Efficient One-Step Aldol-Type Reaction of Ketones with Acetals and Ketals Mediated by Dibutylboron Triflate/ Diisopropylethyl Amine

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ABSTRACT



A highly efficient one-step Mukaiyama aldol-type reaction has been developed for the synthesis of β -alkoxy carbonyl compounds starting from ketones and acetals/ketals. The reaction is mediated by a combination of Bu₂BOTf and *i*-Pr₂NEt affording the products in high yields. Formation of the two possible diastereoisomers of the β -alkoxy ketones from the chiral acetals shows that the condensation takes place by an S_N1 mechanism, involving prior opening of the acetal to an oxonium ion.

Mukaiyama aldol-type reaction of a silyl enol ether with an acetal or ketal providing the corresponding β -alkoxy carbonyl compound¹ has been a subject of extensive investigations.^{2,3} The reaction requires the preformation of silyl enol ether from corresponding carbonyl compounds, which then undergoes a Lewis acid-catalyzed coupling to the acetal or ketal in a separate step (eq 1). In a modified process, both the enol ether formation and the subsequent addition to an acetal or ketal have also been realized in a single-step (eq 2).⁴ In this communication, we describe a new single-step method using dibutylboron triflate/diisopropylethylamine (Bu₂BOTf/*i*-Pr₂NEt) for the Mukaiyama aldol-type reaction between ketones and acetals (or ketals).

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Recently, we have described the Bu₂BOTf/*i*-Pr₂NEtmediated intramolecular cyclization of keto-acetal compounds to afford the cyclic ethers in a single step (eq 3).⁵ In this process, the dibutylboron enolate of ketone reacted with the resident acetal, which was activated by Bu₂BOTf. To check the feasibility of this one-step process for the analogous

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^{(2) (}a) Murata, S.; Suzuki, M.; Noyori, R. *J. Am. Chem. Soc.* **1980**, *102*, 3248–3249. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899–3910. (c) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259–4275.

intermolecular coupling reaction (eq 2, $M = BBu_2$), initially, we examined the condensation of acetone (1a) and hexanone (1f) with acetal 2c, using a procedure similar to that used in the intramolecular reaction (procedure A).⁶ Fortunately, the reaction proceeded smoothly to afford the desired products, 3a, as its semiketal form, and 3b in 44 and 58% yields, respectively (Scheme 1). Compound 3b was obtained as a



^{*a*} Key: (a) **1a** (or **1f**), **2c**, *i*-Pr₂NEt, CH₂Cl₂, -78 °C, then Bu₂BOTf (procedure A); (b) **1f**, *i*-Pr₂NEt, CH₂Cl₂, -78 °C, Bu₂BOTf, 0.5 h, then **2c** (procedure B).

separable mixture of *syn* and *anti* isomers (56:44). Interestingly, when other boron-Lewis acids such as BCl_3 , *c*-Hex₂BCl, or 9-BBNOTf⁷ were used, none of them provided the desired product. Next, we varied the reaction conditions, including the mode of addition of the substrates. In an

(4) For direct formation of silyl enol ether, see: Kobayashi, S.; Nishio, K. J. Org. Chem. 1993, 58, 2647–2649. For direct generation of Titanium enolates, see: (a) Keck, G. E.; Wager, C. A.; Wager, T. T.; Savin, K. A.; Covel, J. A.; McLaw, M. D.; Krishnamurthy, D.; Cee, V. J. Angew. Chem., Int. Ed. 2001, 40, 231–234. (b) Cosp, A.; Romea, P.; Talavera, P.; Urpi, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. Org. Lett. 2001, 3, 615–617. (c) Cosp, A.; Romea, P.; Urpi, F.; Vilarrasa, J.; Font-Bardia, M.; Solans, X. Org. Lett. 2001, 3, 615–617. (c) Cosp, A.; Romea, P.; Urpi, F.; Vilarrasa, J. Tetrahedron Lett. 2001, 42, 4629–4631. (d) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. J. Am. Chem. Soc. 1990, 112, 8215–8216. For BF₃·OEt₂-mediated reaction, see: Hashigaki, K.; Yoshioka, S.; Yamato, M. Synthesis 1986, 1004–1007.

(5) For the Bu₂BOTf/*i*-Pr₂NEt-mediated intramolecular one-step aldoltype coupling of ketones with acetals and ketals, see: Das, S.; Li, L.-S.; Sinha, S. C. *Org. Lett.* **2004**, *6*, 123–126. optimized process (procedure B),⁸ we preformed the dibutyl boron-enolate of **1f** by treatment with Bu_2BOTf/i - Pr_2NEt at -78 °C for 30 min, to complete the enolization,⁹ and then a solution of acetal **2c** was added slowly. Using a workup procedure similar to procedure A led to a cleaner reaction, affording **3b** in 78% yield.

