Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 5775–5786

One-pot cyclization of dilithiated nitriles with isothiocyanates and epibromohydrin. Synthesis of 2-cyano-1-(hydroxymethyl)-cyclopropanes and 2-cyanomethylidene-4-(hydroxymethyl)-thiazolidines

Uwe Albrecht,[a] Ilia Freifeld,[a] Helmut Reinke[b] and Peter Langer[b,c,*]

[a]*Institut für Chemie und Biochemie, Universität Greifswald, Soldmannstr. 16, 17487 Greifswald, Germany*
[b]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany*
[c]*Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany*

Received 10 February 2006; revised 13 March 2006; accepted 22 March 2006
Available online 3 May 2006

Abstract—The cyclization of dilithiated nitriles with epibromohydrin afforded 2-cyano-1-(hydroxymethyl)cyclopropanes. 2-Cyanomethylidene-(4-hydroxymethyl)thiazolidines were prepared by one-pot cyclization of dilithiated nitriles with isothiocyanates and epibromohydrin.

1. Introduction

One-pot cyclizations of dianions with dielectrophiles are of considerable synthetic utility.[1] In this context, epibromohydrin (EBH) has been used as a versatile synthetic building block. In recent years, we reported one-pot cyclizations of epibromohydrin with dilithiated 1,3-dicarbonyl compounds,[2] amides,[3] oximes and hydrazones.[4] The Lewis acid mediated cyclization of EBH with 1,3-bis-silyl enol ethers has been reported.[5] 2-Cyano-1-(hydroxymethyl)cyclopropanes are available by cyclization of epihalohydrins with nitriles in the presence of weak or strong bases.[6,7] Recently, we have shown that the sequential addition of isothiocyanates and EBH to dilithiated nitriles provides a convenient approach to 2-cyanomethylidene-(4-hydroxymethyl)thiazolidines.[8] With respect to our preliminary communications in this field,[6,8] we herein report full details of one-pot cyclizations of EBH with nitriles with[8] or without[6] addition of isothiocyanates.

2. Results and discussion

2.1. Synthesis of 2-cyano-1-(hydroxymethyl)cyclopropanes

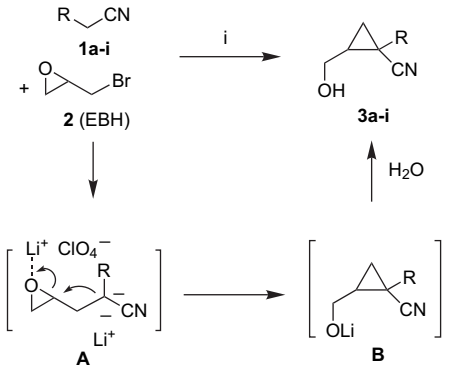
The reaction of the dianion[9] of phenylacetonitrile (**1a**), generated by addition of *n*-BuLi (2.3 equiv), with epibromohydrin (**2**, EBH) afforded the 2-cyano-1-(hydroxymethyl)-cyclopropane **3a**.[10,11] Optimal yields (up to 79%) were obtained when (a) lithium perchlorate was added, (b) an excess of the dianion was used (2.5 equiv) and (c) the reaction mixture was stirred for 10 h at −35 °C and subsequently for 8 h at 20 °C (Scheme 1, Table 1). The use of 1-tosyloxy-2, 3-epoxypropane and epichlorohydrin proved to be unsuccessful. Cyclopropane **3a** was isolated as an inseparable diastereomeric mixture (*cis*/*trans*=8:1, the CN and the CH_2OH group are located cis to each other). The presence of Lewis acid proved to be important for the activation of the epoxide in the cyclization step. The tuning of the temperature proved to be important as the first attack of **1a** onto **2** occurred selectively at −35 °C. Upon warming to 20 °C and stirring at this temperature, the cyclization step occurred. Therefore, selectivity and yield decreased when the temperature of the reaction mixture was not maintained at −35 °C for 10 h. The use of an excess of the dianion was important to achieve a complete conversion of **2**.

The formation of **3a** can be explained by attack of the dianion onto the carbon attached to the bromine atom, cyclization and subsequent protonation upon aqueous work-up. Alternatively, attack of the dianion onto the sterically less encumbered carbon atom of the epoxide and subsequent S_Ni reaction is in principle possible. The diastereoselectivity can be explained by steric interaction of the phenyl and the hydroxymethyl group during the cyclization (Scheme 1).

The cyclization of arylacetonitriles **1a–g** with EBH afforded the 2-cyano-1-(hydroxymethyl)cyclopropanes **3a–g** in

Keywords: Cyclizations; Cyclopropanes; Epibromohydrin; Heterocycles; Isothiocyanates.
* Corresponding author. Tel.: +49 381 4986410; fax: +49 381 4986412; e-mail: peter.langer@uni-rostock.de

0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.03.072



Scheme 1. Cyclization of dilithiated arylacetonitriles with epibromohydrin; *i*: (1) 2.3 *n*-BuLi, (2) **2**, $LiClO_4$, THF, (3) H_2O.

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 non-separable diastereomeric mixtures.

