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Effective procedure for selective ammonolysis of monosubstituted oxiranes: application to E7389 synthesis

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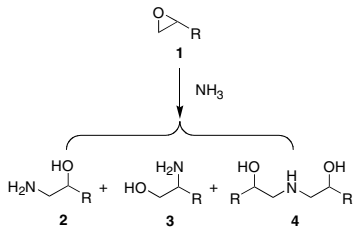
Abstract—A highly effective procedure is reported to synthesize 1,2-aminoalcohols by regio- and chemo-selective ammonolysis of mono-substituted epoxides. Additive- and concentration-effects were studied, revealing that (1) methanesulfonic acid is most effective among the additives tested and (2) formation of bis-adducts is practically eliminated at $[C] \leqslant 40$ mM. The optimum condition thus identified was successfully applied to the final step of the synthesis of potent anti-tumor compound E7389.

1,2-Aminoalcohols **2** (Scheme 1) are important building blocks in the synthesis of natural products, pharmaceuticals, and other substances.[1] Among several synthetic methods known, ammonolysis of 1,2-epoxides **1** is one of the most attractive and commonly used methods,[2] coupled with the fact that optically active 1,2-epoxides have become readily available in recent years.[3–6] However, there are three intrinsic limitations that could potentially make this process impractical. First, the nucleophilic attack of ammonia can take place at the 1- or 2-position, that is, **1**→**2** versus **1**→**3**. Second, the resultant 1,2-aminoalcohols **2** can react with the starting material **1**, to yield the corresponding secondary amines **4**. Because a primary amine is more nucleophilic than ammonia, this side reaction often presents a problem. Usually, this problem is circumvented by use of a large excess of ammonia at low concentration, which is not necessarily ideal for a large-scale synthesis.



Scheme 1.

Third, the ammonolysis is usually slow and often suffers from low conversion. To overcome this difficulty, the microwave assisted method has been reported in recent years.[7] Overall, although ammonolysis of 1,2-epoxides is a direct and attractive synthetic route to 1,2-aminoalcohols, problems still remain to achieve this chemical transformation effectively and economically.

Related to the ammonolysis summarized in Scheme 1, we should note that aminolysis of epoxides with primary and secondary amines has been a subject for extensive research. To overcome the intrinsic limitations noted above, three type of approaches, that is, (1) use of metal amides (aluminum,[8] magnesium,[9] lead,[10] tin,[11] and silicon[12]), (2) use of metal salts such as $LiClO_4$[13] and lanthanide(III) triflates,[14] and (3) use of amines absorbed on alumina,[15] have been introduced.

The potential problems associated with the ammonolysis of epoxides came to our attention in connection with the synthesis of an anti-tumor drug candidate E7389 (**7**), a structurally simplified analog of the marine natural product halichondrins (Scheme 2).[16–18] Namely, the last step in the synthesis of E7389 (**7**) is the ammonolysis of epoxide **6**, generated in situ from the mono-mesylate **5**.[16] Based on the published experimental procedure, we speculate that this step most likely suffers from the problems discussed in a general context.

Basically, we were curious about the possibility of activating 1,2-epoxides by an acid. In this connection, the reports by Crotti and co-workers are instructive; they

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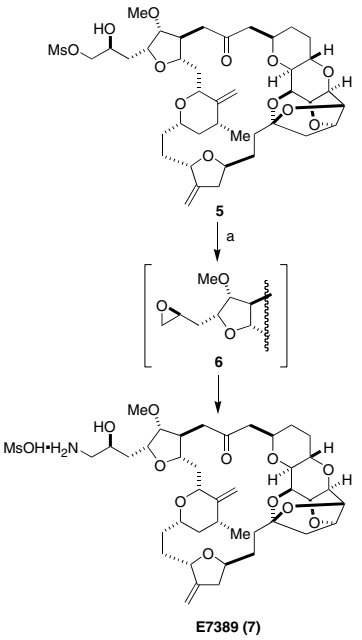


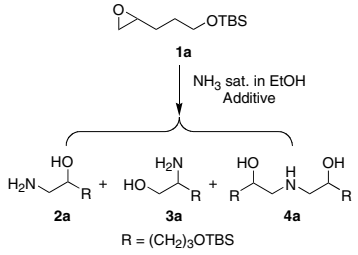
Scheme 2. Reagents and conditions: (a) EtOH saturated with NH_3, MsOH (5 equiv), $[C] = 40$ mM, rt, 3.5 days, 93% yield.

demonstrated that lanthanide(III) triflates such as $Yb(OTf)_3$, $Nd(OTf)_3$, and $Gd(OTf)_3$ catalyze the aminolysis of 1,2-epoxides in a non-protic solvent, to yield the corresponding aminoalcohols in a highly stereo- and regio-selective manner.[14] Reymond and co-workers extended the $Yb(OTf)_3$-mediated method to ammonolysis of 1,2-epoxides in ethanol, to obtain the desired aminoalcohols in high yields.[19] In addition, Koyama and Fujikawa claimed in their patent that ammonium halide improves the ammonolysis of epoxides.[20]

In terms of the enhancement of reactivity and the improvement of regioselectivity, the examples cited above suggest that lanthanide(III) triflates appear to give a solution for the ammonolysis/aminolysis of 1,2-epoxides. To the best of our knowledge, however, there is no study reported to suppress the formation of dimer **4** and conduct the ammonolysis in a practically acceptable concentration. Thus, we decided to study the ammonolysis of a 1,2-epoxide in the presence of acids. Using the epoxide **1a** (Table 1), we examined the effect of acids and concentrations on the product distribution.

