JOC The Journal of Organic Chemistry

NOTE

pubs.acs.org/joc

An Effective Method To Prepare Imines from Aldehyde, Bromide/Epoxide, and Aqueous Ammonia

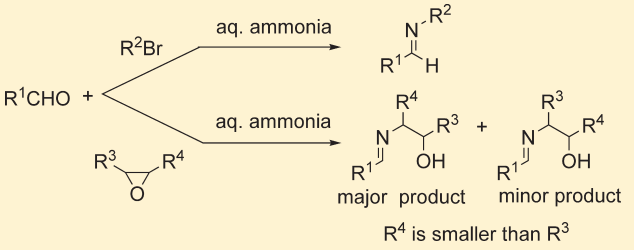
Jing-Mei Huang,*[,†] Jue-Fei Zhang,[†] Yi Dong,[†] and Wen Gong[‡]

[†]School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, People's Republic of China

[‡]Blue Star Xinghuo Silicone Plant, Jiujiang 330319, People's Republic of China

Supporting Information

ABSTRACT: A three-component reaction of aldehydes, alkyl bromides, and ammonia to form imines was studied. Aqueous ammonia was applied as the nitrogen source and solvent in the reaction. For the aromatic aldehyde, the product yields are good to excellent and the reaction conditions are mild to be compatible with a range of functional groups. The reaction of aldehydes and aqueous ammonia with epoxides was also studied and imines bearing a vicinal hydroxyl group can be obtained efficiently and regioselectively. And studies showed that this method allows the synthesis of primary amines and especially 1,2-amino alcohol selectively in high yield. It is proposed that the reaction pathway might involve a key intermediate of hydrobenzamide.

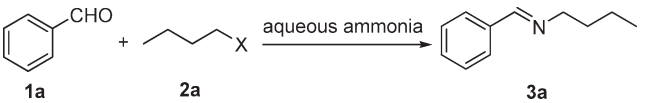


Imines are widely used in the synthesis of natural products, non-natural amino acids, pharmaceutical and medicinal compounds such as β-lactam, as well as polymers and materials.[1] Imines are often obtained by the condensation of amines with the carbonyl compounds,[2] and they can also be obtained by the oxidative condensation of amines,[3] oxidation of amines,[4] and the oxidative coupling of alcohols and amines.[5−7]

For the method of condensation of amines with the carbonyl compounds, although it is a well-established, direct, and attractive synthetic route to prepare imines, problems still remain to achieve this chemical transformation economically. For many years, azeotropic distillation was the most popular technique to remove the liberated water. Molecular sieves, dehydrating solvents, or Lewis acid catalysts have been shown to remove water as well as facilitate nucleophilic attack on the carbonyl compound. These methodologies suffer from high reaction temperatures, prolonged reaction times, high cost, or moisture sensitive reagents/catalysts. Given the importance of imines as intermediates in organic synthesis, the development of convenient procedures for their preparation is of interest. In recent years, aqueous protocols have received considerable attention and developed very fast.[8] In connection with our interests in aqueous medium reactions,[9] herein we disclose a novel three-component tandem reaction to prepare imines from aldehydes, bromides/epoxides, and aqueous ammonia under mild conditions.

The reaction of benzaldehyde and 1-bromobutane was initially investigated in 3.0 M aqueous ammonia at room temperature. However, there was no imine observed. When the reaction was carried out at 60 °C, a 40% yield of desired imine was obtained (entry 2, Table 1). Increase of the concentration of ammonia resulted in an increase of the yield (entries 3 and 4, Table 1). Optimization on the concentration of ammonia showed that the yield reached 91% in 28% (w/w) aqueous ammonia (entry 4, Table 1). When the reaction was carried out at higher temperature (75 °C), the desired imine was isolated with a small decrease of yield (entry 6, Table 1). For 1-iodobutane and 1-chlorobutane,

Table 1. Optimization of the Reaction Conditions for the Three-Component Tandem Reaction to Prepare Imine 3a[a]