The scope of the reaction was explored using a series of ketones, acetals, and ketals. Condensation of various ketones, including acetophenone (1b), propiophenone (1c), 2-methvlbutanone (1d), cyclopentanone (1e), and cyclohexanone (1f), with acetals (2a-g) was examined using procedure B. In all cases, the desired β -alkoxy ketones were obtained in good yields (Table 1). The substituted cyclic acetal, 2b, underwent highly regioselective acetal opening to produce the β -alkoxy ketone (3d) with a primary alcohol (entry 2, Table 1). The isomeric secondary alcohol was not detected. The reaction slightly favored the formation of syn isomer (entries 8-13, Table 1). The highest syn selectivity was obtained when propiophenone was used as the ketone counterpart (entry 9, Table 1). We next investigated reactions of ketones (1b,c) with various ketals (4a-g) using procedure B, which also gave satisfactory results (Table 2). Functionalized ketals such as 4f and 4g also afforded the desired products with high yields.

To check the regioselectivity of this reaction with respect to ketone, two sets of experiments were conducted. In one experiment, 2-butanone (1g) and acetal 2e were used (Scheme 2A). The reaction of 1g with 2e (Scheme 2A) using Bu2BOTf/i-Pr2NEt in CH2Cl2 afforded the two regioisomeric compounds, 6 and 7, in a nearly 1.4:1 ratio. Whereas no change in regioselectivity of the reaction was noticed when the reaction was conducted in ether, a minor improvement in the stereoselectivity of *syn-7* over *anti-7* was realized. In another experiment (Scheme 2B), condensation of 1b with *n*-butyl THP ether was investigated, which predominantly gave the open chain product (8a, 73% yield) and a minor amount of tetrahydropyran derivative (8b, 7%). Use of 3-methyl-2-butanone, on the other hand, exclusively formed the open chain product (9a, 72% yield). Therefore, this method also provides an easy protocol to give 5-alkoxy-7keto-alkan-1-ols (such as 8a and 9a).

To extend the scope of the reaction, we briefly studied the Bu₂BOTf/*i*-Pr₂NEt-mediated coupling of ketone and esters with trialkyl ortho esters and acetals, respectively (Scheme 3). As shown, ketone **1c** reacted with triethyl orthoformate to afford the corresponding β -keto acetal, **11a**. However, under similar conditions, the reaction did not take

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⁽⁶⁾ **Procedure A.** To a solution of acetone (1 mmol) and acetal 2 (1 mmol) in 5 mL of CH_2Cl_2 at -78 °C was added *i*-Pr₂NEt (1 mmol), followed by a rapid addition of Bu₂BOTf (1.2 mmol). The resulting reaction mixture was stirred at -78 °C for 30 min, and then buffer (pH = 7.4, 1.2 mL), methanol (1.2 mL), and H₂O₂ (0.4 mL) were added. Stirring was continued for 1 h at room temperature, and then the mixture was worked up using ether. The organic layer was washed with aqueous NaHCO₃ and brine and dried over MgSO₄. Solvents were removed, and the crude product was purified by column chromatography on silica gel.

⁽⁷⁾ It has been reported that 9-BBNOTf could catalyze the aldol-type reaction between silyl enol ether and acetals. Ishihara, K.; Yamamoto, H.; Heathcock, C. H. *Tetrahedron Lett.* **1989**, *30*, 1825–1828.

⁽⁸⁾ **Procedure B.** Bu₂BOTf (1.0 M, 1.3 mL, 1.3 mmol) was added dropwise to a solution of ketone (1 mmol) and *i*-Pr₂NEt (0.2 mL, 1.15 mmol) in dry CH₂Cl₂ (5 mL) at -78 °C under argon. The resulting mixture was stirred for 30 min, and then a solution of an acetal (1 mmol) in dry CH₂Cl₂ (3 mL) was added slowly. Stirring was continued for 30 min, and then the reaction was quenched by addition of PBS buffer (1.3 mL), methanol (1.3 mL) and H₂O₂ (0.5 mL). The resulting mixture was warmed to room temperature and stirred for 1 hour, extracted with ether, washed with brine and dried over MgSO₄. The crude product was purified by chromatography on silica gel column.

