ORGANIC LETTERS

2011
Vol. 13, No. 13
3534–3537

Mild Nonepimerizing *N*-Alkylation of Amines by Alcohols without Transition Metals

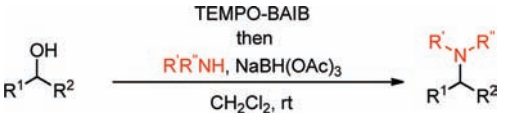
Claire Guérin,[†] Véronique Bellosta,[†] Gérard Guillamot,[‡] and Janine Cossy*,[†]

Laboratoire de Chimie Organique, ESPCI ParisTech, CNRS UMR 7084, 10 rue Vauquelin, 75231-Paris Cedex 05, France, and PCAS, 23 rue Bossuet, Z.I. la vigne aux Loups, 91160-Longjumeau, France

janine.cossy@espci.fr

Received May 19, 2011

ABSTRACT



A one-pot two-step sequence involving an oxidation/imine-iminium formation/reduction allowed the *N*-alkylation of amines by alcohols without any epimerization when optically active alcohols and amines are involved in the process.

As *N*-alkylamines constitute a key functional group in organic chemistry, many synthetic works have been devoted to their synthesis.[1] Traditionally, the *N*-alkylation of amines is achieved either by reaction with alkylating agents or by addition of nucleophiles or radicals on imines.[1] The most commonly used method for the preparation of secondary and tertiary amines is the substitution of alkyl halides by amines, in the presence of a stoichiometric amount of base.[2] However, in this process polyalkylation can occur, leading to a mixture of compounds, and undesired inorganic wastes are produced. Moreover, many alkyl halides are toxic and not commonly encountered in Nature. The use of available, inexpensive, and less hazardous reagents such as alcohols instead of alkyl halides for *N*-alkylation of amines is a challenging and a highly atom-efficient approach which leads only to the formation of water as a byproduct. The "borrowing hydrogen strategy", also called hydrogen autotransfer, has allowed the direct use of alcohols as alkylating agents. This process has been applied to the formation of C−N bonds,[3] and the use of SiO_2[4] and Al_2O_3[5] as catalysts has been reported; however, both the yields and the selectivities (monoalkylation versus bis-alkylation) are poor. The best conditions involve transition-metal based catalysts, including heterogeneous and homogeneous processes. When the reaction is performed with heterogeneous catalysts[3d] such as nickel,[6] copper,[7] platinum, ruthenium,[8] palladium,[9] gold,[10] silver,[11] or iron,[12] the yields are good to excellent, but generally the main drawback is the need for harsh conditions such as high temperature which can be detrimental for highly sensitive compounds. Taylor et al. reported a mild one-pot oxidation/imine-iminium formation/reduction sequence for the conversion of benzylic, allylic, or propargylic alcohols to amines using

[†] ESPCI ParisTech.
[‡] PCAS.

(1) (a) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785–7811. (b) Olsen, C. A.; Franzyk, H.; Jaroszewski, J. W. *Synthesis* **2005**, 2631–2653.

(2) Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; 5th ed.; Wiley-Interscience: New York, 2001; pp 499−501 and references cited.

(3) (a) Hamid, M. H. S.; Slatford, P.; Williams, J. M. *Adv. Synth. Catal.* **2007**, *349*, 1555–1575. (b) Nixon, T. D.; Whittlesey, M. K.; Williams, J. M. J. *Dalton Trans.* **2009**, *38*, 753–762. (c) Dobereiner, G. E.; Crabtree, R. H. *Chem. Rev.* **2010**, *110*, 681–703. (d) Guillena, G.; Ramón, D. J.; Yus, M. *Chem. Rev.* **2010**, *110*, 1611–1641.

(4) (a) Brown, A. B.; Reid, E. E. *J. Am. Chem. Soc.* **1924**, *46*, 1836–1839. (b) Narayanan, S.; Prasad, B. P. *J. Chem. Soc., Chem. Commun.* **1992**, 1204–1205.