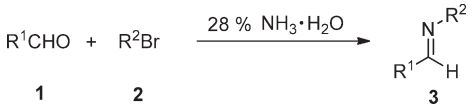


entry	X	solution	temp (°C)	yield (%)[b]
1	Br	3 M aq ammonia	rt	0
2	Br	3 M aq ammonia	60	40
3	Br	9 M aq ammonia	60	80
4	Br	28% (w/w) aq ammonia	60	91
5	Br	28% (w/w) aq ammonia	45	65
6	Br	28% (w/w) aq ammonia	75	82
7	I	28% (w/w) aq ammonia	60	90
8	Cl	28% (w/w) aq ammonia	60	22

[a] Reaction conducted with benzaldehyde (0.5 mmol), **2a** (0.75 mmol) in aqueous ammonia (1 mL), overnight. [b] Isolated yields.

Received: December 11, 2010
Published: March 23, 2011

Table 2. Formation of Imines from Aldehydes and Bromides in Aqueous Ammonia[a]



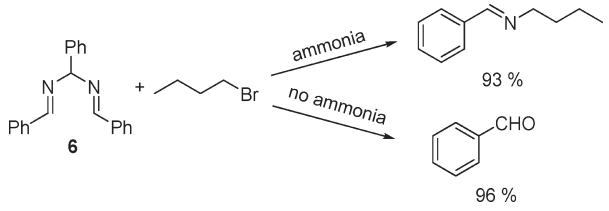
entry	R^1	R^2	product	yield (%)[b]
1	Ph	*n*-Bu	**3a**	91
2	Ph	*i*-Pr	**3b**	86
3	Ph	$PhCH_2$	**3c**	91
4	Ph	CH_2=$CHCH_2$	**3d**	90
5	Ph	CH_3CH=$CHCH_2$	**3e**	85
6	Ph	$CNCH_2CH_2$	**3f**	90
7	4-Cl-C_6H_4	*n*-Bu	**3g**	89
8	4-CN-C_6H_4	*n*-Bu	**3h**	78[c]
9	2-thienyl	*n*-Bu	**3i**	82
10	2-HO-C_6H_4	*n*-Bu	**3j**	85
11	2-Br-C_6H_4	CH_2=$CHCH_2$	**3k**	94
12	4-Cl-C_6H_4	CH_2=$CHCH_2$	**3l**	92
13	2-furyl	CH_2=$CHCH_2$	**3m**	93
14	4-O_2N-C_6H_4	CH_2=$CHCH_2$	**3n**	92[c]
15	PhCH=CH	CH_2=$CHCH_2$	**3o**	89
16	*n*-Pr	*n*-Bu	**3p**	10[d]
17	*n*-Pr	$PhCH_2$	**3q**	32[d]
18	*n*-Pr	CH_2=$CHCH_2$	**3r**	<10[d]

[a] Standard reaction conditions: aldehydes (0.5 mmol), bromides (0.75 mmol), and 28% (w/w) aqueous ammonia (1.0 mL), 60 °C, overnight. When allyl and benzyl bromide were employed, reactions were conducted at rt. [b] Isolated yields. [c] 0.25 mL of THF was added. [d] Yield was determined by NMR of crude product.

the products were obtained in the yields of 90% and 22%, respectively (entries 7 and 8, Table 1). Hence, the best condition is shown in entry 4, Table 1.[10]

Subsequently, a variety of aldehydes and alkyl bromides were examined to generate the desired products under the optimal conditions. Table 2 summarizes the details of the result. For the aromatic aldehydes, the desired imines were prepared smoothly

