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BF_3·OEt_2-Mediated Ring Opening of Oxetanes with Ylides Derived from the Phosphoniosilylation Products of Enones

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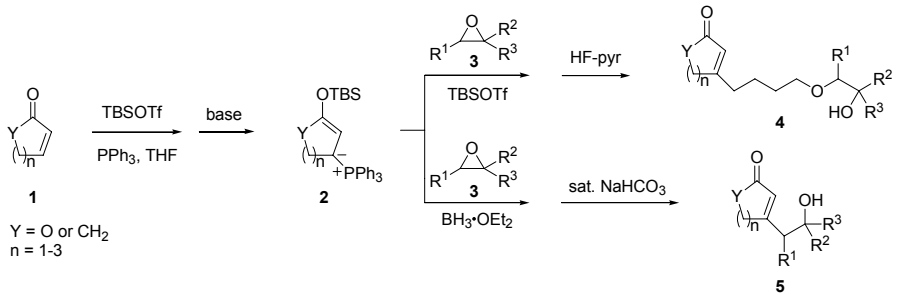
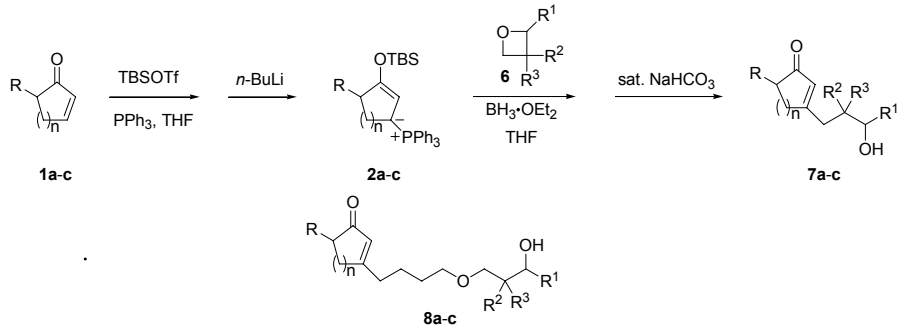
β-Functionalization of α,β-unsaturated carbonyl compounds has been very important topic in synthetic organic chemistry. Among the various methods for effecting β-functionalization of α,β-unsaturated carbonyl compounds we have been interested in the dipole reversal process utilizing the phosphoniosilylation reaction of α,β-unsaturated carbonyl compounds with triphenylphosphine (Ph_3P) and *tert*-butyldimethylsilyl triflate (TBSOTf).[1-4] As a part of research programs exploring the scope and application of this process, we have recently studied the ring-opening reactions of epoxides with ylides **2** obtained from the phosphoniosilylation products of α,β-unsaturated carbonyl compounds (Scheme 1).[5] In the studies we have found that ring-opening reactions of epoxides with ylides **2** in THF proceed in two different pathways depending on the identity of a Lewis acid added as a reaction promoter. While the reaction in the presence of TBSOTf as a Lewis acid yielded three-component coupling products **4** exclusively,[5a] ring-opening products **5** were obtained predominantly with the use of BF_3·OEt_2.[5b] Although less prevalent than the nucleophilic ring-opening of epoxides, the equivalent reaction of oxetanes has also exhibited broad versatility in organic synthesis.[6] Thus, we became interested in investigating the ring-opening reaction of oxetanes with ylides **2** (Scheme 2). Herein, we wish to report the results in these studies.

At the outset, we planned to acquire ring-opening products **7** rather than three-component coupling products **8** (Scheme 2), since compounds **7** are usually more useful than **8** from a synthetic point of view. Upon scrutinizing the results from the ring-opening reactions of epoxides with ylides **2** (*vide supra*)[5b] and examples of nucleophilic ring-opening reactions of oxetanes,[6a-c] we considered BF_3·OEt_2 as a suitable Lewis acid to facilitate the oxetane-ring opening process for the purpose. And although



Scheme 1



For **1-2** & **7-8**, **a**: n = 1, R = H; **b**: n = 2, R = H; **c**: n = 2, R = CH_2Ph

For **6-8**, **p**: R^1=R^2=R^3= H; **q**: R^1= $(CH_2)_7CH_3$, R^2=R^3= H; **r**: R^1= CH_2CH_2Ph, R^2=R^3= H; **s**: R^1= H, R^2=R^3= CH_3.