(5) Valot, F.; Fache, F.; Jacquot, R.; Spagnol, M.; Lemaire, M. *Tetrahedron Lett.* **1999**, *40*, 3689–3692.

(6) For recent reference with Ni, see: García Ruano, J. L.; Parra, A.; Alemán, J.; Yuste, F.; Mastranzo, V. M. *Chem. Commun.* **2009**, 404–406.

(7) For recent references with Cu, see: (a) Martínez-Asencio, A.; Ramón, D. J.; Yus, M. *Tetrahedron* **2011**, *67*, 3140–3149. (b) He, J.; Yamaguchi, K.; Mizuno, N. *Chem. Lett.* **2010**, *39*, 1182–1183. (c) Likhar, P. R.; Arundhathi, R.; Kantam, M. L.; Prathima, P. S. *Eur. J. Org. Chem.* **2009**, 5383–5389.

10.1021/ol201351a
Published on Web 06/08/2011

MnO_2 as the oxidant, a polymer-supported cyanoborohydride as the reductant, and acetic acid as the additive.[13] With homogeneous catalysts[3] such as ruthenium[14] or iridium[15] catalysts, yields in the monoalkylated amines are good but the reaction has to be conducted in refluxing toluene and the reaction times are usually long except under microwave irradiation. By using these catalysts, the main drawbacks are the temperature and the epimerization of optically active alcohols involved in the *N*-alkylation of amines.[14b] Very recently, *N*-alkylation of amines by direct nucleophilic substitution at the sp^3 carbon atom of alcohols was reported using iron and amino acid catalysts, but again, elevated temperature and long reaction times are necessary.[16]

Here, we report a one-pot oxidation/imine-iminium formation/reduction sequence under mild conditions (Scheme 1). This sequence allows the chemoselective *N*-alkylation of amines with various nonactivated primary and secondary alcohols and prevents epimerization of optically active substrates (amines or alcohols). Furthermore, no transition metals are involved which is of importance when medicinal chemists have to prepare amines for biological tests.

Among the various conditions reported for the oxidation of alcohols, we selected the mild 2,2,6,6-tetramethyl-1-piperidinyloxyl and [bis(acetoxy)-iodo]benzene (TEMPO-BAIB) system[17] which releases AcOH in the reaction medium; the latter is known to be an efficient additive for reductive aminations.[18] First, we tested the sequence for the *N*-alkylation of benzylamine **2a** by octanol **1a**. Hence, **1a** was oxidized by TEMPO (0.2 equiv) in the presence of BAIB (1.15 equiv) in CH_2Cl_2 at rt. After 16 h, **2a** (3 equiv) and the reducing agent (2 equiv) were both introduced in the reaction mixture at rt. The results are reported in Table 1. By using $NaBH(OAc)_3$ and $NaBH_3CN$, which are commonly used for reductive amination of aldehydes, the desired *N*-alkylated amine **3a** was formed as well as the corresponding *N*,*N*-bis-alkylated compound **4a** (as a minor product) (Table 1, entries 1 and 2). The use of $NaBH_4$ led to **3a** almost quantitatively with only traces of **4a** (Table 1, entry 3). The use of 2 equiv of benzylamine seems to be a good compromise to obtain **3a** in both good yield (91%) and selectivity (ratio **3a**/**4a** = 95/5) (Table 1, entry 5).

Scheme 1. Oxidation/Imine-Iminium Formation/Reduction

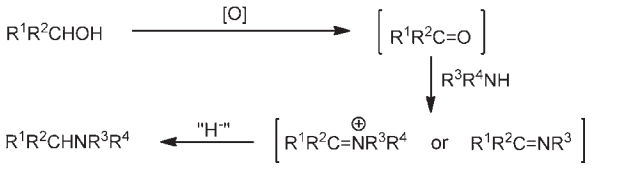
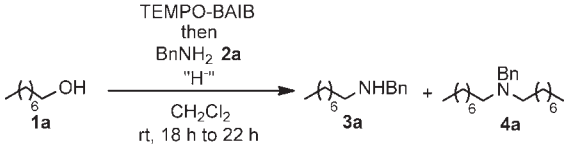


