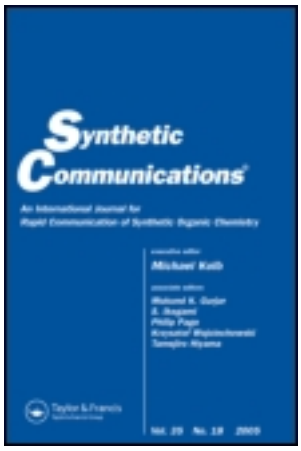

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Facile Syntheses of Azetidin-3-ols by Rearrangement of 2,3-Epoxypropylamines

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ABSTRACT

The *N*-alkyl-2,3-epoxypropylamines (**2**) formed from primary alkylamines (**1**) and epichlorohydrin were chemoselectively rearranged to the four-membered rings, *N*-alkylazetidin-3-ols (**3**), upon treatment of triethylamine in refluxing acetonitrile.

Polynitrated small-size heterocycles and carbocycles are at the forefront of the search for more powerful and less sensitive energetic materials because of the increased performance expected from the additional energy increase upon opening of the strained ring system

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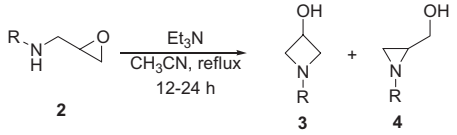
during decomposition. An important new member of this class of energetic materials is 1,3,3-trinitroazetidine (TNAZ), a potentially melt castable explosive has a melting point (m.p. 110°C), moderate density (1.84 gcm^{-3}), good thermal stability (>240°C), and low sensitivity.[1] The principal source of 1,3,3-trinitroazetidine remains the original preparative method starting from *tert*-butylamine and epichlorohydrin.[2]

We have initiated preparation of polymer-bound polynitroazetidines as new energetic materials and hence needed sterically nonbulky *N*-alkylazetidin-3-ols. Although Gaertner's preparation of azetidinols from epichlorohydrin was limited to sterically hindered amines, some important progress has been made toward more productive synthesis of these compounds.[3] Okutani et al. substantially decreased the reaction time for ring-closure and increased the yield of products conducting the reactions in acetonitrile[4] and Gaj reported a modified synthetic method for *N*-alkylazetidin-3-ols from sterically less hindered amines and methoxymethyl ethers of 1,3-dichloro-2-propanols.[5] Jenkins and Higgins successively reported improved method for preparation of the ether derivatives of azetidinols with nonbulky *N*-alkyl substituents.[6]

In searching for the more convenient methods for preparation of 3-azetidinols, the rearrangement of *N*-alkyl-2,3-epoxypropylamines (**2**) was investigated. The 2,3-epoxyamines (**2**) were prepared from epichlorohydrin and various amines according to the known methods as summarized in Table 1.

A solution of the primary amines **1** and epichlorohydrin in isopropanol was stirred for about 24 h to give the *N*-alkyl-2,3-epoxypropylamines **2a–g** without contaminating the corresponding tertiary amines.

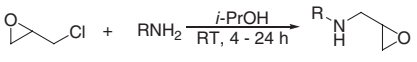
Intramolecular cyclization of 2,3-epoxyamines **2** can lead to azetidin-3-ols (**3**) by nucleophilic attack at the terminal C-3 carbon or to hydroxymethylaziridines **4** as known as the aza-Payne rearrangement via a 3-*exo*-*tet* type pathway (Eq. (1)).



2 3 4 (1)

Recently, Karikomi et al. found that magnesium bromide could be of great utility for the regioselective rearrangement of 2,3-epoxyamines to *N*-alkyl-3-azetidinols.[7] During our preparation of

Table 1. Preparations of *N*-alkyl-2,3-epoxyamines.



1 2

Entry	*R* group	Time (h)	Products	Yield (%)
1	*t*-Butyl-	24	**2a**	98
2	Isopropyl-	24	**2b**	94
3	*n*-Butyl-	16	**2c**	90
4	$HOCH_2CH_2$-	6	**2d**	86
5	Allyl-	24	**2e**	81
6	Benzyl-	24	**2f**	81
7	Diphenylmethyl-	24	**2g**	98

Table 2. Cyclizations of *N*-alkyl-2,3-epoxypropylamine hydrochlorides (**2**) to *N*-alkylazetidin-3-ols (**3**).

Entry	*R* group	Time (h)	Products	Yield (%)
1	*t*-Butyl-	16	**3a**	85
2	Isopropyl-	17	**3b**	47
3	*n*-Butyl-	22	**3c**	40
4	$HOCH_2CH_2$-	12	**3d**	26
5	Allyl-	24	**3e**	50
6	Benzyl-	24	**3f**	56
7	Diphenylmethyl-	24	**3g**	72

N-tert-butylazetidin-3-ol, we found that treatment of triethylamine to *N-tert*-butyl-2,3-epoxypropylamine **2a** in acetonitrile was rearranged to the corresponding azetidinol **3a** in highly efficient manner. Then, we have optimized the reaction conditions applicable to preparation of various alkyl-substituted 3-azetidinols **3b–3g**. When these 2,3-epoxyamines were refluxed in acetonitrile in the presence of triethylamine as a base, they were smoothly cyclized to the *N*-alkylazetidin-3-ols in good yields as summarized in Table 2.

