An efficient method for zinc mediated reduction of norbornyl α-diketones in [bmim][BF$_4$]:H$_2$O

Faiz Ahmed Khan* and Ch. Sudheer

Department of Chemistry, Indian Institute of Technology, Kanpur 208 016, India
E-mail: faiz@iitk.ac.in

Abstract

Efficient reduction of mono- and disubstituted norbornyl α-diketones with zinc in [bmimBF$_4$]:[H$_2$O] to afford the corresponding acyloins in excellent yields and diastereoselectivities is described. In case of the monosubstituted norbornyl α-diketones, very high regioselectivities ranging from 90:10 to 100:0, in favor of diastereomer possessing *endo*-hydroxyl diagonal to *endo*-substituent were observed.

Keywords: Acyloins, zinc, α-diketones, ionic liquid, regioisomers

Introduction

Acyloins or α-hydroxy ketones are important class of intermediates in organic synthesis due to their bifunctional aspect and are abundantly found substructures in various natural products.[1,2] Acyloins are generally prepared by acyloin condensation reactions,[3] oxidation of enolates,[4] α-hydroxylation of ketones,[5] ketohydroxylation of olefins[6] and reduction of α-diketones.[7] However, the problems associated with reduction of α-diketones, such as over reduction to a diol[8] or to an α-methylene ketone,[9] make this procedure less attractive. Usage of Morita-Baylis-Hillman adducts as precursors for the acyloins is the most recent method for obtaining acyloins.[10] To circumvent the problems associated with reduction of α-diketones to acyloins, we have reported an indium mediated regio- and diastereoselective reduction of norbornyl α-diketones to corresponding acyloins.[11] While acyloins were obtained in good yields from norbornyl α-diketones with various *endo* substituents and the selectivities of acyloin formations were dependent on the *endo* substituents, the reductions of monosubstituted norbornyl α-diketones with *endo* oxygen substituents (OAc, OEt) afforded the acyloins in moderate yields.[11] Norbornyl acyloins with *endo* oxygen are potential precursors for norbornyl *C2* symmetric diols with bridge head halogens.

With growing environmental concerns regarding the usage of volatile organic solvents, there has been a greater emphasis on development of greener technologies in the recent years.[12] Ionic liquids have emerged as alternative reaction media for several important reactions.[13] In view of

our interest in imidazolium ionic liquids,[14] we decided to check if usage of these non-covalent solvents as reaction medium circumvents the aforementioned problem.

Results and Discussion

To begin with, we chose symmetrical α-diketone **1a** to standardize the reaction conditions for the reduction of α-diketones and the efforts are detailed in Table 1. Initial reactions of the reductions of α-diketones with zinc under the conditions previously described by us for the indium mediated reactions,[11] namely MeOH-H_2O afforded acyloins in modest yields. In pursuit of developing milder reaction conditions and to improve the yields, reductions were carried out in ionic liquids [bmim][BF_4] and [bmim][PF_6]. It was necessary that water be used as a co-solvent as the reactions did not proceed (starting material recovered) in the absence of water (entries 1 and 2). Between the two ionic liquids used, [bmim][BF_4] was a better solvent as the reaction in [bmim][PF_6] was sluggish (entry 6). This sluggishness could be because [bmim][PF_6] and water are immiscible. The reaction afforded a complex reaction mixture in the absence of NH_4Cl (entry 4) and when the reduction was carried out with indium metal, only 80% of the starting material was

**Table 1.** Zn mediated reduction of diketone **1a** in ionic liquids
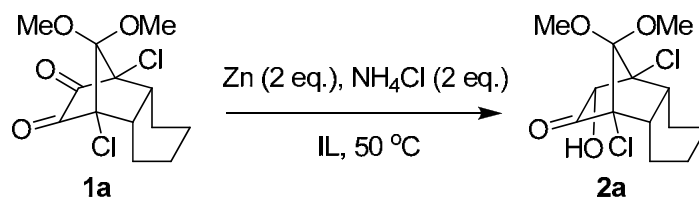
Entry	Solvent	Time	Yield (%)
1	[bmim][PF_6]	15 h	$-^a$
2	[bmim][BF_4]	10 h	$-^a$
3	[bmim][BF_4]:H_2O	3 h	96
4	[bmim][BF_4]:H_2O	6 h	$-^{b,c}$
5	[bmim][BF_4]:H_2O	30 min	93^d
6	[bmim][PF_6]:H_2O	11 h	83 (76)^e
7	[bmim][BF_4]:H_2O	7 h	87 (80)^{e,f}

IL and H_2O were used 10:1. [a]Starting material recovered. [b]NH_4Cl was not used. [c] Complex reaction mixture. [d]4 eq. of Zn and 4 eq. of NH_4Cl were used. [e]Yield is based on the recovered starting material and figures in parenthesis are those of percentage conversions of the diketones. [f] 2 eq. In was used in place of Zn.

consumed even after 7h (entry 7). The optimal condition was to use two equivalents of zinc and two equivalents of NH$_4$Cl in a mixture of [bmim][BF$_4$] and H$_2$O (10:1)[15] at 50°C. The reaction took less time when excess of zinc and NH$_4$Cl were used (entry 5).

