SHORT PAPER

J. Chem. Research (S), 2003, 724–725

Intermolecular aldol type reactions of phenacyl bromide with aldehydes mediated by active metallic indium in aqueous media†

Huayue Wu*, Jinchang Ding, Jing Gao and Miaochang Liu

Department of Chemistry, Wenzhou Normal College, Wenzhou, Zhejiang, 325027, P.R. China

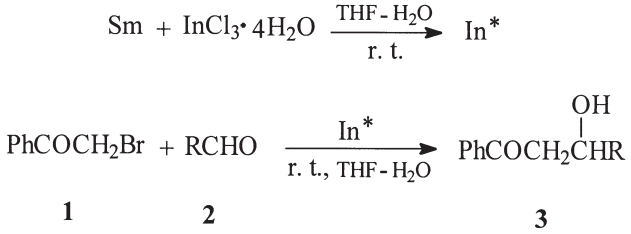
Mediated by active metallic indium generated *in situ* from metallic samarium and $InCl_3.4H_2O$, phenacyl bromide and aldehydes smoothly underwent intermolecular aldol type reaction in aqueous media affording β-hydroxy ketones in good yields and under mild conditions.

Keywords: aldol type reactions, phenacyl bromide, metallic indium

Aldol type reactions have attracted considerable attention in the area of organic synthesis.[1] This is due partly to the fact that a large number of important natural products contain the β-hydroxy carbonyl unit. Several procedures for the preparation of β-hydroxy ketones have appeared in the literature, among which, the intermolecular reaction of α-halogeno ketones with carbonyl compounds is the more commonly used. For example, a cross-aldol reaction based on the generation of an aluminium enolate by the coupling of Et_2AlC1 and metallic zinc was reported by Nozaki and co-workers.[2] This group also developed the $Bu_3SnAlEt_2$- or $Bu_3PbAlEt_2$-mediated reactions of α-halogeno ketones with carbonyl compounds.[3] In another example, reaction of metallic tin with α-halogeno ketones gave the tin(II) enolates, which when treated with carbonyl compounds gave β-hydroxy ketones in good yields.[4] Samarium diiodide has also been used to promote the inter- or intramolecular aldol type reactions of α-halogeno ketones with carbonyl compounds.[5] While these methods mentioned above afford the desired β-hydroxy ketones with good yields, almost all of them have to be carried out under strictly anhydrous conditions.

During the last two decades, there has been considerable interest in performing organometallic reactions in aqueous media.[6] A number of potential advantages have been cited, including: (1) the ease of reactions obviating the need for inflammable anhydrous organic solvents and inert atmosphere; (2) protection of "reactive" hydroxyl functional group is no longer required and (3) compounds (*e.g.* carbohydrates) which are insoluble in organic solvents, can react directly. On the other hand, the choice of metals in organometallic reactions in aqueous media is restricted. The reactive alkali and alkaline earth metals cannot be used because of their vigorous reactions with water itself. Metals, which readily form oxides that are insoluble in water, are also unlikely candidates. Recently, indium has been found to be a metal of choice in place of the metallic zinc and tin.[7] Moreover indium is turning out to be more effective than zinc and tin in that indium mediated reactions require no activation and produce only few side products. As a result, metallic indium mediated carbon–carbon bond-forming reactions have commanded considerable attention in organic synthesis.

Recently, we have begun a program directed toward the application of active metallic indium generated *in situ* from metallic samarium and $InCl_3.4H_2O$ in mediating organic reactions in aqueous media.[8] We would now like to report our new results that may provide a new method for the preparation of β-hydroxy ketones. The reaction is shown in Scheme 1.



