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Synthesis of 1,2,3-trisubstituted cyclopropanes by MIRC reactions of dithianyllithiums with monocarboxylic vinyl epoxide analogues

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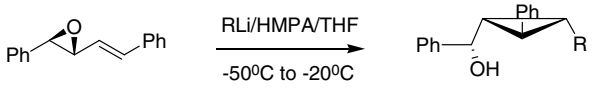
Abstract—A variety of cyclopropane derivatives bearing stereochemistry at all three positions on the ring were readily obtained in a high yield of 76–92% and high stereoselectivity (trans:cis > 95:5) when the monocarboxylic vinyl epoxide analogues reacted with dithianyllithiums in the presence of HMPA. This reaction was supposed to be a tandem conjugation addition-opening epoxide ring sequence.

The smallest cycloalkane, cyclopropane, is found as a basic structure element in a wide range of naturally occurring compounds.[1] Moreover, many cyclopropane-containing unnatural products have been prepared to test the bonding features of this class of highly strained cycloalkanes and to study enzyme mechanism or inhibition. Cyclopropanes have also been used as versatile synthetic intermediates in the synthesis of more functionalized cycloalkanes and acyclic compounds. Especially, the 1,2,3-trisubstituted cyclopropanes are found widely in natural products and biologically active molecules.[2] The Michael induced ring closing reactions (MIRC) play an important role in this field of chemistry and many synthetic applications are described in the literature so far.[3] But in this reaction, in most cases it is necessary to use doubly activated substrates. When only one activating group is present on the substrates, the reaction usually fails due to an unfavourable Michael equilibrium.[4] Kasatkin reported the synthesis of cyclopropane dicarboxylates using MIRC reactions of diethyl 2,3-epoxybutylidene-malonate with methylmagnesium iodide and lithium phenylacetylide in the presence of 5 mol % CuI.[5] However, when Yamamoto et al. studied the reactions of monocarboxylic vinyl epoxide with copper reagents in the similar reaction conditions, they found that only SN_2 or SN_2' products were obtained.[6] So in Kasatkin's reaction conditions, the doubly activate 2,3-epoxybutylidene must be required in the MIRC reaction. There have been few applications of the MIRC reaction to monocarboxylic vinyl epoxide analogues.

Recently, we reported one approach to 1,2,3-trisubstituted cyclopropanes derivatives that were readily obtained using phenylvinyl epoxide with dithianyllithiums in the presence of HMPA.[7] However, this work only suitable for one type of substrate, mono epoxides of diaryl-substituted dienes (Scheme 1).

Encouraged by our previous results, we intend to extend the reaction scope. Initially, (*E*)-methyl 3-(3-methyloxiran-2-yl) acrylate **1a** was chosen as substrate to optimize the reaction condition. The reaction was found to be critically dependent upon temperature and the presence



R=2-alkyl-1, 3-dithiane, Me, Bu up to 97% yield and 99:1 dr

Scheme 1.

Keywords: 1,2,3-Trisubstituted cyclopropanes; MIRC reactions; Vinyl epoxide.
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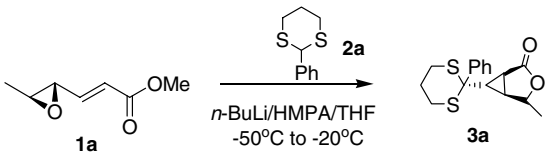
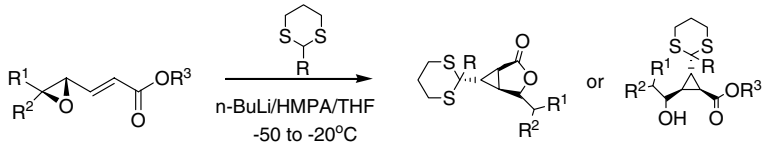
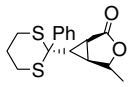
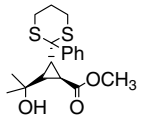
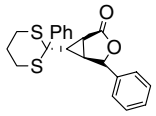
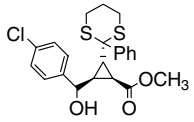
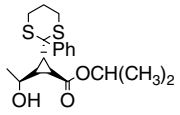
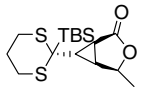
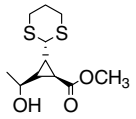
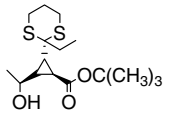
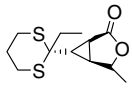


Scheme 2.