Standardized conditions were employed for the reduction of various symmetrically disubstituted norbornyl α-diketones (Table 2). The striking difference compared to the indium mediated reductions that we have reported earlier is the time taken for the completion of reaction. While the reductions of α-diketones with zinc or indium in MeOH-H$_2$O needed reflux conditions (90 ^{o}C) and prolonged reaction times (20–40 h), contrarily the reactions in [bmim][BF$_4$]-H$_2$O were complete in 3 h even at lower temperature (50 ^{o}C) while the yields obtained are similar or better than those obtained by the previously reported protocol.[11]

**Table 2.** Zinc mediated reduction of disubstituted norbornyl α-diketones
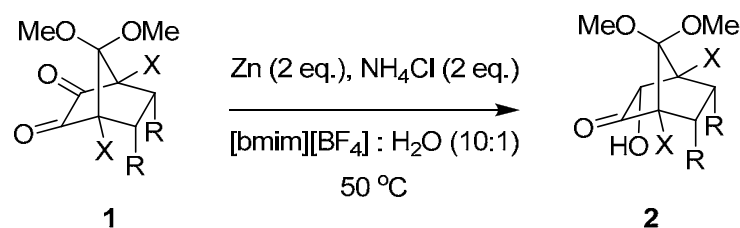
Entry	Substrate	X	R, R	Time (h)	Yield (%)
1	**1b**	Cl	-(CH$_2$)$_3$-	3	92
2	**1c**	Cl	-(CH$_2$)$_6$-	3	98
3	**1d**	Cl	-(CH$_2$-O- CH$_2$-O- CH$_2$)-	3	93
4	**1e**	Cl	-(O- CMe$_2$-O)-	2	85
5	**1f**	Cl	-(CH$_2$-O- CH$_2$)-	3	91
6	**1g**	Cl	CH$_2$OAc	3	88
7	**1h**	Br	CH$_2$OAc	3	77
8	**1i**	Br	-(CH$_2$-O- CH$_2$-O- CH$_2$)-	3	81

The reaction conditions employed were mild and functionalities like acetate and acetonide survived and acyloins were obtained in good yields (entries 4, 6 and 7). The disubstituted bromo α-diketones **1h** and **1i** afforded acyloins (entries 7 and 8) in good yields. The yields in these cases are somewhat lower compared to their corresponding chloro analogues. Similar results were obtained when the reduction was carried out with indium using the conventional solvents.[11] In all the cases, the acyloins obtained were exclusively the ones where the hydroxyl group occupies the *endo* position, an outcome similar to that observed in indium mediated reduction of disubstituted norbornyl α-diketones. The structures were confirmed by comparing the ^{1}H NMR spectra of the acyloins with those reported earlier.[11]

After employing zinc mediated reduction in [bmim][BF$_4$] efficiently to obtain various disubstituted acyloins (Table 2), we turned our attention to the reduction of monosubstituted α-diketones. Herein, apart from the formation of diastereomers as in the disubstituted norbornyl α-diketones, there is also a possibility for the formation of regioisomers (Table 3).

Table 3. Zinc mediated reduction of mono substituted norbornyl α-diketones
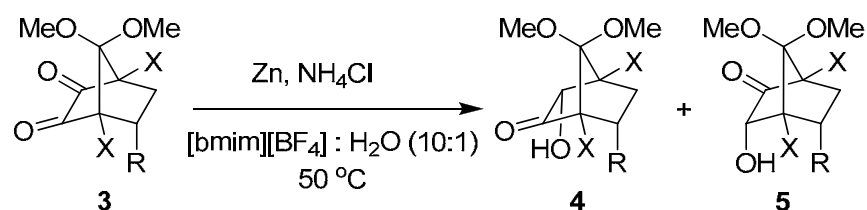
Entry	Substrate	X	R	Time	Yield (%)[a]	Ratio (4:5)[b]
1	**3a**	Cl	Ph	10 min	95	100:0
2	**3b**	Br	Ph	30 min	89	100:0
3	**3c**	Cl	OEt	2 h	91	95:5
4	**3d**	Br	OEt	2 h	82	95:5
5	**3e**	Cl	OAc	1 h	93	100:0
6	**3f**	Cl	OTMS	2 h	92	90:10

