REGIOCONTROLLED CONJUGATE ADDITION OF GERMANIUM-MASKED DIENOLATES TO MICHAEL ACCEPTORS

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Summary: The reaction of Ge-masked dienolates with Michael acceptors in the presence of Lewis acids produced the 1,4- γ adduct regioselectively, whereas the reaction in the presence of Bu₄NF gave the 1,4- α adduct exclusively.

The regioselective carbon-carbon bond formation at the γ -position of dienolates has been a long standing problem in organic synthesis, since dienolates derived from enoates undergo selective alkylation at the α -position under kinetic control in preference to the γ -position.¹ The regioselectivity of the reactions of the ambident nucleophiles with simple electrophiles such as aldehydes, ketones, and alkyl halides has been studied extensively, and the precise experimental conditions necessary for complete α - vs. γ -regioselection have been developed.¹ However, the regiocontrol of the reactions between the ambident nucleophiles and ambident electrophiles, such as allylic halides and α , β -unsaturated carbonyl compounds, has not been studied widely. In the latter case we encounter the potential difficulties associated with controlling the four fold regioselection in comparison with the twofold regioselection in the former case. For example, the reaction of dienolates with enones could give four possible adducts (eq 1). The coupling between cyclopentenone and the lithium dienolate of crotonates has given



regioselectively a $1,4-\alpha$ adduct.³ The addition of the vinylogous Reformatsky reagent derived from ethyl 4bromocrotonate to some enones has produced a $1,4-\gamma$ adduct under the controlled reaction conditions.^{2,4} The $1,2-\gamma$ selectivity was obtained in the reaction of lithium dienolates with certain enones⁵ and enals.⁶ We wish to report a new approach to this problem; the reaction of the Ge-masked dienolates with Michael acceptors gives the $1,4-\gamma$ adduct with the aid of Lewis acids, whereas the $1,4-\alpha$ adduct is obtained with Bu₄NF (eq 2).



The results are summarized in Table 1. The Ge-masked dienolates were obtained easily from the corresponding lithium dienolates as previously described.¹ The reaction of 1 with 2 in the presence of Bu₄NF in THF at -78°C--25°C gave the 1,4- α -adduct 3 regioselectively (entry 1).⁷ On the other hand, the reaction in the presence of TiCl₄ in CH₂Cl₂ at -78°C-0°C produced the 1,4- γ -adduct 4 regioselectively along with the cyclization product 5 (entry 2). Since 5 arose from the 1,4- γ -type conjugate addition, the regiocontrol of the Lewis acid mediated reaction was completely in a 1,4- γ manner. The high selectivity of 4/5 was obtained with AlCl₃·OEt₂ (entry 3). Other Lewis acids such as BF₃·OEt₂, ZnCl₂, and TiCl(OiPr)₃ were ineffective. The use of SnCl₄ gave 4 and 5 in lower yields in comparison with TiCl₄ and AlCl₃. In general, the use of AlCl₃·OEt₂ gave better result than the use of TiCl₄. For example, the use of TiCl₄ in the reaction of 1 with 6 gave 7 in 41% yield and 8 in 32% yield (cf. entry 4). In entries 5 and 6, no cyclization products were produced and only the 1,4- γ adducts were obtained. The 1,4- γ regioselectivity was also produced in the reactions of 13 and 16 (entries 7 and 8). Here also, small amounts of the cyclization products, 15 and 18, were obtained as by-products, but the reaction might be useful for the synthesis of fused bicyclic systems if the conjugate addition-cyclization would become a major reaction course.

The Ge-masked dienolates (1, 13, 16) were obtained by trapping the corresponding lithium dienolates with Me₃GeCl.¹ As shown in eq 3, the reaction with Me₂GeCl₂ gave (α -germylated)₂ product 19 in 29% isolated yield along with small amounts of (α -germylated)(γ -germylated) product. The reaction of 0.6 equiv 19 with 2 in the presence of AlCl₃•OEt₂ also afforded 3 in 78% yield and 4 in 18% yield, indicating that two dienolate groups of 19 could be transfered to the Michael acceptor with the aid of AlCl₃.



In conclusion, we are now in a position to control the regioselectivity of the reactions between the ambident nucleophiles and electrophiles. Such regiocontrol is not so easy if we utilize the ordinary metal enolates such as lithium and zinc dienolates. The present success is primarily owing to the use of the α -germylated masked dienolates, which opens a door to the organic synthesis via organogermanium compounds.⁸

