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# PREPARATION AND REACTION OF NOVEL OXYGEN ESTER ENOLATES, 1, REACTION OF THIOGLYCOLATE WITH ALDEHYDES USING DIALKYLBORYL TRIFLATE

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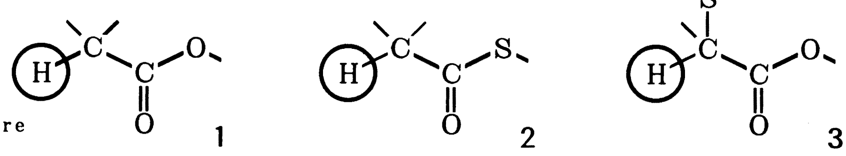
With the assistance of the electron withdrawing effect of divalent sulfur substituent, boron ester enolates were formed from the corresponding oxygen esters in the presence of dialkylboryl trifluoromethanesulfonate. These novel oxygen ester enolates reacted smoothly with aldehydes to produce the usual *syn*-aldol products.

KEYWORDS——aldol condensation; oxygen ester enolate; boron enolate; sulfur substituent; dialkylboryl trifluoromethanesulfonate; α-proton; acidity; thioglycolate; diastereoselectivity

Boron enolate-mediated aldol condensation is one of the most promising reactions for the synthesis of various complex molecules, because of their convenience[1] and high stereoselectivity.[2] We have been interested in the synthetic potency of boron enolates, especially the boron enolates of oxygen ester. However, despite the expected utility, the preparation of boron enolates directly from the corresponding oxygen esters (1) has not been feasible.[3]

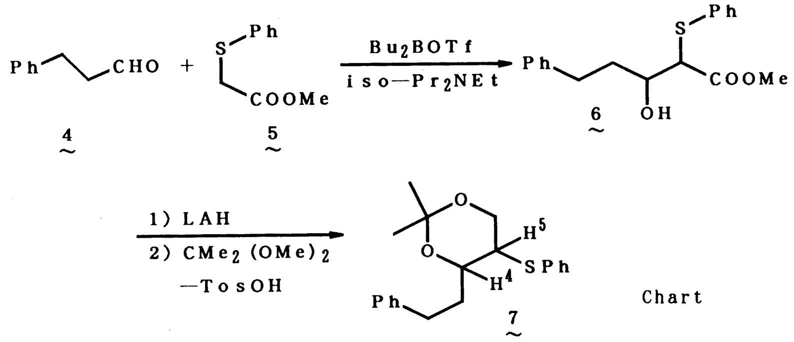
A likely reason for this problematic nature of oxygen esters is the insufficient acidity of their α-proton. For example, the pKa value of acetone is about 20, whereas that value of ethyl acetate is about 24.5.[5] On the other hand, the thiol esters (2) are in a typical class of compounds that can be converted to the corresponding enolates by dialkylboryl trifluoromethanesulfonate (triflate).[6] This chemical property has been interpreted in terms of the appreciable electron withdrawing effect of the alkylthio group.[7] By analogy, the resultant acidity of oxygen esters such as thioglycolate derivatives (3) was expected to be similar to the acidity of 2.[8]



Figure

First, we investigated the preparation of a boron ester enolate and its reaction with phenylpropiponaldehyde (4). Methyl phenylthioacetate (5) was converted into the boron enolate in diethyl ether solvent by its reaction with dibutylboryl triflate in the presence of diisopropylethylamine. The generation of the enolate was confirmed by the development of insoluble ammonium salt.

The enolate was allowed to react with 4 at -78°C. The subsequent usual work-up and purification by silica gel chromatography furnished the *syn*-aldol product (6) with high diastereomeric purity. This reaction may proceed *via* *(Z)*-enolate to produce the *syn* product. The relative stereochemistry of this product was determined *via* the corresponding 1,3-dioxane derivative (7) obtained by LAH reduction and treatment with 2,2-dimethoxypropane and p-toluenesulfonic acid.[9] A 270 MHz NMR spectrum showing a coupling constant between $H^4$ and $H^5$ indicated the 2,3-*syn* stereorelationship of 6.[10]