To begin with, we examined the effects of $Yb(OTf)_3$ on the ammonolysis of **1a**. Thus, **1a** was treated with ammonia in ethanol (ammonia-saturated EtOH, $[C] = 40$ mM) in the presence and absence of $Yb(OTf)_3$ (10 mol %) at 70 °C and the product analysis was conducted after acetylation of the crude product (entry 3a vs entry 13a in Table 1), thereby revealing the following. First, no significant difference in the ammonolysis rate was noticed between the two cases. Considering that a large excess of ammonia was used for these experiments, this observation was not totally unexpected. Second, the

Table 1. Effect of additive and concentration on product distribution



Entry	Additive	Concentration (mM)	Temperature[a]	Ratio **2a**:**4a**
1	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	160	70	100:12
2	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	80	70	100:11
3a	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	40	70	100:3
3b			rt	100:8
4	$Yb(OTf)_3{\cdot}nH_2O$ (0.1 equiv)	20	70	100:2
5	$Sc(OTf)_3$ (0.1 equiv)	20	70	100:4
6a	MsOH (5 equiv)	80	70	100:8
6b			rt	100:9
7a	MsOH (5 equiv)	40	70	100:2
7b			rt	100:3
8a	MsOH (5 equiv)	20	70	100:1.5
8b			rt	100:2
9	MsOH (3 equiv)	40	rt	100:4.5
10	MsOH (1 equiv)	40	rt	100:5
11	NH_4Cl (5 equiv)	40	70	100:5
12	NH_4OAc (5 equiv)	40	70	100:6
13a	No additive	40	70	100:4
13b			rt	100:8

[a] Reaction time at 70 °C and at rt was 10 h and 82 h, respectively.

aminoalcohol corresponding to **3a** was not detected in the crude product for both cases (^{1}H NMR). Third, $Yb(OTf)_3$ appeared to have a small effect on the **2a**:**4a** ratio, that is, the ratio was slightly better for entry 3a than for entry 13a. Interestingly, at room temperature, the $Yb(OTf)_3$-effect on the ratio was not seen (entry 3b vs entry 13b).

We then studied the concentration effect on the dimer formation in the presence of $Yb(OTf)_3$ (entries 1–4), thereby revealing that only a very small amount of **4a** was detected at $[C] \leqslant 40$ mM, whereas a significant amount of dimer **4a** was found at $[C] \geqslant 80$ mM.[21]

Encouraged by these results, we tested other Lewis and Brønsted acids. $Sc(OTf)_3$ (10 mol %) gave the result similar, but slightly inferior, to that with $Yb(OTf)_3$ (entry 5). Among the Brønsted acids tested, methanesulfonic acid (MsOH)[22] was found to be slightly more effective than $Yb(OTf)_3$, but hydrochloric acid (NH_4Cl) and acetic acid (NH_4OAc) were found to be less effective (entry 11 and 12). Notably, 10 mol % of $Yb(OTf)_3$ was sufficient to cause the optimum effect, whereas more than a stoichiometric amount of MsOH was required (entries 7ab, 9, and 10). Practically, approximately 5 equiv of MsOH seemed to be required to achieve the maximum **2a**:**4a** ratio. Overall, the effectiveness order of tested-acids is as follows: MsOH (5 equiv) $\geqslant$ $Yb(OTf)_3$ (0.1 equiv) > NH_4Cl (5 equiv) > NH_4OAc (5 equiv) > $Sc(OTf)_3$ (0.1 equiv). Considering the cost effectiveness and operational simplicity, we recommend the ammonolysis in the presence of excess MsOH over $Yb(OTf)_3$.

The concentration dependency of the product distribution in the presence of MsOH (entries 6–8) was found to be similar to that in the presence of $Yb(OTf)_3$. Namely, only a very small amount of **4a** was detected at $[C] \leqslant 40$ mM, whereas a significant amount of dimer **4a** was found at $[C] \geqslant 80$ mM. The temperature effect on the **2a**:**4a** ratio was found to be negligibly small, although the ratio at 70 °C appeared to be very slightly better than that at room temperature (entries 6a vs 6b, 7a vs 7b, 8a vs 8b). Finally, it is worthwhile noting that no detectable regioisomer **3a** was detected in the crude product (^{1}H NMR).[23] Overall, this ammonolysis can best be achieved in NH_3-saturated EtOH in the presence of MeOH (5 equiv) at $[C] \leqslant 40$ mM. Under this condition, additional two epoxides were selectively converted into the corresponding aminoalcohols in high yields.[24]