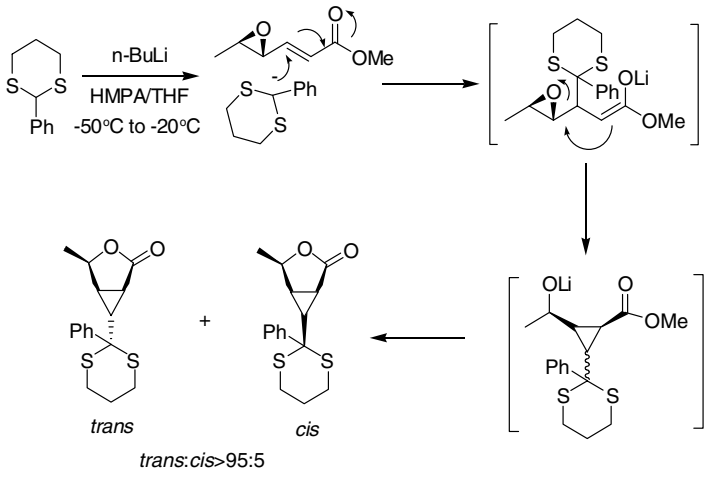
of HMPA.[8] The reaction of **2a** with **1a** proceeded smoothly at −50 to −20 °C in anhydrous THF. When the reaction was performed in a lower temperature, the product of Michael addition was obtained in high yield. When the reaction was performed in the absence of HMPA, the reaction became complicated and the expected product **3a** was obtained in a minor amount. Meanwhile, we found that Lewis acid such as BF_3 did not promote the reaction. Using catalytic amount of BF_3, the starting materials disappeared quickly, very little desired product was detected by TLC and the reaction also became very complicated. It is also worth noticing that this reaction needs anhydrous and oxygen-free conditions. Moreover, the solvents played an important role in this reaction. For example, the use of anhydrous THF as the solvent could lead to the formation of cyclopropane in high yield, whereas the reaction was carried out with difficulty in toluene and ethyl ether. When MeLi or *n*-BuLi was used under the current

Table 1. Cyclopropanation of monocarboxylic epoxide analogues with dithianyllithiums



Entry[a]	R^1	R^2	R^3	R	Product[b]	Yield (%)
1	Me	H	Me	Ph		84
2	Me	Me	Me	Ph		90
3	Ph	H	Me	Ph		89
4	4-Cl–Ph	H	Me	Ph		92
5	Me	H	*i*-Pr	Ph		87
6	Me	H	Me	TBS		76
7	Me	H	Me	H		81
8	Me	H	*t*-Bu	Et		83
9	Me	H	Me	Et		79

[a] All the experiments were done according to Ref. 11.
[b] All the products were identified by ^1H NMR, ^{13}C NMR, HRMS and IR.[12]



Scheme 3. Supposed mechanism.

reaction conditions, the reaction was complex and the desired cyclopropane product was not obtained (Scheme 2).

Having established optimal reaction condition, several racemic monocarboxylic epoxide analogues[9] and a variety of dithianyllithiums were prepared and the reaction results are summarized in Table 1. The substituents of the epoxide terminal did not affect cyclopropanation reaction (Table 1, entries 1–4). When R^3 was a small steric group such as methyl, a tandem reaction occurred and the corresponding cyclopropane-bearing lactones were obtained as the sole products (Table 1, entries 1, 3, 6 and 9). We also found the steric factor of 1,3-dithiane did not obviously affect stereoselectivity of cyclopropanation (Table 1, entries 1, 6, 7 and 8). In all cases, 1,2,3-trisubstrated cyclopropanes were obtained in a high yield of 76–92% and high stereoselectivity (trans:cis > 95:5). The NMR analysis of the crude reaction revealed that in all cases, the trans isomers were formed exclusively and the cis isomers have not been detected by the NMR spectrum.[3,4,10,12]

Based on the experimental results, a plausible mechanism was suggested as follows (Scheme 3). This cyclopropanation reaction was supposed to be a tandem conjugation addition-opening epoxide ring sequence.

In summary, we have developed a new and high stereoselective process for synthesis of 1,2,3-trisubstrate cyclopropanation derivatives in high yields. More importantly, a variety of substituents could be introduced into the resulting cyclopropane monocarboxylic ester derivatives with a highly stereoselective. Further mechanistic and synthetic studies are currently in progress.

