JOC *Note*

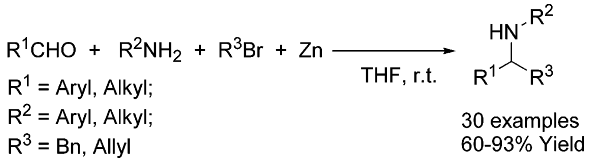
Efficient Three-Component One-Pot Benzylation and Allylation of Aldehydes and Amines for Synthesis of Homobenzylamines and Homoallylamines

Renhua Fan,* Dongming Pu, Luoheng Qin, Fengqi Wen, Guoping Yao, and Jie Wu*

Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China

frenhua@yahoo.com

Received December 20, 2006

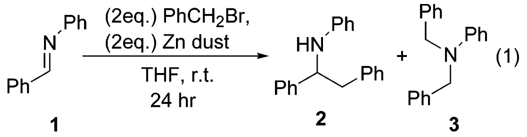


A highly efficient, three-component one-pot benzylation and allylation of aromatic and aliphatic aldehydes and amines affords the corresponding homobenzylamines and homoallylamines in good to excellent yield. The procedure is lauded by its simplicity and manipulability.

In carbon–carbon bond formation reactions, the addition of organometallic reagents to imines provides a versatile method for the synthesis of amines.[1] The versatility, however, was compromised by the poor electrophilicity of the azomethine carbon of imines, which gives rise to the competitive byproducts through reduction, enolization, or coupling reaction as well as to the desirable adducts.[1d] In order to expand the scope of the organometallic addition to imines, several approaches have been exploited. The C═N bond could be activated by an electron-withdrawing group on nitrogen. The use of N-activated imines, however, is generally restricted in nonenolizable aldimines. This approach is further complicated by the harsh deprotection condition if the removal of the N-protecting group is necessary.[2] An alternative method is to activate the N-inactivated imine by coordinating a Lewis acid to the nitrogen of the C═N moiety. The applicability of this approach is possibly hampered by other Lewis basic centers in the imine structure.[3] In most of the cases, imines are mainly restricted to aryl aldimines due to the low reactivity of other imines. The inclination of the α-deprotonation of aliphatic imines significantly reduces the versatility of the reactions involving basic organometallic reagents. The applicability is therefore limited within the scope of the imines derived from nonenolizable or α-alkyl-substituted aliphatic aldehydes.[4]

Significant advances have been made in the Barbier-type imine alkylation in recent years.[5] Most of them, however, have been focused on the imine allylation because of the favorable reactivity of allylic organometallic reagents as the result of the resonance stabilization of the allyl anion.[6] The difficulty in both synthesis and stability of the imines derived from aliphatic aldehydes and amines makes a multicomponent one-pot procedure for allylation of imines preferred in practice. On the other hand, compared to the extensive studies on the allylation of imines,[7] the benzylation of imines has received much less scrutiny until recently.[8] We report herein the results regarding a three-component one-pot benzylation and allylation of aromatic and aliphatic aldehydes and amines under the Barbier-type conditions. The simplicity of the procedure lies in the fact that no further activation of the zinc powder and no isolation of the unstable imine intermediates are necessary.

In 1996, Hou's group has reported an efficient allylation of inactivated aldimines under the Barbier-type conditions using allyl bromide and zinc dust in anhydrous tetrahydrofuran (THF).[7e] However, the benzylation of imine **1** did not give rise to the expected benzylation product **2** under the same conditions but a reduction N-benzylation byproduct **3** in 82% yield (eq 1).



(1)

In the following condition screening experiments, the benzylation product **2** could be detected with moist THF as solvent while the yield of **3** decreased to 26%. When 1 equiv of H_2O

---

[1] For reviews, see: (a) Kleinman, E. F.; Volkmann, R. A. *In Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 975. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Li, A. H.; Dai, L. X.; Aggarwal, V. K. *Chem. Rev.* **1997**, *97*, 2431. (d) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (e) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (f) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163. (g) Davies, A. G. *Organotin Chemistry*; Wiley-VCH: Weinheim, Germany, 2004. (h) Hisashi, Y.; Koichiro, O. *MainGroup Metals in Organic Synthesis*; Wiley-VCH: Weinheim, Germany, 2004; Vol. 2, p 621. (i) Hou, X. L.; Wu, J.; Fan, R. H.; Ding, C. H.; Luo, Z. B.; Dai, L. X. *Synlett* **2006**, 181.

[2] (a) Volkmann, R. A. In *Comprehensive Organic Synthesis: Additions to C*–*X π-Bonds, Part 1*; Schreiber, S. L., Ed.; Pergamon: Oxford, 1991; Vol. 1, p 355. (b) Sisko, J.; Weinreb, S. M. *J. Org. Chem.* **1990**, *55*, 393.