Scheme 1. Studies on the Reaction of Preform 6 with Bromide

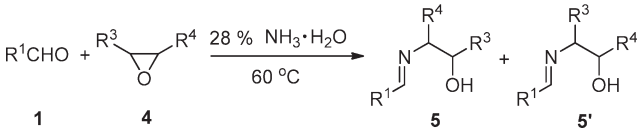


in excellent yields in the method. There was a tolerance for an electron-donating group (−OH) or electron-withdrawing groups (e.g., −Cl, −Br, $-NO_2$, −CN), and thienyl (entry 9, Table 2) and furyl (entry 13, Table 2) groups were not affected in this mild procedure. In further investigations, the transformation of an α,β-unsaturated aldehyde proceeded efficiently to afford the corresponding product in an excellent yield (entry 15, Table 2). In addition, allyl bromide and benzyl bromide performed more actively in this method, and corresponding imines were obtained in excellent yields at room temperature. It is notable that the 3-bromopropionitrile could also be used to give **3f** in a yield of 90% (entry 6, Table 2). However, for the aliphatic aldehyde, the yields of imines obtained were not satisfied (entries 16, 17, and 18, Table 2).

It is noteworthy that epoxides, instead of bromides, were also good substrates for the preparation of imines bearing a vicinal hydroxyl group. As shown in Table 3, epoxides afforded the desired imines regioselectively in excellent yields when aromatic aldehydes were applied, and the ring was opened at the less hindered site predominately. But for the aliphatic aldehyde, the yield obtained was low (entry 7, Table 3).

It was observed that a white precipitate appeared first when benzaldehyde and alkyl bromide were added into aqueous ammonia, then it disappeared slowly during the reaction. The white precipitate had been collected and confirmed by NMR as hydrobenzamide **6**. It was suggested that hydrobenzamide **6** might be an important intermediate in the reaction. Hence, hydrobenzamide **6** was presynthesized[11] and then was treated with the mixture of 1-bromobutane and aqueous ammonia at

Table 3. Formation of Imines from Aldehydes and Epoxides in Aqueous Ammonia[a]

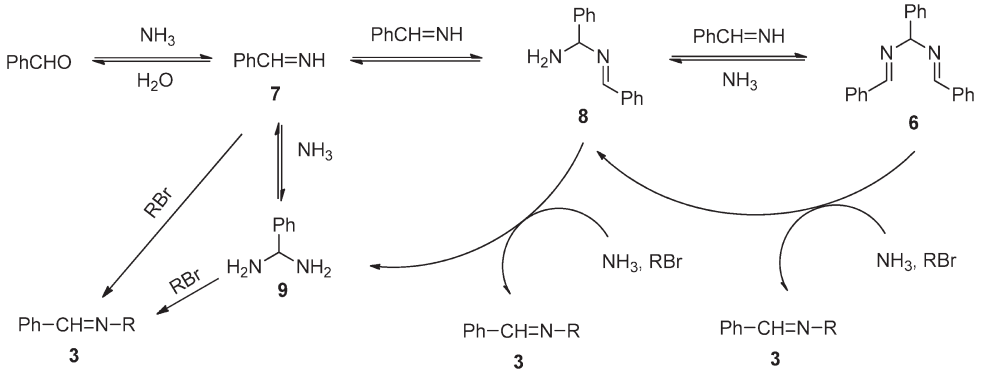


entry	R^1	R^3	R^4	major product	5:5′[b]	yield of 5+5′ (%)[c]	yield of 5 (%)[d]
1	Ph	Me	H	**5a**	97:3	93	87
2	4-Cl-C_6H_4	Me	H	**5b**	98:2	90	81
3	Ph	Ph	H	**5c**	72:28	96	65
4	4-MeO-C_6H_4	Ph	H	**5d**	79:21	86	64
5	Ph	$-(CH_2)_4-$		**5e**		96	90
6	4-MeO-C_6H_4	Me	H	**5f**	98:2	92	—[e]
7	*n*-Pr	$-(CH_2)_4-$		**5g**		32	

