperature. A solution

of dimethylphenylphosphine (8.4 mg, 0.06 mmol) in $CHCl_3$ (1 mL) was added to the reaction mixture and the mixture was stirred at ambient temperature for 1 h. The resulting mixture was purified directly by silica gel column chromatography (hexane–EtOAc, 1:2–1:4) and compound **2** was obtained in 97% yield (132.1 mg, 1.18 mmol) as white crystals; mp 71–73 °C.

IR (KBr): 3368, 1679, 1633 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.40–2.48 (m, 2 H), 2.59–2.66 (m, 2 H), 2.69 (t, *J* = 5.9 Hz, 1 H), 4.32–4.37 (m, 2 H), 7.50–7.57 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8, 35.0, 57.5, 144.9, 159.0, 209.9.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 63.94; H, 7.21.

2-Hydroxymethyl-2-cyclohexen-1-one (4)
Colorless oil.

IR (neat): 3412, 1667 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.96 (quint, *J* = 6.2 Hz, 2 H), 2.31–2.43 (m, 4 H), 2.93 (br s, 1 H), 4.19 (s, 2 H), 6.91 (t, *J* = 4.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 25.5, 38.1, 61.5, 138.2, 146.8, 200.5.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.65; H, 7.99. Found: C, 66.35; H, 7.90.

2-Hydroxymethyl-6-methyl-2-cyclohexen-1-one (6)
Colorless oil.

IR (neat): 3436, 1668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.8 Hz, 3 H), 1.64–1.80 (m, 1 H), 1.98–2.08 (m, 1 H), 2.33–2.48 (m, 3 H), 2.70 (br s, 1 H), 4.21 (s, 2 H), 6.86 (t, *J* = 4.1 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 25.0, 30.7, 41.6, 62.1, 137.6, 146.0, 203.1.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: 68.20; H, 8.69.

2-Hydroxymethyl-5-methyl-2-cyclohexen-1-one (8)
Colorless oil.

IR (neat): 3417, 1668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.2 Hz, 3 H), 1.98–2.29 (m, 3 H), 2.38–2.54 (m, 2 H), 2.69 (br s, 1 H), 4.22 (s, 2 H), 6.85–6.92 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.0, 30.3, 33.9, 46.3, 61.7, 137.9, 146.0, 200.7.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: 68.31; H, 8.51.

2-Hydroxymethyl-4-methyl-2-cyclohexen-1-one (10)
Colorless oil.

IR (neat): 3414, 1668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.14 (d, *J* = 7.2 Hz, 3 H), 1.64 (dddd, *J* = 4.7, 9.5, 12.4, 13.3 Hz, 1 H), 2.03–2.12 (m, 1 H), 2.34 (ddd, *J* = 4.9, 12.4, 16.8 Hz, 1 H), 2.49 (td, *J* = 4.9, 16.8 Hz, 1 H), 2.51–2.63 (m, 1 H), 2.68 (s, 1 H), 4.21 (s, 2 H), 6.72 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.2, 30.7, 31.1, 37.0, 61.8, 136.9, 152.3, 200.5.

2-(1-Hydroxyphenylmethyl)-2-cyclopenten-1-one (12a)
White crystals; mp 93–112 °C.

IR (KBr): 3234, 1691, 1492 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.43–2.50 (m, 2 H), 2.56–2.66 (m, 2 H), 3.46 (d, *J* = 4.0 Hz, 1 H), 5.57 (br s, 1 H), 7.24–7.43 (m, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5, 35.1, 69.4, 126.2, 127.6, 128.3, 141.4, 147.7, 159.3, 209.3.

HR–ESI–MS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{13}O_2$: 189.0916; found: 189.0926.

Anal. Calcd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.74; H, 6.55.

2-(1-Hydroxy-3-phenylpropyl)-2-cyclopenten-1-one (12b)
Colorless oil.

IR (neat): 3418, 1694, 1496 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.96–2.07 (m, 2 H), 2.40–2.46 (m, 2 H), 2.56–2.63 (m, 2 H), 2.65–2.99 (m, 2 H), 3.03 (br s, 1 H), 4.48 (br s, 1 H), 7.14–7.34 (m, 5 H), 7.44 (br s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.6, 31.6, 35.2, 37.1, 67.1, 125.8, 128.4, 128.5, 141.6, 147.5, 158.0, 210.0.

HR–ESI–MS: *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{17}O_2$: 217.1229; found: 217.1232.

2-(1-Hydroxycyclohexylmethyl)-2-cyclopenten-1-one (12c)
Colorless oil.

IR (neat): 3437, 1694 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.90–1.10 (m, 2 H), 1.10–1.32 (m, 3 H), 1.46–1.90 (m, 6 H), 2.41–2.47 (m, 2 H), 2.59–2.65 (m, 2 H), 2.81 (br s, 1 H), 4.18 (d, *J* = 5.8 Hz, 1 H), 7.41 (dt, *J* = 0.9, 2.7 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 26.0, 26.3, 26.6, 27.7, 29.4, 35.2, 42.5, 72.6, 146.4, 159.2, 210.1.

HR–ESI–MS: *m*/*z* $[M + H]^+$ calcd for $C_{12}H_{19}O_2$: 195.1385; found: 195.1381.

2-(1-Hydroxyfurylmethyl)-2-cyclopenten-1-one (12d)
Pale yellow oil.

