An efficient method for the preparation of β-nitroalkanols in room temperature ionic liquids

Weixing Qian, Fengyang Ju, Weiliang Bao and Yongmin Zhang*

Zhejiang University, Xi Xi Campus, Department of Chemistry, Hangzhou, Zhejiang 310028, P. R. China

β-Nitroalkanols were obtained in good to high yields from carbonyl substrates and nitroalkanes in the room temperature ionic liquids using DBU as catalyst under mild reaction conditions and short reaction times.

Keywords: Henry reaction, β-nitroalkanol, ionic liquid, DBU

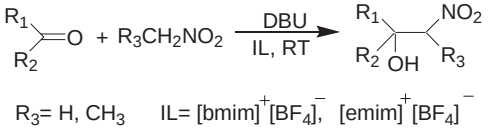
The Henry (nitroaldol) reaction is one of the most important methods for carbon–carbon formation. The adducts may be transformed into valuable building blocks. β-Nitroalkanols are particularly important precursors in the synthesis of nitro alkenes, β-amino alcohols and α-nitro ketones.[1-5] Nitro alkenes have proved to be useful intermediates, which behave both as electron-deficient alkenes and as heterodienes in Diels–Alder reactions,[6-7] while α-nitro ketones are valuable building blocks in the synthesis of several natural products.[8] In addition, β-nitroalkanols are also an important class of compounds for their biological properties as fungicides.[9]

Typical methods for preparing β-nitroalkanols involve nucleophilic addition of a nitroalkane to the carbonyl substrates in the presence of base such as alkali metal hydroxides, carbonates, bicarbonates and alkoxides and also organic non-ionic strong bases like tetramethylguanidine (TMG),[10] 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD).[11] Several heterogeneous catalysts including KG–60–NEt_2,[12] Mg–Al–O–*t*–Bu hydrotalcite,[13] Mg–Al hydrotalcite[14] and amberlyst[15] have also been employed to bring about the Henry reaction. Recently, considerable work about the enantioselective Henry reaction mediated by novel catalyst systems with divalent metals has been reported.[16-18] Although these methods afford high yields of the nitroalkanols with carbonyl compounds, they suffer from long reaction times,[12,14,15] or a large excess of nitoalkane.[10] The latter is a serious drawback, especially when valuable nitro derivatives are used. Thus, the development of new methodologies for the preparation of β-nitroalkanols is very significant.

Room temperature ionic liquids, a set of green solvents with unique chemical and physical properties such as tunable polarity, high thermal stability, negligible vapour pressure, recyclability and reusability, have attracted growing interest.[19] Their ability to solubilise both inorganic and organic compounds can lead to enhanced rates of chemical processes, and moreover, their properties can be adjusted by changing the anion or the alkyl group attached to the cation.[20] Just because of these distinct advantages, ionic liquids have becoming an exciting area of research.

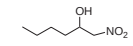
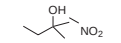
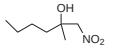
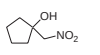
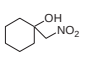
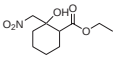
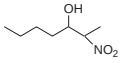
Being attracted by many excellent features of ionic liquids, we decided to investigate the possibility to synthesise the β-nitroalkanols in ionic liquids. The reaction was performed by stirring nitroalkanes and carbonyl compounds in $[emim]^+[BF_4]^-$ (1-ethyl-3-methylimidazolium tetrafluoroborate) and $[bmim]^+[BF_4]^-$ (1-butyl-3-methyl-imidazolium tetrafluoroborate) using DBU as a catalyst (Scheme 1). To investigate the generality of the reaction, a wide variety of substrates were used and good to high yields were obtained as expected (Table 1). The products were readily separated from the ionic liquids.

As shown in Table 1, all these reactions could be completed within 30 minutes with moderate to high yields. This indicated that the Henry reaction in ionic liquids could be accelerated in comparison with traditional methods, which often suffered from long reaction times or low yields. Maybe the high polarity of ionic liquids favoured the rapid formation of the reaction intermediates, so the Henry reaction could be achieved in shorter times than the routine procedures involving conventional organic solvents.



