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Tetrahedron Letters 47 (2006) 1977–1980
Tetrahedron Letters

One-pot, cis-selective synthesis of α-substituted β-trimethylsilyl-α,β-epoxyesters from α-ketoesters and diazo(trimethylsilyl)methyl magnesium bromide

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Received 19 December 2005; revised 11 January 2006; accepted 13 January 2006
Available online 3 February 2006

Abstract—Reaction of α-ketoesters with diazo(trimethylsilyl)methyl magnesium bromide followed by in situ treatment with pivalic acid gave α-substituted β-trimethylsilyl-α,β-epoxyesters in an efficient and cis-selective manner.
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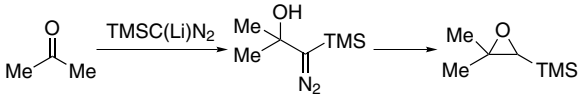
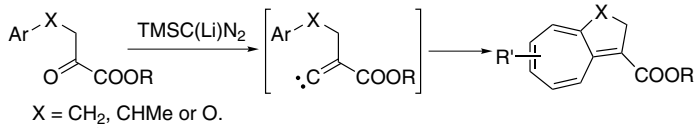
α-Substituted α,β-epoxyesters (α-substituted glycidates) are very promising as bioactive compounds.[1] To date, many synthetic methods of these compounds have been reported;[2–5] for instance, (i) Darzens condensation of α-haloesters with ketones or aldehydes,[2] (ii) epoxidation of α-substituted acrylates,[3] and (iii) addition of nucleophiles to *tert*-butyl 2-ethoxycarbonylprop-2-enyl peroxide followed by S_Ni reaction.[4] However, in most cases of the methods, the synthesis of the substrates is complex and/or laborious, and therefore, development of a new approach to α-substituted α,β-epoxyesters will be valuable.

Recently, we have revealed that reactions of 4-aryl-2-oxobutanoates and aryloxypyruvates with TMSC(Li)N_2 gave 2,3-dihydroazulene-1-carboxylates[6] and 1,2-dihydro-1-oxaazulene-3-carboxylates[7] via alkylidenecarbene intermediates (Scheme 1). Interestingly, in these reactions, TMSC(Li)N_2 chemoselectively reacted with the ketone moiety of α-ketoesters and the ester moiety remained intact. Meanwhile, it has been reported by Schöllkopf and Scholz that reaction of acetone with TMSC(Li)N_2 gave the corresponding diazoalcohol, which was converted to 2,2-dimethyl-3-trimethylsilyloxirane at room temperature in ca. 33% yield in two steps (Scheme 2).[8] These results led us to investigate the synthesis of α-substituted α,β-epoxyesters from α-ketoesters using TMSC(Metal)N_2. As a result of intensive investigation of reaction conditions, we found that α-substituted β-trimethylsilyl-α,β-epoxyesters could be cis-selectively synthesized by reaction of α-ketoesters with the magnesium bromide salt of $TMSCHN_2$ (TMSC(MgBr)N_2)[9] followed by treatment with pivalic



Scheme 2. Report by Schöllkopf and Scholz.



Scheme 1. Our previous reports.

Keywords: Epoxyesters; Glycidates; α-Ketoesters; One-pot synthesis; Trimethylsilyldiazomethane.
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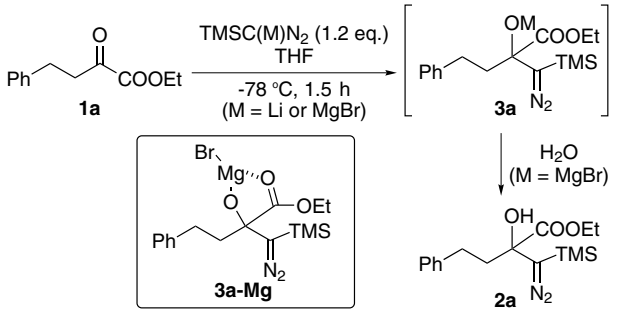
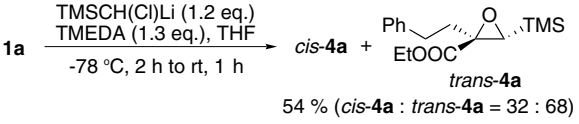
doi:10.1016/j.tetlet.2006.01.067



Scheme 3. Reaction of TMSC(Li)N_2 or TMSC(MgBr)N_2 with **1a**.

acid in a one-pot process. Herein, the details of our results are described.

