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Ultrasound-accelerated synthesis of chiral allylic alcohols promoted by indium metal

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Abstract—The 2-iodomethyl-*O*-isopropylidine acetals undergo smoothly β-elimination by indium metal in methanol under sonication to afford the corresponding allylic alcohols in excellent yields with high selectivity. This method tolerates both acid and base labile functional and protecting groups and also free hydroxyl groups present in the molecule. Improved yields and enhanced rates are the remarkable features obtained by ultrasound.

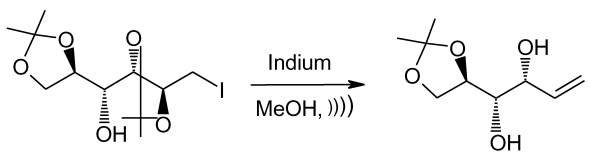
1. Introduction

The synthesis of optically pure building blocks via Chiron approach still continues to attract organic chemists especially if these building blocks are obtained from naturally available carbohydrates, tartaric acid, amino acids, and lactic acid etc. owing to their abundance and easy availability at low cost.[1] Chiral allylic alcohols are versatile intermediates for the synthesis of many biologically active natural products such as leukotrienes, lipoxins, pheromones, sphingolipids, trienomycins and α-lipoic acid, γ-caprolactone, γ-benzyloxymethyl butyrolactone, *exo*-brevicomin and many others.[2,3] Consequently, various methods have been developed for the synthesis of chiral allylic alcohols, which include: sharpless kinetic resolution,[4] asymmetric reduction of vinyl ketones by chiral catalysts[5] or enzymes[6] and enantioselective addition of alkenyl metal reagents to aldehydes.[7] Other methods for the synthesis of chiral allylic alcohols include: reductive elimination of 2,3-epoxy halides and reductive elimination of *O*-isopropyldine acetal tosylhydrazones.[8] However, in spite of their potential utility, many of these methods are involved in the use of strongly acidic or basic conditions, air or moisture sensitive reagents and prolonged reaction times and often produce unsatisfactory yields with low functional group selectivity. Thus, there is need to develop a simple, convenient and practical method for the synthesis of chiral allylic alcohols. In recent years, indium-mediated transformations have attracted great significance because of certain unique properties possessed by indium.[9] Indium metal is quite stable to water or air and does not require any activation or anhydrous reaction conditions. Furthermore, the first ionization potential of indium is much lower than that of zinc or tin, hence it could be a potential reducing agent.[10] Furthermore, there are no reports on the use of indium metal for the synthesis of chiral allylic alcohols from halomethyl isopropylidine acetals. In addition, ultrasound has become a very useful synthetic tool in organic synthesis.[11] It has been used to enhance reaction rates in a large number of classical organic reactions.[12]

2. Results and discussion

In continuation of our interest on the applications of metallic indium for various organic transformations,[13] we report herein a novel and highly efficient method for the synthesis of chiral allylic alcohols from 2-iodomethyl-*O*-isopropylidine acetals using indium metal in methanol under sonication (Scheme 1).

Thus treatment of 4-benzyloxymethyl-5-iodomethyl-1,3-dioxolane with indium metal in methanol under sonic waves resulted in the formation of 1-benzyloxy-3-buten-2-ol in 94% yield. In a similar fashion, a variety of iodomethyl-*O*-isopropylidine acetals underwent smoothly the reductive elimination to afford the corresponding allylic alcohols in high yields. The starting materials were prepared by using literature methods.[8] The method is compatible with various protecting groups such as benzyl, *p*-methoxybenzyl ethers, TBS ethers, acetals, esters and olefins present in the



Scheme 1.

Keywords: indium reagents; isopropylidine acetals; allylic alcohols.