[a]Isolated yields of analytically pure **4**+**5**. [b]Determined by 400 MHz ^{1}H NMR

Zinc mediated reductions of the monosubstituted derivatives **3** proceeded efficiently to furnish the acyloins **4** as the major or exclusive product (entries 1, 2 and 5) and **5** as the minor *endo* alcohols (Table 3). The major acyloins **4** were derived from the formal reduction of the carbonyl group that is diagonal to *endo* substituents R, while the formal reduction of the carbonyl group on the same side of the *endo* substituents R furnished the minor acyloins **5.** The reaction was stereoselective leading to the formation of *endo* alcohols exclusively, and was also highly regioselective. The regioselectivities varied from 90:10 to 100:0 for the two regioisomeric alcohols **4** and **5**. The product distribution of alcohols **4** and **5** was determined by ^{1}H NMR integration at 400 MHz of the products obtained after a short silica gel column filtration. The yields and the regioselectivities obtained for the acyloins **4** and **5** with *endo* oxygen substituents (entries 3-7, Table 3) were better than those obtained from the indium mediated reactions.[11] It was essential that the reaction mixture was well stirred. Failure to do so resulted in decreased

yields and also altered regioselectivities. Efficient mixing is vital because of the viscosity of the ionic liquid used.

The structural assignments in case of the chromatographically purified acyloins **2, 4** and **5** were made based on the observed w-coupling in the ^{1}H NMR spectra.[11] Recovered [bmim][BF$_4$] was recycled without any loss in the yield. Recycling experiments were performed using α-diketone **3c** as it gives a chance not only to check the influence of ionic liquid recycling on the yield but also the regioselectivity during the zinc mediated reductions. The ionic liquid was reused for three cycles with no noticeable change in the regioselectivities and the yields.

Experimental Section

General Procedures. NMR spectra were recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C) on a 400 MHz FT-NMR spectrometer. Samples for NMR were made in CDCl$_3$ and TMS was used as the internal standard. TLC was performed on silica gel coated on microscopic slides. Visualization of spots was effected by exposure to iodine or spraying with 4% ethanolic H$_2$SO$_4$ and charring. Column chromatography was performed using silica gel (100-200 mesh), and ethyl acetate-hexane was used as eluent. Solvents and reagents were purified by standard methods.

General procedure for the zinc mediated reduction of α-diketones
A mixture of α-diketone (0.25 mmol), zinc metal (0.5 mmol, powder) and NH$_4$Cl (0.5 mmol) in [bmim][BF$_4$] (1 mL) and water (0.1 mL) was stirred at 50°C for the specified time (Table 2 and Table 3). After completion of the reaction, as monitored by TLC, the reaction mixture was extracted with 50% ethyl acetate in hexane (4x5 mL). Combined organic layer was concentrated and purified by silica gel column chromatography to give the acyloins in the specified yields. Spectral data for the acyloins were reported earlier.[11] Acyloin **2e** was not reported earlier and its spectral data is given here.

Recycling procedure for [bmim][BF$_4$]
After the completion of the reaction, the residue containing [bmim][BF$_4$] was dissolved in CH$_2$Cl$_2$ (5 mL), filtered through a filter paper, dried over Na$_2$SO$_4$ and the solvent was removed on a rotary evaporator. The ionic liquid was further dried at 70 °C and 0.1 mm Hg for 2 h before using it for the next reaction.
Acyloin 2e. Yield 85%; colorless solid; mp 108 – 109 ^{o}C; ^{1}H NMR (400 MHz, CDCl$_3$) δ 4.95 (dd, 1H, J= 7.9, 2.2 Hz), 4.75 (d, 1H, J= 8.1 Hz), 4.38 (dd, 1H, J= 11.2, 2.0 Hz), 4.27 (d, 1H, J=11.5 Hz, D$_2$O exchangeable), 3.60 (s, 3H, OMe), 3.55 (s, 3H, OMe), 1.44 (s, 3H, Me), 1.29 (s, 3H, Me); ^{13}C NMR (100 MHz, CDCl$_3$) δ 196.8, 115.3, 105.0, 85.0, 80.8, 77.8, 68.6, 51.9, 51.6, 25.4, 23.3; IR (KBr) 3400, 2950, 1770, 1450, 1240 cm^{-1}; Anal. Calcd. for C$_{12}$H$_{16}$Cl$_2$O$_6$: C, 44.05; H, 4.93; found C, 44.11; H, 5.17.

