Base-Catalyzed Direct Transformation of Benzylamines into Benzyl Alcohols

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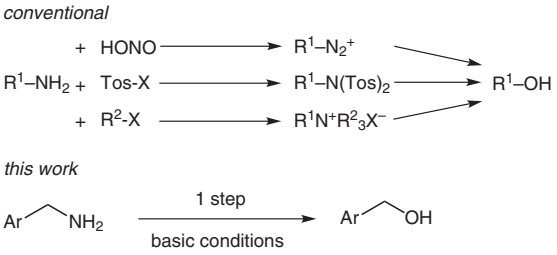
Abstract: Benzylamines were directly transformed into benzyl alcohols in superheated aqueous methanol in the presence of a base catalyst. This process is simple and will provide an alternative industrial route to benzyl alcohols such as xylene glycols.

Key words: alcohols, amines, catalysis, substitution, solid-phase synthesis

Benzyl alcohols are widely used as raw materials for medicines, agrochemicals, plasticizing agents, solvents in paints, and so on.[1] Particularly, xylene glycols, which have two hydroxy groups, have become increasingly important as raw materials for synthetic fibers and synthetic resins, such as polyesters and polyurethanes, and an efficient manufacturing process is desired.[2] Many methods have been proposed for the preparation of xylene glycols, however, there are few that are applicable on an industrial scale. The hydrogen reduction of dimethyl terephthalate, generally used in industrial processes, needs high temperature and high pressure and the yield is relatively low due to over-reduced byproducts.[3]

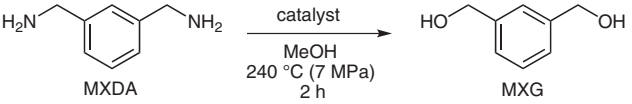
On the other hand, large amounts of xylene diamines are commercially produced for nylon by the hydrogen reduction of xylene dinitriles, which are prepared from xylenes by ammoxidation.[4] It was considered that if an amino group could be easily transformed into a hydroxy group, xylene diamines could become new starting materials for xylene glycols. The amino groups on the benzene ring are relatively easily transformed into hydroxy groups. For example, active anilines can be transformed into phenols by heating under acidic conditions.[5] However, the transformation of aliphatic amines into alcohols is relatively cumbersome. Diazotization of an amino group by nitrite salt,[6] conversion into the quaternary ammonium salt by alkyl halide,[7] sulfonamidation by sulfonyl chloride, and the formation of the pyridinium salt[8] are common methods (Scheme 1). Because the aliphatic amino group is not a good leaving group, transformation of the amino group into a better leaving group is necessary. Therefore, these methods require several steps and it is difficult to apply this to commercialization. With this background, we investigated the direct transformation of amino groups into hydroxy groups and, in this communication, we report a cost-effective and more direct transformation of benzylic amino groups into hydroxy groups under base-mediated conditions.



Scheme 1 Transformation of the aliphatic amino group into a hydroxy group

First, *m*-xylene diamine (MXDA) was adopted as a model compound and its transformation into *m*-xylene glycol (MXG) was examined in methanol at 240 °C (Table 1). Without catalyst, no reaction proceeded (entry 1). Next, solid acid (SiO_2–Al_2O_3) and solid base catalysts (MgO, $Ca(OH)_2$) were investigated, but no product was obtained (entries 2–4). HCl also showed no catalytic activity; however, by using KOH as a catalyst, MXG was obtained in 20% yield (entries 5 and 6). Hence, other homogeneous base catalysts were screened and it was found that NaOMe and NaOH were both effective, and MXG was

Table 1 Effect of Various Bases and Acid Catalysts[a]



Entry	Catalyst	Yield (%)[b]
1	–	0
2	SiO_2–Al_2O_3	0
3	MgO	0
4	$Ca(OH)_2$	0
5	HCl[c]	0
6	KOH	20
7	NaOMe[d]	74
8	NaOH	73

[a] Reaction conditions: MXDA (0.3 g, 2.2 mmol), catalyst (0.1 g), MeOH (7.4 g), 240 °C (autoclave), 2 h.
[b] GC yield. Tridecane was used as an internal standard.
[c] Aqueous solution was used.
[d] Methanol solution was used.

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obtained in 74 and 73% yields, respectively (entries 7 and 8).