Scheme 1

Table 1 Active metallic indium mediated preparation of β-hydroxy ketones

Entry	R	Reaction time/min	Product	Yield/%[a]
1	C_6H_5	5 (120[b])	3a	(o[b])85
2	4-$CH_3C_6H_4$	5	3b	83
3	4-$CH_3OC_6H_4$	5	3c	79
4	3-BrC_6H_4	5	3e	86
5	4-ClC_6H_4	5	3f	93
6	2-ClC_6H_4	5	3g	83
7	2-furyl	5	3h	78
8	C_6H_5CH=CH	5	3i	82
9	*n*-C_4H_9	12	3j	81

[a]Isolated yield of β-hydroxy ketones. [b]In the presence of Sm powder or indium trichloride alone.

In a typical experimental procedure, indium(III) chloride suspended in THF–H_2O (8/1) mixture was treated with metallic samarium. A vigorus reaction took place and a light black species appeared after several minutes which indicated that active metallic indium was readily prepared. At this stage, a mixture of phenacyl bromide and aldehydes was added. Several minutes later, the aldol type reaction was completed as shown by TLC and the desired β-hydroxy ketones were obtained with good yields. The results are listed in Table 1.

A wide range of structurally varied aryl-substituted aldehydes (Table 1, entries 1–7) or alkyl-substituted aldehydes (Table 1, entries 8–9) underwent equally efficient aldol-type reaction with phenacyl bromide by this procedure to provide the corresponding, β-hydroxy ketones in good results. Several sensitive functional groups such as Cl, Br, OMe remained intact under the present reaction condition. No side products arising from the reduction and/or pinacol coupling of the carbonyl compound were found. When unsaturated aldehyde was used, no conjugate addition occurred and only l,2-addition product was obtained (Table 1, entry 8). In addition, it should be noted that no reaction took place with either metal samarium or indium trichloride alone (Table 1, entry 1), although it has been reported that indium trichloride is an effcient catalyst in Mukaiyama type reactions of silyl enol ethers and aldehydes.[9]

* To receive any correspondence.

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

In conclusion, the present procedure may provide a novel, efficient methodology for the preparation of β-hydroxy ketones. To the best of our knowledge, this is the first report of active metallic indium promoted aldol type reaction of phenacyl bromide and aldehydes to afford β-hydroxy ketones, and certainly it may broaden the scope of indium-mediated carbon–carbon bond formation reactions. The advantages of this method include mild conditions which tolerate several sensitive functional groups, high yields, and environmentally benign reaction conditions. Further studies to develop other new reactions using active metallic indium are in progress.

Experimental

General experimental details: Melting points were uncorrected. ^{1}H NMR spectra were recorded on a Bruker AC 300 instrument. All samples were measured in $CDC1_3$ using TMS as internal standard, IR spectra were determined on a Bruker-EQUINOX55 spectrometer. The reactions were performed in the open air.

General procedure for the preparation of β-hydroxy ketones (**3**): In a 25 ml three-necked flask were placed $InCl_3.4H_2O$ (1 mmol), metallic samarium (1 mmol), THF (4 ml), then to the mixture was slowly added H_2O (0.5 ml). Drastic reaction took place, and a kind of light black species appeared in 3 min which indicated that active metallic indium was readily prepared. Then a mixture of phenacyl bromide (1 mmol) and aldehyde (1 mmol) was added to the flask. After stirring for the time given in Table 1, the mixture was quenched with diluted HCl (0.1 M, 2 ml) and extracted with ether (3 × 20 ml). The combined extract was washed with saturated brine (15 ml) and dried over anhydrous Na_2SO_4. After evaporating the solvent under reduced pressure, the resulting crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:8) as eluent.

3-Phenyl-3-hydroxy-1-phenylpropan-1-one (**3a**): m.p. 45–46°C (lit.[10] 44–46°C); IR 3449, 3062, 2930, 1681 cm^{-1}; ^{1}H NMR δ 7.97 (d, *J*= 7.8 Hz, 2H), 7.58–7.63 (m, 1H), 7.29–7.51 (m, 7H), 5.37 (t, *J*= 6.0 Hz, 1H), 3.58 (br s, 1H), 3.39 (d, *J*= 6.0 Hz, 2H).

