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# DUAL ROLES OF TRIMETHYLSILYL GROUP FOR SPECIFIC GENERATION OF ENOLATES FROM β-KETOALKYLTRIMETHYLSILANES. REGIOSPECIFIC PREPARATION OF TWO TYPES OF ACYCLIC ALDOLS

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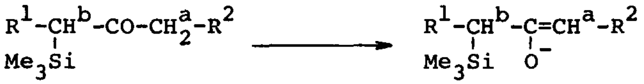
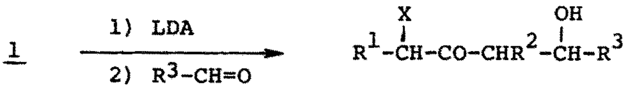
During a past decade, the aldol reaction is one of the most versatile tools for construction of carbon frameworks of organic molecules.[1] Especially, much attensions have recently been focussed on regiospecific preparation of directed aldols and various methods have been devised for generation of specific enolates.[2] Among a lot of precursors of the enolates reported hitherto, silyl enol ethers of ketones have most widely been employed for such purposes.[3] On application to certain synthetic purposes, however, methods using silyl enol ethers have sometimes been useless because the desired starting ethers can not always be prepared regiospecifically.[4]

Recently, we reported a simple synthetic method of β-ketoalkyltrimethylsilanes 1.[5,6] We wish to describe herein a new approach to the aldol synthesis, which involves selective generation of two types of enolates from the common starting material 1. In the first case, regiospecific generation of the enolate 2 was effected efficiently as shown in the following example. β-Ketoalkyltrimethylsilane 1 ($R^1 = C_6H_5CH_2$, $R^2 = H$) was treated with an equimolar amount of LDA at -78 °C for 1 min in THF, followed by quenching with appropriate aldehyde at -78 °C for 10--15 min. Through such a simple procedure, the corresponding aldol adduct 3b was isolated in good yield after acidic work up, without any contamination of the regio-isomer 4. If desired, the aldol could be isolated as the C-silylated one 3a; the C-silylated products 3a were usually stable under non-acidic circumstance and were obtained after work up with phosphate buffer (pH 7.0) followed by bulb to bulb distillation.



$$R^1\text{-}\underset{\mathrm{Me_3Si}}{\mathrm{CH}^b}\text{-CO-CH}_2^a\text{-}R^2 \longrightarrow R^1\text{-}\underset{\mathrm{Me_3Si}}{\mathrm{CH}^b}\text{-}\underset{\mathrm{O^-}}{\mathrm{C}}\text{=CH}^a\text{-}R^2$$

1 2



$$\underline{1} \xrightarrow[\text{2) } R^3\text{-CH=O}]{\text{1) LDA}} R^1\text{-}\overset{X}{\text{CH}}\text{-CO-CHR}^2\text{-}\overset{\text{OH}}{\text{CH}}\text{-}R^3$$

3a; X = $Me_3Si$
3b; X = H

Stereochemical outcome was also examined on the aldol adduct derived from the reaction of ethyl ketone 1 ($R^1 = C_6H_5CH_2$, $R^2 = CH_3$) with benzaldehyde; nmr analysis of the product exhibited a remarkable tendency to the formation of erythro isomer (erythro : threo = 70 : 30),[7] yet the selectivity was much less when compared with the systems of Heathcock et al.[8]

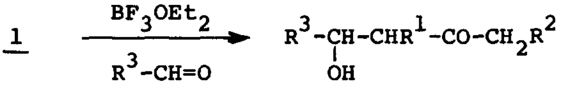
Table 1. Preparation of Aldol 3b.

| $R^1$ | $R^2$ | $R^3$ | 3b[a] Yield (%) |
|---|---|---|---|
| $C_6H_5CH_2$ | H | $C_6H_5$ | 82[b] |
| $C_6H_5CH_2$ | H | $C_8H_{17}$ | 78[b] |
| $C_6H_5CH_2$ | $CH_3$ | $C_6H_5$ | 95[c] |
| $CH_3$ | $CH_3$ | $C_6H_5$ | 95[c] |
| $CH_3$ | $CH_3$ | $C_5H_{11}$ | 78[c] |
| $CH_3CH_2$ | $CH_3$ | $C_6H_5$ | 87[c] |
| $CH_3CH_2$ | $CH_3$ | $C_5H_{11}$ | 72[c] (70[c, d]) |

[a] Absence of the regio-isomer was confirmed by nmr and glpc analysis of the product. [b] The reactions were performed under the conditions described in the text. [c] β-Ketoalkyltrimethylsilane 1 was treated with LDA at -50°C for 3--4 hr and was quenched with an aldehyde at the same temperature for 10 sec. [d] Yield of 3a. Isolated by bulb to bulb distillation (100--105°C/0.2 Torr).