Table 1. *N*-Alkylation of Benzylamine with Octanol



entry	"H$^-$"	$BnNH_2$ **2a** (*x* equiv)	**3a**/**4a**	yield in **3a**[a]
1	$NaBH(OAc)_3$	3	74/26	40%
2	$NaBH_3CN$	3	85/15	69%
3	$NaBH_4$	3	97/3	quant
4	$NaBH_4$	1	n.d.[b]	59%
5	$NaBH_4$	2	95/5	91%

[a] Yield for isolated **3a**. [b] n.d. = not determined.

The reaction is general and allows the monoalkylation of a wide range of amines.[19] The results obtained with various amines and alcohols are reported in Table 2. We have to

(8) (a) Kim, J. W.; Yamaguchi, K.; Mizuno, N. *J. Catal.* **2009**, *263*, 205–208. (b) Yamaguchi, K.; He, J.; Oishi, T.; Mizuno, N. *Chem.—Eur. J.* **2010**, *16*, 7199–7207. (c) Yamaguchi, K.; Mizuno, N. *Synlett* **2010**, 2365–2382.

(9) For recent references with Pd, see: (a) Zhang, Y.; Qi, X.; Cui, X.; Shi, F.; Deng, Y. *Tetrahedron Lett.* **2011**, *52*, 1334–1338. (b) Corma, A.; Ródenas, T.; Sabater, M. J. *Chem.—Eur. J.* **2010**, *16*, 254–260. (c) Xu, C.-P.; Xiao, Z.-H.; Zhuo, B.-Q.; Wang, Y.-H.; Huang, P.-Q. *Chem. Commun.* **2010**, *46*, 7834–7836.

(10) For recent references with Au, see: (a) He, L.; Lou, X.-B.; Ni, J.; Liu, Y.-M.; Cao, Y.; He, H.-Y.; Fan, K.-N. *Chem.—Eur. J.* **2010**, *16*, 13965–13969. (b) Ishida, T.; Kawakita, N.; Akita, T.; Haruta, M. *Gold Bulletin* **2009**, *42*, 267–274.

(11) (a) Shimizu, K.; Nishimura, M.; Satsuma, A. *ChemCatChem* **2009**, *1*, 497–503. (b) Cui, X.; Zhang, Y.; Shi, F.; Deng, Y. *Chem.—Eur. J.* **2011**, *17*, 1021–1028.

(12) (a) Martínez, R.; Ramón, D. J.; Yus, M. *Org. Biomol. Chem.* **2009**, *7*, 2176–2181. (b) Gonzalez-Arellano, C.; Yoshida, K.; Luque, R.; Gai, P. L. *Green Chem.* **2010**, *12*, 1281–1287.

(13) Blackburn, L.; Taylor, R. J. K. *Org. Lett.* **2001**, *3*, 1637–1639.

(14) For recent references with Ru, see: (a) Watson, A. J. A.; Maxwell, A. C.; Williams, J. M. J. *J. Org. Chem.* **2011**, *76*, 2328–2331. (b) Hamid, M. H. S. A.; Allen, C. L.; Lamb, G. W.; Maxwell, A. C.; Maytum, H. C.; Watson, A. J. A.; Williams, J. M. J. *J. Am. Chem. Soc.* **2009**, *131*, 1766–1774. (c) Lamb, G. W.; Watson, A. J. A.; Jolley, K. E.; Maxwell, A. C.; Williams, J. M. J. *Tetrahedron Lett.* **2009**, *50*, 3374–3377. (d) Imm, S.; Bähn, S.; Neubert, L.; Neumann, H.; Beller, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 8126–8129. (e) Bähn, S.; Imm, S.; Mevius, K.; Neubert, L.; Tillack, A.; Williams, J. M. J.; Beller, M. *Chem.—Eur. J.* **2010**, *16*, 3590–3593. (f) Bähn, S.; Tillack, A.; Imm, S.; Mevius, K.; Michalik, D.; Hollmann, D.; Neubert, L.; Beller, M. *ChemSusChem* **2009**, *2*, 551–557. (g) Pingen, D.; Müller, C.; Vogt, D. *Angew. Chem., Int. Ed.* **2010**, *49*, 8130–8133.

