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# The Reaction of *O*-Silylated Enolates of Carboxylic Esters and of Lactones with Aminomethyl Ethers Catalyzed by ZnCl$_2$

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**Synopsis.** It was found that the reaction of *O*-silylated enolates of carboxylic esters and of lactones with aminomethyl ethers proceeds smoothly under a catalytic action of zinc chloride to afford the corresponding *α*-aminomethylated carboxylic esters or lactones, except only one case using *O*-silylated enolate of *δ*-valerolactone, in which the resultant *α*-aminomethyl-*δ*-valerolactone is somewhat unstable and undergoes decomposition, leading to the production of *α*-methylene-*δ*-valerolactone.

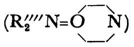
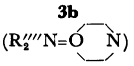
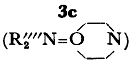
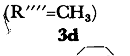
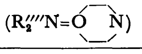
It is well known that Mannich salts and related compounds bearing a structural resemblance are excellent precursors of *α*-methylene carbonyl compounds.[1] In 1980 Miyano and his co-workers[1] were successful in preparing the Mannich salts of carbonyl compounds *via* *O*-silylated enolates of ketones and aldehydes by a combination of chloroiodomethane and *N,N,N′,N′*-tetramethyldiaminomethane. More recently, Hosomi and his co-workers[2] were successful in preparing the salts by the reaction of *O*-silylated enolates of ketones with aminomethyl ethers catalyzed by the use of iodotrimethylsilane or trimethylsilyl trifluoromethanesulfonate. Though these mthods are found superior in many instances to the earlier procedures, such as those using preformed moisture-sensitive iminium salts[3] with enol silyl ethers, they involve the utilization of relatively expensive and not easily available reagents. With these considerations in mind, we have studied the reaction of *O*-silylated enolates of saturated carboxylic esters (**1**) with aminomethyl ethers (**2**) in the presence of easily available zinc chloride. The reaction proceeds smoothly at room temperature in acetonitrile to afford the corresponding *α*-aminomethyl carboxylic esters (**3**) in moderate yields; these esters are not readily, if at all, obtainable by other procedures (Table 1).

The reaction may involve the initial loss of the alkoxyl group of **2** to give the aminomethyl cation and its subsequent (or simultaneous) attack on **1**, accompanied by the release of the trimethylsilyl group.

When this procedure was extended to *O*-silylated enolates of *δ*-valerolactone, *γ*-butyrolactone, and methyl 3-butenoate (**4**, **5**, and **6**), somewhat different results were observed (Table 2).

It was recognized that, in the reaction of **4** with **2**, the initially formed *α*-aminomethyl-*δ*-valerolactones are

Table 1. Reaction of *O*-silylated enolates of saturated carboxylic esters (**1**) with aminomethyl ethers (**2**)

