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A simple and an efficient indium trichloride catalyzed benzyl etherification

G Bhaskar, M Solomon, G Babu, D Muralidharan & Paramasivan T Perumal*

Organic Chemistry Division, Central Leather Research Institute, Adyar, Chennai 600 020, India

E-mail: ptperumal@gmail.com

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An efficient method has been developed for the synthesis of benzyl ethers of alkyl, allyl and propargyl alchols by simple, direct coupling of alcohols in the presence of catalytic amount of $InCl_3$ under solvent-free condition.

Keywords: Indium trichloride, benzyl etherification, solvent free condition

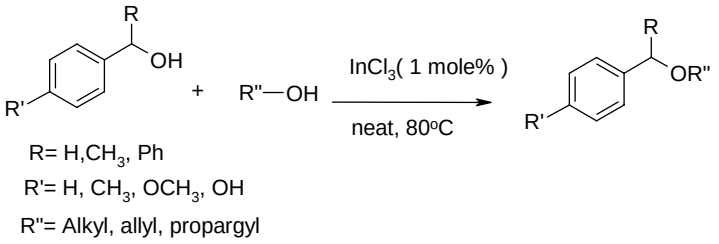
Ethers are prevalent in numerous natural products[1] and are of pharmacological interest[2]. They are one of the most widely used protecting groups for alcohols in organic synthesis. Of the numerous available protecting groups for alcohols, benzyl ethers are the most popular, due to their deprotection conditions being orthogonal to each other[3,4]. The traditional methods employed for the synthesis of ethers involve the reaction between an alkyl halide and alkoxide[5] or an alcohol and base[6]/Lewis acid[7]. These methods require strongly acidic or basic conditions, besides which they produce an acid or salt as the co-product. Later, alcohols were considered attractive electrophiles compared to alkyl halides from atom economical and synthetic viewpoint as they are readily available and the only co-product formed is water. This direct coupling of alcohols is conducted in the presence of catalytic amounts of organic or inorganic acids[8]. However, the activation of alcohols is difficult because of the poor leaving group ability of the hydroxyl group. On the other hand, Lewis acids are reported to be effective in the catalytic activation of alcohols resulting in the formation of ethers[9-11]. Conventional Lewis acids suffer from the drawback in requiring high catalyst to substrate ratio, Lewis acid undergo decomposition with water which form as a byproduct in the reaction.

On the other hand, indium(III) salts are stable in air, inexpensive, nontoxic and water-tolerant which make them efficient catalysts in aqueous[12] and non-aqueous media. In addition indium(III) salts are mild Lewis acids, by the virtue of which, other functionalities present in the substrate remain intact in the reaction[13]. These intrinsic properties of indium(III) salts, resulted in their increased and widespread application, as a efficient Lewis acid catalyst for various organic transformations[14-20] including the catalytic activation of alcohols[21-23]. In continuation of this work[24-27], a simple and efficient method for the synthesis of benzyl ethers using catalytic amounts of indium trichloride under solvent free condition (**Scheme I**) is reported.

Results and Discussion

The benzylation of *n*-butanol with *p*-methoxy-benzyl alcohol, as a model reaction in the presence of catalytic amount (1 mole%) of indium trichloride was carried out. The reaction proceeded smoothly, and the corresponding ether was obtained in 85% yield after 4 hr at 80°C, under neat condition. The same reaction yielded only 21% yield after 24 hr at RT. In the absence of the indium trichloride, the reaction did not proceed even when the reaction was extended to 48 hr at 80°C. Hence the optimized condition was found that mixing of *n*-butanol and *p*-methoxybenzyl alcohol in the presence of 1 mole% of indium trichloride catalyst, heated at 80°C under sealed condition without any solvent. This protocol was extended to the reaction between the primary and secondary benzyl alcohols and the alkyl, allyl and propargyl alcohols. The results are summarized in **Table I**.

The results revealed that the primary benzyl alcohols having electron donating substituent like hydroxy and methoxy react smoothly with various alcohols like alkyl, allyl and propargyl alcohols giving the corresponding ethers in good to excellent yield (**Table I**, entries **1-12**). But simple and electron