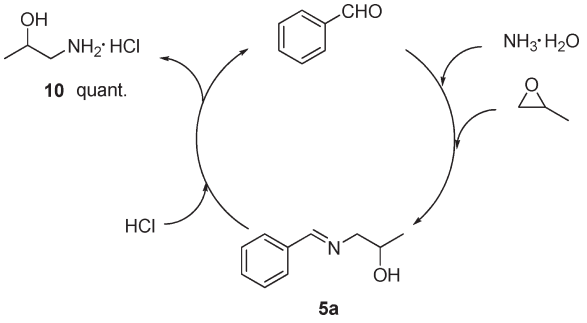
[a] Standard reaction conditions: aldehyde (2 mmol), epoxide (2.5 mmol), and 28% (w/w) aqueous ammonia (3.0 mL), overnight, 60 °C. [b] Determined by ^1H NMR of crude product. [c] NMR yield of 5:5′; internal standard: nitrobenzene. [d] Isolated yields of **5** by crystallization. [e] Unstable in column and failed to be crystallized.

dx.doi.org/10.1021/jo102455q |*J. Org. Chem.* 2011, 76, 3511–3514

Scheme 2. Proposed Reaction Pathway through Intermediate 6



Scheme 3. Application on the Synthesis of Primary Amine



60 °C overnight, and **3a** was obtained in a yield of 93% (Scheme 1). However, if the preformed **6** was added into the mixture of 1-bromobutane and water in the absence of ammonia, benzaldehyde was collected and none of the desired product was obtained, which indicated the importance of ammonia as a necessary partner in the reaction for the formation of imines from hydrobenzamide **6**.

Thus, the following reaction pathway was tentatively proposed to rationalize the formation of imines in aqueous ammonia (Scheme 2). In the mixture of benzaldehyde and aqueous ammonia, an equilibrium[12] was established that involved intermediates **7**, **8**, **9**, and **6**, and bromide might react with each of the intermediates to produce the desired imine **3**.

Another mechanism could not be neglected, in which the in situ formation of a primary alkylamine from the reaction of alkyl bromide with ammonia is followed by the condensation of primary alkylamine with aldehyde to produce imine. From the above experimental results, it was hypothesized that the route through Scheme 2 predominated in the two pathways.

It can be envisioned that the easy hydrolysis of imines renders this method a new protocol for the synthesis of primary amines.[13,14] Compared with reported methods of direct ammonolysis of bromides and 1,2-epoxides, this procedure avoids the production of secondary and tertiary amines as byproduct. Meanwhile the employed aldehyde can be recycled. As an example, in the treatment of imine **5a**[15] with 0.1 N HCl at room temperature for 3 h, the hydrolysis occurred smoothly to produce benzaldehyde and 1,2-amino alcohol **10**[16] quantitatively by NMR analysis (Scheme 3).

In conclusion, an efficient method for the preparation of imines from alkyl bromides/epoxides and aldehydes in aqueous ammonia has been developed. The obvious advantages of this synthetic procedure are simplicity and efficiency. This method also provided a new protocol for the synthesis of primary amines, especially for the synthesis of 1,2-amino alcohol regioselectively in high yields. Further investigation to determine a precise mechanism and expand the scope of this reaction is underway in our laboratory.

EXPERIMENTAL SECTION

Procedure for the Preparation of Compound 3a. A mixture of benzaldehyde (53 mg, 0.5 mmol) and 1-bromobutane (102 mg, 0.75 mmol) in 28% (w/w) aqueous ammonia (1.0 mL) was stirred in a sealed tube at 60 °C overnight. The reaction mixture was extracted with diethyl ether (2 × 10 mL). The combined organic layer was washed with water (5 mL) and brine (5 mL) and then dried over anhydrous magnesium sulfate. The organic solvent was removed on a rotary evaporator under vacuum, and the crude product was purified by column chromatography on silica gel (hexane/ethyl acetate/triethylamine 100:10:1) to afford **3a** as a colorless oil (73 mg, 91% yield). The silica gel was preneutralized with 1% (v/v) of triethylamine in hexane before packing. δ_H (300 MHz; $CDCl_3$; Me_4Si) 0.96 (3 H, t, J = 7.1 Hz, 3 × $CH_2CH_2CH_2CH_3$), 1.34−1.46 (2 H, m, $CH_2CH_2CH_2CH_3$), 1.65−1.75 (2 H, m, $CH_2CH_2CH_2CH_3$), 3.63 (2 H, dt, J = 1.2, 7.0 Hz, $CH_2CH_2CH_2CH_3$), 7.40−7.42 (3 H, m, 3 × *Ph*), 7.72−7.75 (2 H, m, 2 × *Ph*), 8.28 (1 H, s, N=C*H*). δ_C (75 MHz; $CDCl_3$; Me_4Si) 13.8, 20.3, 32.9, 61.3, 127.9, 128.4, 130.3, 136.3, 160.5. HRMS (ESI) m/z ($M + H^+$) calcd for $C_{11}H_{16}N$ 162.1283, found 162.1278.