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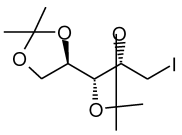
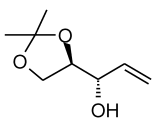
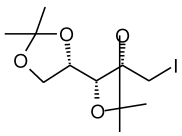
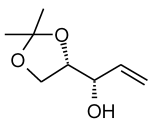
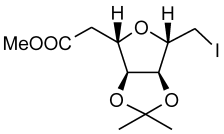
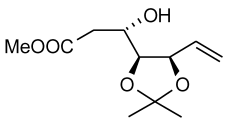
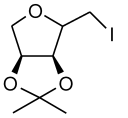
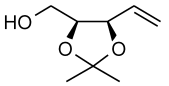
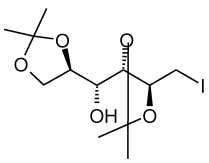
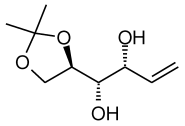
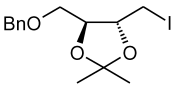
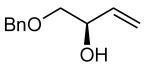
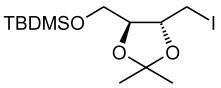
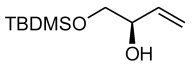
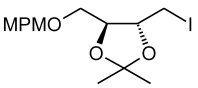
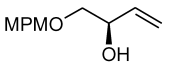
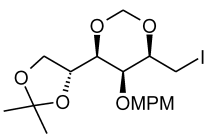
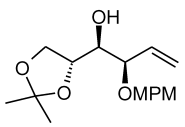
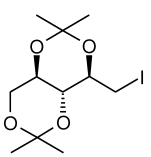
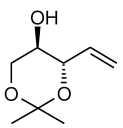
molecule. The reactions are clean and no side products or decomposition of the products are observed. The cyclic ethers like 2-iodomethyltetrahydro-2*H*-pyran and 2-iodomethyltetrahydrofuran also gave the corresponding 5-hexen-1-ol and 4-penten-1-ol in 95 and 90% yields, respectively, over 4.5 h under similar reaction conditions. The scope and generality of this procedure is illustrated with respect to various iodomethyl ketals and the results are presented in the Table 1. The experimental procedure is quite simple and the products are obtained in high yields. Unlike tin or zinc, indium does not require any acidic promoters or activators or anhydrous solvents to promote the reactions. Methanol appears to be the solvent of choice, giving best results. Among various metals such as indium, zinc, samarium and tin used for this transformation, indium was found to be more effective than others in terms of yields and reaction times, for example, the treatment of 1-iodomethyl-2,3,4,5-di-*O*-isopropylidine derivative of D-arabinose (entry **1a**) with different metals such as indium, zinc and tin for 5.5 h gave the corresponding chiral allylic

Table 1. Indium-mediated efficient synthesis of chiral allylic alcohols

Entry	Substrate **1**	Product[a] **2**	Time (h)	Yield (%)[b]
a			5.5	92
b			5.5	90
c			6.0	86
d			5.5	89
e			6.5	87
f			6.5	94
g			6.0	87
h			6.5	85
i			6.0	91
j			5.5	89

[a] All products were characterized by ^{1}H NMR, IR and mass spectra.
[b] Isolated and unoptimized yields.

alcohol (entry **2a**) in 92, 89, and 65% yield respectively under these reaction conditions. The reaction proceeds smoothly under mild conditions under sonic waves to give the products in high yields. Owing to vibrational energy of water, the bath temperature reached 60–65°C under sonication. The reaction rates and yields were dramatically enhanced by ultrasound. The rate enhancement under sonication may be attributed to the cavitation and the activation of the metal surface by sonic waves.[12] In the absence of sonic waves, longer reaction times and high temperature conditions are typical to achieve comparable yields those that are obtained by ultrasound. Zinc metal was also found to be equally effective for this transformation.