Scheme I — Benzylation of alcohols

deficient benzyl alcohols are inefficient under these experimental conditions. This might be due to the presence of electron withdrawing groups on these substrates disfavour the formation of carbocation intermediate. Also primary, secondary and tertiary alcohols react well and produce the corresponding ethers in moderate to good yields. However, the reaction between isopropyl alcohol **2b**, and *p*-methoxybenzyl alcohol **1a** afforded the ether product **3b** (**Table I**, entry **2**) only 32% in yield even after 12 hr. The *n*-butanol **2c** (**Table I**, entry **3**) reacts smoothly with *p*-methoxybenzyl alcohol **1a** produce the respective ether 85% in 4 hr, whereas *sec*-butanol **2d** and *t*-butanol **2e** afford the corresponding ethers (**Table I**, entry **4**,**5**) 81% and 67% respectively in 2 hr. Likewise, the cyclic secondary alcohols such as cyclohexanol **2f** and cyclocheptanol **2g** reacted with *p*-methoxybenzyl alcohol **1a** to yield the corresponding ethers **6,7** in good yields. Allyl alcohol **2h** reacted cleanly with *p*-methoxybenzyl alcohol to yield allyl(*p*-methoxybenzyl)ether **3h** in 87% yield. Propargyl alcohol **2**i which was reported to be unreactive with benzyl alcohols in the presence of $PdCl_2$, (ref 9d) and $Cu(acac)_2$, (ref 6), reacted smoothly with *p*-methoxybenzyl alcohol (**Table I, 1a**) and *p*-hydroxybenzyl alcohol **1b** in the presence of $InCl_3$ and afforded the corresponding ethers in attractive yields. (**Table I**, **9**,**11**). Further, **1a** reacted with similar type of alcohol **2j** to produce the respective ether in 83%. (**Table I**,**10**,**11**). Also *p*-hydroxybenzyl alcohol **1b** reacted with 2-isopropoxy ethanol **2k** to yield the corresponding ether **3l**, which is an intermediate in the synthesis of bisoprolol[28], a selective β-1 adrenergic receptor blocker, used primarily in cardiovascular disorders. In this reaction, the benzylic –OH was selectively etherificated and the phenolic –OH was untouched. Similarly in compound **8-12** alkyne, olefin, and methoxy functional groups were intact. This indicates that $InCl_3$ is a mild Lewis acid catalyst.

Experimental Section

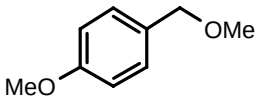
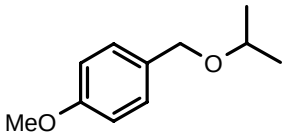
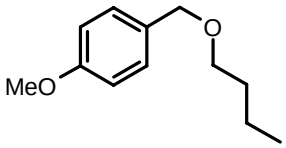
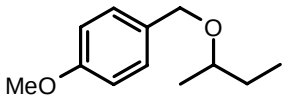
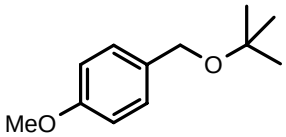
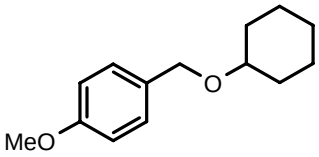
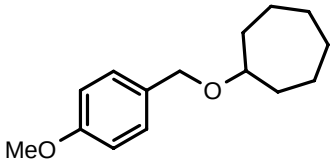
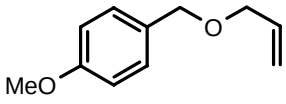
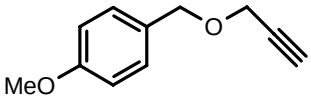
Various alcohols and benzyl alcohols were obtained from S.D. Fine Chemicals. Indium(III) chloride was purchased from Aldrich. IR spectra were recorded on a Perkin-Elmer FT-IR spectrophotometer. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as an internal standard on a JEOL spectrometer at 500 MHz and 125 MHz, respectively. Mass spectra were recorded on a Perkin-Elmer EI GC-MS spectrometer. Column chromatography was performed on silica gel (100–200 mesh, SRL, India). Analytical TLC was performed on precoated plastic sheets of silica gel G/UV-254 of 0.2 mm thickness (Macherey-Nagel, Germany).

Benzylation of alcohols

A typical experimental procedure for the benzylation of alcohols taking *p*-hydroxybenzyl alcohol **1b** and propargyl alcohol **2i** as a representative was carried out. To a stirred solution of *p*-hydroxybenzyl alcohol (10 mmole, 1.26 g) and propargyl alcohol (30 mmole, 1.68 g) at RT $InCl_3$ (1 mole%, 22 mg) was added. The reaction-mixture was stirred at 80°C for 0.45 min. under sealed condition. The completion of the reaction was monitored by TLC, and the reaction-mixture was diluted with ethylacetate and washed with water. The organic layer was dried over anhydrous magnesium sulphate and the excess solvent was removed in vacuum. The crude mixture obtained was purified by column chromatography on silica gel using petroleum ether-ethyl acetate as the eluent.