Acknowledgments

References and Notes

1. (a) Kido, F.; Kitahara, H.; Yoshikoshi, A. *J. Org. Chem.* **1986**, *51*, 1478. (b) Murahashi, S.-I.; Saito, T.; Hanaoka, H.; Murakami, Y.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *J. Org. Chem.* **1993**, *58*, 2929. (c) Piers E.; Renaud, J. *J. Org. Chem.* **1993**, *58*, 11. (d) Money, T. *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier: New York, 1989, Vol. 4, p 625.

2. (a) Whitesell, j. K.; Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443. (b) Chandhary, A. G.; Kingston, D. G. I. *Tetrahedron Lett.* **1993**, *34*, 4921. (c) Gala, D.; DiBenedetto, D. J.; Clark, J. E.; Murphy, B. L.; Schumacher, D. P.; Steinman, M. *Tetrahedron Lett.* **1996**, *37*, 611. (d) Monneret, C. *Eur. J. Med. Chem.* **2001**, *36*, 483.

3. (a) Schräpler, U.; Rühlmann, K. *Chem. Ber.* **1964**, *97*, 1383. (b) Mori, T.; Nakahara, T.; Nozaki, H. *Can. J. Chem.* **1969**, *47*, 3266.

4. (a) Bailey, E. J.; Barton, D. H. R.; Elks, J.; Templeton, J. F. *J. Chem. Soc.* **1962**, 1578. (b) Adam, W.; Müller, M.; Prechtl, F. *J. Org. Chem.* **1994**, *59*, 2358.

5. (a) Masui, M.; Ando, T.; Shiori, T. *Tetrahedron Lett.* **1988**, *29*, 2835. (b) Morikawa, K.; Park, J.; Andersson, P. G.; Hashiyama, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 8463. (c) Marcune, B. F.; Karady, S.; Reider, P. J.; Miller, R. A.; Biba, M.; DiMichele, L.; Reamer, R. A. J. Org. Chem. 2003, 68, 8088.

6. (a) Murahashi, S.-I.; Saito, T.; Hanaoka, H.; Murakami, Y.; Naota, T.; Kumobayashi, H.; Akutagawa, S. *J. Org. Chem.* **1993**, *58*, 2929. (b) Murahashi, S.-I.; Naota, T.; Hanaoka, H. *Chem. Lett.* **1993**, *1767*; (c) Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1499.

7. (a) Hayakawa, R.; Sahara, T.; Shimizu, M. *Tetrahedron Lett.* **2000**, *41*, 7939 and references therein. (b) de Oliveira, L. F.; Costa, V. E. U. *Tetrahedron Lett.* **2006**, *47*, 3565.

8. (a) Clerici, A.; Porta, O. *J. Org. Chem.* **1985**, *50*, 76. (b) Yamada, M.; Horie, T.; Kawai, M.; Yamamura, H.; Araki, S. *Tetrahedron* **1997**, *53*, 15685.

9. Reusch, W.; Lemahieu, R. *J. Am. Chem. Soc.* **1964**, *86*, 3068.

10. Amarante, G. W.; Rezende, P.; Cavallaro, M.; Coelho, F. *Tetrahedron Lett.* **2008**, *49*, 3744.

11. (a) Khan, F. A.; Dash, J.; Sudheer, Ch. *Chem.Eur. J.* **2004**, *10*, 2507. (b) Khan, F. A.; Dash, J.; Sahu, N.; Gupta, S. *Org. Lett.* **2002**, *4*, 1015.

12. Li, C.-J.; Trost, B. M.; *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 13197 and references therein.

13. For recent reviews on ionic liquids, see (a) Binnemans, K. *Chem. Rev.* **2007**, *107*, 2592-2614. (b) Ranke, J.; Stolte, S.; Stormann, R.; Arning, J.; Jastorff, B. *Chem. Rev.* **2007**, *107*, 2183-2206. (c) Van Rantwijk, F.; Sheldon, R. A. *Chem. Rev.* **2007**, *107*, 2757-2785. (d) Parvulescu, V. I.; Hardacre, C.

Chem. Rev. **2007**, *107*, 2615-2665. (e) Rogers, R. D.; Voth, G. A. *Acc. Chem. Res.* **2007**, *41*, 1077. and articles therein on the special issue, "Ionic Liquids".

14. (a) Khan, F. A.; Dash, J.; Sudheer, Ch.; Gupta, R. K. *Tetrahedron Lett.* **2003**, *44*, 7783. (b) Khan, F. A.; Dash, J.; Satapathy, R; Upadhyay, S. K. *Tetrahedron Lett.* **2004**, *45*, 3055. (c) Khan, F. A.; Sudheer, Ch.; Sahu, N. *Synth. Commun.* **2005**, *35*, 201.

15. A 10:1binary mixture of [bmim][BF$_4$] and H$_2$O was used as we have used a similar mixture for the zinc mediated reductions reported in reference 14a.