Scheme 2

less reactive than epoxides, oxetanes were envisaged to undergo the desired ring-opening reaction under the similar reaction conditions to those in the $BF_3{\cdot}OEt_2$-assisted ring-opening of epoxides with **2**. Thus, we began to examine $BF_3{\cdot}OEt_2$-promoted ring-opening reactions of oxetanes using ylide **2b** derived *in situ* from 2-cyclohexen-1-one **1b** and trimethylene oxide **6p** as model substrates. When the ylide **2b** was reacted with the model oxetane **6p** in the presence of $BF_3{\cdot}OEt_2$ in THF at −78 °C, and the resulting reaction mixture was then treated with saturated aqueous $NaHCO_3$ solution at −78 °C to rt in the same reaction vessel, an oxetane ring-opening product **7bp** was obtained in high 88% yield.

Encouraged by the success of the ring-opening of an oxetane **6p** with the ylide **2b**, the procedure was employed to various oxetanes and ylides (Scheme 2). The whole process involves four steps: (1) phosphoniosilylation of enones **1a-c** with Ph_3P and TBSOTf, (2) ylide formation with *n*-BuLi, (3) oxetane ring-opening reaction in the presence of $BF_3{\cdot}OEt_2$ and (4) desilylative elimination of Ph_3P. However, since this four-step sequence is carried out in the single reaction vessel, the resulting β-(3-hydroxy)alkylated products of enones can be obtained in very efficient and practical sense. The selected results are shown in Table 1 and demonstrate the efficacy and applicability of the process. This process works well in cyclopentenone and cyclohexenone series such as **1a-c**. With trimethylene oxide **6p** (entries 1, 4, and 7), the alcohols **7a-c** were obtained in good to high yields (78 - 88%). With oxetanes **6q**[7] and **6r**[7] possessing an alkyl substituent at the 2-position of oxetanes (entries 2, 3, 5, 6, 8, and 9), the alcohols **7a-c** were obtained as exclusive products in good yields (66 - 82%). The results indicate that the ring-opening reactions of oxetanes **6q** and **6r** with ylides **2** in the presence of $BF_3{\cdot}OEt_2$ also proceed with high regioselectivities, similarly to the previously reported ring-opening reactions of epoxides **3** with the ylides **2** in the presence of $BF_3{\cdot}OEt_2$.[5b] 3,3-Dimethyloxetane **6s** was also subjected to the reaction sequence. However, the results attending this procedure were disappointing. No significant amounts of products were obtained. These results can be understood, considering the reacting center of 3,3-dimethyloxetane **6s** to be neopentyl-like. Although the applicability of this process to acyclic enones was also tested, such efforts proved fruitless. Either no significant amounts or poor yields of products were obtained. Either lower reactivity of ylides or decomposition of oxetanes and ylides might be responsible for such unsuccessful outcomes in those cases.

Table 1. Oxetane ring-opening at the β-position of cyclic enones in the presence of $BF_3{\cdot}OEt_2$

Entry	Enone	Oxetane	Product	Yield(%)[a]
1	**1a**	**6p**	**7ap**	80
2	**1a**	**6q**	**7aq**	75
3	**1a**	**6r**	**7ar**	73
4	**1b**	**6p**	**7bp**	88
5	**1b**	**6q**	**7bq**	72
6	**1b**	**6r**	**7br**	82
7	**1c**	**6p**	**7cp**	78
8	**1c**	**6q**	**7cq**	68
9	**1c**	**6r**	**7cr**	66

[a]Overall isolated yields.

In summary, we have shown that ring-opening reactions of oxetanes with ylides, derived from the phosphoniosilylation products of cyclic enones, can be successfully executed by the use of $BF_3{\cdot}OEt_2$ as a Lewis acid. The whole four-step one pot process provides an efficient tool for the access of β-(3-hydroxy)-alkylation of cyclic enones.

Experimental Section

Preparation of 3-(3-hydroxypropyl)cyclohex-2-enone 7bp (General procedure). To a solution of triphenylphosphine (87 mg, 0.33 mmol) in tetrahydrofuran (1.5 mL) was added TBSOTf (76 μL, 0.33 mmol) and 2-cyclohexen-1-one (29 μL, 0.30 mmol). After being stirred at room temperature for 1.5 h, the reaction mixture was cooled to −78 °C and *n*-butyllithium (267 μL, 1.46 M in hexanes, 0.39 mmol) was added dropwise to give a dark brown-colored solution. After the mixture being stirred for 1 h, trimethylene oxide (29 μL, 0.45 mmol) and $BF_3{\cdot}OEt_2$ (57 μL, 0.45 mmol) was added dropwise. The reaction mixture was stirred for 1 h and saturated $NaHCO_3$ solution was added. After being warmed to room temperature, the reaction mixture was stirred for 1 h. The usual extractive work-up and flash column chromatography (hexane:$CHCl_3$:EtOAc = 1:1:4) gave **7bp** (40 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (s, 1H), 3.80-3.74 (m, 2H), 3.63-3.61 (t, J = 6.0 Hz, 2H), 2.40-2.38 (m, 2H), 2.32-2.28 (m, 2H), 2.26-2.24 (m, 2H), 1.96-1.93 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.2, 125.9, 85.1, 67.5, 53.1, 40.9, 36.8, 36.0, 25.8, 22.0. IR (film) 3457, 2946, 2877, 1700, 1650, 1606, 1454, 1427, 1375, 1351, 1261, 1162, 1031, 966, 889, 755, 638 cm^{-1}. ESI MS (*m/z*) 155.1 $[M+1]^+$.