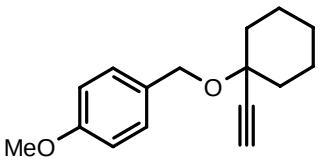
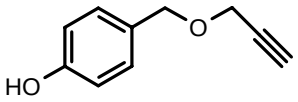
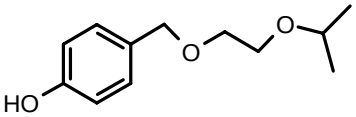
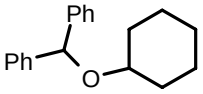
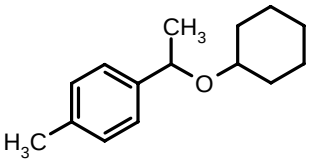
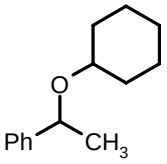
1-Methoxy-4-methoxymethyl-benzene (3a, ref 11d**)**: Colourless oil, IR (neat): 3000, 2929, 2822, 1612, 1513, 1461, 1247, 1096, 1034, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.35 (3H, s), 3.80 (3H, s), 4.38 (2H, s), 6.87 (2H, d, *J* = 8.4Hz), 7.25 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.0, 57.6, 74.3, 113.7, 129.3, 130.3, 159.2; M^+ : 152; For $C_9H_{12}O_2$: Calcd C, 71.03; H, 7.95. Found: C, 71.09; H, 7.87%.

Table I — Indium trichloride catalysed benzylation of alcohols

1	4-Methoxybenzylalcohol **1a**	Methanol **2a**	 **3a**	6.0	59
2	4-Methoxybenzylalcohol **1a**	Isopropylalcohol **2b**	 **3b**	12.0	32
3	4-Methoxybenzylalcohol **1a**	n-Butanol **2c**	 **3c**	4.0	85
4	4-Methoxybenzylalcohol **1a**	*sec*-butanol **2d**	 **3d**	2.0	81
5	4-Methoxybenzylalcohol **1a**	*t*-butanol **2e**	 **3e**	2.0	67
6	4-Methoxybenzylalcohol **1a**	Cyclohexanol **2f**	 **3f**	1.0	85
7	4-Methoxybenzylalcohol **1a**	Cycloheptanol **2g**	 **3g**	1.75	81
8	4-Methoxybenzylalcohol **1a**	Allyl alcohol **2h**	 **3h**	1.50	87
9	4-Methoxybenzylalcohol **1a**	Propargyl alcohol **2i**	 **3i**	0.75	84

— Contd

Table I — Indium trichloride catalysed benzylation of alcohols — *Contd*

10	4-Methoxybenzylalcohol **1a**	1-Ethynyl-cyclohexanol **2j**	 **3j**	0.75	83
11	4-Hydroxybenzylalcohol **1b**	Propargyl alcohol **2i**	 **3k**	0.75	89
12	4-Hydroxybenzylalcohol **1b**	2-Isopropoxy-ethanol **2k**	 **3l**	3.25	87
13	Diphenyl-methanol **1c**	Cyclohexanol **2f**	 **3m**	2.0	84
14	1-*p*-Tolyl-ethanol **1d**	Cyclohexanol **2f**	 **3n**	2.5	78
15	1-Phenyl-ethanol **1e**	Cyclohexanol **2f**	 **3o**	3.0	71

1-Isopropoxymethyl-4-methoxy-benzene (3b, ref 9c**)**: Colourless oil, IR (neat): 2970, 2842, 1612, 1511, 1462, 1247, 1125, 1174, 1037, 818 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.19 (6H, d, *J* = 6.1Hz), 3.65 (1H, sept, *J* = 6.1Hz), 3.80 (3H, s), 4.43 (2H, s), 6.86 (2H, d, *J* = 8.4Hz), 7.25 (2H, d, *J* = 7.6Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.1, 54.9, 69.6, 70.5, 113.7, 128,9, 131.3, 159; M^+: 180; For $C_{11}H_{16}O_2$: Calcd C, 73.30; H, 8.95. Found: C, 71.24; H, 8.91%.