[3] (a) Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1994**, *59*, 7947. (b) Katritzky, A. R.; Hong, Q.; Yang, Z. *J. Org. Chem.* **1995**, *60*, 3405.

[4] (a) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178. (b) Huet, J. *Bull. Soc. Chim. Fr.* **1964**, 952.

[5] For selected recent examples, see: (a) Sain, B.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1992**, *33*, 4795. (b) Bhuyan, P. J.; Prajapati, D.; Sandhu, J. S. *Tetrahedron Lett.* **1992**, *33*, 7975. (c) Lu, W.; Chan, T. H. *J. Org. Chem.* **2001**, *66*, 3467. (d) Lu, W.; Chan, T. H. *J. Org. Chem.*, **2000**, *65*, 8589.

[6] For selected recent examples, see: (a) Shen, K. H.; Yao, C. F. *J. Org. Chem.* **2006**, *71*, 3980. (b) Han, R.; Choi, S.; Son, K.; Jun, Y. Lee, B.; Kim, B. *Synth. Commun.* **2005**, *35*, 1725. (c) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Green Chem.* **2004**, *6*, 119. (d) Andrews, P. C.; Peatt, A. C.; Raston, C. L. *Tetrahedron Lett.* **2004**, *45*, 243. (e) Hilt, G.; Smolko, K. I.; Waloch, C. *Tetrahedron Lett.* **2002**, *43*, 1437. (f) Kim, B. H.; Han, R.; Park, R. J.; Bai, K. H.; Jun, Y. M.; Baik, W. *Synth. Commun.* **2001**, *31*, 2297. (g) Su, W. K.; Li, J. H.; Zhang, Y. M. *Synth. Commun.* **2001**, *31*, 273.

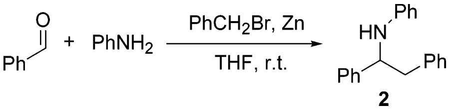
[7] For selected recent examples, see: (a) Sun, X. W.; Xu, M. H.; Lin, G. Q. *Org. Lett.* **2006**, *8*, 4979. (b) Zhang, W. X.; Ding, C. H.; Luo, Z. B.; Hou, X. L.; Dai, L. X. *Tetrahedron Lett.* **2006**, *47*, 8391. (c) Zhang, W. X.; Hou, X. L. *Chin. Chem. Lett.* **2006**, *17*, 1037. (d) Liu, X. Y; Zhu, S. Z; Wang, S. W. *Synthesis* **2004**, 683. (e) Wang, D. K.; Dai, L. X.; Hou, X. L.; Zhang, Y. *Tetrahedron Lett.* **1996**, *37*, 4187.

[8] Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc.* **2006**, *128*, 9998.

10.1021/jo062616y CCC: $37.00

was added into the reaction mixture in anhydrous THF, the reaction gave product **2** in 10% yield. The yield of **2** increased to 64% while imine **1** was treated with 1 equiv of H_2O in anhydrous THF for 30 min before zinc and benzyl bromide were added. Drastic decrease in yield (only 30%) occurred, however, when 2 equiv of H_2O was used while the other kept constant. Further experiments showed that the ratio of benzyl bromide and zinc relative to imine (2:1) was crucial for the completion of the reaction.

The further improvement of the specific reaction cannot be done without the elucidation of the reaction mechanism. In order to understand the reaction pathway, imine **1** and 1 equiv of H_2O were mixed in THF-d_4, and the mixture was stirred at room temperature for 30 min. The ^1H NMR showed that imine **1** decomposed to the benzaldehyde, aniline, and another compound. The obtained spectrum was similar to that of the mixture of benzaldehyde and aniline in THF-d_4. Under the Barbier-type conditions, benzaldehyde, aniline, benzyl bromide, and zinc dust were mixed in a 1:1:2:2 ratio in anhydrous THF, and the mixture was stirred at room temperature for 24 h (eq 2). The benzylation



(2)

occurred with product **2** in 54% yield while the benzaldehyde did not disappear. Only a trace amount of byproduct **3** was detected while another byproduct from the reaction of aniline and benzyl bromide was isolated in 24% yield. The optimization of the reaction conditions showed that the best ratio among benzaldehyde, aniline, benzyl bromide, and zinc was 1:2:3:3, in which the yield of **2** increased to 74%. The ^1H NMR for the crude reaction product showed that, except the known byproducts, toluene was formed in the reaction. As a control experiment, 8% yield of **2** and 61% yield **3** were obtained when anhydrous $MgSO_4$ was used as an additive in the three-component procedure.