Various reaction conditions were examined to increase the yield (Table 2). When the amount of NaOH was reduced to 0.8 molar equivalent against MXDA (0.4 molar equivalent with respect to the amino group), the reaction was retarded and the yield was reduced. On the other hand, the yield was not improved when the amount of NaOH was increased to 2.7 molar equivalents (entries 1–3). Excess methanol was needed; when the amount of methanol was reduced to 14 molar equivalents against MXDA, the yield was decreased (entries 2, 4, and 5). Concerning the temperature, 240 °C was found to be optimal. The reaction was retarded at 220 °C and some undesired byproducts were observed at 260 °C, thus the yields were decreased in both cases (entries 2, 6, and 7).

Table 2 Reaction Conditions for MXDA[a]

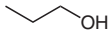
Entry	NaOH/MXDA ratio[b]	MeOH/MXDA ratio	Temp (°C)	Yield (%)[c]
1	0.80	110	240	15
2	1.4	110	240	73
3	2.7	110	240	71
4	1.4	56	240	71
5	1.4	14	240	60
6	1.4	110	220	28
7	1.4	110	260	63

[a] Reaction conditions: MXDA (0.3 g, 2.2 mmol), NaOH in MeOH, 2 h, autoclave.
[b] When NaOH/MXDA molar ratio was 0.8, the NaOH/amino group molar ratio was 0.4.
[c] GC yield. Tridecane was used as internal standard.

Next, protic solvents were examined (Table 3). Primary alcohols, such as methanol, ethanol, and 1-propanol, gave similar results (entries 1–3). In contrast, almost no reaction proceeded in a secondary alcohol such as 2-propanol (entry 4). The reaction also did not proceed in H_2O (entry 5). However, it was found that the addition of water to methanol reduced the amount of byproducts and improved the yield. When the reactions were performed in mixed solvents (MeOH–H_2O, 97:3 and 70:30 wt%), the GC yields were improved to 83 and 93%, respectively (entries 6 and 7). The crude MXG (93% GC yield) was easily purified by Kugelrohr distillation to afford the pure product in 89% yield. These strong solvent effects of alcohols and water clearly indicated that alcohols took part in the reaction and played a significant role.

Reactions in supercritical and subcritical aqueous (protic) media have recently garnered a lot of attention, and the reactions of benzylamines in such media were frequently reported.[9] However, there have been no reports in which benzyl alcohols were obtained in high yield. For example, Deka and coworkers reported that when benzylamine and an equivalent amount of HCl were heated in supercritical methanol, benzyl methyl ether was produced as a main product and benzyl alcohol was afforded in 25% yield as a byproduct.[10] Katritzky and coworkers reported that when benzylamine was heated in aqueous formic acid at 350 °C, benzyl alcohol was obtained in 41% yield.[9c] It seems that a key for improving the yield in the process reported here was that basic catalysts were used instead of acidic catalysts.[11] In order to examine whether subcritical conditions were important or not, a reaction was performed in 1-undecanol at reflux (235 °C) under atmospheric pressure. Since, under these conditions, MXG was produced in 36% yield, it was considered that pressure was not so important and that the reaction temperature was more critical.

Table 3 Effects of Protic Solvents[a]

Entry	Solvents	Yield (%)[b]
1	MeOH	73
2	EtOH	77
3		74
4		0.7
5	H_2O	0
6	MeOH–H_2O (93:7 wt)	83
7	MeOH–H_2O (70:30 wt)	93 (89)[c]

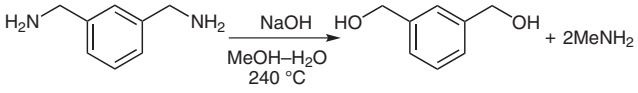
[a] Reaction conditions: MXDA (0.3 g, 2.2 mmol), NaOH (0.1 g, 2.5 mmol), alcohol (7.4 g), 240 °C (autoclave), 2 h.
[b] GC yield. Tridecane was used as internal standard.
[c] Isolated yield is shown in parenthesis.

Through the use of these optimized conditions, a variety of benzyl amine derivatives were investigated (Table 4). To examine the substituent effect on the nitrogen atom, benzylamine, *N*-methylbenzylamine, and *N*,*N*-dimethylbenzylamine were tested. Benzyl alcohol was obtained in high yield from benzylamine, however, the yields were very low for the other amines. Hence, it was found that only the primary amino group could be transformed into the hydroxy group (entries 1–3). Alkyl groups on the benzene ring were tolerated, and *o*-, *m*-, *p*-methyl and *p*-*tert*-butyl benzylamine gave the corresponding products in high yields (entries 4–7). *m*-Chlorobenzylamine reacted in high yield, although the yields of *o*- and *p*-chlorobenzylamines were lower, due to partial methoxylation (entries 8–10). In the case of methoxybenzylamines, the yield was moderate because hydroxybenzyl alcohols were obtained as byproducts (entries 11–13). The yield of 1-phenylethanol was also low. It is considered that the steric bulk around the amino group encumbered the reaction (entry 14). No product was obtained from aniline or 1,3-bis(aminomethyl)cyclohexane (entries 15 and 16).

