Generation of 2-Substituted-2-metallo-1,3-dithianes and Their Coupling with 1,2-Disubstituted Epoxides at Room Temperature

Mitsuaki Ide, Minoru Yasuda, Masaya Nakata*

Department of Applied Chemistry, Faculty of Science and Technology, Keio University, 3-14-1 Hiyoshi, Kohoku-ku, Yokohama 223-8522, Japan

Fax: +81-45-563-0446; E-mail: msynktxa@applc.keio.ac.jp

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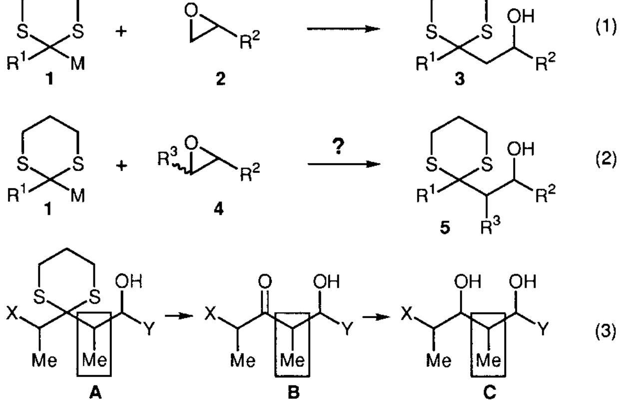
Abstract: 2-Substituted-1,3-dithianes were subjected to lithiation by *n*-BuLi at room temperature and the resulting anions reacted with 1,2-disubstituted epoxides at room temperature, giving the coupling products in satisfactory yield. In addition, a mixed organometallic reagent, *n*-BuLi/Bu_2Mg, was found to be an effective metallation reagent for 2-substituted-1,3-dithianes.

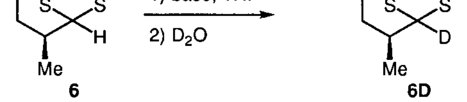
Since the introduction of 2-lithio-1,3-dithiane derivatives by Corey and Seebach in 1965,[1] synthetic organic chemists have been using them as the excellent acyl anion equivalents for carbon-carbon bond formation.[2] Representative examples are the coupling of 2-lithio-1,3-dithiane derivatives with epoxides. In general, 2-lithio-1,3-dithiane itself and 2-substituted-2-lithio-1,3-dithianes **1** (M = Li) react with monosubstituted epoxides **2** to afford the coupling products **3** in satisfactory yield (eq 1). Even in such a case, however, problems still remain; when anions are short-lived and/or epoxides are relatively poor electrophiles, the coupling reaction is capricious.[3] Moreover, it has been considered that 1,2-disubstituted epoxides **4** can not react efficiently with 2-substituted-2-lithio-1,3-dithianes **1** (M = Li, eq 2). Therefore, such coupling reactions have scarcely been attracted attention[4] and, to the best of our knowledge, have not been used in natural product syntheses. We now report in this letter the effective coupling reactions of 2-substituted-2-metallo-1,3-dithianes **1** with 1,2-disubstituted epoxides **4** at room temperature to afford the coupling products **5** in satisfactory yield. Compared with **3**, the compound **5** includes the additional substituent R^3 in its structure. Therefore, in the case of **5** having the partial structure (R^1 = Me-branched unit, R^3 = Me: eq 2) such as **A** (eq 3), it would be possible to obtain a sequential array of alternate Me and OH groups, such as **C**, via de-dithioacetalization (**A** to **B**) and reduction (**B** to **C**).