| Silylated enolate | Amino ether[a)] | Product | Yield % [b)] | Bp $\theta_b$/°C (Torr)† | $^1$H-NMR(60 MHz, $\delta$, CDCl$_3$) | MS (40 eV) *m/e*(M$^+$) |
|---|---|---|---|---|---|---|
| **1a** | **2a** | **3a** (R$''''$=C$_2$H$_5$) | 52[c)] | 74—78 (5) | 0.8—1.4 (m, 12H), 1.3—1.8 (m, 2H), 2.3—2.8 (m, 7H), 4.13(t, 2H) | 201 |
| **1a** | **2b** | **3a** (R$''''$=CH$_3$) | 79 | 50—53 (6.5) | 0.91 (t, 3H), 1.25 (t, 3H), 1.3—1.8 m, 2H), 2.19 (s, 6H), 2.3—2.8 (m, 3H), 4.14 (q, 2H) | 173 |
| **1a** | **2c** | **3a**  (R$_2''''$N=O N) | 51 | 62—65 (2.5) | 0.89 (t, 3H), 1.25 (t, 3H), 1.3—1.8 (m, 2H), 2.1—2.7 (m, 7H), 3.60 (t, 4H), 4.13 (t, 2H) | 215 |
| **1b** | **2a** | **3b** (R$''''$=C$_2$H$_5$) | 51 | 84—86 (18.5) | 0.93 (t, 6H), 1.14s, 6H), 2.47 (q, 4H), 2.53 (s, 2H), 3.63 (s, 3H) | 187 |
| **1b** | **2b** | **3b** (R$''''$=CH$_3$) | 32 | 77—81 (19) | 1.21 (s, 6H), 2.28 (s, 6H), 2.50 (s, 2H), 3.70 (s, 3H) | 159 |
| **1b** | **2c** | **3b**  (R$_2''''$N=O N) | 64 | 84—88 (7) | 1.14 (s, 6H), 2.3—2.7 (m, 4H), 2.43 (s, 2H), 3.4—3.8 (m, 4H), 3.60 (s, 3H) | 201 |
| **1c** | **2a** | **3c** (R$''''$=C$_2$H$_5$) | 88 | 68—69 (6.5) | 0.93 (t,9H), 1.33 (s, 3H), 1.1—2.0 (m, 2H), 2.23 (d, 1H), 2.49 (q, 4H), 2.73 (d, 1H), 3.61 (s, 3H) | 201 |
| **1c** | **2b** | **3c** (R$''''$=CH$_3$) | 81 | 55—59 (7.5) | 0.80 (t, 3H), 1.16 (s, 3H), 1.2—1.8 (m, 2H), 2.20 (s, 6H), 2.25 (d, 1H), 2.62 (d, 1H), 3.64 (s, 3H) | 173 |
| **1c** | **2c** | **3c**  (R$_2''''$N=O N) | 82 | 67—68 (3) | 0.83 (t, 3H), 1.16 (s, 3H), 1.46 (q, 2H), 2.29 (d, 1H), 2.3—2.6 (m, 4H), 2.64 (d, 1H), 3.5—3.8 (m, 4H), 3.62 (s, 3H) | 215 |
| **1d** | **2a** | **3d** (R$''''$=C$_2$H$_5$) | 90 | 118—121 (6.5) | 0.91 (t, 6H), 0.7—1.8 (m, 8H), 1.8—2.3 (m, 2H), 2.43 (q, 4H), 2.48 (s, 2H), 3.63 (s, 3H) | 227 |
| **1d** | **2b** | **3d** (R$''''$=CH$_3$) | 63 | 131—133 (26) | 0.7—1.7 (m, 8H), 1.9—2.2 (m, 2H), 2.17 (s, 6H), 2.39 (s, 2H), 3.61 (s, 3H) | 199 |
| **1d** | **2c** | **3d**  (R$_2''''$N=O N) | 89 | 145—148 (6.5) | 0.9—1.8 (m, 8H), 1.8—2.2 (m, 2H), 2.3—2.6 (m, 2H), 2.44(s, 2H), 3.5—3.7 (m, 4H), 3.63 (s, 3H) | 241 |
| **1e** | **2a** | **3e** (R$''''$=C$_2$H$_5$) | 89 | 57—62 (3) | 0.92 (t, 6H), 1.4—1.9 (m, 6H), 1.9—2.2 (m, 2H), 2.47 (q, 4H), 2.60 (s, 2H), 3.62 (s, 3H) | 213 |
| **1e** | **2b** | **3e** (R$''''$=CH$_3$) | 62 | 35—36 (3) | 1.4—2.3 (m, 8H), 2.20 (s, 6H), 2.52 (s, 2H), 3.64 (s, 3H) | 185 |
| **1e** | **2c** | **3e**  (R$_2''''$N=O N) | 91 | 91—94 (4) | 1.4—2.0 (m, 6H), 2.0—2.3 (m, 2H), 2.3—2.7 (m, 4H), 2.55 (s, 2H), 3.6—3.8 (m, 4H) 3.64 (s, 3H) | 227 |

