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Chemo-, Regio-, and Diastereoselective Synthesis of Functionalized Cyclopropanes by Cyclization of Dilithiated Nitriles with Epibromohydrin

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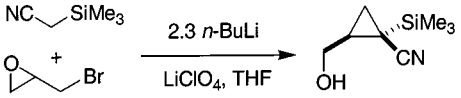
ABSTRACT



The cyclization of 1,1-dianions with epibromohydrin results in chemo-, regio-, and diastereoselective formation of functionalized hydroxymethyl cyclopropanes.

Cyclopropanes are present in a number of pharmacologically relevant natural and unnatural products and also represent useful synthetic building blocks.[1] Although a number of cyclopropane syntheses are known today, very few examples have been reported for the most simple synthetic approach—the direct cyclization of dimetalated substrates (dianions) with dielectrophiles. The reason for this lies in the low reactivity matching of the starting materials giving rise to many side reactions. The cyclization of dilithiated dialkyl succinates (1,2-dianions) with bromochloromethane has been reported to result in formation of symmetrical 1,2-disubstituted cyclopropanes.[2] Cyclization reactions of 1,1-dianions with 1,*n*-dielectrophiles (n = 2, 3, 4) are relatively rare.[3] In the course of our interest in the development of new cyclization reactions of dianions with 1,2-dielectrophiles, we have recently reported the synthesis of 2-alkylidene-3-iminoindoles by cyclization of 1,1-dianions with oxaldiimidoyl dichlorides[4] and the synthesis of functionalized tetrahydrofurans by cyclization of 1,3-dicarbonyl dianions with epibromohydrin.[5] Herein, we wish to report cyclization reactions of epibromohydrin with dilithiated nitriles.[6−8] This methodology allows an efficient synthesis of a variety of functionalized cyclopropanes which represent useful synthetic building blocks.

Our first attempts to induce a cyclization of the dianion of phenylacetonitrile **1a** with 1-tosyloxy-2,3-epoxypropane resulted in the formation of a complex mixture. Reaction of the dianion of **1a** with epibromohydrin **2** at 0 °C afforded 1-cyano-2-hydroxymethylcyclopropane **3a**, but only in a low yield. We eventually found that optimal yields were obtained when the reaction was carried out in the presence of the

(1) (a) *Houben-Weyl, Methoden der Organischen Chemie*, 4th ed., Vol. E17, Carbocyclic Three-Membered Ring Compounds; de Meijere, A., Ed.; Thieme: Stuttgart, 1996. (b) *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: Chichester 1987.

(2) Misumi, A.; Iwanaga, K.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1985**, *107*, 3343.

(3) For cyclization reactions of 1,1-dianions, see: (a) Müller, J. F. K.; Neuburger, M.; Zehnder, M. *Helv. Chim. Acta* **1997**, *80*, 2182. (b) Eisch, J. J.; Dua, S. K.; Behrooz, M. *J. Org. Chem.* **1985**, *50*, 3674. (c) Mussatto, M. C.; Savoia, D.; Trombini, C.; Umani-Ronchi, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 260. The sodium alkoxide mediated cyclization of malonates with 1,2-dibromoethane or 1,2-bromochloroethane proceeds by stepwise deprotonation of the nucleophile rather than by formation of a dianion: see ref 1a.

(4) Langer, P.; Wuckelt, J.; Döring, M.; Görls, H. *J. Org. Chem.* **2000**, *65*, 3603.

(5) Langer, P.; Freifeld, I. *Chem. Eur. J.* **2001**, *7*, 565.

(6) For a review of the structures of lithiated and dilithiated nitriles and sulfones, see: Boche, G. *Angew. Chem.* **1989**, *101*, 286; *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 277.

(7) For cyclizations of nitrile monoanions with epibromohydrin and epichlorohydrin, see: (a) Grangier, G.; Aitken, D. J.; Guillaume, D.; Husson, H.-P. *Tetrahedron Lett.* **1994**, 4355. (b) Benedetti, F.; Berti, F.; Risaliti, A. *Tetrahedron Lett.* **1993**, 6443. (c) Aitken, D. J.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1990**, *55*, 2814. (d) Aitken, D. J.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1988**, 3315. (e) Mouzin, G.; Cousse, H.; Bonnaud, *Synthesis* **1978**, 304.

(8) For the synthesis of vinylcyclopropanes by reaction of lithiated nitriles with ethyl 4-bromocrotonate, see: Ghera, E.; Ben-David, Y. *Tetrahedron Lett.* **1979**, 4603.