Initially, under similar reaction conditions reported by Schöllkopf,[8] we performed the reaction of TMSC(Li)N_2 with commercially available ethyl 4-phenyl-2-oxobutanoate **1a** as an α-ketoester (Scheme 3). The α-ketoester **1a** easily underwent the reaction with TMSC(Li)N_2, but the product was a complex mixture and the desired diazoalcohol **2a** was not detected.[10] Interestingly, under the same reaction conditions, replacement of TMSC(Li)N_2 by TMSC(MgBr)N_2, prepared from TMSC(Li)N_2 and $MgBr_2$ etherate, dramatically affected the reaction and the desired **2a** was obtained quantitatively.[11] The result suggests that the diazoalkoxide **3a-Mg** might be stabilized by the strong coordination of a magnesium ion with the carbonyl group of an ester moiety. Thus, the one-pot synthesis of α,β-epoxyesters by successive treatment of the formed diazoalkoxide **3a-Mg** with an acid was examined (Table 1).[12–14] When AcOH (1.5 equiv) as an acid was used, the desired ethyl α-(2-phenethyl)-β-trimethylsilylglycidate **4a** was obtained in 50% yield with cis-selectivity (cis:trans = 78:22) (entry 1). An increased amount (5 equiv) of AcOH significantly improved the cis-selectivity (cis:trans = 87:13) (entry 2). The use of 10-camphorsulfonic acid (CSA) or $CHCl_2COOH$ in place of AcOH led to a complex mixture or a decrease of the yield (entries 3 and 4). However, treatment with pivalic acid, a mild acid, was quite effective and the best results were obtained in both the yield (88%) and selectivity (cis:trans = 96:4) (entry 5). Although the amount of pivalic acid was increased to 10 equiv, no improvement was observed in the selectivity (entry 6). Incidentally, for a comparison of the method using TMSC(MgBr)N_2 with as another synthetic approach to **4a**, reaction of **1a** with chloro(trimethylsilyl)methyl lithium[15] was carried out (Scheme 4).[16] However, the yield of **4a** was 54% with low trans-selectivity (cis:trans = 32:68).

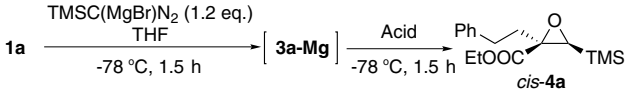


Scheme 4. Synthesis of **4a** using chloro(trimethylsilyl)methyl lithium.

Next, the generality of substrates was examined (Table 2).[12–14] Various α-ketoesters **1a–e** bearing alkyl groups, such as a 2-phenethyl, 3-phenylpropyl, isopropyl, or methyl group, smoothly underwent the reaction with TMSC(MgBr)N_2 to give **4a–e** in good to high yields with high cis-selectivity (entries 1–5). Especially, the diisopropylamide derivative **1b** gave almost complete cis-selectivity compared to that of ethyl ester **1a** (entries 1 and 2). The phenyl and phenylethynyl derivatives **1f** and **1i** also gave the epoxides **4f** and **4i** in good to high yields, but little diastereoselectivity was observed (entries 6 and 9). Thus, reaction with **1g**, **1h**, and **1j** bearing a bulky diisopropylamide or *tert*-butyl ester moiety was examined (entries 7, 8, and 10). However, the amide **1g** did not undergo the reaction, while reaction with **1h** and **1j** smoothly proceeded giving the corresponding **4h** and **4j** in high yields. Unfortunately, **1h** and **1j** had almost no effect on the selectivity (entries 8 and 10).