3-(4-Methyphenyl)-3-hydroxy-1-phenylpropan-1-one (**3b**): m.p. 47–49°C (lit.[10] 47–48°C); IR 3448, 3061, 2921, 1685 cm^{-1}; ^{1}H NMR δ 7.96 (d, *J*= 7.8 Hz, 2H), 7.57–7.62 (m, 1H), 7.45–7.50 (m, 2H), 7.28–7.36 (m, 2H), 7.20 (d, *J*= 7.9 Hz, 2H), 5.33 (t, *J*= 6.0 Hz, 1H), 3.61 (br s, 1H), 3.37–3.39 (m, 2H), 2.37 (s, 3H).

3-(4-Methoxyphenyl)-3-hydroxy-1-phenylpropan-1-one (**3c**): oil (lit.[10]); IR 3399, 3061, 2935, 1681 cm^{-1}; ^{1}H NMR δ 7.98 (d, *J*= 7.2 Hz, 2H), 7.58–7.62 (m, 1H), 7.37–7.51 (m, 4H), 6.91–6.96 (m, 2H), 5.32 (t, *J*= 6.1 Hz, 1H), 3.83 (s, 3H), 3.58 (br s, 1H), 3.37–3.40 (m, 2H).

3-(3-Bromophenyl)-3-hydroxy-1-phenylpropan-1-one (**3e**): oil (lit.[11]); IR 3437, 3062, 2903, 1680 cm^{-1}; ^{1}H NMR δ 7.96 (d, *J*= 7.8 Hz, 2H), 7.59–7.63 (m, 2H), 7.36–7.51 (m, 3H), 7.25–7.27 (m, 2H), 5.31–5.35 (m, 1H), 3.60 (br s, 1H), 3.35–3.37 (m, 2H).

3-(4-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (**3f**): m.p. 95–96°C (lit.[10] 96–96.5°C); IR 3466, 3058, 2947, 1667 cm^{-1}; ^{1}H NMR δ 7.94–7.97 (m, 2H), 7.58–7.64 (m, 1H), 7.46–7.51 (m, 2H), 7.34–7.41 (m, 4H), 5.32–5.36 (m, 1H), 3.58 (br s, 1H), 3.34–3.37 (m, 2H).

3-(2-Chlorophenyl)-3-hydroxy-1-phenylpropan-1-one (**3g**): m.p. 78–81°C (lit.[5b] 80–81°C); IR 3528, 3063, 2907, 1669 cm^{-1}; ^{1}H NMR δ 7.99 (d, *J*= 7.8 Hz, 2H), 7.59–7.75 (m, 2H), 7.34–7.51 (m, 4H), 7.25–7.27 (m, 1H), 5.69–5.73 (m, 1H), 3.75 (br s, 1H), 3.56–3.62 (m, 1H), 3.13–3.22 (m, 1H).

3-Furyl-3-hydroxy-1-phenylpropan-1-one (**3h**): oil (lit.[12]); IR 3449, 3062, 2914, 1683 cm^{-1}; ^{1}H NMR δ 8.01 (d, *J*= 7.5 Hz, 2H), 7.59–7.65 (m, 1H), 7.41–7.53 (m, 3H), 6.35–6.38 (m, 2H), 5.37–5.41 (m, 1H), 3.51–3.66 (m, 2H), 3.36 (br s, 1H).

1,5-Diphenyl-3-hydroxy-4-penten-1-one (**3i**): m.p. 51–52°C (lit.[2b] 51–53°C); IR 3373, 3061, 2979, 1680 cm^{-1}; ^{1}H NMR δ 7.98 (d, *J*= 7.5 Hz, 2H), 7.30–7.63 (m, 8H), 6.72 (d, *J*= 15.9 Hz, 1H), 6.33 (dd, *J*= 15.9, 6.0 Hz, 1H), 4.95–5.01 (m, 1H), 3.31–3.42 (m, 2H), 3.10 (br s, 1H).