Equation 1, 2, 3

We first selected **6**[5,6] and **7**[6,7] as a dithiane and a 1,2-disubstituted epoxide component, respectively (eq 4). *t*-BuLi in pentane (1 equiv for **6**) was added at -78 °C to a solution of **6** in 10% HMPA-THF (0.2 M for **6**)[8] and to this was added **7** (1 equiv for **6**) in THF; the mixture was stirred at -78 °C for 1 d. But only the starting materials were recovered. *n*-BuLi/*t*-BuONa complex, which was used for metallation of 2-substituted-1,3-dithianes by Lipshutz,[9] was of no effect on this coupling at -78 °C. It was decided to investigate the lithiation conditions (in THF) by D_2O quenching. Representative data are shown in Table 1. HMPA was needed for the anion generation at -78 °C by using *n*-BuLi or *t*-BuLi as a base (entries 1, 2, 6, and 7). Metallation with *t*-BuLi/HMPA and *n*-BuLi/*t*-BuONa effectively occurred at -78 °C (entries 1 and 5). These results suggested that the inertness of the reaction of eq 4 was due to the poor electrophilicity of **7**. We considered that it was necessary to raise the reaction temperature to overcome this problem. The use of HMPA in metallation at room temperature (rt: 20 - 25 °C) was less satisfactory (entries 3, 4, 11, and 12). We found that the anion was best generated by treatment of **6** with *n*-BuLi (1 equiv for **6**) at rt for 5 min; D_2O quenching furnished 90% deuterium incorporation (entry 11). This gratified result promoted us to re-examine the reaction of eq 4. Namely, to the anion generated as above was added **7** (1 equiv for **6**) in THF at rt. After 3 h at rt, **8**[6,10] was obtained in 61% isolated yield along with **6** (36%) and **7** (32%).[11] When 1.2 equiv of *n*-BuLi and 1.3 equiv of **7** were used, the yield of **8** increased to 73%.

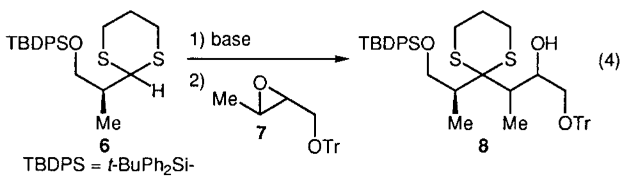
Table 1. Generation of the anion of **6** and D_2O quenching[a]



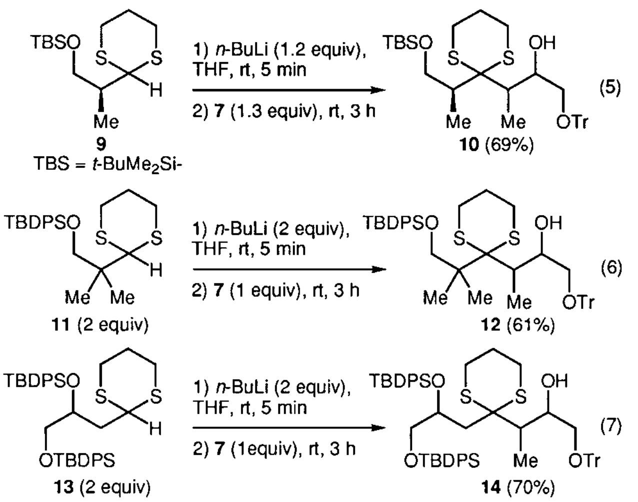
entry	base	additive	temp/°C	time/min	% D[b]
1	*t*-BuLi	HMPA	-78	5	82
2	*t*-BuLi	none	-78	60	0
3	*t*-BuLi	HMPA	rt	5	16[c]
4	*t*-BuLi	none	rt	5	54
5	*n*-BuLi/*t*-BuONa	none	-78	60	72
6	*n*-BuLi	HMPA	-78	5	46
7	*n*-BuLi	none	-78	60	0
8	*n*-BuLi	none	-40	60	32
9	*n*-BuLi	none	0	60	79
10	*n*-BuLi	none	rt	60	86[d]
11	*n*-BuLi	none	rt	5	90[d]
12	*n*-BuLi	HMPA	rt	5	14[c]

[a] Base (1 equiv for **6**) was added to a solution (0.2 M for **6**) of **6** in THF or 10% HMPA/THF at the specified temperature. After the specified time, D_2O was added and the mixture was worked up as usual. [b] Determined by ^1H NMR (270 MHz) analysis of the crude products. [c] Contaminated with decomposed products. [d] When 1.2 equiv of base was used, % D was >95

Encouraged by this success, we next examined the coupling reactions of other 2-substituted-1,3-dithianes, **9**,[5,6] **11**,[6,12] and **13**,[6,13] with **7** (eqs 5, 6, and 7). In the case of eqs 6 and 7, 2 equiv of dithiane components were required to obtain satisfactory yield.[6,10]