In this reaction, the protonation step of the resulting diazoalcohol with an acid was crucial for induction of diastereoselectivity as shown in Scheme 5. The cis-selectivity was probably due to less steric repulsion of a trimethylsilyl group for a hydroxyl group than an alkyl group. The reason for little selectivity in the reaction

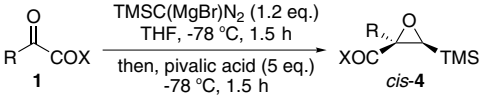
Table 1. Screening of acids



Entry	Acid (equiv)	Yield (%)	Cis:trans[b]
1	AcOH (1.5)	50	78:22
2	AcOH (5)	55	87:13
3	CSA (5)	—[a]	—
4	$CHCl_2COOH$ (5)	39	93:7
5	Pivalic acid (5)	88	96:4
6	Pivalic acid (10)	90	95:5

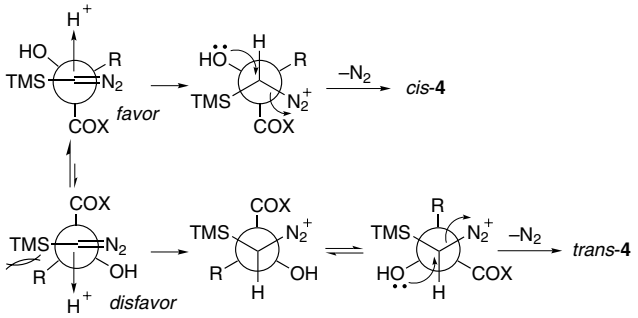
[a] Complex mixture was given.
[b] The ratio of regioisomers was calculated by ^{1}H NMR measurement.

Table 2. Generality of substrates



Entry	Substrate	Yield (%)	Cis:trans[c]
1[a]	**1a** (R = $Ph(CH_2)_2$, X = OEt)	88 (**4a**)	96:4
2	**1b** (R = $Ph(CH_2)_2$, X = NPr^i_2)	80 (**4b**)	>99:1
3	**1c** (R = $Ph(CH_2)_3$, X = OEt)	86 (**4c**)	>99:1
4	**1d** (R = Me_2CH, X = OEt)	83 (**4d**)	94:6[d]
5	**1e** (R = Me, X = OEt)	69 (**4e**)	93:7[d]
6	**1f** (R = Ph, X = OEt)	98 (**4f**)	57:43
7	**1g** (R = Ph, X = NPr^i_2)	—[b]	—
8	**1h** (R = Ph, X = OBu^t)	85 (**4h**)	61:39
9	**1i** (R = PhC≡C, X = OEt)	79 (**4i**)	54:46
10	**1j** (R = PhC≡C, X = OBu^t)	91 (**4j**)	55:45[d]

[a] Shown in entry 5 of Table 1.
[b] Almost no reaction.
[c] The ratio of regioisomers was calculated by ^{1}H NMR measurement.
[d] The cis- and trans-isomers were inseparable by column chromatography.



Scheme 5. Plausible mechanism for induction of diastereoselectivity.

of **1f** and **1h–j** (entries 6 and 8–10 in Table 2) might be that a phenyl or phenylethynyl group for R was similar to an ester or hydroxy group in size, respectively.

In conclusion, we have succeeded in the one-pot cis-selective synthesis of α-substituted β-trimethylsilyl-α,β-epoxyesters from α-ketoesters using $TMSC(MgBr)N_2$ and this synthetic method will provide a new access to α-substituted α,β-epoxyesters.

Acknowledgments

This work was financially supported by a Grant-in-Aid for Scientific Research (KAKENHI) (to T.A.), and a Grant-in-Aid from The Japan Securities Scholarship Foundation (to Y.H.).