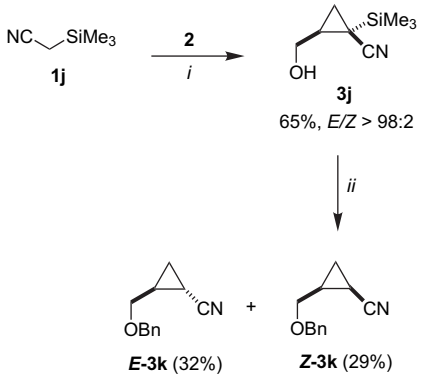
moderate to good yields and with good diastereoselectivity (Scheme 1, Table 2). The reaction of (*N*-methylpyrrol-2-yl)acetonitrile with EBH afforded the cyclopropane **3h**. The cyclopropyl-substituted thiophene **3i** was prepared from (thien-2-yl)acetonitrile; the trans-diastereomer could be isolated in pure form. The yields of **3a–i** were generally good (except for **3f** containing a substituent at the *ortho* position of the aryl group). For all products (except for **3h**, dr=3:1) good diastereoselectivities in favour of the cis configured products were observed (dr=5:1–8:1). The selectivity can be explained by steric interaction of the aryl group with the oxygen atom of the epoxide in intermediate **A** (Scheme 1). An electronic impact on the stereoselectivity cannot be excluded.

Table 2. Synthesis of 2-cyano-1-(hydroxymethyl)cyclopropanes **3a–i**

3	R	(%)[a]	*cis*/*trans*[b]
a	Ph	79	8:1
b	4-MeC_6H_4	56	7:1
c	4-(MeO)C_6H_4	52	7:1
d	3-MeC_6H_4	71	7:1
e	3-(MeO)C_6H_4	75	6:1
f	2-MeC_6H_4	34	5:1
g	2-Naphthyl	81	5:1
h	*N*-Methylpyrrol-2-yl	83[c]	3:1
i	Thien-2-yl	39[c]	<2:98[d]

[a] Isolated yields of non-separable diastereomeric mixtures.
[b] By ^1H NMR of the isolated product.
[c] LDA was used.
[d] Besides, a mixture of diastereomers (*cis*/*trans*=1:4) was isolated (43%).

The cyclization of dilithiated (trimethylsilyl)acetonitrile (**1j**) with EBH afforded the TMS-substituted cyclopropane **3j** with excellent diastereoselectivity (Scheme 2).[12,13] Notably, this transformation required the use of freshly prepared **1j**. Treatment of **3j** with TBAF afforded **3k**; however, the yield was low, due to decomposition and volatility of the product. The reaction of **3j** with NaH (2.4 equiv) and benzylic bromide (1.2 equiv) afforded the benzylated TMS-free cyclopropane **3k** as a separable mixture of diastereomers. The formation of **3k** can be explained by benzylation of the hydroxyl group, nucleophilic attack of NaH onto the TMS-group, extrusion of $HSiMe_3$ and formation of a cyclopropyl carbanion, which was protonated during the aqueous work-up. The use of 2 equiv (rather than only one) of NaH proved to be important. The configuration of cyclopropanes **3a**, **3j**, *cis*-**3k** and *trans*-**3k** was proved by NOESY experiments.



Scheme 2. Cyclization of dilithiated (trimethylsilyl)acetonitrile with epibromohydrin; *i*: (1) 2.3 LDA, (2) **2**, $LiClO_4$, THF, (3) H_2O; *ii*: BnBr (1.2 equiv), NaH (2.4 equiv), THF, 20 °C, 48 h.

2.2. Synthesis of 2-cyanomethylidene-(4-hydroxymethyl)thiazolidines

One-pot cyclizations often rely on the addition of a nucleophile onto a relais species (e.g., a nitrile or cumulene) and subsequent cyclization with a dielectrophile. Isothiocyanates represent interesting relais species in this type of transformation.[14] For example, one-pot cyclizations of arylmethylnitriles (dinucleophile) with isothiocyanates (relais species) and 1,2-dibromoethane, chloroacetic chloride[15] or ethyl 2-chloro-2-oxoacetate (dielectrophile) have been reported.[16] Recently, we have found that the reaction of the dianion of arylacetonitriles with isothiocyanates and epibromohydrin (EBH) afforded 2-alkylidene-(4-hydroxymethyl)thiazolidines.[8] Notably, (4-hydroxymethyl)thiazolidines and -oxazolidines are present in a variety of pharmacologically relevant compounds.[17] Related compounds have been employed as building blocks in the synthesis of penicillinic derivatives, D-biotin and allokainic acid.[18] Previous syntheses of (4-hydroxymethyl)thiazolidines and -oxazolidines rely on cyclization reactions with direct formation of the hydroxymethyl group. This includes, for example, cyclizations of aziridines with carbon disulfide,[19] hydrolysis of 4-thioxo-2-azetidinones[20] or cyclizations of ketenethioacetals with 1,3-propanedioles.[21] Other syntheses are based on the reduction of carboxylic derivatives and include, for example, condensations of aldehydes or ketones with L-cysteine,[22a,b] cyclizations of L-serinal derivatives,[23] cyclizations of potassium