3. Conclusion

In summary, this paper describes a novel, convenient and practical method for the synthesis of chiral allylic alcohols from 2-iodomethyl-*O*-isopropylidine acetals using indium metal in methanol under sonic waves. This method is compatible with acid sensitive 1,2-isopropylidine acetals, silyl ethers, esters and *p*-methoxybenzyl ethers. In addition to its simplicity and milder reaction conditions, this method provides high yields of products with high selectivity, which makes it a useful and attractive strategy for the synthesis of chiral allylic alcohols.

4. Experimental

IR spectra were recorded on a Perkin–Elmer FT-IR 240-c spectrophotometer using KBr optics. ^{1}H NMR spectra were recorded on Gemini-200 spectrometer in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV. CHN analyses were recorded on a Vario EL analyzer. The optical rotations were measured on a Jasco Dip 360 Digital polarimeter. The Bransonic model 2210R-DTH ultrasound was operated at 335 W (47 KHz).

4.1. General procedure

A mixture of 2-iodomethyl-*O*-isopropylidine acetals (2 mmol) and indium powder (4 mmol) in methanol (10 mL) was sonicated (Bransonic model 2210R-DTH) for the appropriate time (Table 1). The reaction temperature was raised to 60–65°C after sonication for 3–5 h. On completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with methanol (10 mL). The combined extracts were concentrated in vacuo and purified by column chromatography on silica gel (Merck, 100–200 mesh, ethyl acetate–hexane, 1:9) to afford pure allylic alcohol.

4.1.1. Compound 2a. Oil, $[\alpha]_D^{25}$=4.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.45 (s, 3H), 2.08 (brs, OH), 3.82–3.90 (m, 2H), 4.0–4.15 (m, 1H), 4.24–4.32 (m, 1H), 5.25 (dd, 1H, *J*=10.2, 1.9 Hz), 5.45 (dd, 1H, *J*=17.3, 1.9 Hz), 5.70–5.90 (ddd, 1H, *J*=17.3 10.2, 6.8 Hz). EIMS: *m/z*: 158 [M$^+$], 144, 130, 103, 85, 55, 43. IR (KBr) ν: 3475, 2853, 1649, 1451, 1114, 929, 741 cm^{-1}. Anal. calcd for $C_8H_{14}O_3$ (158.19): C, 60.74; H, 8.92. Found: C, 60.78; H, 8.95.

4.1.2. Compound 2b. Oil, $[\alpha]_D^{25}$=6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.33 (s, 3H), 1.45 (s, 3H), 2.35 (brs, OH), 3.68–3.80 (m, 1H), 3.90–4.05 (m, 3H), 5.10 (dd, 1H, *J*=10.3, 1.9 Hz), 5.45 (dd, 1H, *J*=17.2, 1.9 Hz), 5.67–5.88 (ddd, 1H, *J*=17.2, 10.3, 6.9 Hz). EIMS: *m/z*: 158 [M$^+$], 145, 130, 102, 85, 55, 43. IR (KBr) ν: 3457, 2891, 1665, 1443, 1115, 935, 743 cm^{-1}. Anal. calcd for $C_8H_{14}O_3$ (158.19): C, 60.74; H, 8.92. Found: C, 60.78; H, 8.98.

4.1.3. Compound 2c. Colourless liquid, $[\alpha]_D^{25}$=−15.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.43 (s, 3H), 2.38–2.53 (m, 1H), 2.68–2.80 (m, 1H), 2.95 (brs, OH), 3.78 (s, 3H), 3.95–4.02 (m, 2H), 4.63–4.67 (m, 1H), 5.25 (dd, 1H, *J*=10.2, 2.0 Hz), 5.50 (dd, 1H, *J*=17.3, 2.0 Hz), 5.72–5.90 (ddd, 1H, *J*=17.3, 10.2, 6.8 Hz). EIMS: *m/z*: 230 [M$^+$], 215, 127, 98, 69, 43. IR (KBr) ν: 3465, 2890, 1649, 1465, 1114, 931, 740 cm^{-1}. Anal. calcd for $C_{11}H_{18}O_5$ (230.25): C, 57.37; H, 7.88. Found: C, 57.40; H, 7.91.