3-(3-Hydroxypropyl)cyclopent-2-enone (7ap, entry 1): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 3.74-3.72 (t, J = 6.5 Hz, 2H), 2.63-2.61 (m, 2H), 2.53-2.52 (m, 2H), 2.44-2.43 (m, 2H), 1.90-1.89 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.6, 182.2, 129.7, 62.2, 35.5, 31.9, 30.1, 26.0. IR (film) 3415, 2939, 2881, 1700, 1668, 1608, 1436, 1405, 1340, 1268, 1240, 1191, 1058, 919, 844, 723 cm^{-1}. ESI MS (*m/z*) 141.1 $[M+1]^+$.

3-(3-Hydroxyundecyl)cyclopent-2-enone (7aq, entry 2): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (s, 1H), 3.68-3.64 (br, 1H), 2.62-2.61 (m, 2H), 2.52-2.48 (m, 2H), 2.44-2.42 (m, 2H), 1.80-1.74 (m, 1H), 1.71-1.64 (m, 1H), 1.31-1.26 (br, 14H), 0.91-0.88 (t, J = 6.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.4, 183.1, 129.6, 71.6, 38.0, 35.6, 34.8, 33.3, 32.1, 31.2, 30.0, 29.8, 29.5, 25.9, 22.9, 14.4. IR (KBr) 3401, 2927, 2858, 1700, 1670, 1612, 1463, 1434, 1405, 1340, 1276, 1191, 1083, 1027, 939, 894, 846, 721, 617, 539, 493 cm^{-1}. ESI MS (*m/z*) 253.2 $[M+1]^+$.

3-(3-Hydroxy-5-phenylpentyl)cyclopent-2-enone (7ar, entry 3): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.13 (m, 5H), 5.88 (s, 1H), 3.62-3.60 (br, 1H), 2.74-2.72 (m, 2H), 2.65-2.63 (m, 2H), 2.53-2.51 (m, 2H), 2.43-2.39 (m, 2H), 2.35-2.33 (m, 2H), 1.78-1.72 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.3, 182.9, 141.9, 132.3, 129.7, 128.8, 126.3, 70.9, 39.4, 35.4, 34.9, 32.3, 31.9, 31.2, 30.0. IR (KBr) 3371, 3025, 2941, 2906, 1704, 1664, 1614, 1494, 1432, 1328, 1295, 1255, 1195, 1093, 912, 846, 773, 713, 636 cm^{-1}. ESI MS (*m/z*) 245.1 $[M+1]^+$.

3-(3-Hydroxyundecyl)cyclohex-2-enone (7bq, entry 5): ^{1}H

NMR (500 MHz, $CDCl_3$) δ 5.90 (s, 1H), 3.62-3.59 (br, 1H), 2.38-2.36 (t, J = 6.5 Hz, 2H), 2.33-2.30 (t, J = 6.0 Hz, 2H), 2.01-1.98 (m, 2H), 1.69-1.58 (m, 2H), 1.47-1.45 (m, 2H), 1.34-1.24 (br, 14H), 0.90-0.87 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.2, 166.7, 125.8, 71.6, 37.9, 37.6, 34.6, 34.5, 32.1, 31.2, 30.1, 29.9, 29.8, 29.5, 25.9, 22.9, 14.4. IR (KBr) 3438, 2927, 2856, 1654, 1623, 1457, 1421, 1375, 1344, 1322, 1257, 1191, 1081, 964, 902, 885, 757, 719 cm^{-1}. ESI MS (*m/z*) 267.2 $[M+1]^+$.