Equation 4

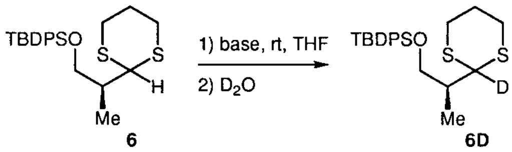


Equation 5, 6, 7

Next, we turned our attention to make use of *n*-BuLi/Bu$_2$Mg complex as a metallating reagent. During the course of our synthetic studies on biscembranoids,[14] we found that *n*-BuLi/Bu$_2$Mg complex (Bu$_2$Mg: *n*-Bu:*s*-Bu = 1:1, Aldrich) was an effective anion generator for the Ito-Kodama cyclization and/or the Biellmann-type reaction,[15] which are the coupling reaction of phenylthio-stabilized allylic anions with epoxides. We anticipated that this mixed reagent would stabilize the anions generated from 1,3-dithiane derivatives.[16] We investigated the metallation conditions (using **6** in THF) at rt by D$_2$O quenching. Relevant data are shown in Table 2. An increase of the ratio of Bu$_2$Mg/*n*-BuLi decreases % D (entries 2, 3, 4, and 5). As we would expect, the anion generated with *n*-BuLi/Bu$_2$Mg is long-lived at rt and % D is unchangeable after 3 h (entries 2 and 8). In contrast, % D decreases from 86 (1 h) to 73 (3 h) in the case of the anion generated with only *n*-BuLi (entries 1 and 7). To the anion generated at rt for 1 h from **6** (1 equiv) by treatment with a pre-mixed reagent of 1 equiv of *n*-BuLi and 0.25 equiv of Bu$_2$Mg was added **7** (1 equiv) in THF; the mixture was stirred at rt for 3 h, giving **8** in 71% yield. When 1.2 equiv of *n*-BuLi, 0.3 equiv of Bu$_2$Mg, and 1.3 equiv of **7** were used, the yield of **8** increased to 85%. This result is superior to that of the aforementioned coupling using only *n*-BuLi. It is not yet clear what the active species of *n*-BuLi/Bu$_2$Mg complex are.[17,18]

The results presented in this letter would broaden the synthetic usefulness of 1,3-dithiane chemistry. Studies toward the application of this methodology to natural product syntheses as well as efforts to rationalize the role of the mixed reagents system (*n*-BuLi/Bu$_2$Mg) are now in progress.

Table 2. Generation of the anion of **6** and D$_2$O quenching[a]



entry	base	time/min	% D[b]
1	*n*-BuLi	60	86
2	*n*-BuLi/Bu$_2$Mg (0.25)[c]	60	85
3	*n*-BuLi/Bu$_2$Mg (0.50)[c]	60	74
4	*n*-BuLi/Bu$_2$Mg (0.75)[c]	60	67
5	*n*-BuLi/Bu$_2$Mg (1.00)[c]	60	62
6	Bu$_2$Mg	60	0
7	*n*-BuLi	180	73
8	*n*-BuLi/Bu$_2$Mg (0.25)[c]	180	85

[a] Base (1 equiv for **6**) was added to a solution of **6** in THF (0.2 M for **6**) at rt (20 - 25 °C). After the specified time, D$_2$O was added and the mixture was worked up as usual. [b] Determined by ^{1}H NMR (270 MHz) analysis of the crude products. [c] Bu$_2$Mg in heptane (equiv indicated in parenthesis) was added to *n*-BuLi (1 equiv for **6**) in hexane at rt; this mixed reagent was used as a base

References and Notes

(1) (a) Corey, E. J.; Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 1075-1077. (b) Seebach, D.; Corey, E. J. *J. Org. Chem.* **1975**, *40*, 231-237.

(2) For reviews, see: (a) Seebach, D. *Synthesis* **1969**, 17-36. (b) Gröbel, B.-T.; Seebach, D. *Synthesis* **1977**, 357-402. (c) Page, P. C. B.; van Niel, M. B.; Prodger, J. C. *Tetrahedron* **1989**, *45*, 7643-7677. (d) Kolb, M. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 5; Paquette, L. A., Ed.; John Wiley & Sons: Chichester, 1995; p2983-2989.

