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Improved method of an unusual conversion of aliphatic amines into alcohols

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Abstract—An improved method for the synthesis of alcohols from amines was achieved using a degassed diethylene glycol and KOH. Utilizing this method, facile conversion of a cyano group, even a sterically hindered one, to a hydroxy-methyl group was also accomplished. © 2001 Elsevier Science Ltd. All rights reserved.

Although synthesis of alcohols from amines seems to be a simple conversion, practically efficient synthesis of aliphatic alcohols from the corresponding amines is extremely difficult. It is well known that aromatic amines can be converted into the alcohols via a diazonium salt; however, a successful conversion of aliphatic amines to the corresponding alcohols via diazonium salts is rare.[1a–d] In some cases, reaction of aliphatic amines with nitrous acid led to a number of rearranged products with very low yields of the desired alcohols.[1e–k] Other methods require more than one step and sometimes suffer from low yields.[2]

In the course of our synthetic studies of scopadulin,[3] we found an efficient one-step reaction for conversion of primary aliphatic amines into alcohols mediated by KOH.[3a] However, our previously reported method provided moderate yields of alcohols from amines. Herein, we present an improved method for this conversion and utilization of this method for convenient and efficient conversion of a cyano group into a hydroxymethyl group. Results of experimentation to obtain some information on the reaction mechanism are also presented.

As a result of the optimization of the reaction conditions, we found that increased yields were observed when the reaction was conducted in degassed diethylene glycol under a nitrogen atmosphere.[4] Table 1 shows the results of the conversion of amines **1**–**6** to the corresponding alcohols **7**–**12**. Phenylbutylamine **1** (entry 1) and benzylic amine **2** (entry 2) afforded the corresponding alcohols **7** and **8** in 76 and 77% yields, respectively,[5] upon treatment with KOH in degassed diethylene glycol at 210°C.[6] The reaction temperature should be controlled precisely.[7] Similarly, the amine **3** provided the alcohol **9** in 69% yield. (±)-α-Phenylethylamine **4** and (±)-α-naphthylethylamine **5** furnished the alcohols **10** and **11** in 70 and 47% yields, respectively. Aliphatic amine **6** provided the known alcohol **12**, albeit in a low yield (42%). In contrast, secondary and tertiary amines were inert to this reaction conditions.[8]

Next, utilization of this reaction to the conversion of hindered nitriles **13**–**16** to the alcohols **9** and **17**–**19** was investigated. As shown in Table 2, the nitrile **13** was converted into the corresponding amine by treating with $LiAlH_4$, and the resulting amine, without further purification,[9] was then subjected to the improved method of amine-to-alcohol reaction conditions to provide the corresponding alcohol **9** in 67% yield in two steps.[10] Similarly, **14** also gave the diol **17** in moderate yield. The nitrile **15**[11] and **16**, the cyano group of which is highly hindered due to the presence of both the axial methyl group and the oxygen functionality, also yielded **18** and **19** in 79%[12] and 66% yields, respectively. Although hydrous zirconium oxide-mediated direct conversion of the cyano group to a hydroxy methyl group was reported,[13] this method is limited to unhindered nitrile under vapor-phase conditions. Alternatively, the conversion of a cyano group into a hydroxymethyl group is possible via an aldehyde or a carboxylic acid; however, conversion of the hindered cyano group into the corresponding aldehyde,[14] acid[15] or ester[16] is quite difficult. Moreover, most of these methods required purification of aldehydes and carboxylic acid formed. In contrast, our method is suitably

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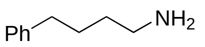
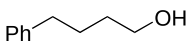
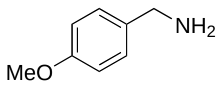
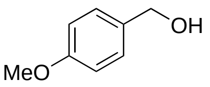
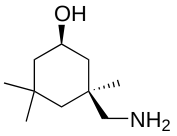
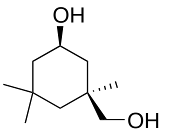
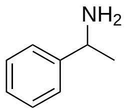
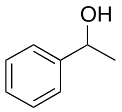
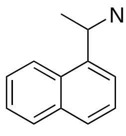
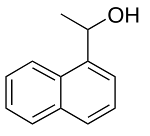
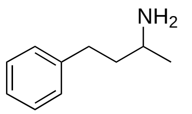
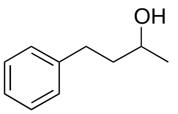
Table 1. Improved synthesis of alcohols from amines