Scheme 1

Table 1 β-Nitroalkanol products and the yields in $[emim]^+[BF_4]^-$

Entry	Substrate	Products	Time	Yield[a,b]/%
1			2 min	98
2	*p*-$NO_2C_6H_4CHO$	*p*-$NO_2C_6H_4CHOHCH_2NO_2$	10 min	90
3	*p*-$CH_3C_6H_4CHO$	*p*-$CH_3C_6H_4CHOHCH_2NO_2$	30 min	50
4			15 min	70
5			10 min	80
6			5 min	90
7			10 min	87
8			30 min	60
9			15 min	95
10	*p*-$NO_2C_6H_4CHO$	*p*-$NO_2C_6H_4CHOHCH(CH_3)NO_2$	20 min	80
11	*p*-ClC_6H_4CHO	*p*-$ClC_6H_4CHOHCH(CH_3)NO_2$	30 min	60

[a]Isolated yield after chromatographic purification; [b]All the products characterised by elemental analysis, IR and NMR spectrometer.

To search for further evidence, we attempted the Henry reaction in $[bmim]^+[BF_4]^-$ and found that the result was not very satisfactory (Table 2). Though the reaction of *p*-$O_2NC_6H_4CHO$ with CH_3NO_2 was not affected because of its high reactivity, the reaction of *p*-$CH_3C_6H_4CHO$ (CH_3 could be seen as an electron-donating group) with CH_3NO_2 was greatly affected. Cyclopentanone even could not react with CH_3NO_2 in 4hs. As $[bmim]^+[BF_4]^-$ has lower polarity than $[emim]^+[BF_4]^-$ [21], it verified our previous conclusion that the high polarity of ionic liquids plays an important role in accelerating the reaction, which indicated that the structure of ionic liquids could influence the Henry reaction.[20] Note that the reaction of $CH_3CH_2NO_2$ is restricted to aldehydes for the reactivity of nitroethane is lower than that of nitromethane due probably to its steric hindrance.

In conclusion, we provided a novel and convenient method for high-efficient synthesis of β-nitroalkanols using ionic liquids as reaction media as well as promoters. The remarkable features of

* Correspondence. E-mail: yminzhang@mail.hz.zj.cn

Table 2 Substrates and the yields in $[bmim]^+[BF_4]^-$

Entry	Substrate 1	Sbustrate 2	Time	Yield/%
1'	*p*-$NO_2C_6H_4CHO$	CH_3NO_2	10min	90
2'	*p*-$CH_3C_6H_4CHO$	CH_3NO_2	1h	20
3'		CH_3NO_2	4h	0

this procedure are mild reaction conditions, enhanced rates, improved yields and lower consumption of nitroalkanes, which permit an easy work up and convey environmental advantages.

Experimental

^{1}H NMR spectra were determined in $CDCl_3$ on a Bruker 400 MHz spectrometer with TMS as the internal standard. IR spectra were recorded on a Bruker Vector-22 infrared spectrometer. C, H, N were analysed on a Carlo Erba 1110 elemental analyser. Reactions were carried out in a 10ml flask equipped with a magnetic stirring bar with no special precaution in the fume cupboard.

Typical procedure: To a stirred solution of nitromethane (0.12 g, 2 mmol) in $[emim]^+BF_4^-$ (2 ml) was added two drops of DBU (catalyst) at room temperature. Then *p*-$NO_2C_6H_4CHO$ (0.18g, 1 mmol) was added and stirred for 10 min. The reaction mixture was diluted with brine, acidified with 0.1 mol/l HCl solution, and then extracted with ether (3×10 ml). The ether layer was separated. The product was further purified by flash chromatography (5:1, petroleum/ethyl acetate), yield: 90%.

1-Nitrohexan-2-ol (*product* **1**)[22]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 0.92 (t, *J* = 7.2Hz, 3H), 1.32–1.61(m, 6H), 2.70(br, 1H), 4.28–4.34(m, 1H), 4.37(d, *J* = 12.8Hz, 1H), 4.43(dd, *J* = 12.8, 2.8Hz, 1H). IR(KBr)ν(cm^{-1}) 3496, 2931, 2860, 1551, 1418, 1381. Anal. calcd. for $C_6H_{13}NO_3$: C 48.97, H 8.90, N 9.52. Found: C 48.71, H 8.92, N 9.61.