1-Butoxymethyl-4-methoxy-benzene (3c, ref 29**)**: Colourless oil, IR (neat): 2953, 2862, 1612, 1513, 1461, 1362, 1247, 1174, 1098, 1038, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.90 (3H, t, *J* = 6.8Hz), 1.38 (2H, sextet, *J* = 7.6Hz), 1.58 (2H, q, *J* = 6.1Hz), 3.43 (2H, t, *J* = 6.9Hz), 3.79 (3H, s), 4.42 (2H, s), 6.87 (2H, d, *J* = 8.4Hz), 7.25 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 13.9, 19.4, 31.9, 55.2, 69.9, 72,5, 113.8, 129.2, 130.8, 159.1; M^+ : 194; For $C_{12}H_{18}O_2$: Calcd C, 74.19; H, 9.34. Found: C, 74.14; H, 9.39%.

1-*sec*-Butoxymethyl-4-methoxy-benzene (3d, ref 29**)**: Colourless oil, IR (neat): 2967, 2937, 2870, 1612, 1513, 1461, 1300, 1247, 1174, 1069, 1033, 821 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 0.93 (3H, t, *J* = 7.7Hz), 1.19 (3H,d, *J* = 6.1Hz), 1.44-1.53 (1H, m), 1.57-1.65 (1H, m), 3.41-3.48 (1H, m), 3.79 (3H, s), 4.41 (1H, d, *J* = 11.4Hz), 4.50 (1H, d, *J* = 11.5Hz), 6.86 (2H, d, *J* = 8.4Hz), 7,28 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 9.9, 19.2, 29.3, 55.1, 69,9. 75.8, 113.7, 129.1, 131.3, 159.1; M^+: 194; For $C_{12}H_{18}O_2$: Calcd C, 74.19, H, 9.34. Found: C, 74.13;H, 9.31%, .

1-*tert*-Butoxymethyl-4-methoxy-benzene (3e, ref 9c**)** : Colourless oil, IR (neat): 2967, 1610, 1511, 1372, 1243, 1195, 1058, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.34 (9H, s), 3.80 (3H, s), 4.41 (2H, s), 6.90 (2H, d, *J* = 8.4Hz), 7.31 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 27.7, 55.2, 63.8, 73.2, 113.7, 128.9, 132.0, 158.9; M^+: 194; For $C_{12}H_{18}O_2$: Calcd C, 74.19; H, 9.34. Found: C, 74.12; H, 9.37%.

1-Cyclohexyloxymethyl-4-methoxy-benzene (3f, ref 30**)**: Colourless oil, IR (neat): 2995, 2928, 2851, 1612, 1513, 1451, 1360, 1299, 1247, 1174, 1088, 1036, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.18-1.38 (5H, m), 1.50-1.56 (1H, m), 1.72-1.78 (2H, m), 1.91-1.97 (2H, s), 3.29-3.36 (1H, m), 3.79 (3H, s), 4.47 (2H, s), 6.87 (2H, d, *J* = 8.4Hz), 7.27 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.2, 25.9, 32.3, 55.1, 69.3, 76.6, 113.7, 129.0, 131.4, 159.1; M^+: 220; For $C_{14}H_{20}O_2$: Calcd C, 76.33; H, 9.15. Found: C, 76.27; H, 9.19%.

(4-Methoxy-benzyloxy)-cycloheptane 3g: Colourless oil, IR (neat): 2930, 2858, 1512, 1449, 1365, 1092, 1024, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.35-1.48 (2H, m), 1.55-1.65 (4H, m), 1.65-1.78 (4H, m), 1.92-1.21 (2H, m), 3.52-3.58 (1H, m), 3.79 (3H, s), 4.66 (2H, s), 6.89 (2H, d, *J* = 8.4Hz), 7.29 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.1, 28.6, 34.0, 55.3, 69.8, 79.2, 113.8, 129.1, 131.5, 159.0; M^+: 234; For $C_{15}H_{22}O_2$: Calcd C, 76.88; H, 9.46. Found: C, 76.83; H, 9.41%.

1-Allyloxymethyl-4-methoxy-benzene (3h, ref 9b**)**: Colourless oil, IR (neat): 3071, 3004, 2947, 2841, 1612, 1513, 1461, 1248, 1081, 1035, 820 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 3.79 (3H, s), 3.99 (2H, d, *J* = 6.1Hz), 4.45 (2H, s), 5.19 (1H, d, *J* = 10.7Hz), 5.29 (1H, d, *J* = 17.6Hz), 5.94 (1H, m), 6.87 (2H, d, *J* = 8.4Hz), 7.26 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.0, 70.8, 71.7, 113.7, 116,7, 129.3, 130.5, 135.1, 159.3; M^+: 178; For $C_{11}H_{14}O_2$: Calcd C, 74.13; H, 7.92. Found: C, 74.07; H, 7.87%.