3-n-Buty1-3-hydroxy-1-phenylpropan-1-one (**3j**): oil(lit.[13]); IR 3440, 2980, 1705, 1620 cm^{-1}; ^{1}H NMR δ 7.35–7.75 (m, 5H), 3.85–4.10 (m, 1H), 2.95 (br s, 1H), 2.40 (d, *J*=6.0Hz,2H),0.80–1.40(m, 9H).

Received 3 June 2003; accepted 22 June 2003
Paper 03/1948

References

1 H.O. House, *Modern Synthetic Reactions*, 2nd edn.; Menlo Park, Benjamin 1972, pp. 629-682.
2 (a) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto and H. Nozaki, *J. Am. Chem. Soc.*, 1977, **99**, 7705; (b) K. Maruoka, S. Hashimoto, Y. Kitagawa, H. Yamamoto and H. Nozaki, *Bull. Chem. Soc. Jpn*., 1980, **53**, 3301.
3 (a) N. Tsuboniwa, S. Matsubara, Y. Morizawa, K. Oshima and H. Nozaki, *Tetrahedron Lett.*, 1984, **25**, 2569; (b) S. Matsubara, N. Tsuboniwa, Y. Morizawa, K. Oshima and H. Nozaki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3242.
4 T. Harada and T. Mukaiyama, *Chem. Lett.*, 1982, 467.
5 (a) P. Girard, J.L. Namy and H.B. Kagan, *J. Am. Chem. Soc.*, 1980, **102**, 2693; (b) Y. Aoyagi, M. Yoshimura, M. Tsuda, T. Tsuchibuchi, S. Kawamata, H. Tateno, K. Asano, H. Nakamura, M. Obokata, A. Ohta and Y. Kodama, *J. Chem. Soc., Perkin Trans.* 1, 1995, 689.
6 (a) C.J. Li, *Chem. Rev.*, 1993, **93**, 2203; (b) A. Lubineau, J. Auge and Y. Queneau, *Synthesis*, 1994, 741; (c) C.J. Li, *Tetrahedron*, 1996, **52**, 5643; (d) T.H. Chan, C.J. Li, M.C. Lee and Z.Y. Wei, *Can. J. Chem.*, 1994, **72**, 1181.
7 (a) C.J. Li and T.H. Chan, *Tetrahedron Lett.*, 1991, **32**, 7071; (b) T.H. Chan and M.B. Isaac, *Pure. Appl. Chem.*, 1996, **68**, 919; (c) J. Auge, N.L. Germain and A.T. Woaye, *Tetrahedron Lett.*, 1999, **40**, 9245; (d) F.A. Khan and B. Prabhudas, *Tetrahedron*, 2000, **56**, 7595; (e) G.C. Lloyd-Jones, M. Murray, R.A. Stentiford and P.A. Worthington, *Eur. J Org. Chem*., 2000, 975.
8 H.Y. Wu and J.C. Ding, *J. Chem. Res.*, 2002, **9**, 461.
9 (a) T.P. Loh, J. Pei and G.Q. Cao, *J. Chem. Soc., Chem. Commun.*, 1996, 1819; (b) T.P. Loh, J. Pei, K.S.V. Koh, G.Q. Cao and X.R. Li, *Tetrahedron Lett*., 1997, **38**, 3465.
10 E. Hasegawa, K.Ishiyama, T. Horoguchi and T. Shimizu, *J Org. Chem.*,1991, **56**, 1631.
11 J. Zhou, Y. Jia, Q. Shao and S. Wu, *Synth. Commun.*, 1996, **26**, 769.
12 S. Fukuzawa, T. Tsuruta, T. Fujinami and S. Sakai, *J. Chem. Soc., Perkin Trans.* 1, 1987, 1476.
13 D.P. Curran, *J. Am. Chem. Soc.*, 1983, **105**, 5826.