4.1.4. Compound 2d. Oil, $[\alpha]_D^{25}$=+15.1 (*c* 1.05, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.45 (s, 3H), 2.05 (brs, OH), 3.58 (d, 2H, *J*=6.7 Hz), 4.20 (q, 1H, *J*=6.7 Hz), 4.60 (t, 1H, *J*=6.5 Hz), 5.25 (dd, 1H, *J*=10.3, 2.0 Hz), 5.50 (dd, 1H, *J*=17.3, 2.0 Hz), 5.72–5.90 (ddd, 1H, *J*=17.3, 10.3, 6.5 Hz). EIMS: *m/z*: 158 [M$^+$], 144, 130, 102, 85, 55, 43. IR (KBr) ν: 3450, 2871, 1647, 1459, 1107, 937, 741 cm^{-1}. Anal. calcd for $C_8H_{14}O_3$ (158.19): C, 60.73; H, 8.91. Found: C, 60.76; H, 8.94.

4.1.5. Compound 2e. Viscous liquid, $[\alpha]_D^{25}$=6.1 (*c* 2.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 3H), 1.42 (s, 3H), 2.08 (brs, OH, 2H), 3.65–3.82 (m, 3H), 4.10 (q, 1H, *J*=6.5 Hz), 4.40 (t, 1H, *J*=6.5 Hz), 5.20 (dd, 1H, *J*=10.2, 1.9 Hz), 5.45 (dd, 1H, *J*=17.3, 1.9 Hz), 5.70–5.90 (ddd, 1H, *J*=17.3, 10.2, 6.5 Hz). EIMS: *m/z*: 188 [M$^+$], 174, 160, 144, 103, 85, 55. IR (KBr) ν: 3441, 2861, 1650, 1450, 1100, 925, 737 cm^{-1}. Anal. calcd for $C_9H_{16}O_4$ (188.22): C, 57.42; H, 8.56. Found: C, 57.45; H, 8.59.

4.1.6. Compound 2f. Colourless liquid, $[\alpha]_D^{25}$=3.8 (*c* 1.2, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.37 (brs, OH), 3.30–3.58 (m, 2H), 4.28 (m, 1H), 4.55 (s, 2H), 5.10 (dd, 1H, *J*=10.3, 1.7 Hz), 5.40 (dd, 1H, *J*=17.4, 1.7 Hz), 5.72–5.90 (ddd, 1H, *J*=17.4, 10.3, 6.8 Hz), 7.20–7.40 (m, 5H). EIMS: *m/z*: 178 [M$^+$], 91, 87, 77. IR (KBr) ν: 3440, 2860, 1610, 1529, 1460, 1310, 1255, 1105, 930, 825 cm^{-1}. Anal. calcd for $C_{11}H_{14}O_2$ (178.23): C, 74.12; H, 7.92. Found: C, 74.15; H, 7.97.

4.1.7. Compound 2g. Oil, $[\alpha]_D^{25}$=4.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.02 (s, 6H), 0.95 (s, 9H), 2.37 (brs, OH), 3.40 (dd, 1H, *J*=12.3, 6.5 Hz), 3.65 (dd, 1H, *J*=12.3, 6.8 Hz), 4.15–4.20 (m, 1H), 5.15 (dd, 1H, *J*=10.3, 1.8 Hz), 5.40 (dd, 1H, *J*=17.4, 1.8 Hz), 5.72–5.90 (ddd, 1H, *J*=17.4, 10.3, 6.9 Hz). EIMS: *m/z*: 202 [M$^+$], 184, 155, 135, 107, 67, 55, 43. IR (KBr) ν: 3445, 2860, 1645, 1455, 1104, 927, 738, 698 cm^{-1}. Anal. calcd for $C_{10}H_{22}O_2Si$ (202.36): C, 59.35; H, 10.96; Si, 13.88. Found: C, 59.51; H, 10.99; Si, 13.92.

