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Mukaiyama Aldol Reaction of 1, 2-Bis(trimethylsiloxy) Cyclobutene Catalyzed by Magnesium(II) Iodide

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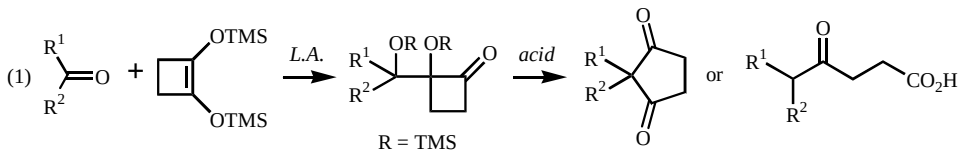
Abstract: Efficient Mukaiyama-type aldol reaction of 1, 2-bis(trimethylsiloxy)cyclobutene with aromatic aldehydes catalyzed by MgI_2 is reported. The resulting succinoylation product of aldehyde was converted into the synthetic useful γ-lactone and butenolide derivatives.

Keywords: Mukaiyama aldol reaction, 1, 2-bis(trimethylsiloxy)cyclobutene, magnesium iodide.

The unique reactivity of 1, 2-bis(trimethylsiloxy)cyclobutene (BTCB) towards carbonyl substrate or its acetal equivalent under Lewis acid catalysis was first recognized by Kuwajima and Nakamura in 1977[1]. The reaction generally led to the *geminal acylation* or *reductive succinoylation* of carbonyl substrate *via* the acid-catalyzed pinacol-type rearrangement (acyl migration) of the Mukaiyama aldol adduct as illustrated in **Eq. 1**[2].



Further development of this reaction has been carried out extensively by Burnell and his co-workers[3]. The usefulness of this method has been demonstrated in a number of natural product syntheses[4]. Strong Lewis acids, such as $TiCl_4$, $SnCl_4$ and BF_3 etherate, have been usually employed[2] to promote the initial Mukaiyama-type aldol addition. For example, large excess BF_3 etherate was used frequently as the (Lewis) acidic catalyst for the aldol coupling as well as for the subsequent rearrangement in improved one-pot procedure[3]. In connection with our exploration on the reaction catalyzed by *Lewis acidic* magnesium (II) in selective carbon–carbon bond forming reactions[5], we report herein a facile Mukaiyama-type aldol reaction of BTCB with aldehydes catalyzed by MgI_2.

As shown in **Scheme 1**, the aldol addition of BTCB with aromatic aldehyde **1** was

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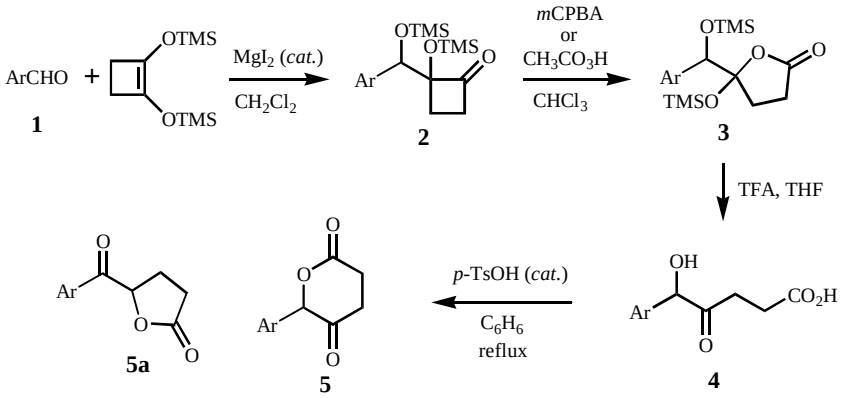
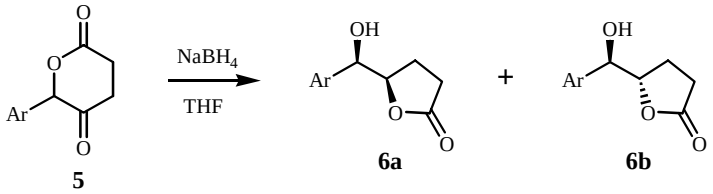
conducted in CH_2Cl_2 in the presence of catalytic amount (1–3 mol%) of freshly prepared[6] MgI_2 under ambient temperature over a period of hours. The bis(trimethylsiloxy) adduct **2** was usually obtained in high isolated yield (95–100%) as a mixture of diastereomers after usual aqueous workup and chromatography on silica gel[7]. Aromatic ketones and aliphatic aldehydes were unreactive in this reaction system even with the excess MgI_2 as catalyst. The use of $MgBr_2$ or $MgCl_2$ as reaction catalyst is much less effective. Substituted aldehyde **1** with electron-donating groups [*i.e.*, Ar = 2-(MeO)Ph, 4-(MeO)Ph, 3,4-(methylenedioxy)Ph] reacted much fast with BTCB than the aldehyde **1** with electron-withdrawing substituents [*i.e.*, Ar = 2-(Cl)Ph, 2-(CF_3)Ph, 4-(NO_2)Ph] catalyzed by MgI_2. This interesting catalytic reactivity is under further investigation in our laboratory. It is apparent that the carbonyl function of aromatic aldehyde was selectively activated through the coordination with the Lewis acidic magnesium (II) species, like $[MgI]^+$, although BTCB is one of the least reactive enol silane nucleophile.