Several features are to be noted. First, the present method allows for the control of chemoselective rearrangement of 2,3-epoxypropylamines to azetidin-3-ols (**3**) without using magnesium bromide. Second, simple modification of the known reaction conditions has shown to be applicable to synthesis of various *N*-alkyl-azetidin-3-ols from sterically nonhindered amines. Especially, triethylamine might help the nucleo-

Table 3. ^{1}H NMR and ^{13}C NMR data (in $CDCl_3$) for **3a–g**.

Compds.	^{1}H NMR, δ	^{13}C NMR, δ
3a	1.22 (s, 9H), 3.58 (dd, $J=8.0$, 6.0 Hz, 2H), 3.98 (dd, $J=8.0$, 8.0 Hz, 2H), 4.65 (m, 1H)	23.79, 57.07, 57.47, 58.33
3b	0.94 (d, $J=6.0$ Hz, 6H), 2.36 (m, 1H), 2.89 (dd, $J=7.6$, 4.0 Hz, 1H), 2.89 (dd, $J=7.6$, 5.6 Hz, 1H), 3.59 (dd, $J=8.0$, 4.4 Hz, 1H), 3.59 (dd, $J=8.0$, 6.4 Hz, 1H), 4.35 (m, 1H)	19.45, 58.68, 60.16, 62.35
3c	0.89 (t, $J=6.8$Hz, 3H), 1.30 (m, 4H), 2.42 (t, $J=7.2$ Hz, 2H), 2.88 (dd, $J=8.4$, 6.0 Hz, 1H), 2.88 (dd, $J=6.8$, 4.4 Hz, 1H), 3.58 (dd, $J=8.4$, 6.0 Hz, 1H), 3.58 (dd, $J=6.8$, 4.4 Hz, 1H), 4.37 (m, 1H)	14.04, 20.49, 29.71, 59.53, 61.69, 64.00
3d	2.65 (t, $J=5.2$ Hz, 2H), 3.10 (dd, $J=8.8$, 4.8 Hz, 2H), 3.32 (bs, 1H), 3.53–3.56 (m, 2H), 3.57–3.61 (m, 2H), 4.41 (m, 1H)	59.65, 61.45, 62.98, 64.27
3e	2.93 (m, 1H), 3.08 (d, $J=6.4$ Hz, 1H), 3.58 (dd, $J=8.8$, 6.0 Hz, 1H), 4.38 (quintet, 1H, $J=6$ Hz, 1H), 5.10 (dd, 1H, $J=10.4$, 1 Hz, 1H), 5.15 (dd, 1H, $J=17.2$, 2.0 Hz, 1H), 5.65–5.76 (m, 1H)	61.67, 61.94, 63.56, 117.51, 133.40
3f	2.92 (dd, 1H, $J=8.4$, 6.0 Hz, 1H), 3.54 (dd, 1H, $J=6.8$, 4.4 Hz, 1H), 3.58 (s, 2H), 4.33 (quintet, 1H, $J=6.0$ Hz), 7.19–7.30 (m, 5H)	61.83, 63.42, 63.75, 127.10, 128.19, 128.41, 137.01
3g	2.88 (dd, 1H, $J=8.0$, 5.6 Hz, 1H), 3.49 (dd, 1H, $J=6.8$, 4.4 Hz, 1H), 4.32 (s, 1H), 4.39 (quintet, 1H, $J=6.0$ Hz), 7.13–7.46 (m, 10H)	61.99, 63.55, 78.43, 127.01, 127.27, 128.30, 141.71

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philic nitrogen of 2,3-epoxypropylamines attack to the epoxide at the less hindered end. In summary, this facile azetidinol synthesis could be a good method for nonbulky alkyl-substituted azetidin-3-ols (**3**).

GENERAL EXPERIMENTAL

1. General Procedure

All reactions were performed under an atmosphere of dry argon. Commercial reagents were used as received without further purification. All products were purified by flash column chromatography using silica gel 60 (79–230 mesh, Merck). The purified products were identified with ^{1}H and ^{13}C NMR spectral data obtained from a Varian Mercury 400 MHz NMR spectrometer using tetramethylsilane as an internal standard.

2. A Typical Procedure for Synthesis of *N*-Alkyl-2,3-epoxyamines 2

To a solution of diphenylmethylamine (**1g**, 1.00 g, 5.46 mmol) in isopropylalcohol (10 mL) was added dropwise epichlorohydrine (430 μL, 5.46 mmol) at 0°C. Then, this mixture was stirred at RT for 24 h, concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate = 10/1) to give *N*-diphenylmethyl-2,3-epoxypropylamine **2g** (1.28 g, 98% yield).

3. A Typical Procedure for Synthesis of *N*-Alkylazetidin-3-ols 3

To a solution of *N*-diphenylmethyl 2-3-epoxypropylamine (**2g**, 1.30 g, 5.43 mmol) in acetonitrile (10 mL) was added triethylamine (2.3 mL, 16.3 mmol) at 0°C. Then, this mixture was refluxed for 24 h, cooled to room temperature. The solution was concentrated under reduced pressure and the residue was purified by flash column chromatography in silica gel (hexane/ethyl acetate = 2/1) to give a *N*-diphenylmethyl-azetidin-3-ol (**3g**, 0.93 g, 3.91 mmol, 72% yield) as a white solid. M.p.: 110–113°C (Lit.[2b] 113°C). ^{1}H NMR and ^{13}C NMR data for **3a–g** are tabulated in Table 3.

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