1-(p-Nitrophenyl)-2-nitroethan-1-ol (*product* **2**)[23]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 3.24(br, 1H), 4.57(dd, *J* = 11.6, 4.0Hz, 1H), 4.61(dd, *J* = 11.6, 8.0Hz, 1H), 5.61(dd, *J* = 8.0, 4.0Hz, 1H), 7.61–7.65(m, 2H), 8.25–8.29(m, 2H). IR(KBr)ν(cm^{-1}) 3528, 2964, 2925, 1559, 1521, 1348. Anal. calcd. for $C_8H_8N_2O_5$: C 45.29, H 3.80, N 13.20. Found: C 45.35, H 3.81, N 13.03.

1-(p-Methylphenyl)- 2-nitroethan-1-ol (*product* **3**)[24]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 2.39(s, 3H), 2.85(br, 1H), 4.53(dd, *J* = 13.2, 3.2Hz, 1H), 4.62(dd, *J* = 13.2, 9.6Hz, 1H), 5.45(dd, *J* = 9.6, 3.2Hz, 1H), 7.24(d, *J* = 8.0Hz, 2H), 7.31(d, *J* = 8.0Hz, 2H,). IR(KBr)ν(cm^{-1}) 3377, 2977, 2871, 1556, 1378, 1114, 819. Anal. calcd. for $C_9H_{11}NO_3$: C 59.66, H 6.12, N 7.73. Found: C59.69, H 6.12, N 7.52.

2-Methyl-1-nitrobutan-2-ol (*product* **4**)[25]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 0.99(t, *J* = 7.6Hz, 3H), 1.30(s, 3H), 1.59–1.65(m, 2H), 2.82(s, 1H), 4.41(d, *J* = 11.6Hz, 1H), 4.46(d, *J* = 11.6Hz, 1H). IR(KBr)ν(cm^{-1}) 3442, 2926, 2854, 1552, 1467, 1380. Anal. calcd. for $C_5H_{11}NO_3$: C 45.10, H 8.33, N 10.52. Found: C 45.17, H 8.31, N 10.75.

2-Methyl-1-nitroheptan-2-ol (*product* **5**): Oil. ^{1}H NMR ($CDCl_3$) δ_H 0.92(t, *J* = 7.2Hz, 3H), 1.30(s, 3H),1.33–1.41(m, 4H), 1.55–1.58(m, 2H), 2.82(s, 1H), 4.40(d, *J* = 9.6Hz, 1H), 4.46(d, *J* = 9.6Hz, 1H). IR(KBr)ν(cm^{-1}) 3439, 2924, 2853, 1553, 1463, 1378, 1086. Anal. calcd. for $C_7H_{15}NO_3$: C52.16, H 9.38, N 8.69. Found: C 52.21, H 9.40, N 8.86.

1-Nitromethylcyclopentanol (*product* **6**)[26]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 1.49–1.60(m, 4H), 1.63–1.74(m, 4H), 2.79(br, 1H), 4.44(s, 2H). IR(KBr)ν(cm^{-1}) 3495, 1550, 1420, 1390. Anal. calcd. for $C_6H_{11}NO_3$: C 49.65, H 7.64, N 9.65. Found: C 49.60, H 7.63, N 9.59.

1-Nitromethylcyclohexanol (product **7**)[23]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 1.87–1.92(m, 5H), 2.07–2.11(m, 5H), 2.96(br, 1H), 4.26(s, 2H). IR(KBr)ν(cm^{-1}) 3486, 1545, 1422, 1382. Anal. calcd. for $C_7H_{13}NO_3$: C52.82, H 8.23, N 8.80. Found: C52.78, H 8.23, N 8.94.