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9. Reaction using $TMSC(MgBr)N_2$. Ogawa, H.; Aoyama, T.; Shioiri, T. *Heterocycles* **1996**, *42*, 75–82.
10. Spectroscopic data of the crude product showed the presence of 1,3-Brook rearrangement product formed by the intermediate **3a-Li**.
11. Data for **2a**. IR (neat) *v*: 3496, 2045 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 0.19 (s, 9H), 1.32 (t, 3H, $J = 7.1$ Hz), 2.15 (t, 2H, $J = 8.2$ Hz), 2.47–2.58 (m, 1H), 2.77–2.88 (m, 1H), 3.57 (s, 1H, disappeared with D_2O), 4.20–4.29 (m, 2H), 7.17–7.31 (m, 5H).
12. Typical procedure (entry 5 in Table 1). To a solution of $TMSCHN_2$ (1.50 M in hexane solution, 0.39 ml, 0.58 mmol) in THF (3.5 ml), *n*-BuLi (1.58 M in hexane solution, 0.37 ml, 0.58 mmol) was added dropwise at −78 °C under argon atmosphere, and the mixture was stirred for 20 min. $MgBr_2$ (1.07 M in Et_2O–benzene (2:1) solution, 0.54 ml, 0.58 mmol) was added dropwise, and the

mixture was stirred at −78 °C for 10 min. To the mixture, a solution of ethyl 4-phenyl-2-oxobutanoate **1a** (100 mg, 0.49 mmol) in THF (1.3 ml) was added dropwise. The whole mixture was stirred at −78 °C for 1.5 h, then pivalic acid (248 mg, 2.43 mmol) in THF (1.0 ml) was added and the mixture was stirred for an additional 1.5 h. After being quenched with saturated $NaHCO_3$aq, the mixture was extracted with EtOAc (three times). The extracts were washed with water and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (BW-200MH, 10 g, hexane–EtOAc = 30:1) to afford **4a** (125 mg, 88%, cis:trans = 96:4).