Not only benzylamine but other aromatic and hetero aromatic methylamines could also be used. Naphthylmethyl-

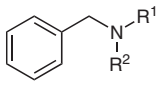
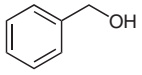
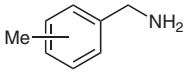
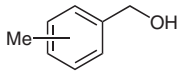
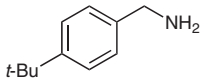
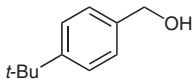
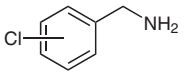
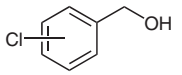
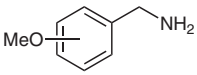
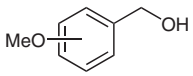
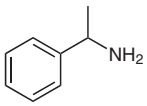
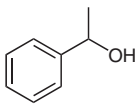
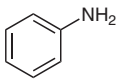
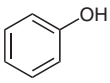
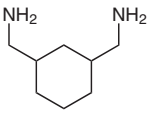
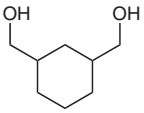
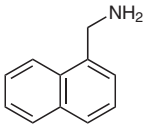
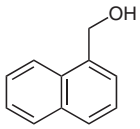
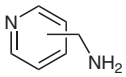
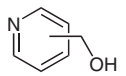
amine and pyridinylmethylamine gave the corresponding alcohols in high yields (entries 17–20).[12]

In order to obtain information about the reaction mechanism,[13] the time course of the reaction of MXDA was analyzed (Scheme 2). Soon after the reaction started, the amount of MXDA reduced and the amount of mono alcohol increased. After 50 min, the amount of mono alcohol decreased and MXG increased. From these observations, it was apparent that the amino groups were being transformed into hydroxy group in a stepwise manner. As the reaction proceeded, an equimolar amount of methylamine compared to reacted amino group was generated.[14–16] The reaction was catalyzed by NaOH in H_2O–MeOH in Figure 1, however, when the reaction was performed in MeOH by using NaOMe as a catalyst, no benzyl methyl ether derivatives were produced (Table 1, entry 7). When *m*-bis(methoxymethyl)benzene was reacted, no reaction occurred and almost all the starting material was recovered, which showed that the benzyl methyl ethers were stable under the reaction conditions. Based on these results, it was concluded that the reaction did not proceed through the normal S_N2 mechanism. A more precise analysis of the reaction is ongoing.



Scheme 2

Table 4 Substrates Scope and Limitations[a]

Entry	Amine	Product	Substituent	Yield (%)[b]
1			R^1 = H, R^2 = H	91 (86)
2			R^1 = Me, R^2 = H	6
3			R^1 = Me, R^2 = Me	2
4			*o*-Me	92[c] (89)
5			*m*-Me	93 (79)
6			*p*-Me	96 (93)
7				93 (91)
8			*o*-Cl	74[d]
9			*m*-Cl	91 (86)[e]
10			*p*-Cl	35[f]
11			*o*-OMe	48[e]
12			*m*-OMe	65[e,g]
13			*p*-OMe	32
14				23
15				0
16				0
17				93 (85)
18			2-	82 (75)
19			3-	99 (94)
20			4-	70

[a] Reaction conditions: Amine/MeOH/H_2O/NaOH = 1:110:70:1.4 (molar ratio), 240 °C, 2 h.
[b] GC yield. Tridecane was used as internal standard. Isolated yields after distillation or column chromatography are shown in parentheses.
[c] Tetradecane was used as an internal standard.
[d] *o*-Methoxybenzylalcohol was observed in 11% yield.
[e] Amine/MeOH/H_2O/NaOH = 1:55:35:0.7 (molar ratio),
[f] *p*-Methoxybenzylalcohol was observed in 32% yield.
[g] *m*-Hydroxybenzylalcohol was observed in 14% yield.

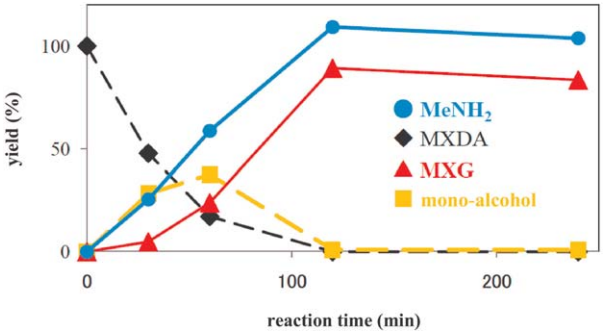


Figure 1 Time course of the reaction. Reaction conditions: MXDA/MeOH/H_2O/NaOH = 1:110:70:1.4 (molar ratio), 240 °C. Methylamine yield = (methylamine mol/MXDA mol) × 0.5.