2-Hydroxy-2-nitromethylcyclohexanecarboxylic acid ethyl ester (*product* **8**): Oil. ^{1}H NMR ($CDCl_3$) δ_H 1.30(t, *J* = 6.8Hz, 3H), 1.37–1.90(m, 8H), 2.52 (dd, *J* = 11.0, 5.6Hz, 0.6H), 2.69(dd, *J* = 9.6, 4.4Hz, 0.4H), 3.61(br, 1H), 4.16–4.30(m, 2H), 4.43(d, *J* = 10.8Hz, 0.6H), 4.51(d, *J* = 10.8Hz, 0.6H), 4.72(d, *J* = 12.4Hz, 0.4H), 4.83(d, *J* = 12.4Hz, 0.4H). IR(KBr)ν(cm^{-1}) 3470, 2940, 2867, 1705, 1552, 1380, 1193. Anal. calcd. for $C_{10}H_{17}NO_5$: C51.94, H 7.41, N 6.06. Found: C51.85, H 7.42, N 5.91.

2-Nitroheptan-3-ol (*product* **9**)[28]: Oil. ^{1}H NMR ($CDCl_3$) δ_H 0.90 (t, *J* = 7.2Hz, 3H), 1.25–1.48(m, 6H), 1.49(d, *J* = 0.8Hz, 1.35H), 1.51(d, *J* = 0.8Hz, 1.65H), 2.76(s, 1H), 3.85–3.90(m, 0.55H), 4.12–4.16(m, 0.45H), 4.45–4.55(m, 1H). IR(KBr)ν(cm^{-1}) 3485, 2927, 2854, 1554, 1455, 1376. Anal. calcd. for $C_7H_{15}NO_3$: C 52.16, H 9.38, N 8.69. Found: C 52.19, H 9.41, N 8.62.

1-(p-Nitrophenyl)-2-nitropropan-1-ol (*product* **10**): m.p. 85–87°C (Lit.[29] 87°C) ^{1}H NMR ($CDCl_3$) δ_H 1.38(d, *J* = 7.2Hz, 2.61H), 1.49 (d, *J* = 7.2Hz, 0.39H), 3.38(br, 1H), 4.70–4.81(m, 1H), 5.19(d, *J* = 8.4Hz, 0.87H), 5.56(d, *J* = 3.2Hz, 0.13H), 7.58–7.62(m, 2H), 8.23–8.27(m, 2H). IR(KBr)ν(cm^{-1}) 3400, 1530, 1385, 1102. Anal. calcd. for $C_9H_{10}N_2O_5$: C 47.79, H 4.46, N 12.39. Found: C 47.85, H 4.47, N 12.31.

1-(p-Chlorophenyl)-2-nitropropan-1-ol (*product* **11**)[30]: Oil ^{1}H NMR ($CDCl_3$) δ_H 1.29(d, *J* = 7.2Hz, 1.9H), 1.46(d, *J* = 7.2Hz, 1.1H), 3.20 (s, 1H), 4.61–4.66(m, 0.36H), 4.67–4.71(m, 0.64), 4.98(d, *J* = 8.8Hz, 0.64H), 5.34(t, *J* = 3.2Hz, 0.36H), 7.28–7.31(m, 2H), 7.33–7.37 (m, 2H). IR(KBr)ν(cm^{-1}) 3447, 1552, 1491, 1390, 1092. Anal. calcd. for $C_9H_{10}ClNO_3$: C 50.13, H 4.67, N 6.50. Found: C 50.06, H 4.67, N 6.52.