Scheme 1



Baeyer–Villiger oxidation of cyclobutanone adduct **2** with *m*-CPBA or peracetic acid in $CHCl_3$ gave the corresponding lactone **3** in 75–80% isolated yield. Keto acid **4**, the succinoylation product of aldehyde **1**, was obtained quantitatively by acidic hydrolysis with 10% aqueous TFA in THF. Acid **4** was lactonalized in refluxing benzene in the presence of catalytic amount of *p*-TsOH to give the δ-lactone **5**[8] in 70–76 % yield.

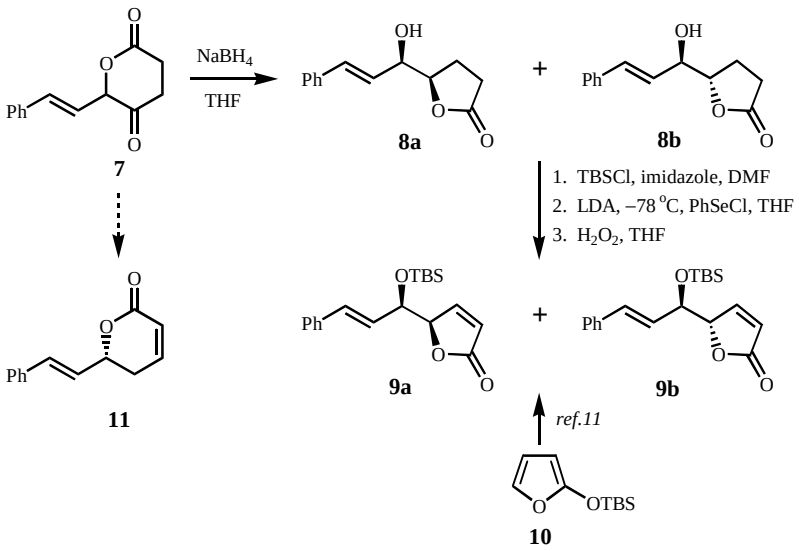
Scheme 2



Reduction of lactone **5** with $NaBH_4$ in THF afforded the rearranged diastereomeric γ-lactones **6a** and **6b**[9] quantitatively in a ratio of 88:12 which were readily separated by

flash chromatography on silica gel (**Scheme 2**). The structures of **6a** and **6b** were assigned[10] as *syn* (or *threo*) and *anti* (or *erythro*) respectively based on their characteristic IR and ^{1}H NMR spectroscopic data[9].

Scheme 3



Mukaiyama aldol adition of BTCB to *trans*-cinnamaldehyde catalyzed by 1 mol% of MgI_2 is equally effective to give the corresponding succinoylation product δ-lactone **7**[9] *via* an analogous synthetic sequence as described in **Scheme 1**, and diastereomeric γ-lactones **8a** and **8b**[9] were obtained in a ratio of 3:2 by $NaBH_4$ reduction. The *tert*-butyldimethylsiloxy ethers of γ-lactones **8a** and **8b** were converted to the corresponding butenolide derivatives **9a** and **9b**[9] respectively by standard method in 50−55% overall yield (**Scheme 3**). The butenolides **9a** and **9b** can be generated formally from the vinylogous Mukaiyama aldol reaction of aldehyde with cyclic siloxy diene **10** which have been studied extensively by Casiraghi and his co-workers[11]. Studies toward the synthesis of goniothalamin **11**[12], an antimicrobial natural product of the class of 5, 6-dihydro-2*H*-pyran-2-one, from styrenyl δ-lactone **7**, is underway.

In summary, a facile and selective Mukaiyama-type aldol addition of BTCB to aromatic or unsaturated aromatic aldehyde catalyzed by MgI_2 was developed. This process coupled with Baeyer−Villiger oxidation of the resultant cyclobutanone adduct provided a facile method for the succinoylation of aldehyde (to δ-lactone **5**) and an alternative access to butenolide derivatives of the vinylogous aldol adduct of siloxy diene **10**.