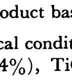
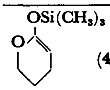
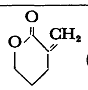
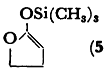
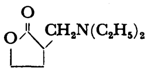
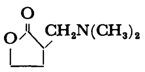
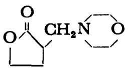
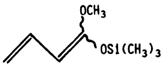
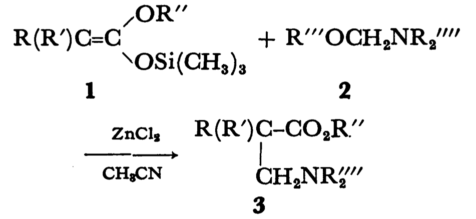
a) **2a**: *n*-C$_2$H$_9$OCH$_2$N(C$_2$H$_5$)$_2$, **2b**: *i*-C$_2$H$_9$OCH$_2$N(CH$_3$)$_2$, **2c**: C$_2$H$_5$OCH$_2$N  O b) Yield of the isolated product based on **1**. c) When the reaction of **1a** with **2a** was accomplished by the following combination of a catalyst and a solvent under otherwise identical conditions, **3a** (R$''''$=C$_2$H$_5$) was obtained in the yields shown in parentheses: ZnBr$_2$/CH$_3$CN (52%), BF$_3$·O(C$_2$H$_5$)$_2$/CH$_3$CN (43%), AlCl$_3$/CH$_3$CN (34%), TiCl$_2$/CH$_3$CN (26%), ZnCl$_2$/CH$_2$Cl$_2$ (43%), ZnCl$_2$/C$_6$H$_6$(45%), ZnC$_2$/(C$_2$H$_5$)$_2$O (36%). d) Yield in the reaction using the CH$_2$Cl$_2$ solvent. †1 Torr≈133.322 Pa.

Table 2. Reaction of $O$-silylated enolates of $\delta$-valerolactone, $\gamma$-butyrolactone, and methyl 3-butenoate (**4**, **5**, and **6**) with aminomethyl ethers (**2**)

| $O$-Silylated enolate | Aminomethyl ether | Product[b] | Yield %[c] | Bp $\theta_b$/°C (Torr) | MS(40 eV) $m/e$(M+) |
|---|---|---|---|---|---|
|  (**4**) | **2a** |  (**7**) | 64 | 76—77(6.5) [lit,[4] 56.5(0.07)] | 112 |
| **4** | **2b** | **7** | 31 | | |
| **4** | **2c** | **7** | 49 | | |
|  (**5**) | **2a** |  (**8a**) | 35 | 59—62(3) | 171 |
| **5** | **2b** |  (**8b**) | 40 | 54—57(2.5) [lit,[5] 72—73(0.05)] | 143 |
| | **c** |  (**8c**) | 60 | Mp 134—135 (Hexane) | 185 |
|  (**6**) | **2a** |  (**9a**)[d] | 55[e] | 49—50(3) | 185 |
| **6** | **2b** |  (**9b**)[d] | 31[e] | 50—51(4) | 157 |
| **6** | **2c** |  (**9c**)[d] | 34[e] | 76—77(2.5) | 199 |