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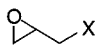
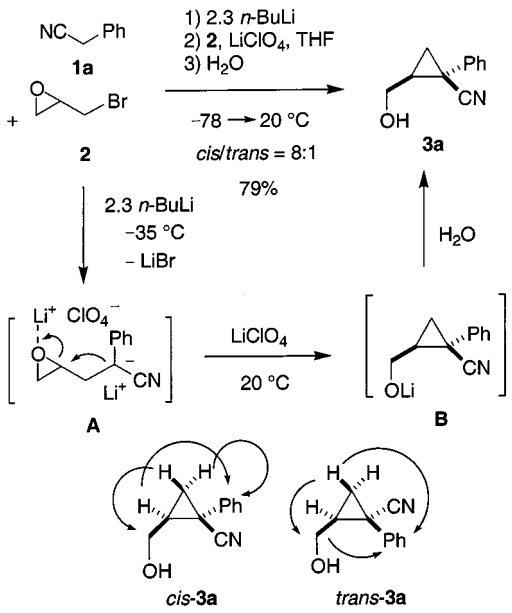
Table 1. Optimization of the Reaction of Dilithiated **1a** with Functionalized Epoxides

Entry		Lewis acid	(equiv.)	**1a** (equiv.)	*t* [h] [a]	(%) [b]
1	OTos	-		2.5	10 + 8	0
2	OTos	$LiClO_4$	(2.5)	2.5	10 + 8	0
3	Cl	$LiClO_4$	(2.5)	2.5	10 + 8	36
4	Br	-		1.0	10 + 8	22
5	Br	-		2.5	10 + 8	30
6	Br	LiCl	(2.5)	2.5	10 + 8	35
7	Br	$LiClO_4$	(2.5)	2.5	10 + 8	79
8	Br	$LiClO_4$	(2.5)	1.0	10 + 8	48
9	Br	$LiClO_4$	(2.5)	2.5	1 + 12	24

[a] Reaction time at −35 °C + reaction time at 20 °C. [b] Isolated yield of nonseparable diastereomeric mixtures.

Lewis acid lithium perchlorate and when an excess of the dianion was used (Table 1).[9] A thorough tuning of the temperature also proved important for the optimization. The reaction mixture was stirred for 10 h at −35 °C and subsequently for 8 h at 20 °C. The use of epichlorohydrin was less effective than that of **2**. Cyclopropane **3a** was formed with good diastereoselectivity (*cis*/*trans* = 8:1). However, the isomeric mixture could not be separated by chromatography. The configuration was established by NOESY experiments carried out on the diastereomeric mixture of **3a**. The diagnostic NOE effects are depicted in Scheme 1.

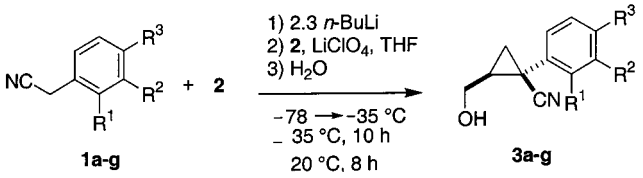
Scheme 1. Cyclization of Dilithiated Phenylacetonitrile with Epibromohydrin



The formation of cyclopropane **3a** can be explained by the following mechanism: at low temperature, the dianion chemoselectively attacked the carbon attached to the bromine atom. Warming of the mixture to 20 °C resulted in attack of the monoanion onto the central carbon atom of the epoxide. The epoxide was activated by the Lewis acid $LiClO_4$. Alternatively, the formation of **3a** can be explained by attack of **1a** onto the epoxide, Payne rearrangement and subsequent cyclization. The regioselectivity (formation of a three- rather than a four-membered ring) can be explained on the basis of stereoelectronic considerations.[10−12] The diastereoselectivity can be explained by steric interaction of the phenyl and the hydroxymethyl group during the cyclization (Scheme 1).