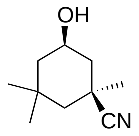
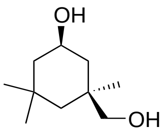
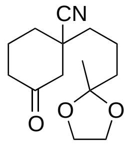
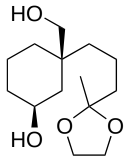
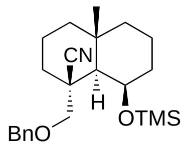
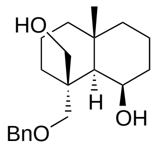
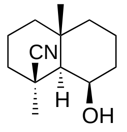
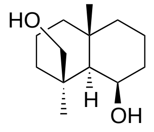
$$R{-}NH_2 \xrightarrow[210\ °C]{\text{KOH, diethylene glycol}} R{-}OH$$

Entry	Substrate	Reaction time (Yield)	Product
1	 **1**	12 h (76%)	 **7**
2	 **2**	1 h (77%)	 **8**
3	 **3**	2.5 h (69%)	 **9**
4	 **4**	1.5 h (70%)	 **10**
5	 **5**	4.5 h (47%)	 **11**
6	 **6**	8 h (42%)	 **12**

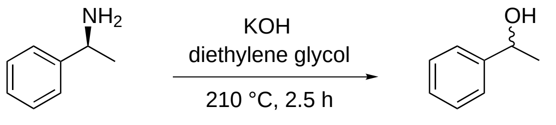
applicable to various hindered nitriles, and requires no purification of the intermediate amines.

Table 2. Conversion of a hindered cyano group to a hydroxymethyl group

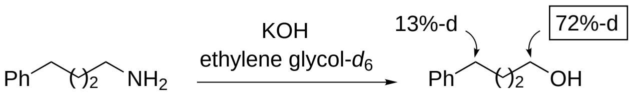
$$R{-}CN \xrightarrow[\text{2) KOH, diethylene glycol, 210 °C}]{\text{1) LiAlH}_4\text{, THF–Et}_2\text{O}} R{-}CH_2OH$$

Substrate	Product	Yield
 **13**	 **9**	67%
 **14**	 **17**	54%
 **15**	 **18**	79%
 **16**	 **19**	66%

To reveal the mechanical aspect of this unusual conversion, the stereochemical course of the reaction was investigated. When (+)-α-phenylethylamine **4** was subjected to the amine-to-alcohol reaction conditions, the optical rotation of the resulting alcohol **10** was considerably low (<5% ee, Eq. (1)). We next probed into the solvent effect using some involatile solvents. The reaction of phenylbutylamine **1** in alcoholic solvents such as ethylene glycol (197°C for 40 h) or glycerin (210°C for 8 h) yielded the desired **7**, although in low yields (25 and 22%, respectively). In contrast, when HMPA, diphenyl ether, or 1-methyl-2-pyrrolidone was used as solvent, the reaction did not proceed. Assuming that the alcoholic solvent would be the key to the progress of the reaction, we finally conducted a labeling experiment using a deuterated solvent (Eq. (2)). According to the ^{1}H NMR spectra of the alcohol **7** obtained by the reaction of **1** in ethylene glycol-d_6,[17] 72% of the carbinol protons was deuterated. At the present stage of our understanding, it is difficult to conclude the mechanism of this reaction; however, it is apparent that the alcoholic solvent exerts a significant role in the present transformation.[18]



4 **10** (<5% ee) (1)



1 **7**-d (2)

In conclusion, we have developed an improved method for an efficient one-step synthesis of alcohols from amines. Use of a degassed solvent increased the reaction yield. This method is superior to all other reported methods for the related conversion in terms of yield, convenience, cost, and synthetic usefulness. A facile conversion of the hindered cyano group into a hydroxymethyl group was achieved utilizing this method. Detailed study of the mechanistic pathway is now under investigation.