(15) For recent references with Ir, see: (a) Suzuki, T. *Chem. Rev.* **2011**, *111*, 1825–1845. (b) Saidi, O.; Blacker, A. J.; Farah, M. M.; Marsden, S. P.; Williams, J. M. J. *Chem. Commun.* **2010**, *46*, 1541–1543. (c) Saidi, O.; Blacker, A. J.; Lamb, G. W.; Marsden, S. P.; Taylor, J. E.; Williams, J. M. J. *Org. Process Res. Dev.* **2010**, *14*, 1046–1049. (d) Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2010**, *16*, 13193–13198. (e) Blank, B.; Michlik, S.; Kempe, R. *Chem.—Eur. J.* **2009**, *15*, 3790–3799. (f) Blank, B.; Michlik, S.; Kempe, R. *Adv. Synth. Catal.* **2009**, *351*, 2903–2911. (g) Kawahara, R.; Fujita, K.; Yamaguchi, R. *J. Am. Chem. Soc.* **2010**, *132*, 15108–15111. (h) Yamaguchi, R.; Mingwen, Z.; Kawagoe, S.; Asai, C.; Fujita, K. *Synthesis* **2009**, 1220–1223.

(16) Zhao, Y.; Foo, S. W.; Saito, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 3006–3009.

(17) De Mico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli G. *J. Org. Chem.* **1997**, *62*, 6974–6977.

(18) Baxter, E. W.; Reitz, A. B. *Reductive Aminations of Carbonyl Compounds with Borohydride and Borane Reducing Agents*; John Wiley & Sons, Inc.: 2004; Vol. 59.

(19) For all experiments, the completion of the oxidation was checked by TLC or GC/MS and, if necessary, additional BAIB (up to 0.75 equiv) was introduced. The amount of BAIB necessary for the oxidation may be related to its quality.

Table 2. *N*-Alkylation of Primary and Secondary Amines by Primary and Secondary Alcohols

1 3

entry	R'R''NH_2 2	R^1OH 1	product 3 yield
1	$BnNH_2$ **2a**	**1b**	**3b** 60% (70%)[a]
2	**2b**	**1c**	**3c** 85%
3	*t*-Bu-NH_2 **2c**	**1c**	**3d** 96% (31%)[a]
4	*t*-Bu-NH_2 **2c**	**1d**	**3e** 80%
5	$BnNH_2$ **2a**	**1e**	**3f** 83%[b] (43%)[a]
6	$BnNH_2$ **2a**	**1f**	**3g** quant
7	**2b**	**1g**	**3h** 84%
8	**2d**[c]	**1c**	**3i** 88%
9	**2e**	**1b**	**3j** 70%
10	Bn_2NH **2f**[c]	**1a**	**3k** 92% (82%)[a]
11	Bn_2NH **2f**	**1h**	**3l** 90%[d]

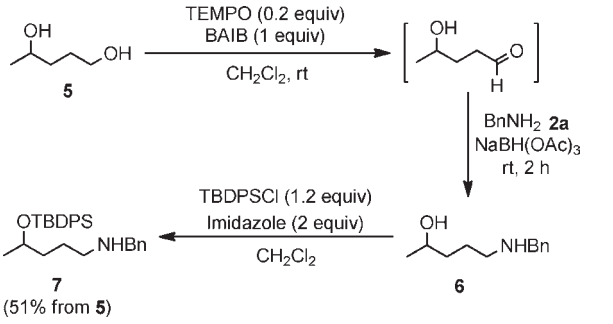
[a] Yields given in parentheses refer to similar experiments performed with 2 equiv of $NaBH_4$ instead of $NaBH(OAc)_3$. [b] Yield estimated by ^1H NMR from a mixture of **3f** and Bn_2NH. [c] Only 1 equiv of amine was used for this experiment. [d] Yield estimated by ^1H NMR from a mixture of **3l** and Bn_3N.