To study the preparative scope of the reaction, the substituents of the arylacetonitrile were systematically varied (Scheme 2, Table 2). Cyclopropanes **3b** and **3c** were prepared

Scheme 2. Cyclization of Dilithiated Arylacetonitriles with Epibromohydrin



with good diastereoselectivity from 4-tolyl- and 4-methoxyphenylacetonitrile, respectively. The reaction of **2** with 3-tolyl- and 3-methoxyphenylacetonitrile afforded cyclopropanes **3d** and **3e**, respectively, in good yields and with good diastereoselectivity. The use of 2-tolylacetonitrile **1f** resulted in formation of the expected product **3f**, but only in a low

(9) **Representative experimental procedure:** To a THF solution (20 mL) of phenylacetonitrile (0.58 g, 5.00 mmol) was added *n*-BuLi (10.48 mmol, 4.23 mL, solution in *n*-hexane) at 0 °C. The solution was stirred for 1 h, and subsequently a THF solution (20 mL) of $LiClO_4$ (0.34 g) and of epibromohydrin (0.33 g, 2.40 mmol) was added at −78 °C. The temperature was increased to −35 °C during 2 h, and the solution was stirred at this temperature for 10 h. The solution was warmed to ambient during 1 h and stirred for 8 h. To the solution was added a saturated aqueous solution of NH_4Cl (40 mL) and ether (50 mL). The organic layer was separated, and the aqueous layer was extracted with ether (2 × 50 mL) and dichloromethane (2 × 50 mL). The combined organic layers were extracted with a saturated aqueous solution of brine, dried (Na_2SO_4), and filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, petroleum ether/ether = 4:1 → 1:1) to give **3a** as a colorless oil (330 mg, 79%, *Z*/*E* = 8:1). Spectroscopic data for **3a**: ^1H NMR ($CDCl_3$, 250 MHz) δ = 1.55 (m, 1 H, CH_2), 1.91 (m, 1 H, CH), 3.34 (br, 1 H, OH), 3.76 (dd, J = 12 Hz, J = 5 Hz, CH_2OH), 3.98 (dd, J = 12 Hz, J = 5 Hz, CH_2OH), 7.28 (m, 5 H, Ph); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 16.08 (C), 21.23 (CH_2), 31.30 (CH), 62.62 (CH_2OH), 120.57 (C, CN), 125.82, 127.56, 128.73 (CH, Ph), 135.52 (C); MS (EI, 70 eV) 173 (M^+, 18), 143 (24), 129 (100), 115 (26), 103 (34); the exact molecular mass *m*/*z* = 173.0841 ± 2 mD (M^+) for $C_{11}H_{11}NO$ was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{11}H_{11}NO$: C 76.28, H 6.40. Found: C 76.46, H 6.28. All compounds were prepared as racemic material and gave satisfactory spectroscopic and analytical and/or high-resolution mass data. The diastereomers of **3a**−**g** and **5** could not be separated.

(10) For comparison, see: (a) Corbel, B.; Decesare, J. M.; Durst, T. *Can. J. Chem.* **1978**, *56*, 505. (b) Benedetti, F.; Berti, F.; Risaliti, A. *Tetrahedron Lett.* **1993**, 6443.

(11) For the synthesis of hydroxycyclobutanes, see: Jeffery, J. E.; Kerrigan, F.; Miller, T. K.; Smith, G. J.; Tometzki, G. B. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2583.

(12) Brown, A. C.; Carpino, L. A. *J. Org. Chem.* **1985**, *50*, 1749.

Table 2. Synthesis of separate Cyclopropanes **3**

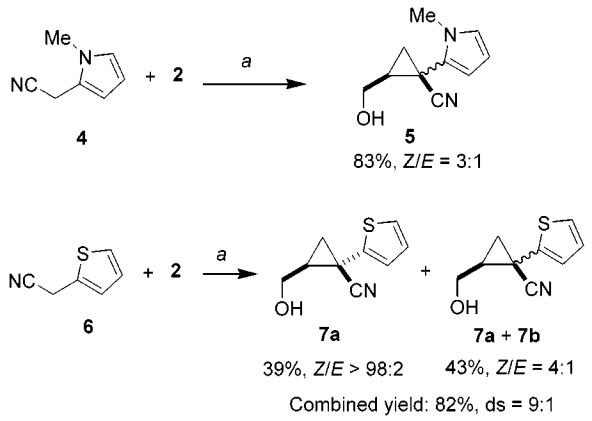
3	R^1	R^2	R^3	*cis/trans*[a]	(%)[b]
a	H	H	H	8:1	79
b	H	H	Me	7:1	56
c	H	H	OMe	7:1	52
d	H	Me	H	7:1	71
e	H	OMe	H	6:1	75
f	Me	H	H	5:1	34
g		$-C_4H_4-$	H	5:1	81

[a] By ^{1}H NMR of the isolated product. [b] Isolated yield of nonseparable diastereomeric mixtures.

yield. The nitrile **1f** was recovered in 46% yield. The reaction of **2** with 2-naphthylacetonitrile gave cyclopropane **3g**.