IR (neat): 3396, 1694, 1253, 1070 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 2.45–2.51 (m, 2 H), 2.62–2.69 (m, 2 H), 3.48 (br s, 1 H), 5.58 (s, 1 H), 6.28 (d, *J* = 3.2 Hz, 1 H), 6.34 (dd, *J* = 1.9, 3.2 Hz, 1 H), 7.38 (br s, 1 H), 7.53 (dt, *J* = 1.1, 2.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.8, 35.1, 63.9, 107.3, 110.4, 142.5, 144.7, 153.7, 160.1, 209.2.

Anal. Calcd for $C_{10}H_{10}O_3$: C, 67.41; H, 5.66. Found: C, 67.25; H, 5.80.

References

(1) (a) Joseph, E.; Eiseman, J. L.; Hamilton, D. S.; Wang, H.; Tak, H.; Ding, Z.; Ganem, B.; Creighton, D. J. *J. Med. Chem.* **2003**, *46*, 194. (b) Banwell, M. G.; Crasto, C. F.; Easton, C. J.; Karoli, T.; March, D. R.; Nairn, M. R.; O'Hanlon, P. J.; Oldham, M. D.; Willis, A. C.; Yue, W. *Chem. Commun.* **2001**, 2210. (c) Kerr, W. J.; McLaughlin, M.; Pauson, P. L.; Robertson, S. M. *J. Organomet. Chem.* **2001**, *630*, 104. (d) Kabat, M. M.; Kiegiel, J.; Cohen, N.; Toth, K.; Wovkulich, P. M.; Uskokovic, M. R. *J. Org. Chem.* **1996**, *61*, 118. (e) Wexler, B. A.; Toder, B. H.; Minaskanian, G.; Smith, A. B. III *J. Org. Chem.* **1982**, *47*, 3333. (f) Smith, A. B. III; Branca, S. J.; Pilla, N. N.; Guaciaro, M. A. *J. Org. Chem.* **1982**, *47*, 1855. (g) Smith, A. B. III; Guaciaro, M. A.; Schow, S. R.; Wovkulich, P. M.; Toder, B. H.; Hall, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 219.

(2) (a) Guaciaro, M. A.; Wovkulich, P. M.; Smith, A. B. III *Tetrahedron Lett.* **1978**, 4661. (b) Smith, A. B. III; Branca, S. J.; Guaciaro, M. A.; Wovkulich, P. M.; Korn, A. *Org. Synth., Coll. Vol. VII*; Wiley: New York, **1990**, 271.
(3) (a) Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc.* **2004**, *126*, 4520. (b) Ito, H.; Konishi, M.; Iguchi, K. *Tetrahedron Lett.* **2004**, *45*, 1941. (c) Ito, H.; Kobayashi, T.; Hasegawa, M.; Iguchi, K. *Tetrahedron Lett.* **2003**, *44*, 1259.
(4) For reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811. (b) Rezgui, F.; Amri, H.; El Gaied, M. M. *Tetrahedron* **2003**, *59*, 1369. (c) Iwabuchi, Y.; Hatakeyama, S. *J. Synth. Org. Chem., Jpn.* **2002**, *60*, 2. (d) Langer, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3049. (e) Ciganek, E. *Org. React. (N.Y.)* **1997**, *51*, 201. (f) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001. (g) Drewes, S. E.; Roots, G. H. P. *Tetrahedron* **1988**, *44*, 4653.
(5) (a) Shi, M.; Chen, L.-H. *Chem. Commun.* **2003**, 1310. (b) Zanardi, F.; Appendino, G.; Casiraghi, G. *Chemtracts* **2002**, *15*, 490. (c) Frank, S. A.; Mergott, D. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 2404. (d) Leadbeater, N. E.; van der Pol, C. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2831. (e) Shi, M.; Jiang, J.-K.; Cui, S.-C.; Feng, Y.-S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390. (f) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4295. (g) Jenner, G. *Tetrahedron Lett.* **2000**, *41*, 3091. (h) Li, W.; Zhang, Z.; Xiao, D.; Zhang, X. *J. Org. Chem.* **2000**, *65*, 3489. (i) Yamada, Y. M. A.; Ikegami, S. *Tetrahedron Lett.* **2000**, *41*, 2165. (j) Hayase, T.; Shibata, T.; Soai, K.; Wakatsuki, Y. *Chem. Commun.* **1998**, 1271. (k) Morita, K.; Suzuki, Z.; Hirose, H. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2815.
(6) (a) Luo, S.; Zhang, B.; He, J.; Janczuk, A.; Wang, P. G.; Cheng, J.-P. *Tetrahedron Lett.* **2002**, *43*, 7369. (b) Gatri, R.; El Gaied, M. M. *Tetrahedron Lett.* **2002**, *43*, 7835. (c) Lee, K.-Y.; GowriSankar, S.; Kim, J.-N. *Tetrahedron Lett.* **2004**, *45*, 5485. (d) Sugahara, T.; Ogasawara, K. *Synlett* **1999**, 419; see also references 1b and 1d.
(7) (a) Rezgui, F.; El Gaied, M. M. *Tetrahedron Lett.* **1998**, *39*, 5965. (b) Aggarwal, V. K.; Dean, D. K.; Mereu, A.; Williams, R. *J. Org. Chem.* **2002**, *67*, 510. (c) Yadav, V. K.; Senthil, G.; Babu, G.; Parvez, M.; Reid, J. L. *J. Org. Chem.* **2002**, *67*, 1109; see also references 6b and 6c.
(8) Chong, B.-D.; Ji, Y.-I.; Oh, S.-S.; Yang, J.-D.; Baik, W.; Koo, S. *J. Org. Chem.* **1997**, *62*, 9323.