point out that both $NaBH_4$ and $NaBH(OAc)_3$ were tested as reducing agents and in most cases $NaBH(OAc)_3$ was revealed to be the best reducing agent. Benzylamine[20] **2a** was alkylated with ω-unsaturated primary alcohol **1b** as well as with secondary alcohols such as **1e** in good yields ($\geq$70%) (Table 2, entries 1 and 5). It is worth noting that *N*-Boc-3-hydroxypiperidine **1f** was quantitatively transformed to the corresponding *N*-Boc-3-aminopiperidine **3g** when primary amine **2a** was used (Table 2, entry 6). Allylamine **2b** was *N*-alkylated in good yields by primary or secondary alcohols without any isomerization of the double bond (Table 2, entries 2 and 7). Furthermore, a sterically hindered amine such as *tert*-butylamine **2c** can be alkylated by benzyl alcohol **1c** or solketal **1d** to produce the monoalkylated amines **3d** and **3e** in good yields (Table 2, entries 3 and 4).

Secondary amines **2d**–**f** were also *N*-alkylated by primary or secondary alcohols **1a**, **1b**, **1c**, and **1h**, and the corresponding tertiary amines **3i**–**l** were isolated in good to excellent yields (Table 2, entries 8–11). It is worth mentioning that benzyl alcohol **1c** can be used to protect primary or secondary amines by a benzyl group under very mild conditions, in good yields (Table 2, entries 2, 3, and 8).

This one-pot process is chemoselective, and diols such as **5** can be transformed selectively[21] to the amino-alcohol **6** which, after silylation, led to **7** in 51% overall yield, without isolation of any intermediates (Scheme 2).

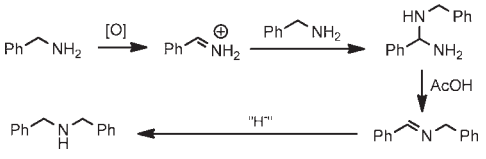
Scheme 2. Chemoselective Amination of Diol **5**



When the *N*-alkylation of amines was realized with optically active alcohols possessing a stereogenic center in the β position such as (*S*)-solketal **1d**, the use of a transition metal catalyst such as a ruthenium catalyst led to an epimerization of the stereogenic center.[14b] By using our conditions, no epimerization of the stereogenic center present in the alcohol was noticed as the *N*-alkylated amines **8a**–**d** were isolated in good yields and excellent enantiomeric excesses (Table 3).

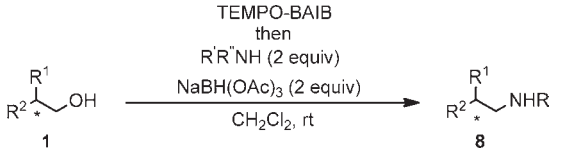
Optically active amines can also be involved in this oxidation/imine-iminium formation/reduction sequence, without any racemization. Thus, when this sequence was applied to benzyl alcohol **1c** and optically active amine **9a**

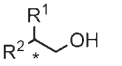
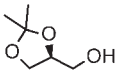
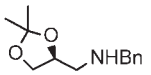
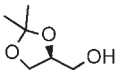
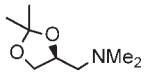
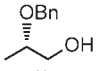
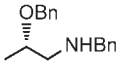
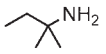
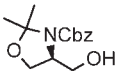
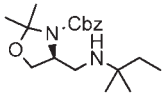
(20) In some cases when $BnNH_2$ or Bn_2NH was used, the formation of Bn_2NH or Bn_3N as byproduct was observed (Table 2, entries 5 and 11). The formation of Bn_2NH (respectively Bn_3N) may be explained by a partial oxidation of $BnNH_2$ (repectively Bn_2NH) followed by imine formation and reduction.