ASSOCIATED CONTENT

Supporting Information. General experimental procedures, characterization data, and ^1H, ^{13}C NMR spectra of the synthesized compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: chehjm@scut.edu.cn.

ACKNOWLEDGMENT

This work was financially supported by the National Natural Science Foundation of China (Grant 20972055).

REFERENCES

(1) (a) Thomas, G. *Medicinal Chemistry*: Wiley: New York, 2000. (b) Patai, S. *The Chemistry of the Carbon-Nitrogen Double Bond (Chemistry of Functional Goups)*: Wiley-Interscience: New York, 1970. (c) Ajamian, A.; Gleason, J. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 3754. (d) Doyle, M. P.; Hu, W.; Timmons, D. J. *Org. Lett.* **2001**, *3*, 3741. (e) Adams, J. P. *J. Chem Soc., Perkin Trans.1* **2000**, *2*, 125. (f) Higuchi, M.; Yamamoto, K. *Org. Lett.* **1999**, *1*, 1881. (g) Hadjipavlou-Litina, D. J.; Eronikaki, A. A. *Drug Des. Discovery* **1998**, *15*, 199. (h) Cushman, M.; He, H. M.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1993**, *36*, 2817. (i) Hart, D. J.; Ha, D. C. *Chem. Rev.* **1989**, *89*, 1447.

(2) Selected examples: (a) Billman, J. H.; Tai, K. M. *J. Org. Chem.* **1958**, *23*, 535. (b) White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. (c) Castellano, J. A.; Goldmacher, J. E.; Barton, L. A.; Kane, J. S. *J. Org. Chem.* **1968**, *33*, 3501. (d) Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570. (e) Texier-Boullet, F. *Synthesis* **1985**, 679.

(3) Selected examples: (a) Orito, K.; Hatakeyama, T.; Takeo, M.; Uchiito, S.; Tokuda, M.; Suginome, H. *Tetrahedron* **1998**, *54*, 8403. (b) Yi, C. S.; Lee, D. W. *Organometallics* **2009**, *28*, 947. (c) Largeron, M.; Chiaroni, A.; Fleury, M.-B. *Chem.—Eur. J.* **2008**, *14*, 996. (d) Landge, S. M.; Atanassova, V.; Thimmaiah, M.; Torok, B *Tetrahedron Lett.* **2007**, *48*, 5161. (e) Kodama, S.; Yoshida, J.; Nomoto, A.; Ueta, Y.; Yano, S.; Ueshima, M.; Ogawa, A. *Tetrahedron Lett.* **2010**, *51*, 2450.

(4) Selected examples: (a) Samec, J. S. M.; Ell, A. H.; Backvall, J.-E. *Chem.—Eur. J.* **2005**, *11*, 2327. (b) Murahashi, S.-I.; Okano, Y.; Sato, H.; Nakae, T.; Komiya, N. *Synlett* **2007**, 1675. (c) Jiang, G.; Chen, J.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2009**, *11*, 4568. (d) Ell, A. H.; Samec, J. S. M.; Brasse, C.; Backvall, J.-E. *Chem. Commun.* **2002**, 1144. (e) Choi, H.; Doyle, M. P. *Chem. Commun.* **2007**, 745. (f) Mukaiyama, T.; Kawana, A.; Fukuda, Y.; Matsuo, J.-I. *Chem. Lett.* **2001**, *5*, 390. (g) Zhu, B.; Lazar, M.; Trewyn, B. G.; Angelici, R. J. *J. Catal.* **2008**, *260*, 1.