(3) For example, see: (a) Hanessian, S.; Pougny, J.-R.; Boessenkool, I. K. *Tetrahedron* **1984**, *40*, 1289-1301. (b) Oppong, I.; Pauls, H. W.; Liang, D.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1986**, 1241-1244. (c) Kinoshita, M.; Taniguchi, M.; Morioka, M.; Takami, H.; Mizusawa, Y. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 2147-2156. (d) Jones, T. K.; Reamer, R. A.; Desmond, R.; Mills, S. G. *J. Am. Chem. Soc.* **1990**, *112*, 2998-3017. (e) Okamura, H.; Kuroda, S.; Ikegami, S.; Tomita, K.; Sugimoto, Y.; Sakaguchi, S.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Tetrahedron* **1993**, *49*, 10531-10554. (f) Nicolaou, K. C.; Ajito, K.; Patron, A. P.; Khatuya, H.; Richter, P. K.; Bertinato, P. *J. Am. Chem. Soc.* **1996**, *118*, 3059-3060. (g) Nicolaou, K. C.; Patron, A. P.; Ajito, K.; Richter, P. K.; Khatuya, H.; Bertinato, P.; Miller, R. A.; Tomaszewski, M. J. *Chem. Eur. J.* **1996**, *2*, 847-868. (h) Smith, A. B., III; Condon, S. M.; McCauley, J. A.; Leazer, J. L., Jr.; Leahy, J. W.; Maleczka, R. E., Jr. *J. Am. Chem. Soc.* **1997**, *119*, 947-961. (i) Smith, A. B., III; Zhuang, L.; Brook, C. S.; Lin, Q.; Moser, W. H.; Trout, R. E. L.; Boldi, A. M. *Tetrahedron Lett.* **1997**, *38*, 8671-8674.

(4) For only one example of the coupling of 2-substituted-2-lithio-1,3-dithiane with 1,2-disubstituted epoxide, see: (a) Sher, F.; Isidor, J. L.; Taneja, H, R.; Carlson, R. M. *Tetrahedron Lett.* **1973**, 577-580. For three examples of the coupling of 2-aryl- and 2-

vinyl-stabilized 2-lithio-1,3-dithianes with 1,2-disubstituted epoxides, see: (b) Amrein, W.; Schaffner, K. *Helv. Chim. Acta* **1975**, *58*, 380-397. (c) Bennasar, M.-L.; Torrens, A.; Rubiralta, M.; Bosch, J.; Grierson, D. S.; Husson, H.-P. *Heterocycles* **1989**, *29*, 745-760. (d) Rubiralta, M.; Diez, A.; Reig, I.; Castells, J.; Bettiol, J.-L.; Grierson, D. S.; Husson, H.-P. *Heterocycles* **1990**, *31*, 173-186.

(5) The chiral compounds **6** and **9** were prepared from methyl (*S*)-3-hydroxy-2-methylpropionate by the following five steps: (1) TrCl, Et_3N, DMAP, CH_2Cl_2, rt, 24 h; (2) $LiAlH_4$, THF, 0 °C, 2 h; (3) Swern oxid.; (4) 1,3-propanedithiol, BF_3**.**OEt_2, CH_2Cl_2, -30 °C, 0.5 h, then CSA, MeOH, rt, 1 h; (5) to **6**: TBDPSCl, imidazole, DMF, rt, 0.5 h, 58% for five steps. to **9**: TBSCl, imidazole, DMF, 0 °C, 0.5 h, 55% for five steps. The enantiomer of **6** was prepared by Smith et al., see ref 3h.

(6) Satisfactory analytical data (NMR spectra and elemental analyses) were obtained for all new compounds.

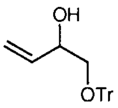
(7) The racemic **7** was prepared from (*E*)-2-buten-1-ol via tritylation (TrCl, Et_3N, CH_2Cl_2, rt, 2 h, 61%) and epoxidation (*m*-CPBA, CH_2Cl_2, rt, 3 h, 74%).

(8) For examples of lithiation of 2-substituted-1,3-dithiane derivatives by *n*-BuLi or *t*-BuLi in the presence of HMPA, see: (a) Sum, P.-E.; Weiler, L. *Can. J. Chem*. **1978**, *56*, 2700-2702. (b) Brown, C. A.; Yamaichi, A. *J. Chem. Soc., Chem. Commun.* **1979**, 100-101. (c) Sum, P.-E.; Weiler, L. *Can. J. Chem*. **1982**, *60*, 327-334. (d) Williams, D. R.; Sit, S.-Y. *J. Am. Chem. Soc.* **1984**, *106*, 2949-2954. (e) Lipshutz, B. H.; Kotsuki, H.; Lew, W. *Tetrahedron Lett.* **1986**, *27*, 4825-4828. (f) Davey, A. E.; Taylor, R. J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 25-27. (g) Solladie, G.; Hutt, J. *Tetrahedron Lett*. **1987**, *28*, 797-800. (h) Toshima, H.; Suzuki, T.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1989**, *30*, 6725-6728. (i) Khandekar, G.; Robinson, G. C.; Stacey, N. A.; Thomas, E. J.; Vather, S. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1507-1519. (j) Ohmori, K.; Suzuki, T.; Miyazawa, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1993**, *34*, 4981-4984. (k) Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869-5880. See also refs 3b, 3c, 3d, 3f, 3g, 3h, and 3i.