(21) No trace of the products coming from *N*-alkylation by the secondary alcohol was detected by either ^1H NMR or GC/MS at any step of the sequence.

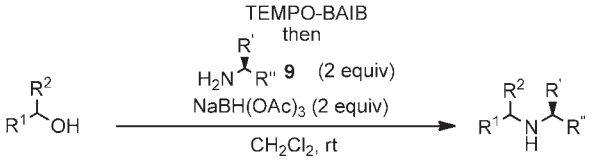
Table 3. *N*-Alkylation of Amines by Alcohols Possessing a Stereogenic Center in the β Position

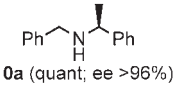
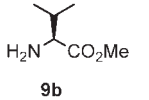
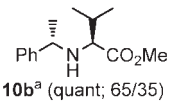
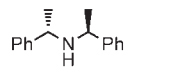
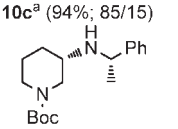
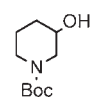
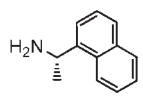
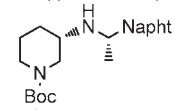


entry	R'R"NH		product **8** (yield; ee)
1	$BnNH_2$ **2a**	 **1d**	 **8a** (70%; >96%)
2	Me_2NH **2g**[a]	 **1d**	 **8b** (60%; >96%)
3	$BnNH_2$ **2a**	 **1i**	 **8c** (92%; >96%)
4	 **2h**	 **1j**	 **8d** (91%; 94%)

[a] 10 equiv of Me_2N were used because of its volatility.

Table 4. *N*-Alkylation of Amines Possessing a Stereogenic Center in the α Position



entry	alcohol **1**	amine **9**	product **10** (yield; dr)
1	 **1c**	 **9a**	 **10a** (quant; ee >96%)
2	 **1g**	 **9b**	 **10b**[a] (quant; 65/35)
3	 **1g**	 **9a**	 **10c**[a] (94%; 85/15)
4	 **1f**	 **9a**	 **10d**[b] (quant; 75/25)
5	 **1f**	 **9c**	 **10e**[c] (93%; 80/20)

[a] Relative configuration of stereogenic centers was attributed by comparison of NMR data with those described in literature. [b] Relative configuration of stereogenic centers was attributed after hydrogenation, as the (+)-(*S*)-3-amino-1-(*tert*-butoxycarbonyl)piperidine is a known coumpound. [c] Relative configuration of stereogenic centers was attributed by analogy with **10d**.

(possessing a stereogenic center in the α position), **10a** was isolated in quantitative yield and with an excellent enantiomeric excess (ee >96%) (Table 4, entry 1). When optically active amines **9a** and **9b** were alkylated with secondary alcohol **1g**, the corresponding amines **10b**–**c** were isolated in good yields and with diastereoisomeric ratios varying from 65/35 to 85/15 (Table 4, entries 2 and 3). In the case of *N*-Boc-3-hydroxypiperidine **1f**, the *N*-Boc-3-aminopiperidine **10e** was obtained with a diastereoisomeric ratio of 80/20 in favor of the (3*S*)-isomer when (*S*)-α-naphthylethylamine **9c** was used (Table 4, entry 5).

In conclusion, we have shown that amines can be alkylated by nonactivated alcohols in a one-pot oxidation/imine-iminium formation/reduction sequence at rt without any transition metal. This sequence of reactions, easy to carry out, allows the formation of secondary and tertiary amines under mild conditions in good yields and with good functional group tolerance. Optically active amines and alcohols can be involved in this sequence without epimerization. We are currently investigating this sequence of reactions in order to have access to biologically active amino compounds.

Acknowledgment. C.G. thanks PCAS for a grant, and PCAS is gratefully acknowledged for financial support.

Supporting Information Available. Experimental procedure and characterization data of compounds **3a**–**l**, **7**, **8a**–**d**, and **10a**–**e**. This material is available free of charge via the Internet at http://pubs.acs.org.