a) The structures of the aminomethyl ethers (**2a**, **2b**, and **2c**) are shown in Table 1. b) The $^1$H-NMR spectra of these products (60 MHz, $\delta$, in $CDCl_3$) are as follows: **7**: 1.7—2.2(m, 2H), 2.5—2.8 (m, 2H), 4.36 (t, 2H), 5.4—5.7 (m, 1H), 6.2—6.5 (m, 1H). **8a**: 0.97 (t, 3H), 1.01 (t, 3H), 2.2—3.1 (m, 9H), 4.1—4.5 (m, 2H). **8b**: 2.09 (s, 6H), 2.0—2.5 (m, 5H), 4.0—4.4 (m, 2H). **8c**: 2.0—3.0 (m, 2H), 3.5—3.8 (m, 4H), 4.0—4.5 (m, 9H). **9a**: 1.01 (t, 6H), 2.2—2.7 (m, 8H), 3.68 (s, 3H), 5.83 (d, 1H), 6.96 (dt, 1H). **9b**: 2.20 (s, 6H), 2.1—2.5 (m, 4H), 3.64 (s, 3H), 5.82 (d, 1H), 6.6—7.1 (m, 1H). **9c**: 2.3—2.6 (m, 8H), 3.5—3.8 (m, 4H), 3.68 (s, 3H), 5.84 (d, 1H), 6.7—7.2 (m, 1H). c) Yield of isolated product based on **4**, **5**, or **6**. d) Presumably, **9a**, **9b**, and **9c** are *trans*-isomers. e) Yield in the reaction using the $CH_2Cl_2$ solvent.



$$\underset{\mathbf{1}}{R(R')C{=}C\begin{matrix}\diagup OR''\\ \diagdown OSi(CH_3)_3\end{matrix}} + \underset{\mathbf{2}}{R'''OCH_2NR_2''''} \xrightarrow[CH_3CN]{ZnCl_2} \underset{\mathbf{3}}{\begin{matrix}R(R')C{-}CO_2R''\\ |\\ CH_2NR_2''''\end{matrix}}$$

**a**: R=H, R′=R″=$C_2H_5$ **b**: R=R′=R″=$CH_3$
**c**: R=$C_2H_5$, R′=R″=$CH_3$ **d**: R(R′)=$-(CH_2)_5-$, R″=$CH_3$
**e**: R(R′)=$-(CH_2)_4-$, R″=$CH_3$

rather unstable under the present reaction conditions; therefore, they partially undergo decomposition, leading to the production of $\alpha$-methylene–$\delta$-valerolactone (**7**). The remaining $\alpha$-aminomethyl-$\delta$-valerolactones, unchanged during the reaction, were converted into **7** in the work-up procedure involving repeated distillation, which causes the thermal decomposition of the aminomethylated compounds (see Experimental section). In contrast, in the cases of **5**, $\alpha$-aminomethyl-$\gamma$-butyrolactone (**8a**, **8b**, and **8c**) were isolated, suggesting that the aminomethylated compounds are stable under the given reaction conditions, as well as during distillation under reduced pressure. The reaction of **6** with **2** proceeded smoothly to afford the products **9a**, **9b**, and **9c** resulting from the attack on the $\gamma$-position of **6**.

The general availability of $O$-silylated enolates[6] from carboxylic esters and from lactones, and of aminomethyl ethers from secondary amines, formaldehyde, and primary alcohols, along with the simple work-up procedures required for these reactions, indicates that this procedure may provide a useful method for the preparation of $\alpha$-aminomethylated carboxylic esters or lactones.

## Experimental

Into a solution of zinc chloride (1.36 g, 10 mmol) in dry acetonitrile (20 ml), we added with stirring a mixture of an $O$-silylated enolate (10 mmol) and an aminomethyl ether (10 mmol). The stirring was continued at room temperature for about 24 h under nitrogen. The resultant reaction mixture was poured into dilute aq $NaHCO_3$ and extracted with ether. The ethereal solution was extracted with 5% aq HCl, and the resultant aq layer was basified with 5% NaOH. The basified aq phase was extracted with ether, then dried over $MgSO_4$ and evaporated *in vacuo* to give a residue. The distillation of this residue yielded the product. In the reaction using **4** as the starting substrate, the following work-up procedure was adopted: the resultant reaction mixture was poured into dilute aq $Na_2CO_3$ and extracted with ether. The ethereal solution was dried over $MgSO_4$ and evaporated *in vacuo* to give a residue, which was repeatedly distilled under reduced pressure.

## References

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