The above results suggested that the reaction might not proceed via an imine intermediate. A plausible pathway was shown in Figure 1. The intermediate **A** was first formed either from the reaction of benzaldehyde with aniline or from reaction of imine **1** with H_2O. One $PhCH_2ZnBr$ then acted as a base to deprotonate **A** to form an intermediate **B** and $PhCH_3$. Intermediate **B** would react with the second $PhCH_2ZnBr$ via a transition-state **C** to give rise to the desirable adduct **2** in the last step.

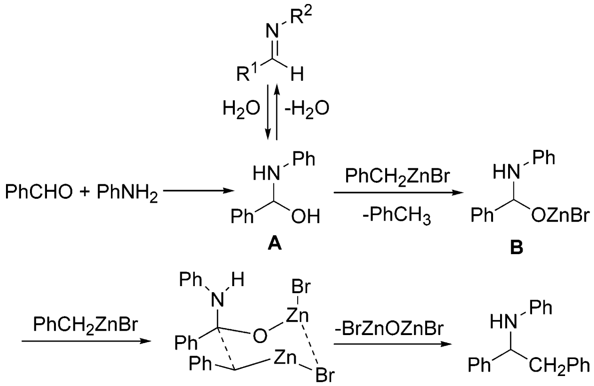
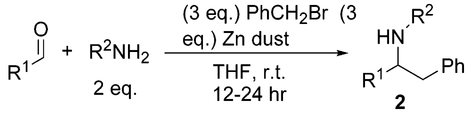


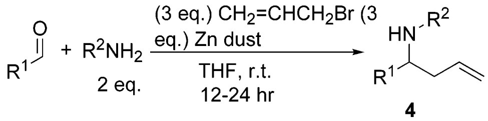
FIGURE 1. Plausible pathway.

TABLE 1. Three-Component One-Pot Benzylation



entry	R^1	R^2	**2** (%)
1	Ph	Ph	**2a** (74)
2	*p*-CH_3O-C_6H_4	Ph	**2b** (76)
3	*p*-CH_3-C_6H_4	Ph	**2c** (72)
4	*p*-Cl-C_6H_4	Ph	**2d** (80)
5	*p*-F-C_6H_4	Ph	**2e** (77)
6	*o*-Cl-C_6H_4	Ph	**2f** (66)
7	2-furan	Ph	**2g** (80)
8	2-thiophen	Ph	**2h** (63)
9	$PhCH_2$	Ph	**2i** (82)
10	*n*-C_6H_{13}	Ph	**2j** (73)
11	*i*-C_4H_9	Ph	**2k** (93)
12	Ph	*p*-CH_3O-C_6H_4	**2l** (67)
13	Ph	*p*-F-C_6H_4	**2m** (60)
14	Ph	$PhCH_2$	**2n** (61)
15	Ph	*n*-C_6H_{13}	**2o** (66)

TABLE 2. Three-Component One-Pot Allylation



entry	R^1	R^2	**4** (%)
1	Ph	Ph	**4a** (70)
2	*p*-CH_3O-C_6H_4	Ph	**4b** (77)
3	*p*-CH_3-C_6H_4	Ph	**4c** (87)
4	*p*-Cl-C_6H_4	Ph	**4d** (85)
5	*p*-F-C_6H_4	Ph	**4e** (71)
6	*o*-Cl-C_6H_4	Ph	**4f** (77)
7	2-furan	Ph	**4g** (85)
8	2-pyridin	Ph	**4h** (93)
9	*n*-C_3H_7	Ph	**4i** (65)
10	*i*-C_4H_9	Ph	**4j** (89)
11	Ph	*p*-CH_3O-C_6H_4	**4k** (73)
12	Ph	*p*-F-C_6H_4	**4l** (69)
13	Ph	*p*-CF_3-C_6H_4	**4m** (67)
14	Ph	$PhCH_2$	**4n** (60)
15	Ph	*n*-C_6H_{13}	**4o** (77)

The scope of the one-pot benzylation reaction of aryl and aliphatic aldehydes and amines was examined (Table 1). For aryl and heteroaryl aldehydes, the reactions proceeded smoothly giving rise to the desirable benzylation products in moderate to good yield (Table 1, entries 1−8). It turned out that our proposed reaction system could adapt to various combinations of aldehydes and amines. Aliphatic aldehydes were good candidates (Table 1, entries 9−11) despite the inherent instability, low reactivity, and often preferable enolization of their respective imine derivatives. Benzylation to the aryl amine with an electron-withdrawing group or electron-donating group, benzyl amine, and aliphatic amine also gave the corresponding products in moderate yield (Table 1, entries 12−15). In all the cases, only a trace amount of reduction N-benzylation byproduct **3** was observed, and the major byproduct (<10%yield) was the material resulting from the further benzylation on the nitrogen site of the expected product.