3-(3-Hydroxy-5-phenylpentyl)cyclohex-2-enone (7br, entry 6): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.20 (m, 5H), 5.89 (s, 1H), 3.65 (br, 1H), 2.80-2.72 (m, 2H), 2.71-2.69 (m, 2H), 2.38-2.35 (m, 2H), 2.28-2.20 (m, 2H), 1.98-1.96 (m, 2H), 1.81-1.79 (m, 2H), 1.71-1.68 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 166.5, 141.9, 128.8, 128.6, 126.2, 125.9, 70.9, 39.4, 37.6, 34.8, 34.4, 32.3, 30.1, 22.9. IR (film) 3425, 3023, 2939, 2861, 1654, 1619, 1602, 1494, 1452, 1425, 1371, 1348, 1324, 1253, 1191, 1130, 1079, 964, 889, 754, 698, 663 cm^{-1}. ESI MS (*m/z*) 259.1 $[M+1]^+$.

6-Benzyl-3-(3-hydroxypropyl)cyclohex-2-enone (7cp, entry 7): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 5.93 (s, 1H), 3.71-3.68 (t, J = 6.5 Hz, 2H), 3.40-3.35 (dd, J_2 = 13.5 Hz, J_1 = 5 Hz, 1H), 2.51-2.47 (m, 2H), 2.31-2.28 (m, 2H), 1.98-1.95 (m, 2H), 1.80-1.75 (m, 2H), 1.64-1.62 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.4, 162.6, 137.8, 126.9, 126.0, 123.8, 123.0, 59.8, 45.4, 33.1, 31.7, 27.5, 26.9, 24.7. IR (film) 3415, 3025, 2937, 2863, 1654, 1602, 1492, 1448, 1419, 1351, 1268, 1214, 1051, 925, 887, 744, 703 cm^{-1}. ESI MS (*m/z*) 245.1 $[M+1]^+$.

6-Benzyl-3-(3-hydroxyundecyl)cyclohex-2-enone (7cq, entry 8): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.11 (m, 5H), 5.85 (s, 1H), 3.56-3.54 (br, 1H), 3.33-3.27 (dd, J_2 = 14.0 Hz, J_1 = 5.0 Hz, 1H), 2.42-2.40 (m, 2H), 2.32-2.29 (m, 2H), 2.21-2.20 (m, 2H), 1.91-1.83 (m, 2H), 1.60-1.53 (m, 2H), 1.26-1.19 (br, 14H), 0.83-0.80 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.0, 165.7, 140.4, 129.5, 128.6, 126.3, 125.5, 71.6, 47.9, 37.9, 35.6, 34.7, 34.2, 34.1, 32.1, 29.9, 29.8, 29.5, 27.3, 25.9, 22.9, 14.4. IR (KBr) 3425, 3023, 2923, 1654, 1454, 1419, 1357, 1328, 1297, 1270, 1211, 1180, 1087, 1027, 892, 732, 698, 528, 505 cm^{-1}. ESI MS (*m/z*) 357.2 $[M+1]^+$.

6-Benzyl-3-(3-hydroxy-5-phenylpentyl)cyclohex-2-enone (7cr, entry 9): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23-7.10 (m, 10H), 5.83 (s, 1H), 3.56 (br, 1H), 3.30-3.26 (dd, J_2 = 14.0 Hz, J_1 = 5.0 Hz, 1H), 2.72-2.69 (m, 1H), 2.64-2.61 (m, 1H), 2.42-2.38 (m, 2H), 2.21-2.16 (m, 2H), 1.88-1.86 (m, 2H), 1.74-1.71 (m, 2H), 1.61-1.58 (m, 2H), 1.20-1.18 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.9, 165.5, 141.9, 129.5, 128.8, 128.6, 126.3, 126.2, 125.5, 70.9, 47.9, 39.4, 35.6, 34.8, 32.3, 29.5, 27.3, 21.3. IR (KBr) 3493, 3029, 2919, 2861, 1645, 1627, 1494, 1452, 1394, 1365, 1270, 1213, 1180, 1147, 1093, 1049, 904, 736, 694, 509 cm^{-1}. ESI MS (*m/z*) 349.2 $[M+1]^+$.

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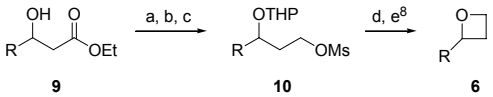
7. Oxetanes **6q** and **6r** were prepared as follows:



9 **10** **6**

For **9**, **10**, **6**, **q**: R = C_8H_{17}; **r** = CH_2CH_2Ph

Reagents: (a) DHP, PPTS(cat.), CH_2Cl_2, rt (b) DIBAL-H, CH_2Cl_2, 0 °C (c) MsCl, Et_3N, CH_2Cl_2, 0 °C, for **10q**, 57%; for **10r**, 49% (d) MeOH, TsOH(cat.), rt (e) KO^{t}Bu, THF, 50 °C, for **6q** & **6r**, 68%.

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