Another utility of 1 as the synthetic intermediate exists in efficacy of the regiospecific preparation of an isomer 4. Thus, treatment of 1 with aldehydes in the presence of Lewis acid[9] (equimolar amount ) in methylene chloride at -78°C led to the formation of 4.

The specific formation of 4 mediated by Lewis acid may be explicable by assuming an intermediary formation of enolate coordinated to Lewis acid. Such types of species are recently regarded as advantageous enolates for the preparation of aldol products because of the stabilized intermediates formation.[9,10] Several Lewis acids were examined and the regiospecific formation of 4 was found to be achieved most effectively by employing $BF_3OEt_2$. A catalytic amount of tetrabutylammonium fluoride also effected such kind of aldol addition,[11] but usually gave less satisfactory results.



$$\underline{1}\ \xrightarrow[R^3\text{-CH=O}]{BF_3OEt_2}\ R^3\text{-}\underset{\text{OH}}{\text{CH}}\text{-CHR}^1\text{-CO-CH}_2R^2$$

4

The isolated product exhibited the complete inversion of the regiospecificity to the one achieved by use of LDA, and the yields lie in high degree.

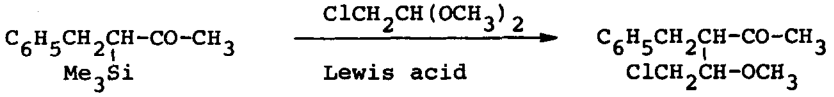
Similar tendency for the former mentioned one for threo-erythro selection was also observed in this case; the ratio of erythro to threo was 71 to 29 for the product derived from ethyl ketone 1 ($R^1 = CH_3CH_2$, $R^2 = CH_3$) with benzaldehyde.[12]

Table 2. Preparation of Aldol 4 Catalyzed by Lewis Acid

| $R^1$ | $R^2$ | $R^3$ | Lewis Acid | 4[a] Yield (%) |
|---|---|---|---|---|
| $C_6H_5CH_2$ | H | $C_6H_5$ | $TiCl_4$ | 71[b] |
| $C_6H_5CH_2$ | H | $C_6H_5$ | $SnCl_4$ | 81[b] |
| $C_6H_5CH_2$ | H | $C_6H_5$ | $BF_3OEt$ | 87[b] |
| $C_6H_5CH_2$ | H | $C_8H_{17}$ | $BF_3OEt_2$ | 78[b] |
| $C_6H_5CH_2$ | $CH_3$ | $C_6H_5$ | $BF_3OEt_2$ | 73[c] |
| $CH_3$ | $CH_3$ | $C_6H_5$ | $BF_3OEt_2$ | 78[c] |
| $CH_3$ | $CH_3$ | $C_5H_{11}$ | $BF_3OEt_2$ | 78[c] |
| $CH_3CH_2$ | $CH_3$ | $C_6H_5$ | $BF_3OEt_2$ | 81[c] |
| $CH_3CH_2$ | $CH_3$ | $C_5H_{11}$ | $BF_3OEt_2$ | 76[c] |

[a] Absence of the regio-isomer was confirmed by nmr and glpc analysis of the product. [b] The reactions were performed at -78 ∿ -50°C for 1.5 hr in the presence of Lewis acid in methylene chloride. [c] The reactions were performed at -50°C for 3--4 hr under the same conditions described above.

Diversed behavior of the acid catalyst was observed about the reaction with chloroacetaldehyde dimethylacetal under similar conditions. Among the Lewis acid examined, the effect of $SnCl_4$ and $TiCl_4$[13] notably outdoes that of $BF_3OEt_2$ which was most suitable one in the reaction with aldehydes.



$$C_6H_5CH_2\underset{Me_3Si}{\text{CH}}\text{-CO-CH}_3\ \xrightarrow[\text{Lewis acid}]{ClCH_2CH(OCH_3)_2}\ C_6H_5CH_2\underset{ClCH_2CH\text{-}OCH_3}{\text{CH}}\text{-CO-CH}_3$$

72% (with $SnCl_4$)
57% (with $TiCl_4$)
not detected (with $BF_3OEt_2$)

These results may indicate that the chemospecific reaction can be achieved simply by changing the reaction conditions, e.g. Lewis acid.

We are currently exploring ways of application of the feature of β-ketoalkyltrimethylsilanes to another types of carbon-carbon bond forming reactions.

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(11) On treatment of β-ketoalkyltrimethylsilane 1 ($R^1$ = $C_6H_5CH_2$, $R^2$ = H) with at -78∼-40°C in THF, the corresponding aldol 4 was obtained in 57% yield. For fluoride catalyzed aldol reactions of silyl enol ethers, see ref 3d and 8.

(12) Determined by an absorption due to the benzylic proton. $CCl_4$; δ 4.87, J = 5 Hz (erythro), δ 4.53, J = 9 Hz (threo).

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