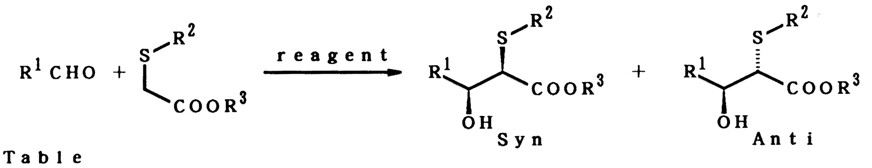


Chart

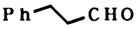
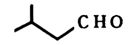
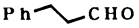
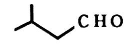
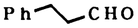
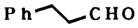
To survey the generality of this reaction, we examined the reactivity with several aldehydes. As shown in the table, most of substrates afforded aldol products with high diastereomeric purity and the yields were quite good. Even highly enolizable aldehyde (entries 3 and 4) also reacted fully satisfactorily. This supported the generation of boron enolate, and the aldol reaction progressed faster than the self condensation of these aldehydes. Mostly, the preferred formation was *syn*-isomer, in contrast to the lithium enolate-mediated reactions (entries 12, 13 and 14). Particularly, the best result was obtained in both yield and diastereoselectivity when dibutylboryl triflate was used. The use of dicyclopentylboryl triflate led to lower selectivity (entry 7) because of the steric effect of bulky cyclopentyl substitution. Furthermore, when *tert*-butyl ester was used as substrate, the ratio improved to 83:17 (entry 8). The poor stereoselectivity in experiments with aromatic (entries 9 and 11) and α,β-unsaturated (entry 10) aldehydes may be attributable to the epimerization of the products by the high acidity of their α-proton.

Conversion of the aldol product to a variety of useful compounds was also tried. The phenylthio group was easily reduced without any side reactions by treating them with tributyltin hydride and a catalytic amount of azoisobutyronitrile in benzene solvent at 80°C. Conversion to the 2,3-epoxypropionate is easily carried out in a straightforward manner by alkylyzing sulfide with methyl iodide and the subsequent treatment with silver tetrafluoroborate.[11] The corresponding *(Z)*-acrylic acid derivatives are also formed by the reaction with 1-ethyl-2-fluoropyridinium tetrafluoroborate and lithium iodide.[12]

Our method offers the possibility of applying dialkylboryl triflate to alkyl esters under much milder reaction conditions. We will report on the scope of the related reactions of these enolates and on their applications to the synthesis of various compounds.



Table

| Entry | $R^1CHO$ | $R^2$ | $R^3$ | Reagent[a)] | Yield[b)] | syn : anti[c)] |
|---|---|---|---|---|---|---|
| 1 |  | Ph | Me | $Bu_2BOTf$ | 87% | 96 : 4 |
| 2 |  | Ph | Me | $Bu_2BOTf$ | 89% | 95 : 5 |
| 3 |  | Ph | Me | $Bu_2BOTf$ | 86% | 94 : 6 |
| 4 | $CH_3CHO$ | Ph | Me | $Bu_2BOTf$ | 74% | 96 : 4 |
| 5 |  | Ph | $Bu^t$ | $Bu_2BOTf$ | 90% | 86 : 14 |
| 6 |  | Ph | $Bu^t$ | $Bu_2BOTf$ | 91% | 91 : 9 |
| 7 |  | Ph | Me | $Pen^c{}_2BOTf$ | 80% | 40 : 60 |
| 8 |  | Ph | $Bu^t$ | $Pen^c{}_2BOTf$ | 69% | 83 : 17 |
| 9 | PhCHO | Ph | Me | $Bu_2BOTf$ | 86% | 60 : 40 |
| 10 |  | Ph | Me | $Bu_2BOTf$ | 82% | 64 : 36 |
| 11 | PhCHO | $PhCH_2$ | Et | $Bu_2BOTf$ | 91% | 35 : 65 |
| 12 |  | Ph | Me | LDA | 81% | 32 : 68 |
| 13 |  | Ph | Me | LDA | 80% | 37 : 63 |
| 14 | PhCHO | $PhCH_2$ | Et | LDA | 87% | 33 : 67 |

a) Dialkylboryl triflate was used with diisopropylethylamine. Reactions using LDA were carried out in $Et_2O$ at -78°C.
b) The isolated yield is described, and all products gave satisfactory NMR, IR and MS data.
c) The ratio was determined by $^1H$ NMR spectra, and both isomers were isolated to confirm the minor isomer.

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10) The coupling constant between $H^4$ and $H^5$ of 7 was 3 Hz. Accordingly, it was concluded that 6 had a 2,3-*syn* stereorelationship according to the reported analogous compounds.[9)] The stereochemical integrity was established rigorously by converting the separated minor isomer into the corresponding 1,3-dioxane derivative. In this case, the coupling constant was 10 Hz and the 2,3-*anti* stereorelationship of the minor isomer was verified.
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