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Regio-selective synthesis of 1,2-aminoalcohols from epoxides and chlorohydrins

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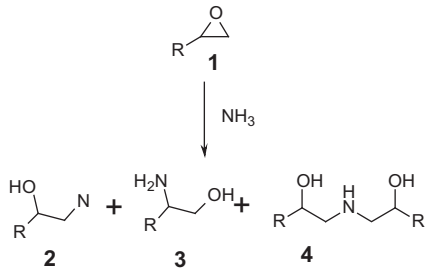
ABSTRACT

A simple and efficient procedure for the regio-selective synthesis of 1,2-aminoalcohols from terminal epoxides and chlorohydrins by using NaHMDS as the source of amine is reported. The wider scope and utility of this method is demonstrated.

1,2-Aminoalcohols are important building blocks in the synthesis of natural products, pharmaceuticals, and other materials.[1] Generally, these 1,2-aminoalcohols are prepared by nucleophilic ring opening of epoxides with nitrogen based nucleophiles.[2–5] Simple ammonolysis of epoxides **1** (Scheme 1) is one of the most commonly used methods[6] but frequently suffers from poor regio-selectivity (**2** vs **3**) and over alkylation (**4**).

To circumvent these challenges, alternative methods to synthesize this important functional group have received an immense amount of attention over the years. Widely used methods include epoxide opening with (i) azides followed by reduction,[2] (ii) phthalimides followed by deprotection[3] (iii) *N,N*-dibenzylamine followed by debenzylation[4], (iv) benzhydrilamine followed by deprotection.[5] Despite these advancements, there are still some drawbacks associated with these previously reported methods, such as involvement of energetic intermediates (azides), toxic reagents (hydrazine for phthalimide deprotection in [ii]), requirement of additional steps for deprotection, and in some cases unsatisfactory selectivity. Therefore, the development of an efficient alternative method is highly desirable.

In one of our developmental projects, during an effort to ring open epoxide with a secondary amine using NaHMDS as base, we observed traces of 1,2-aminoalcohol having primary amine function. This observation prompted us to explore the possibility of using NaHMDS as the source of amine for the epoxide ring opening. When we looked into the literature, we came across a couple of reports indicating the possibility of epoxide ring opening with NaHMDS.[7] To our surprise, this methodology has not been explored by the synthetic community. We anticipated that the sterically-large HMDS group might give better regio-control. Herein we report our results on a highly efficient method for the preparation of 1,2-aminoalcohols from epoxides and chlorohydrins.



Scheme 1.

We began by probing the ability of NaHMDS to open the epoxides. Accordingly, the treatment of styrene oxide (**5**) with NaHMDS in THF at 0 °C overnight gave 15% conversion to intermediate **6**. The rate of the reaction increased considerably when the temperature was raised to 20–25 °C and the reaction was complete in 14–15 h. Aqueous work-up gave 1,2-aminoalcohol **7** in excellent

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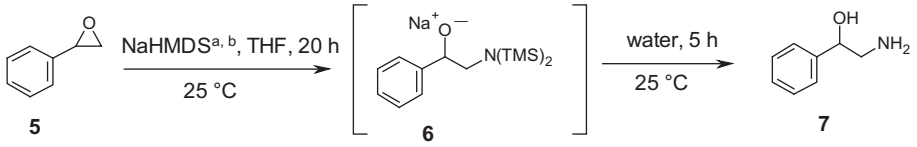
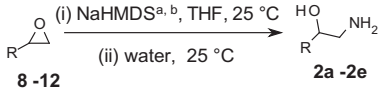


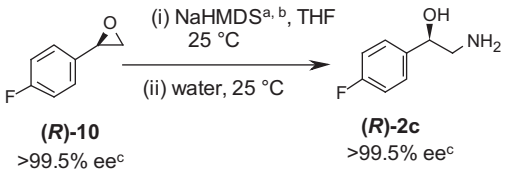
Scheme 2. (a) 3 Equivalents of 1 M NaHMDS solution in THF was used. (b) NaHMDS was added at 0–5 °C.

Table 1
Substrate scope of nucleophilic ring opening of epoxide with NaHMDS

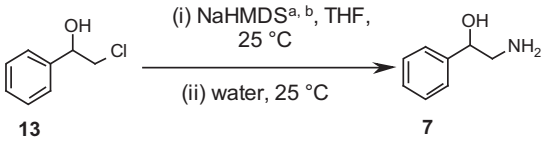


Entry	Substrate	R	Product	Time (h)	Yield[c] (%)
1	8	4-ClC_6H_4	**2a**	17	81
2	9	4-BrC_6H_4	**2b**	14	87
3	10	4-FC_6H_4	**2c**	17	80
4	11	$C_6H_5OCH_2$	**2d**	5	83
5	12	C_4H_9	**2e**	6	70

[a] 3 Equivalents of 1 M NaHMDS solution in THF was used.
[b] NaHMDS was added at 0–5 °C.
[c] Isolated yields.