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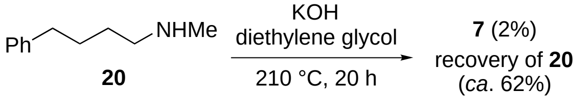
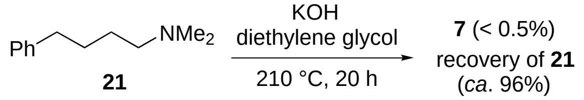
4. Diethylene glycol was degassed by evacuating the reaction vessel and nitrogen flushing (several times).
5. Our previous method for this reaction provided **7** and **8** in 59 and 54% yields, respectively.[3a]
6. *Typical experimental procedure*: Amine, KOH pellets (about 20 equiv.), and diethylene glycol (0.05–0.1 M solution) were placed in a round-bottomed flask equipped with a refluxing condenser, and the flask was evacuated and flushed by nitrogen several times. The mixture was then heated at 210°C[7] for the indicated time (Table 1). After the dark solution obtained was cooled to rt, Et_2O and H_2O were added and stirred for few minutes. The organic phase was separated and the aqueous layer was extracted several times with Et_2O.[19] The combined organic layers were then washed with water, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by column chromatography provided the desired alcohol. The alcohol was further purified by passing it through a short column of Al_2O_3 where necessary.
7. We found that the reaction proceeds quite slowly at a temperature below 200°C. When the temperature was raised to 220°C, an undesired intensely UV positive spot was detected on TLC.
8. Reactions of the secondary and tertiary amines **20** and **21** with KOH in diethylene glycol at 210°C gave a trace amount of the desired alcohol **7** (2% and less than 0.5%, respectively). In both cases, most of the starting materials were recovered unchanged.





9. The reaction product of $LiAlH_4$ was simply filtered through a filter paper and subjected to the reaction conditions.
10. Although Fraud and Lenze investigated the conversion of neopentyl amines into alcohols, neopentylamines gave only the rearranged product.[1e]
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12. Our previously-reported overall yield for the conversion of **15** to **18** was 49% (three steps).[3a]
13. Takahashi, K.; Shibagaki, M.; Matsushita, H. *Chem. Lett.* **1990**, 311.
14. For the conversion of nitriles to aldehydes, see: (a) Rabinovitz, M. In *The Chemistry of the Cyano Group*; Rapport, Z., Ed.; Interscience: New York, 1970; pp. 307–340; (b) Nagata, W. *Tetrahedron* **1961**, *13*, 287; (c) Nagata, W.; Hirai, S.; Itazaki, H.; Takeda, K. *Liebigs Ann. Chem.* **1961**, *641*, 196; (d) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1964**, *86*, 1085; (e) Fry, J. L.; Ott, R. A. *J. Org. Chem.* **1981**, *46*, 602; (f) Corriu, R. J. P; Moreau, J. J. E.; Pataud-Sat, M. *J. Org. Chem.* **1981**, *46*, 3372; (g) Goering, H. L.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5250; (h) Málek, J.; Cerny, M. *Synthesis* **1972**, 217.
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16. In our synthetic studies of scopadulin, we experienced variable yields of acid/ester from a hindered nitrile.[11]
17. Diethylene glycol-d_{10} is not commercially available.
18. The deuterium incorporation can be rationalized by the solvent-mediated redox mechanism: for example, (1) imine formation, hydrolysis by KOH and solvent-mediated Meerwein–Ponndorf–Verley type reduction (MPV reduction) of the resulting aldehyde, or (2) aldehyde formation from the solvent, transamination and MPV reduction by the solvent. Although less than 50% of *d*-incorporation would be theoretically expected only by the MPV reduction, we observed 72%-*d* at the carbinol position (Eq. (2)). So, we speculate that there would be a reversible process that enables an additional deuteration

(for example, reversible oxidation of an amine to the imine mediated by ethylene glycol-d_8). However, more detailed investigations will be necessary to establish the mechanism of the reaction.

19. Usually Et_2O extraction instead of EtOAc extraction is preferred. However, in some cases (for example, entry 2 in Table 2), the alcohol could not be completely extracted by several Et_2O extractions.