(9) Lipshutz, B. H.; Garcia, E. *Tetrahedron Lett.* **1990**, *31*, 7261-7264.

(10) Each compound of **8** and **10** is a 1:1 mixture of diastereomers. The compound **14** is a 1.9:1 mixture of diastereomers. In the structures of **8**, **10**, **12**, and **14**, Me and OH substituents originated from **7** are arranged to syn.

(11) Besides them, the compound **i** was produced as a by-product derived from epoxide **7** in less than 5% yield.



i

Figure 1

(12) The compound **11** was prepared from 2,2-dimethyl-1,3-propanediol by the following four steps: (1) TrCl, NaH, THF, rt, 3 h; (2) Swern oxid.; (3) 1,3-propanedithiol, BF_3**.**OEt_2, CH_2Cl_2, 0 °C, 0.5 h, then CSA, MeOH, rt, 1 h; (4) TBDPSCl, imidazole, DMF, rt, 3 h, 49% for four steps.

(13) The racemic **13** was prepared from glycidol via silylation (TBDPSCl, imidazole, CH_2Cl_2, rt, 1 h, 88%), 1,3-dithiane addition (1,3-dithiane, *n*-BuLi, THF, -30 °C, 1 h) and silylation (TBDPSCl, DMAP, DMF, 100 °C, 36 h, 89% for two steps).

(14) (a) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Synlett* **1997**, 899-902. (b) Yasuda, M.; Ide, M.; Matsumoto, Y.; Nakata, M. *Bull. Chem. Soc. Jpn.* in press.

(15) (a) Kodama, M.; Matsuki, Y.; Ito, S. *Tetrahedron Lett.* **1975**, 3065-3068. (b) Biellmann, J.-F.; Ducep, J.-B. *Org. React.* **1982**, *27*, 1-344.

(16) 2-Metallo-1,3-dithiane derivatives other than lithium, see: (a) Kruse, C. G.; Wijsman, A.; van der Gen, A. *J. Org. Chem*. **1979**, *44*, 1847-1851. (b) Weidmann, B.; Widler, L.; Olivero, A. G.; Maycock, C. D.; Seebach, D. *Helv. Chim. Acta* **1981**, *64*, 357-361. (c) Carre, M. C.; Ndebeka, G.; Riondel, A.; Bourgasser, P.; Caubere, P. *Tetrahedron Lett*. **1984**, *25*, 1551-1554. (d) Jones, A. B.; Villalobos, A.; Linde, R. G., II; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2786-2797. (e) Cer_, V.; Angelis, S. D.; Pollicino, S.; Ricci, A.; Reddy, C. K.; Knochel, P.; Cahiez, G. *Synthesis*, **1997**, 1174-1178. See also refs 8g and 9.

(17) BuLi/Bu_2Mg complex has been used, as a catalyst, for polymerization of monomers. For example, see: Kamienski, C. W.; Gastonia, N. C.; Eastham, J. F. U. S. Patent 3847883 (1974); *Chem. Abstr.* **82**, 58590 (1975). The same complex has been used for metallation of substituted trifluoromethylbenzenes, see: Castaldi, G.; Borsotti, G. European Patent 0491326A2; *Chem. Abstr.* **117**, 150667 (1992).

(18) The structrue elucidation of diorganomagnesium-organolithium complexes, see: (a) Seitz, L. M.; Brown, T. L. *J. Am. Chem. Soc*. **1966**, *88*, 4140-4147. (b) Seitz, L. M.; Little, B. F. *J. Organometal. Chem.* **1969**, *18*, 227-241. (c) Malpass, D. B.; Eastham, J. F. *J. Org. Chem.* **1973**, *38*, 3718-3723. (d) Ashby, E. C.; Chao, L.-C.; Laemmle, J. *J. Org. Chem*. **1974**, *39*, 3258-3263. (e) Greiser, T.; Kopf, J.; Thoennes, D.; Weiss, E. *Chem. Ber.* **1981**, *114*, 209-213. (f) Richey, H. G., Jr.; Farkas, J., Jr. *Organometallics* **1990**, *9*, 1778-1784.

Addendum

The Editorial Office would like to apologise for unnecessary changes in text made to the letter by Heaney, H.; Simcox, M.; Slawin, A.; Giles, R. *Synlett* **1998**, 640 during the editorial process.