Scheme 3. (a) 3 Equivalents of 1 M NaHMDS solution in THF was used. (b) NaHMDS was added at 0–5 °C. (c) Enantiomeric excess was determined by chiral HPLC; see Supplementary data for details.



Scheme 4. (a) 3 Equivalents of 1 M NaHMDS solution in THF was used. (b) NaHMDS was added at 0–5 °C.

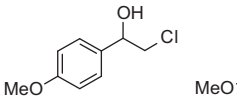
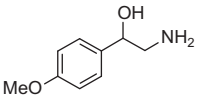
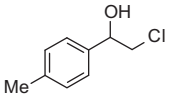
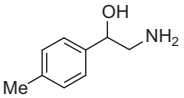
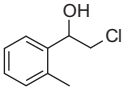
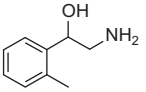
yield (81%) as a single regio-isomer. HPLC analysis of the reaction mixture did not show any traces of regio-isomer. All our efforts to characterize the *N,N*-diTMS intermediate **6** proved to be unsuccessful owing to its instability. It was found that 2.5–3 mole equivalents of NaHMDS was necessary to get a complete reaction. Increasing the temperature to 50 °C resulted in complex reaction mixtures. Use of LiHMDS and KHMDS resulted in lower yields. As anticipated, the sterically demanding HMDS moiety provided a single regio-isomer as shown in Scheme 2.

On the basis of the optimized conditions used, a variety of other epoxides were examined the results are collected in Table 1.

As shown in Table 1, under these conditions[8], a wide range of epoxides, both aromatic as well as aliphatic, underwent nucleophilic ring opening with NaHMDS in high yields.

Mechanistically we do not anticipate any possibility of racemization at C2 position of the epoxide, but to confirm the stereochemical integrity of the reaction, we employed enantiopure (*R*)-4-fluorostyrene oxide (**10**) as starting material (Scheme 3). The product **(*R*)-2c**, as anticipated, did not suffer any loss of chirality during the course of reaction.

Table 2
Examples for the synthesis of amino alcohol from chlorohydrin

S. No.	Substrate	Product	Yield[a] (%)	Time (h)
1			85	15
2			82	16
3			83	15

[a] Isolated yields.

Encouraged by the above results, we extended this methodology to chlorohydrins, one of the general precursors for epoxides. Moreover epoxides with electron-releasing substituents in the aryl ring are generally unstable and are difficult to handle. A method to convert 1,2-chlorohydrins directly to 1,2-aminoalcohols would be advantageous. To test this idea, we attempted the reaction with chlorohydrin **15** (Scheme 4) and demonstrated that upon treatment with NaHMDS, both epoxidation and ring-opening were achieved to afford the desired product in excellent yield.

To assess the scope of this reaction, we carried out further experiments with substituted aryl-halohydrins as shown in Table 2.

From the results shown in Table 2, it is proved that this methodology allows direct access to the desired 1,2-aminoalcohols from 1,2-chlorohydrins without the requirement to handle unstable epoxide intermediates.

In summary, a simple, high-yielding, and regio-selective method for the preparation of 1,2-aminoalcohols from terminal epoxides and 1,2-chlorohydrins has been demonstrated. The method appears to be of general value and works well with both aryl and alkyl substituted epoxides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.013.

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8. *Representative procedure*: To a stirred solution of 2-phenyloxirane **5** (1 g, 8.31 mmol) in anhydrous tetrahydrofuran was added sodium bis(trimethylsilyl) amide (1 M solution in THF, 29.08 mL, 29.08 mmol, 3.0 equiv) at 0–5 °C. The resultant mixture was allowed to warm to 25 °C and stirred for 20 h, by which time the reaction was completed as indicated by TLC. The reaction mixture was then quenched with water (2.5 mL) and stirred for 5 h. The solvent was removed by distillation under reduced pressure bringing the total volume to one-fourth. The content of the reaction mixture was extracted with dichloromethane (2×10 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the crude product. The crude product was purified by column chromatography on silica gel to obtain the pure product as pale yellow solid.