Acknowledgments

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References and Notes

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7. *Representative experimental procedure:* To a stirred solution of piperonal (5 mmol) in CH_2Cl_2 (8 mL) was added a stock solution of MgI_2 in 1:1 Et_2O/benzene (0.2 M/L, 0.5 mL) at 22ºC. After stirring for 10min, a solution of BTCB (6 mmol) in CH_2Cl_2 (5 mL) was introduced dropwise *via* a syringe under N_2. The resulting mixture was stirred at room temperature for 1.5 hr and quenched with saturated aqueous $NaHCO_3$. Extractive workup with ether and chromatographic purification of the crude product on silica gel gave the *bis*-TMS-silylated aldol adducts in 96% yield as a mixture of diastereomers.
8. The structure of δ-lactone **5** was ensured based on the following spectroscopic data and the isomeric γ-lactone **5a** was excluded. **5** [Ar = 3,4-(methylenedioxy)phenyl], IR(film) ν_{max} 1757, 1736, 1491, 1250 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.75–2.95 (m, 4H), 5.59 (s, 1H), 5.99 (s, 2H), 6.82 (br s, 3H, ArH) *ppm*; EIMS *m/z* 234 (M^+, 38), 206 (50), 151 (100).
9. Spectral data [Ar = 3,4-(methylenedioxy)phenyl]: **6a** (88%, *syn or threo*), IR (film) ν_{max} 3400, 1768, 1600, 1492, 1443, 1033 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90–2.10 (m, 2H), 2.48 (dd, 2H, *J* = 9.0, 7.8 Hz), 2.90 (br, OH), 4.50–4.65 (m, 2H), 5.96 (s, 2H), 6.75–6.95 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.8, 147.9, 147.8, 132.3, 120.6, 108.3, 107.2, 101.2, 83.5, 60.4, 28.4, 24.0 *ppm*; EIMS *m/z* 236 (M^+, 28), 151 (100); **6b** (12%, *anti or erythro*) IR ν_{max} 3406, 1768, 1608, 1492, 1443, 1037 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90–2.60 (m, 4H), 4.64 (ddd, 1H, *J* = 7.6, 6.4, 3.4 Hz), 5.01 (br t, 1H, *J* = 6.6 Hz), 5.97 (s, 2H), 6.80–6.90 (m, 3H); **7**, IR ν_{max} 1759, 1737(s), 1605, 1260, 1164 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.83 (t, 2H, *J* = 6.8 Hz), 2.95 (t, 2H, *J* = 7.2 Hz), 5.36 (dd, 1H, *J* = 4.8, 1.6 Hz), 6.25 (dd, 1H, *J* = 16, 4.8 hz), 6.75 (dd, 1H, *J* = 16, 1.6 Hz), 7.25–7.50 (m, 5H); EIMS *m/z* 216 (M^+, 8), 188 (9), 160 (13), 131 (100); HRMS(ESI) calcd for $C_{13}H_{13}O_3$ 217.0859, found for [M+1] 217.0852; **8a** (60%, *syn or threo*) IR ν_{max} 3409 (br s), 1767(s), 1188, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.15–2.35 (m, 2H), 2.50–2.70 (m, 2H), 4.33 (br t, 1H, *J* = 6.2 Hz), 4.57 (m, 1H), 6.24 (dd, 1H, *J* = 16, 6.8 Hz), 6.74 (d, 1H, *J* = 16 Hz), 7.20–7.40 (m, 5H); EIMS *m/z* 218 (M^+, 2), 200 (1), 133 (100); HRMS(FAB) calcd for $C_{13}H_{14}O_3Na$ 241.0835, found for [M+Na] 241.0834; **8b** (40%, *anti or erythro*) IR ν_{max} 3423 (br s), 1766(s), 1189, 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.15–2.20 (m, 1H), 2.25–2.35 (m, 1H), 2.45–2.55 (m, 1H), 2.60–2.70 (m, 1H), 2.98 (br, OH), 4.55–4.70 (m, 2H), 6.13 (dd, 1H, *J* = 16, 5.6 Hz), 6.76 (d, 1H, *J* = 16 Hz), 7.20–7.45 (m, 5H); HRMS(FAB) calcd for $C_{13}H_{14}O_3Na$ 241.0835, found for [M+Na] 241.0829; **9a** (*syn or threo*) IR ν_{max} 1778, 1758(s), 1600, 1468, 1256 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.11 (s, 3H), 0.92 (s, 9H), 4.57 (br t, 1H, *J* = 5.8 Hz), 5.05 (m, 1H), 6.03 (dd, 1H, *J* = 16, 6.3 Hz), 6.16 (dd, 1H, *J* = 5.8, 1.8 Hz), 6.61 (d, 1H, *J* = 16 Hz), 7.20–7.40 (m, 5H), 7.50 (dd, 1H, *J* = 5.8, 1.4 Hz); EIMS *m/z* 315 (M–15), 273, 247, 113; **9b** (*anti or erythro*) IR ν_{max} 1789, 1758(s), 1602, 1468, 1264 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 4.61 (m, 1H), 5.00 (m, 1H), 6.19 (dd, 1H, *J* = 5.8, 1.8 Hz), 6.22 (dd, 1H, *J* = 16, 5.6 Hz), 6.71 (d, 1H, *J* = 16 Hz), 7.15–7.45 (m, 5H), 7.49 (dd, 1H, *J* = 5.8, 1.6 Hz); EIMS *m/z* 315 (M–15).
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