(5) Selected examples: (a) Kwon, M. S.; Kim, S.; Park, S.; Bosco, W.; Chidrala, R. K.; Park, J. *J. Org. Chem.* **2009**, *74*, 2877. (b) Kim, J. W.; He, J.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2009**, *38*, 920. (c) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637. (d) Sun, H.; Su, F.-Z.; Ni, J.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4390. (e) Kegnas, S.; Mielby, J.; Mentzel, U. V.; Christensen, C. H.; Riisager, A. *Green Chem.* **2010**, *12*, 1437. (f) Sithambaram, S.; Kumar, R.; Son, Y.-C.; Suib, S. L. *J. Catal.* **2008**, *253*, 269.

(6) Gnanaprakasam, B.; Zhang, J.; Milsten, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 1468.

(7) Zanardi, A.; Mata, J. A.; Peris, E. *Chem.—Eur. J.* **2010**, *16*, 10502.

(8) (a) Tanaka, K.; Shiraishi, R. *Green Chem.* **2000**, *2*, 272. (b) Simion, A.; Simion, C.; Kanda, T.; Nagashima, S.; Mitoma, Y.; Yamada, T.; Mimura, K.; Tashiro, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2071.

(9) (a) Huang, J.-M.; Ren, H.-R. *Chem. Commun.* **2010**, *46*, 2286. (b) Huang, J.-M.; Dong, Y. *Chem. Commun.* **2009**, 3943. (c) Huang, J.; Zhou, L.; Jiang, H. *Angew. Chem., Int. Ed.* **2006**, *45*, 1945. (d) Huang, J.-M.; Wang, X.-X.; Dong, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 924.

(10) Studies were carried out by running the reaction of benzaldehyde and 1-bromobutane with ammonia in D_2O in a NMR tube. In situ reaction monitoring showed that imine product was formed and benzaldehyde disappeared in the tube before the workup.

(11) (a) Hunter, D. H.; Sim, S. K. *Can. J. Chem.* **1972**, *50*, 669. (b) Francis, F. *Ber.* **1909**, *42*, 2216. (c) Laurent, M. A. *Liebigs Ann. Chem.* **1837**, *21*, 130.

(12) Crowell, T. I.; McLeod, R. K. *J. Org. Chem.* **1967**, *32*, 4030.

(13) General references for the synthesis of primary amines, see: (a) Larock, R. C. *Comprehensive Organic Transformations: a guide to functional group preparation*, 2nd ed.; Wiley-VCH: New York, 1999. (b) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; p 768 and references cited therein. (c) Collman, J. P.; Trost, B. M.; Veroeven, T. R. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, p 892 and references cited therein. (d) Gibson, M. S. *The Chemistry of Amino Group*; Patai, S., Ed.: Interscience: New York, 1968; p 61 and references cited therein.

(14) Recent examples for the synthesis of amines from imines: (a) Kitamura, M.; Suga, T.; Chiba, S.; Narasaka, K. *Org. Lett.* **2004**, *6*, 4619. (b) Gunanathan, C.; Milstein, D. *Angew. Chem., Int. Ed.* **2008**, *47*, 8661. (c) Huang, X.; Ortiz-Marciales, M.; Huang, K.; Stepanenko, V.; Merced, F. G.; Ayala, A. M.; Correa, W.; Jesús, M. D. *Org. Lett.* **2007**, *9*, 1793. (d) Kadyrov, R.; Riermeier, T. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 5472.

(15) **5a** can be easily separated from the product mixture of **5a** and **5a′** by simple recrystallization.

(16) For the synthesis of 1,2-amino alcohol by ammonolysis of oxiranes, see: Kaburagi, Y.; Kishi, Y. *Tetrahedron Lett.* **2007**, *48*, 8967 and references cited herein.