In summary, we have discovered that benzylamines can be easily transformed into benzyl alcohols in high yields by simple heating in aqueous methanol under basic conditions.[17,18] The method is straightforward and cost-effective. Hence, we hope it will become a useful alternative industrial route to benzyl alcohols such as xylene glycols.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(11) (a) After our patent application,[11b] another patent application[11c] was published. It was reported that when benzylamine and an equivalent amount of glycolic acid were heated in supercritical methanol, the amide was probably generated in situ, and then it was converted into benzyl alcohol with good yield. (b) Kanbara, Y.; Abe, T.; Fushimi, N. Jpn. Patent Appl. 288352, **2010**. (c) Kamimura, A.; Kaiso, K.; Sugimoto, T. PCT Int. Appl. WO 016409, **2011**.

(12) We examined the reaction of MXG and methylamine as a representative of the reverse reaction, that is, transformation of benzyl alcohols into benzylamines. So far, MXDA was not obtained.

(13) In order to check metal leaching from the stainless-steel autoclave, ICP analysis of the reaction solution was performed [reaction conditions: MXDA/MeOH/H_2O/NaOH = 1:110:70:1.4 (molar ratio), 240 °C, 2 h]. The concentrations of Fe, Cr, Ni, and Mo were 0.018, 0.058, 0.0, and 3.0 ppm, respectively. The reaction also conducted in a glass vessel when it was carried out in 1-undecanol under reflux at atmospheric pressure. Therefore, it was considered that metal leaching from the reaction vessel was minute and its effect was marginal.

(14) MXDA, mono-alcohol, MXG, MeOH, and methylamine were only observed, and no other byproducts or intermediates were detected in the time-course GC analysis of the reaction.

(15) Reactions under N_2 and H_2 (initial pressure: 1 MPa) were investigated and compared with those at 1 atm N_2. Even under H_2 pressure, the reaction smoothly proceeded and no differences were observed. Combined with the fact that no byproducts or intermediates were detected, it was thus not considered probable that the reaction proceeded via imine or aldehyde intermediates.

(16) From the fact that the yields of *N*-methyl and *N*,*N*-dimethyl benzylamine were very low, it was apparent that N-methylation by methanol did not occur during the reaction

(17) **Preparation of *m*-xylene glycol (MXG); Typical Procedure (Table 1)**
To a 30-mL autoclave was added MXDA (0.30 g, 2.2 mmol), catalyst (0.1 g), and MeOH (7.4 g), and then the inner gas was replaced by N_2. The mixture was heated at 240 °C for 2 h, and then cooled in an ice–water bath. The yield was determined by GC analysis using tridecane as internal standard. The crude products were purified by Kugelrohr distillation.
Spectral data of MXG (Table 3, entry7): ^{1}H NMR (500 MHz, CD_3OD): δ = 4.60 (s, 4 H), 7.24–7.34 (m, 4 H). ^{13}C NMR (126 MHz, CD_3OD): δ = 65.2, 126.6, 126.9, 129.4, 142.8.

(18) **Preparation of benzyl alcohol derivatives (Table 4):** To a 30-mL autoclave was added benzylamine derivative (4.4 mmol for entry 9, 11, and 12, and 2.2 mmol for the others),

powdered NaOH (0.1 g, 2.5 mmol), MeOH (7.4 g), and H_2O (2.9 g), then the inner gas was replaced by N_2. The mixture was heated at 240 °C for 2 h, and then cooled in an ice–water bath. The reaction mixture was neutralized with 1 M HCl (2.5 mL, 2.5 mmol). GC yield was determined by GC analysis using tetradecane (entry 4) and tridecane (for the others) as internal standard. For entry 1, the solutions were dried over Na_2SO_4, concentrated, and purified by silica-gel column chromatography (hexane–EtOAc, 75:25 v/v). The other products were purified by Kugelrohr distillation.

Spectral data of benzyl alcohol (Table 4, entry1): ^{1}H NMR (500 MHz, CD_3OD): δ = 4.59 (s, 2 H), 7.23–7.33 (m, 5 H). ^{13}C NMR (126 MHz, CD_3OD): δ = 65.2, 126.6, 126.9, 129.4, 142.8.

All other products were characterized by comparison of GC retention time with chemical reagents purchased from commercial suppliers.