Received 10 December 2003; accepted 30 January 2004
Paper 03/2242

References

1 R. Tamura, M. Sato and D. Oda, *J. Org. Chem.*, 1986, **51**, 4368.
2 K. Iseki, S. Oishi, H. Sasai and M. Shibasaki, *Tetrahedron Lett.*, 1996, **37**, 9081.
3 A. Barco, S. Benetti, C. Risi and G. Polloni, *Tetrahedron Lett.*, 1996, **37**, 7599.
4 H. Sasai, M. Hiroi, Y. Yamada and M. Shibasaki, *Tetrahedron Lett.*, 1997, **38**, 6031.
5 M. Shibasaki, H. Sasai and T. Arai, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**,1236.
6 D.C.B.Rao.Ranganathan, S. Ranganathan, A.M. Mehrotra and R. Iyengar, *J. Org. Chem.*, 1980, **45**, 1185.
7 S.E. Denmark and A. Thorarensen, *Chem. Rew.*, 1996, **96**,137.
8 (a) R. Ballini and G. Bosica, *J. Org. Chem.*, 1994, **59**, 5466; (b) R. Ballini and G. Bosica, *J. Chem. Res. (S)*, 1993, 371.
9 G. Mikite, K. Jakucs, F. Darvas and A. Lopata, *Pestic. Sci.*, 1982, **13**, 557.
10 D. Simoni, F.P. Invidiata and S. Manfredini, *Tetrahedron Lett.*, 1997, **38**, 2749.
11 D. Simoni, R. Rondanin and M. Morini, *Tetrahedron Lett.*, 2000, **41**, 1607.
12 R. Ballini, G. Bosica and D. Livi, *Tetrahedron Lett.*, 2003, **44**,2271.
13 B. M. Choudary, M. L. Kantam and B. Kavita, *J. Mol. Catal. A: Chemical*, 2001, **169**, 193.
14 V. J. Bulbule, V. H. Deshpande and S. Vela, *Tetrahedron*, 1999, **55**, 9325.
15 R. Ballini, G. Bosica and P. Forconi, *Tetrahedron*, 1996, **52**,1677.
16 D. A. Evans, D. Seidel and M. Rueping, *J. Am. Chem. Soc.*, 2003, **125**, 12692.
17 (a) B. M. Trost and V. S. C. Yeh, *Angew. Chem. Int. Ed.*, 2002, **41**, 861; (b) B. M. Trost, V. S. C. Yeh and H. Ito, *Org. Lett.*, 2002, **4**, 2621.
18 (a) T. Risgaard, K. V. Gothelf and K. A. Jorgensen, *Org. Biomol. Chem.*, 2003, 153; (b) C. Christensen, K. Juhl, R. G. Hazell and K. A. Jorgensen, *J. Org. Chem.*, 2002, **67**, 4875; (c) C. Christensen, K. Juhl and K.A. Jorgensen, *Chem. Commun.*, 2001, 2222.
19 (a) T. Welton, *Chem. Rev.* 1999, **99**, 2071; (b) P. Wasserscheidand and W. Keim, *Angew. Chem. Int. Ed.* 2000, **39**, 3772.
20 J.S. Yadav, B.V.S. Reddy, A.K. Basak and A.V. Narsaiah, *Tetrahedron Lett.*, 2003, **44**, 2217.
21 (a) T.S. Welton, *Chem Rev*., 1999, **99**, 2071; (b) P.H Shetty, P.J. Youngberg, B.R. Kersten and C.F. Poole, *J. Chromatogr*., 1987, **411**, 61; (c) K.G. Furton and R. Morales, *Anal. Chim. Acta*., 1991, **246**, 171.
22 Z. Eckstein, P. Gluzinski, W.Sobótka and T. Urbański, *J. Chem. Soc.*, 1961, 1370.
23 G.A. Amadei, M.H. Dickman, R.A. Wazzeh, P.L. Dimmock and J.E. Earley, *Inorg. Chim. Acta.* , 1999, **288**, 40.
24 C.U. Zhou, Y.Q. Zhou and Z.Y. Wang, *Chinese Chem. Lett.*, 2003, **14**(4), 355.
25 N.N. Levy, C.W. Scaife and A.E. Wilder-Smith, *J. Chem. Soc.*, 1948, 52.
26 L.W. Kozlov, E.F. Fink and G.B. Liorber, *Truky Kazan. Khim. Tekhnol. Inst. im. S. M. Kirova*, 1957, **23**, 148.
27 A.R. Kon. George, *J. Chem. Soc.*, 1951, 843.
28 D.Y. Nightingale and J.R. Janes, *J. Am. Chem. Soc*., 1944, **66**, 352
29 (a) T.S. Welton, *Chem Rev*., 1999, **99**, 2071; (b) P.H. Shetty, P.J. Youngberg, B.R. Kersten and C.F. Poole, *J. Chromatogr*., 1987, **411**, 61; (c) K.G. Furton and R. Morales, *Anal. Chim. Acta*., 1991, **246**, 171
30 C. Szantay and R. Soós, *Magyar Kém. Folyóiral*, 1958, **64**, 470.