The synthesis of heterocyclic cyclopropane derivatives, which are of pharmacological relevance, was next studied. The reaction of *N*-methyl-2-cyanomethylpyrrole **4** with epibromohydrin **2** afforded the cyclopropyl-substituted pyrrole **5** in good yield (Scheme 3). Similarly, the cyclopropyl-

Scheme 3. Synthesis of Cyclopropyl-Substituted Pyrrole **5** and Thiophene **7**[a]

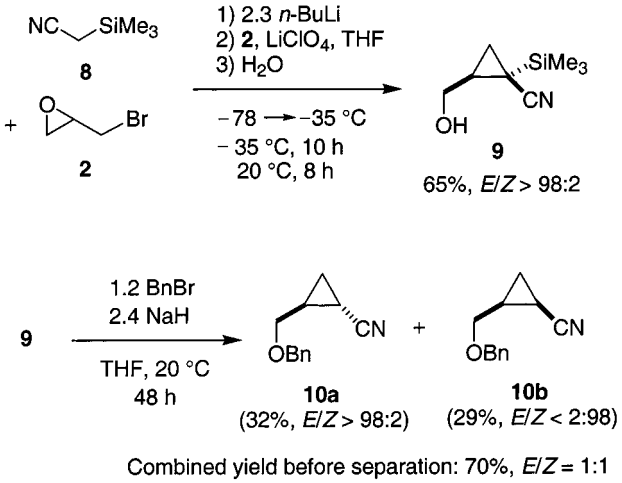


[a] (1) 2.3 *n*-BuLi, THF; (2) **2**, $LiClO_4$; (3) H_2O; −78 → −35 °C, −35 °C 10 h, 20 °C 8 h.

substituted thiophene **7** could be prepared from 2-cyanomethylthiophene **6** in 82% combined yield. The *Z*-diasteromer could be isolated in pure form.

The cyclization of dilithiated trimethylsilylacetonitrile **8** with epibromohydrin afforded the TMS-substituted cyclopropane **9** with excellent diastereoselectivity (Scheme 4). The cyclization was carried out by following the procedure developed for the synthesis of **3a** (vide supra). The configuration of **9** was established by NOESY experiments. Functionalized 1,2-disubstituted cyclopropanes containing a TMS group have to our knowledge not yet been prepared. However, more simple silyl-substituted cyclopropanes are known and their desilylation using tetrabutylammonium fluoride (TBAF) has been studied.[13,14] In fact, the silyl group of **9** could be removed using TBAF. However, the yield was low (ca. 10%), due to decomposition during chromatography

Scheme 4. Cyclization of Dilithiated Trimethylsilylacetonitrile with Epibromohydrin



and due to the volatility of the product. Optimal results were eventually obtained when **9** was treated with NaH (2 equiv) and benzylic bromide. The benzylated TMS-free cyclopropane **10** was isolated in good yield as a mixture of diastereomers (70%, ds = 1:1). The diastereomers **10a** and **10b** could be readily separated by chromatography. The configuration of the pure isomers was assigned by NOESY experiments. Variation of the conditions did not result in any improvement of the stereoselectivity. Deprotonation of the diastereomeric mixture of **10** with LDA and subsequent protonation with hydrochloric acid or 2,6-di(*tert*-butyl)phenol did not change the diastereomeric ratio. The formation of **10** can be explained by benzylation of the hydroxy group, S_N-reaction of NaH with the TMS group, extrusion of $HSiMe_3$, and formation of a cyclopropyl carbanion which was protonated during the aqueous workup. The presence of TBAI (0.1 equiv) resulted in a minor decrease in yield.

In summary, we have reported a new and convenient synthesis of functionalized cyclopropyl nitriles. The reactions are easy to carry out and proceed with very good chemo- and regioselectivity and with good diastereoselectivity.

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Supporting Information Available: Details of the experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL010207C

(13) For the preparation of cyclopropanes by the reaction of silyl/sulfur-stabilized carbanions with epoxides, see: Schaumann, E.; Friese, C. *Tetrahedron Lett.* **1989**, 7033.

(14) For the synthesis and reactions of silyl-substituted cyclopropanes, see: (a) Paquette, L. A.; Blankenship, C.; Wells, G. J. *J. Am. Chem. Soc.* **1984**, *106*, 6442. (b) Wells, G. J.; Yan, T.-H.; Paquette, L. A. *J. Org. Chem.* **1984**, *49*, 3604. (c) Blankenship, C.; Wells, G. J.; Paquette, L. A. *Tetrahedron* **1988**, 4023.