4.1.8. Compound 2h. Colourless liquid, $[\alpha]_D^{25}=3.6$ (*c* 1.5, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 2.25 (brs, OH), 3.25 (dd, 1H, *J*=6.7, 12.0 Hz), 3.45 (dd, 1H, *J*=12.0, 6.9 Hz), 3.80 (s, 3H), 4.20–4.25 (m, 1H), 4.45 (s, 2H), 5.18 (dd, 1H, *J*=10.2, 1.7 Hz), 5.40 (dd, 1H, *J*=17.3, 1.7 Hz), 5.72–5.90 (ddd, 1H, *J*=17.3, 10.2, 6.8 Hz), 6.80 (d, 2H, *J*=8.0 Hz), 7.20 (d, 2H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$, proton decoupled): δ 54.9, 71.1, 72.6, 73.5, 113.5, 115.8, 129.1, 129.6, 136.6, 159.0. EIMS: *m*/*z*: 208 [M^+], 167, 137, 121, 109, 95, 83, 69, 57, 43. IR (KBr) ν: 3441, 2859, 1612, 1514, 1461, 1303, 1251, 1103, 928, 822 cm^{-1}. Anal. calcd for $C_{12}H_{16}O_3$ (208.25): C, 69.20; H, 7.74. Found: C, 69.23; H, 7.78.

4.1.9. Compound 2i. Oil, $[\alpha]_D^{25}=-24.9$ (*c* 2.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.25 (s, 3H), 1.30 (s, 3H), 2.25 (brs, OH), 3.38–3.45 (m, 1H), 3.80 (s, 3H), 3.90–4.10 (m, 4H), 4.30 (d, 1H, *J*=13.5 Hz), 4.50 (d, 1H, *J*=13.5 Hz), 5.15 (dd, 1H, *J*=10.3, 1.9 Hz), 5.40 (dd, 1H, *J*=17.3, 1.9 Hz), 5.80–6.0 (ddd, 1H, *J*=17.3, 10.3, 6.5 Hz), 6.80 (d, 2H, *J*=8.0 Hz), 7.20 (d, 2H, *J*=8.0 Hz). ^{13}C NMR ($CDCl_3$, decoupled): δ 25.4, 26.6, 55.2, 66.4, 70.3, 74.6, 75.6, 79.2, 108.9, 113.7, 118.7, 129.4, 130.0, 135.3. EIMS: *m*/*z*: 308 [M^+], 293, 241, 137, 121, 108, 91, 77. IR (KBr) ν: 3476, 2932, 1612, 1514, 1460, 1376, 1248, 1065, 930, 845, 770 cm^{-1}. Anal. calcd for $C_{17}H_{24}O_5$ (308.37): C, 66.21; H, 7.83. Found: C, 66.25; H, 7.86.

4.1.10. Compound 2j. Oil, $[\alpha]_D^{25}=18.3$ (*c* 1.7, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.50 (s, 3H), 2.25 (brs, OH), 3.44 (dd, 1H, *J*=10.3, 4.9 Hz), 3.49 (m, 1H), 3.85 (dd, 1H, *J*=7.5, 7.3 Hz), 4.20 (dd, 1H, *J*=10.3, 10.1 Hz), 5.20–5.35 (m, 2H), 5.75–5.90 (m, 1H). EIMS: *m*/*z*: 158 [M^+], 140, 130, 118, 102, 85, 70, 55, 43. IR (KBr) ν: 3475, 2940, 1616, 1521, 1475, 1250, 1070, 931, 773 cm^{-1}. Anal. calcd for $C_8H_{14}O_3$ (158.96): C, 60.73; H, 8.92. Found: C, 60.76; H, 8.95.

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