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 Table 1.
 Bu₂BOTf/*i*-Pr₂NEt-Mediated Aldol-Type

 Condensation of Ketones with Acetals

R R	$Ph \rightarrow O \rightarrow R$	Ph─ OMe OMe
H 1 h: P - Ph P' - H	2a ∵n – 1 B – H	2e
1c: R = Ph, R = Me	2b : n = 1, R = Me	R', OEt
1d: R = Me ₂ CH, R ['] = Me	2 d : n = 3, R = H	R OEt
$10.11,11 = (012)_3^{-1}$		21. B - Ft B' - H

	···-=	
2g:	R = MeCC, R' = H	Н

entry	ketone	acetal/ ketal	major product/ number	yield (%) ^a (<i>syn:anti</i>) ^b
1	1b	2a	O Ph Ph O OH	72
2	1b	2b	Ph OH 3d	78
3	1b	2c	O Ph Ph O OH 3e	83
4	1b	2d	O Ph Ph O OH	82
5	1b	2e	O OMe Ph Ph 3g	88
6	1b	2f	Ph OEt 3h	90 ^c
7	1b	2g	O OEt Ph 3i	82
8	1c	2c	Ph Ph 3i	85 (4:1)
9	1c	2e	O OMe Ph Ph 3k	91° (6:1)
10	1d	2e	O OMe Y Ph 3I	89 (3:1)
11	1e	2c	O Ph O OH 3m	86 (2:1)
12	1f	2a	O H Ph O OH 3n	64 (14:11)
13	1f	2d		72 (2:1)

^{*a*} Isolated yield. ^{*b*} Ratio of *syn* and *anti* isomers was determined by ¹HNMR, and the relative configuration was determined by comparing the corresponding NMR data with the literature. ^{*c*} Performed with 1.2 mol of ketone.

 Table 2.
 Bu₂BOTf/*i*-Pr₂NEt-Mediated Aldol-Type

 Condensation between Ketones and Ketals



			(2/3 C	
entry	ketone	ketal	major product/ number	yield (%) ^a (<i>syn:anti</i>) ^b
1	1b	4b	Ph OMe 5a	94 ^c
2	1b	4c	Ph O 5b O OH	90
3	1b	4d	Ph OH 5c	80
4	1b	4e	Ph O OH	82
5	1c	4a	Ph OMe 5e	68
6	1c	4b	Ph OMe 5f	87
7	1c	4c	Ph O OH	90
8	1c	4b	O OMe 5h	76
9	1c	4f	O O OH Ph Cl 5i	48 (3.3:1)
10	1c	4g	O OMe Ph CO ₂ Et	84
11	1e	4b	O O O Me 5k	64

^{*a*} Isolated yield. ^{*b*} Ratio of *syn* and *anti* isomers was determined by ¹HNMR, and the relative configuration was determined by comparing the corresponding NMR data with the literature. ^{*c*} Performed with 1.2 mol of ketone.

place when triethyl orthoacetate was used. Esters such as methylpropionate (10), on the other hand, reacted efficiently with 2c and 4b to afford 12a and 12b, respectively.¹⁰

The Bu₂BOTf/*i*-Pr₂NEt-mediated intermolecular aldol-type reaction of a ketone with acetals ketals can be rationalized

⁽¹⁰⁾ Enolization was carried out at $-78\ ^{\rm o}{\rm C}$ for 2 h before the acetal or ketal was added.



as shown in Scheme 4A. Analogous to the TiCl₄-mediated reaction of silyl enol ether with acetal,¹¹ the reaction takes place via an S_N1 mechanism. Presumably, boron enolate (I) of a ketone reacts with the intermediate II that is generated by the Bu₂BOTf-catalyzed activation to afford the product. In the overall process, more than 1 equiv of Bu₂BOTf is required for both the enolization of a ketone and activation of an acetal or ketal. That the reaction takes place by the



 S_N1 mechanism, was evident from an examination of the reaction of **1b** with the chiral acetals, **2h**-**j**. The products obtained from these acetals were mixtures of both diastereomers of **3p**, **3q**, and **3r**, respectively (eqs 4 and 5). Since only primary alkoxy is the leaving group, only an S_N1 pathway could explain the formation of the diastereoisomeric mixtures of the products. The S_N2 pathway, on the other hand, would provide only one stereoisomer in each case.

In conclusion, we have developed a highly efficient onestep intermolecular aldol-type reaction of ketones and acetals or ketals using $Bu_2BOTf/i-Pr_2NEt$. Evidence has been provided to support the S_N1 -type mechanism for this onepot, operationally simpler method. Further development of this process to carry out the reaction in a highly stereoselective manner is in progress.

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Supporting Information Available: Typical experimental procedure and analytical data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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