entry	Ge-masked dienolate	Michael acceptor	additive	product (isolated yield)
1	GeMe ₃	CO ₂ Et	Bu₄NF	$3 (1,4-\alpha) (61\%)^{a}$
2	1	2	TiCl ₄	$\begin{array}{c} CO_{2}Et \\ CH(CO_{2}Et)_{2} \\ CU_{2}Et \\ CO_{2}Et \\ CO_{2}E$
3	1	2	AICI ₃	4 (93%) [°] 5 (6%)
4	1	CO ₂ Et CO ₂ Et Ph 6	AICI ₃	$\begin{array}{c} CO_2Et \\ CH(CO_2Et)_2 \\ Ph \\ 7 (86\%)^d \\ \end{array} \begin{array}{c} 0 \\ CO_2Et \\ Ph \\ CO_2Et \\ 8 (4\%) \\ \end{array}$
5	1		TiCl ₄	CO_2Et COMe CO_2Et CO_2Et CO_2Et
6	1	COMe COMe	AICI ₃	COMe COMe 12 (51%) ^e
7	GeMe ₃ CO ₂ Me	2	AICI ₃	$\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} $
8	GeMe ₃ CO ₂ Et	2	TiCl ₄	$\begin{array}{c} CO_2 Et \\ CH_1(CO_2 Et)_2 \end{array} \xrightarrow{(CO_2 Et)_2} CH_1(CO_2 Et)_2 \\ 17 (69\%)^{f} \\ 18 (6\%)^{9} \end{array}$

Table 1. Regiocontrolled Conjugate Addition of Ge-masked Dienolates

^aA 7:3 mixture of two diastereomers. The stereochemistry was not determined. ^bThe trans/cis ratio was 88/12. ^cThe trans/cis ratio was 76/24. ^dThe trans/cis ratio was >99/1. ^aThe trans/cis ratio was 55/45. ¹The stereochemistry of diastereomers was not determined. ^gThe 1,4- α adduct was obtained in 7% yield.

The reaction of 1 with 2 is representative. To a 50 ml flask cooled at -78°C under N₂ were placed dry THF (6 ml) and 2 (0.18 ml, 1.0 mmol). To this solution was added 1.0 M Bu₄NF in THF (1.5 ml, 1.5 mmol) and the resulting mixture was stirred for 15 min. A CH₂Cl₂ solution of 1 (1.14 M×1ml, 1.14 mmol) was placed in a 10 ml flask and the solvent was evaporated under vacuum. Dry THF (4 ml) was added, and the THF solution was transfered to the reaction flask via a double ended needle. The mixture was allowed to warm to room temperature, and the reaction was quenched with aq. NH₄Cl. The usual work-up gave crude 3 (292 mg). Purification with silica-gel (30 g) column chromatography using hexane/ether (10/1) as an eluent gave 3 (191 mg, 61% yield) (fr. 6-13).

To a 30 ml flask was placed 0.5 ml of 1M AlCl₃/Et₂O (0.5 mmol), and the ether was removed under vacuum. Dry CH₂Cl₂ (2 ml) was added and the flask was cooled to -78°C. The Michael acceptor 2 (90 μ l, 0.5 mmol) was added and the mixture was stirred for 15 min. A 0.45 M CH₂Cl₂ solution of 1 (1.35 ml, 1.2 equiv.) was added, and the resulting mixture was warmed to 10°C. The reaction was quenched with aq. NH₄Cl. The usual work-up gave crude products (470 mg). Purification with silica-gel (10 g) column chromatography using hexane/ether (20/1) as an eluent gave 4 (146.3 mg, 93% yield, fr. 5~13), and then the use of hexane/ether (10/1) afforded 5 (7.9 mg, 6% yield, fr. 22~32).

References and notes

- For the most recent paper on this subject, see Y. Yamamoto, S. Hatsuya, J. Yamada, J. Org. Chem., 55, 3118 (1990), and references cited therein.
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- 3) W. Oppolzer, R. Pitteloud, J. Am. Chem. Soc., 104, 6478 (1982).
- 4) I. Casinos, R. Mestres, J. Chem. Soc. Perkin I, 1651 (1978).
- 5) K. Suga, S. Watanabe, T. Fujita, Aust. J. Chem., 25, 2393 (1972).
- 6) G. Cardillo, M. Orena, S. Sandri, Tetrahedron, 32, 107 (1976).
- 7) Normally, the 1,4-α product can be obtained by the reaction of lithium dienolates with Michael acceptors. Regioselective synthesis of the 1,4-γ product is more difficult than that of the 1,4-α isomer. Therefore, we mostly listed the results on the synthesis of the 1,4-γ adduct in Table 1, and emphasized the synthetic utility of our method. The Bu₄NF mediated reactions of the Ge masked dienolates with the Michael acceptors, for example, 1 and 6, or 1 and 9, gave the 1,4-α adducts in good yields.
- For the most recent Ge mediated organic synthesis, see (a) S. Kiyooka, Y. Kaneko, H. Matsue, M. Hamada, R. Fujiyama, J. Org. Chem., 55, 5562 (1990), and references cited therein. (b)N. Chatani, N. Horiuchi, T. Hanafusa, J. Org. Chem., 55, 3393 (1990). (c) S. Inoue, Y. Sato, Organometallics, 7, 739 (1988). (d) J. A. Soderquist, A. Negron J. Org. Chem., 54, 2462 (1989).

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