Acknowledgements

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References and notes

1. (a) Faust, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2251; (b) Djerassi, C.; Doss, G. A. *New J. Chem.* **1990**, *14*, 713; (c) Salaün, J. *Curr. Med. Chem.* **1995**, *2*, 511; (d) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1; (e) Wiberg, K. B. *Acc. Chem. Res.* **1996**, *29*, 229.
2. (a) *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Springer: Berlin, 2000; Vol. 207; (b) Houben-Weyl. *Methods of Organic Chemistry*; Thieme: Stuttgart, 1997; Vol. E 17c.
3. (a) Little, R. D.; Dawson, J. R. *Tetrahedron Lett.* **1980**, *21*, 2609–2612; (b) Little, R. D.; Dawson, J. R. *J. Am. Chem. Soc.* **1978**, *100*, 4607; For reviews see: (c) Lebel, H.; Marcoux, J. F.; Molinaro, C.; Charette, A. B. *Chem. Rev.* **2003**, *103*, 1015–1036; Caine, D. *Tetrahedron* **2001**, *57*, 2643–2684.
4. (a) Verhe, R.; De Kimpe, N. In *Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley & Sons: New York, 1987, Part 1, Chapter 9, pp 471–505; (b) Walborsky, H. M.; Topolski, M. *Tetrahedron Lett.* **1993**, *34*, 7681–7684; (c) Little, R. D.; Verhe, R.; Monte, W. T.; Nugent, S.; Dawson, J. R. *J. Org. Chem.* **1982**, *47*, 362.
5. Kasatkin, A. N.; Biktimirov, R. Kh.; Tolstikov, G. A. *Tetrahedron Lett.* **1990**, *31*, 4915.
6. (a) Marshall, J. A. *Chem. Rev.* **1989**, *89*, 1503–1511; (b) Ibuka, T.; Tanaka, M.; Nemoto, H.; Yamamoto, Y. *Tetrahedron* **1989**, *45*, 435.
7. Xie, X.; Yue, G.; Tang, S.; Huo, X.; Liang, Q.; She, X.; Pan, X. *Org. Lett.* **2005**, *7*, 4057–4059.
8. For an insightful discussion of the ion pair solution structures of 2-lithio-1,3-dithianes in THF and HMPA/THF, see: (a) Reich, H. J.; Borst, J. P.; Dykstra, R. R. *Tetrahedron* **1994**, *50*, 5869; (b) Sikorski, W. H.; Reich, H. J. *J. Am. Chem. Soc.* **2001**, *123*, 6527–6535; (c) Reich, H. J.; Sikorski, W. H. *J. Org. Chem.* **1999**, *64*, 14–15; (d) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948.
9. Racemic vinyl expoxides were easily obtained in high yield starting from the corresponding allyl alcohols via *m*-CPBA epoxidation, Swern oxidation and Horner–Emmons condensation sequences or from the Darzens

condensation of bromocrotonate; see: (a) Ireland, R. E.; Norbeck, D. W. *J. Org. Chem.* **1985**, *50*, 2198; (b) Koppel, G. A. *Tetrahedron Lett.* **1972**, *15*, 1507–1509.

10. Although there are exceptions, cyclopropanations via the MIRC reaction of acyclic olefins are usually nonstereospecific, and both (*E*)- and (*Z*)-olefins give the *trans*-cyclopropanes. Kasatkin et al. observed a 5 Hz coupling for the trans isomers and 8 Hz for the corresponding cis isomer. And the ^{1}H NMR spectral analysis showed that the *trans*-cyclopropanes were the product: Funaki, I.; Bell, R. P. L.; Thijs, L.; Zwanenburg, B. *Tetrahedron* **1996**, *52*, 12253–12274.
11. General procedure: A solution of the dithiane (1 mmol) and HMPA (0.30 mL, 1.65 mmol) in anhydrous THF (3 mL) was cooled to −50 °C. *n*-BuLi (2.5 M in petroleum ether, 0.6 mmol) was added dropwise via syringe, and the reaction mixture allowed to warm to −20 °C while stirring for 0.5 h. The mixture was re-cooled to −50 °C and a solution of the monoactivated epoxide analogues (0.50 mmol) in anhydrous THF (3 mL) was added dropwise via syringe. The mixture was warmed to −20 °C over 1 h. After stirring an additional 19 h the reaction was quenched with saturated aqueous NH_4Cl (6 mL) and then diluted with Et_2O (20 mL). The organic layers were separated, the aqueous phase extracted with Et_2O (3×5 mL), and the combined organic layers dried over anhydrous Na_2SO_4, filtered and concentrated. Flash chromatography (petroleum ether/ethyl acetate as eluent) provided cyclopropane derivatives as either colourless oil or white solid.
12. The spectral data of some products. Product 1: White crystal, mp 126–127 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 7.93 (d, $J = 8.1$ Hz, 2H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.29 (t, $J = 7.5$ Hz, 1H), 4.63–4.59 (m, 1H), 2.70–2.62 (m, 4H), 2.01 (m, 1H), 1.98 (m, 1H), 1.89 (m, 2H), 1.84 (m, 1H), 1.33 (d, $J = 6.3$ Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.4, 137.2, 129.9, 128.8, 127.9, 75.6, 57.54, 32.0, 27.9, 27.7, 25.7, 24.5, 23.2, 17.5. IR (ν cm^{-1}): 1762, 1192, 971, 901, 784, 712, 615, 571, 513. HRMS (ESI) Calcd for $C_{16}H_{18}O_2S_2Na$ $(M+Na)^+$: 329.0640. Found: 329.0646. Product 6: White crystal, mp 97–98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (m, 1H), 2.89 (m, 2H), 2.48 (m, 2H), 2.45 (dd, $J = 7.8$, 4.5 Hz, 1H), 2.23 (dd, $J = 4.2$, 3.0 Hz, 1H), 2.08 (m, 1H), 1.90 (m, 2H), 1.42 (d, $J = 6.3$ Hz, 3H), 0.99 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.3, 77.4, 36.6, 32.3, 28.5, 27.0, 26.4, 24.0, 23.7, 23.6, 19.8, 17.7, −6.0, −6.4. IR (ν cm^{-1}): 2959, 2857, 1768, 1187, 1085, 970, 824. HRMS (ESI) Calcd for $C_{16}H_{28}O_2S_2Si$ $(M+NH_4)^+$: 362.1638. Found: 362.1645.