13. The stereochemistry of the compounds **4** was determined by NOESY measurement.
14. Data for **4**. *cis*-**4a**, ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 9H), 1.32 (t, 3H, $J = 7.2$ Hz), 1.92 (ddd, 1H, $J = 5.2$, 10.4, and 15.1 Hz), 2.25 (s, 1H), 2.43 (ddd, 1H, $J = 6.4$, 10.4, and 14.8 Hz), 2.74 (ddd, 1H, $J = 6.4$, 10.4, and 15.1 Hz), 2.86 (ddd, 1H, $J = 5.2$, 10.4, and 14.8 Hz), 4.13 (dq, 1H, $J = 7.2$ and 10.9 Hz), 4.20 (dq, 1H, $J = 7.2$ and 10.9 Hz), 7.17–7.20 (m, 3H), 7.25–7.30 (m, 2H). *trans*-**4a**, ^{1}H NMR ($CDCl_3$) δ: 0.17 (s, 9H), 1.30 (t, 3H, $J = 7.1$ Hz), 1.67 (ddd, 1H, $J = 4.9$, 11.4, and 15.1 Hz), 2.48 (s, 1H), 2.55–2.60 (m, 1H), 2.74–2.79 (m, 1H), 2.86 (ddd, 1H, $J = 4.9$, 11.4, and 15.0 Hz), 4.16–4.22 (m, 2H), 7.18–7.21 (m, 3H), 7.26–7.30 (m, 2H). *cis*-**4b**, ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 9H), 1.20 (d, 3H, $J = 6.5$ Hz), 1.23 (d, 3H, $J = 6.8$ Hz), 1.42 (d, 3H, $J = 7.0$ Hz), 1.44 (d, 3H, $J = 6.8$ Hz), 1.62–1.74 (m, 1H), 2.10 (s, 1H), 2.35–2.46 (m, 1H), 2.70–2.75 (m, 1H), 2.78–2.80 (m, 1H), 3.36–3.40 (m, 1H), 4.49–4.62 (m, 1H), 7.18–7.22 (m, 3H), 7.24–7.28 (m, 2H). *cis*-**4c**, ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 9H), 1.29 (t, 3H, $J = 7.2$ Hz), 1.54–1.59 (m, 1H), 1.70–1.74 (m, 1H), 1.85–1.88 (m, 1H), 2.20–2.25 (m, 1H), 2.26 (s, 1H), 2.62–2.69 (m, 1H), 4.13–4.24 (m, 2H), 7.16–7.19 (m, 3H), 7.26–7.28 (m, 2H). As a mixture of *cis*-**4d** and *trans*-**4d**. *cis*-**4d**, ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 9H), 1.00 (d, 3H, $J = 6.9$ Hz), 1.08 (d, 3H, $J = 6.9$ Hz), 1.32 (t, 3H, $J = 7.1$ Hz), 1.89–1.99 (m, 1H), 2.25 (s, 3H), 4.10–4.29 (m, 2H), and the characteristic signal of *trans*-**4d**, ^{1}H NMR ($CDCl_3$) δ: 0.18 (s, 9H). As a mixture of *cis*-**4e** and *trans*-**4e**. *cis*-**4e**, ^{1}H NMR ($CDCl_3$) δ: 0.11 (s, 9H), 1.31 (t, 3H, $J = 7.1$ Hz), 1.62 (s, 3H), 2.25 (s, 1H), 4.08–4.28 (m, 2H), and the characteristic signal of *trans*-**4e**, ^{1}H NMR ($CDCl_3$) δ: 0.17 (s, 9H). *cis*-**4f**, ^{1}H NMR ($CDCl_3$) δ: −0.20 (s, 9H), 1.25 (t, 3H, $J = 7.1$ Hz), 2.83 (s, 1H), 4.15–4.24 (m, 2H), 7.31–7.33 (m, 3H), 7.49–7.53 (m, 2H). *trans*-**4f**, ^{1}H NMR ($CDCl_3$) δ: 0.16 (s, 9H), 1.31 (t, 3H, $J = 7.1$ Hz), 2.43 (s, 1H), 4.11–4.28 (m, 2H), 7.32–7.35 (m, 3H), 7.51–7.54 (m, 2H). *cis*-**4h**, ^{1}H NMR ($CDCl_3$) δ: −0.21 (s, 9H), 1.44 (s, 9H), 2.76 (s, 1H), 7.29–7.33 (m, 3H), 7.47–7.51 (m, 2H). *trans*-**4h**, ^{1}H NMR ($CDCl_3$) δ: 0.19 (s, 9H), 1.47 (s, 9H), 2.37 (s, 1H), 7.31–7.35 (m, 3H), 7.48–7.51 (m, 2H). *cis*-**4i**,^{1}H NMR ($CDCl_3$) δ: 0.17 (s, 9H), 1.34 (t, 3H, $J = 7.1$ Hz), 2.80 (s, 1H), 4.19–4.33 (m, 2H), 7.30–7.32 (m, 3H), 7.45–7.48 (m, 2H). *trans*-**4i**, ^{1}H NMR ($CDCl_3$) δ: 0.26 (s, 9H), 1.32 (t, 3H, $J = 7.1$ Hz), 2.80 (s, 1H), 4.25–4.32 (m, 2H), 7.32–7.34 (m, 3H), 7.44–7.47 (m, 2H). As a mixture of *cis*-**4j** and *trans*-**4j**. *cis*-**4j**, ^{1}H NMR ($CDCl_3$) δ: 0.19 (s, 9H), 1.55 (s, 9H), 2.76 (s, 1H), 7.31–7.34 (m, 3H), 7.43–7.46 (m, 2H), and *trans*-**4j**, ^{1}H NMR ($CDCl_3$) δ: 0.24 (s, 9H), 1.53 (s, 9H), 2.76 (s, 1H), 7.31–7.34 (m, 3H), 7.43–7.46 (m, 2H).
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16. Reaction using chloro(trimethylsilyl)methyl lithium (Scheme 4). To a solution of chloromethyltrimethylsilane (81 μl, 0.58 mmol) in THF (1 ml), *s*-BuLi (0.61 ml, 1.03 M in pentane, 0.61 mmol) was added dropwise at −78 °C under argon atmosphere, and the mixture was stirred for 5 min. TMEDA (95 μl, 0.63 mmol) was added and the mixture was stirred at −78 °C for 30 min. To the mixture, **1a** (100 mg, 0.49 mmol) in THF (1.3 ml) was added dropwise. The whole mixture was stirred at −78 °C for 2 h, then at room temperature for 1 h. After being quenched with 0.2 N HCl, the mixture was extracted with EtOAc (three times). The extracts were washed with water and saturated brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (BW-200MH, 6 g, hexane–EtOAc = 30:1) to afford **4a** (77 mg, 54%, cis:trans = 32:68).