With these results in hand, we then applied the MsOH-mediated ammonolysis to the synthesis of E7389 (**7**). In this case, epoxide **6** was prepared in situ by ammonia treatment of the corresponding mono-mesylate **5**;[16] with respect to the amount of MsOH present in the reaction media, the reported ammonolysis condition corresponds to entry 10 in Table 1. In extrapolating the optimal conditions found in substrate **1a**, we anticipated the optimum condition for the ammonolysis of **5** to be 'in the presence of additional four or more equivalents of MsOH in EtOH at $[C] = 40$ mM'.[25] Thus, the mono-mesylate **5** was treated with ammonia in ethanol in the presence of 5 equiv of MsOH at 70 °C[27] and at room temperature at $[C] = 40$ mM, to furnish E7389 (**7**) methanesulfonate[16] in 93% yield.[28] The ^{1}H NMR analysis of **7** and its *O*,*N*-diacetate revealed that the product thus obtained was not contaminated with a detectable amount of side-product(s).

In summary, we reported an effective MsOH-mediated ammonolysis of mono-substituted epoxides. Under the optimum condition, that is, EtOH saturated with NH_3 in the presence of MsOH (5 equiv) at $[C] \leqslant 40$ mM, the ammonolysis of **1a** can be achieved in a highly selective manner, to furnish the desired 1,2-aminoalcohol **2a** in excellent chemical yields. The usefulness of this procedure was demonstrated by the case of E7389 (**7**) synthesis.

Acknowledgments

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Supplementary data

^{1}H NMR spectra of **5** and **7** can be found in the online version. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.116.

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developed by Jacobsen (Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063) and by Katsuki (Irie, R.; Noda, K.; Ito, Y.; Matsumoto, N.; Katsuki, T. *Tetrahedron Lett.* **1990**, *31*, 7345), hydrolytic kinetic resolutions of racemic epoxides pioneered by Jacobsen (Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936), and chiral ketone-based asymmetric epoxidation developed by Shi (Tu, Y.; Wang, Z.-X.; Shi, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9806) and others. There are numerous reviews published to cover these subjects. For a recent review, see: Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603. For recent monographs, see: *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I. Ed.; Wiley-VCH: New York, 2000; *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York, 1999; *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Pergamon: New York, 1995; Vol. 12. (volume edited by Hegedus, L. S.). For asymmetric epoxidation of homoallylic alcohols, see: Zhang, W.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 286.

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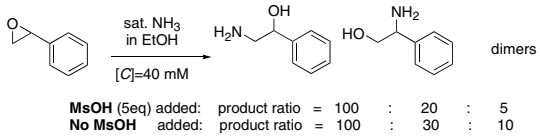
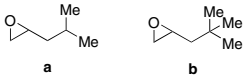
22. *p*-Toluenesulfonic acid was shown to be as effective as MsOH.
23. As anticipated, stylene oxide gave a significant amount of the regioisomer, along with the dimers. Even for this case, the effect of MsOH on the formation of both regioisomer and dimers was noticed.

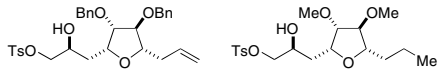


24. Additional two substrates **a** and **b** were subjected to ammonolysis under the optimum condition, to give the expected aminoalcohols in almost quantitative yields.



a **b**

25. Two model substrates **c** and **d** were first used to demonstrate that the identified optimum condition is effective for the transformation of **5** into **7**. Substrates **c** and **d** were synthesized from the known crystalline dibenzoate, that is, dibenzoate **15** reported in Ref. 17b, in 3 (1. BnBr/TBAI/Ag_2O/CH_2Cl_2/rt, 2. aq KOH/MeOH–THF/rt, 3. *p*-TsCl/*n*-$Bu_2SnO/Et_3N/CH_2Cl_2$/rt[26]) and 4 (1. $H_2/Pd(OH)_2$ on C/EtOH/rt, 2. MeI/Ag_2O/MS 4Å/rt, 3. aq KOH/MeOH–THF/rt, 4. *p*-TsCl/*n*-$Bu_2SnO/Et_3N/CH_2Cl_2$/rt[26]) steps, respectively.



c **d**

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27. This ammonolysis was conducted also at 70 °C for 10 h at $[C] = 20$ mM in a 9.4-mg scale, to furnish the desired product over 95% yield. The purity of the crude product thus obtained was found to be as good as that of the product obtained at room temperature (^{1}H NMR analysis of the crude product and its *O*,*N*-diacetate).
28. A 10-mL vial equipped with a magnetic stirbar and a rubber septum fitted with an ammonia inlet needle and a pressure equilibrating needle was charged with **5** (18.8 mg, 0.0232 mmol, 1.0 equiv) and EtOH (0.58 mL). Ammonia gas was bubbled through the needle for 5 min, and then

MsOH (10 vol % in EtOH, 75 μL, 0.116 mmol, 5 equiv) was added. The vial was tightly capped. The mixture was stirred at room temperature for 3.5 days. All volatiles were removed under reduced pressure. To the residue was added EtOAc, and the suspension was passed through a pad of Celite. The filtrate was concentrated and dried under vacuum to give **7** (17.8 mg, 93%) as a colorless amorphous solid.