Addition of allylic organometallic species to the imine constitutes a potentially valuable method for the preparation of homoallylamines. Certain drawbacks of the approach such as unsatisfactory yields with aliphatic aldehydes and amines and the requirement of an additional Lewis acid or other additives limit its range of application.[9] Motivated by the efficient benzylation of aryl and aliphatic aldehydes and amines, a three-component allylation reaction under the same conditions was examined (Table 2). As expected, for aryl, heteroaryl, and aliphatic aldehydes, the allylation proceeded smoothly to produce the desirable adducts in good to excellent yield (Table 2, entries 1−10). Moreover, the scalability of this reaction was also proved to be good by the 73% yield of **4a** when the reaction of benzaldehyde and aniline run in 10 mmol scale.

In summary, we have developed a highly efficient, three-component benzylation and allylation of aromatic and aliphatic aldehydes and amines with the aid of commercially available zinc powder under the Barbier-type conditions. The potential of this reaction system can be evaluated by its adaptability to a wide variety of reagents. In addition, the one-pot procedure offers extra manipulability by avoiding the isolation of the unstable imine intermediates. The further development of asymmetric reactions is ongoing and will be reported in due course.

Experiment Section

Typical Procedure for the Three-Component One-Pot Reaction. A solution of R^1CHO (1 mmol) and R^2NH_2 (2 mmol) in anhydrous THF (3 mL) was stirred at rt under N_2 for 30 min, and then R^3Br (3 mmol) and Zn dust (3 mmol) were added in. The resultant mixture was stirred at rt for 12−24 h (determined by TLC), then quenched with 1% HCl, extracted by DCM, and dried by anhydrous Na_2SO_4, and the crude product was purified by flash column chromatography to provide the corresponding product.

***N*-(1,2-Diphenylethyl)benzenamine 2a.** ^1H NMR (300 MHz, $CDCl_3$) δ 2.99 (dd, $J = 13.2, 8.4$ Hz, 1H), 3.12 (dd, $J = 13.2, 8.4$ Hz, 1H), 4.10 (br, 1H), 4.56 (t, $J = 8.4$ Hz, 1H), 6.42 (d, $J = 8.8$ Hz, 2H), 6.62 (t, $J = 8.2$ Hz, 1H), 6.98−7.38 (m, 12H). The spectral data are consistent with those reported in the literature.[8]

***N*-(1-Phenylbut-3-enyl)benzenamine 4a.** ^1H NMR (400 MHz, $CDCl_3$) δ 2.49−2.55 (m, 1H), 2.59−2.63 (m, 1H), 4.17 (br, 1H), 4.39 (dd, $J = 7.8, 4.8$ Hz, 1H), 5.15−5.22 (m, 2H), 5.74−5.81 (m, 1H), 6.50 (d, $J = 8.2$ Hz, 2H), 6.65 (t, $J = 7.2$ Hz, 1H), 7.09 (t, $J = 8.2$ Hz, 2H), 7.22−7.26 (m, 1H), 7.31−7.39 (m, 4H). The spectral data are consistent with those reported in the literature.[9g]

Acknowledgment. We thank Professor Xue-Long Hou for his invaluable advice during the course of this research. Financial support from National Natural Science Foundation of China (20642006, 20502004), the Science and Technology Commission of Shanghai Municipality (05ZR14013), and Fudan University is gratefully acknowledged.

Supporting Information Available: General experimental information, characterization data of the isolated compounds, and ^1H and ^{13}C NMR spectra for **2** and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO062616Y

---

[9] For selected recent examples, see: (a) Das, B.; Ravikanth, B.; Thirupathi, P.; Vittal Rao, B. *Tetrahedron Lett.* **2006**, *47*, 5041. (b) Das, B.; Ravikanth, B.; Laxminarayana, K.; Vittal Rao, B. *J. Mol. Catal. A: Chem.* **2006**, *253*, 92. (c) Shimizu, M.; Kimura, M.; Watanabe, T.; Tamaru, Y. *Org. Lett*. **2005**, *7*, 637. (d) Yadav, J. S.; Reddy, B. V. S.; Raju, A. K. *Synthesis* **2003**, 883. (e) Akiyama, T.; Iwai, J.; Onuma, Y.; Kagoshima, H. *J. Chem. Soc., Chem. Commun*. **1999**, 2191. (f) Kobayashi, S.; Busujima, T.; Nagayama, S. *J. Chem. Soc., Chem. Commun.* **1998**, 19. (g) Yin, Y. Y.; Zhao, G.; Li, G. L *Tetrahedron* **2005**, *61*, 12042.