1-Methoxy-4-prop-2-ynyloxymethyl-benzene (3i, ref 31**)** : Colourless oil, IR (neat): 3286, 2937, 2851, 1614, 1509, 1452, 1248, 1080, 819 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.46 (1H, t, *J* = 2.3Hz), 3.80 (3H, s), 4.13 (2H, d, *J* = 2.3Hz), 4.54 (2H, s), 6.88 (2H, d, *J* = 8.4Hz), 7.28 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 55.2, 56.7, 71.1, 74.5, 79.8, 113.8, 129.3, 129.8, 159.4; M^+: 176; For $C_{11}H_{12}O_2$: Calcd C, 74.98, H, 6.86. Found: C, 74.92, H, 6.81%.

1-(1-Ethynyl-cyclohexylloxymethyl)-4-methoxy-benzene (3j,ref 32**)**: Colourless oil, IR (neat): 3291, 3004, 2937, 2858, 2056, 1613, 1585, 1513, 1447, 1247, 1175, 949, 820, 645 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.34-1.46 (1H, m), 1.56-1.72 (3H, m), 1.73-1.84 (4H, m), 2.01-2.09 (2H, m), 2.62 (1H, s), 3.82 (3H, s), 4.66 (2H, s), 6.94 (2H, d, *J* = 8.4Hz), 7.38 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 22.8, 25.5, 37.3, 55.2, 65.2, 73.8, 74.1, 85.6, 113.8, 129.3, 131.3, 159.1; M^+ : 244; For $C_{16}H_{20}O_2$: Calcd C, 78.65; H, 8.25. Found: C, 78.58, H, 8.19%.

4-Prop-2-ynyloxymethyl-phenol 3k: White solid, m.p. 72-74°C; IR (KBr) 3397, (br, -OH), 3272, 2872, 2124, 1899, 1609, 1517, 1444,1412, 1352, 1208 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 2.47 (1H, t, *J* = 2.2Hz), 4.14 (2H, d, *J* = 2.2Hz), 4.53 (2H, s), 6.77 (2H, d, *J* = 8.6Hz), 7.21 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 56.7, 71.3, 74.8, 79.5, 115.4, 128.8, 130.2, 155.7; M^+ : 162; For $C_{10}H_{10}O_2$: Calcd C, 74.06; H, 6.21. Found: C, 74.12, H, 6.27%.

4-(2-Isopropoxy-ethoxymethyl)-phenol (3l, ref 11d**)** : Colourless oil, IR (neat): 3305, 1622, 1528, 1224, 1032, 1082 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.17 (6H, d, *J* = 6.1 Hz), 3.55-3.67 (5H, m), 4.46 (2H, s), 5.58 (1H, -OH, s), 6.76 (2H, d, *J* = 8.4Hz), 7.16 (2H, d, *J* = 8.4Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 21.9, 67.3, 69.1, 72.4, 73.1, 115.4, 128.9, 129.8, 156.1; M^+ : 210; For $C_{12}H_{18}O_3$: Calcd C, 68.54; H, 8.63. Found: C, 68.59; H, 8.57%.

Cyclohexyloxy-diphenyl-methane(3m, ref 33**)** : Colourless oil, IR (neat): 3029, 2930, 2851, 1497, 1450, 1344, 1183, 1075, 957,748, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.18-1.31 (3H, m), 1.41-1.58 (3H, m), 1.72-1.82 (2H, m), 1.92-1.98 (2H, m), 3.38 (1H, m), 5.57 (1H, s), 7.23-7.41 (10H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 24.1, 25.9, 32.4, 75.1, 80.0, 127.1, 127.2, 128.3, 143.2; M^+ : 266; For $C_{19}H_{22}O$: Calcd C, 85.67; H, 8.32. Found: C, 85.61; H, 8.26%.

1-(1-Cyclohexyloxy-ethyl)-4-methyl-benzene 3n: Colourless oil, IR (neat): 2930, 2858, 1512, 1449, 1365, 1092, 1024, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.14-1.27 (3H, m), 1.30-1.39 (2H, m), 1.46 (3H, d, *J* = 7.6Hz), 1.52-1.59 (1H, m), 1.69-1.84 (3H, m), 2.00-2.06 (1H, m), 2.39 (3H, s), 3.18-3.25 (1H, m,), 4.62 (1H, quartet, *J* = 7.6Hz), 7.19 (2H, d, *J* = 7.6Hz), 7.27 (2H, d, *J* = 7.6Hz); ^{13}C NMR ($CDCl_3$,125 MHz): δ 21.1, 24.4, 25.93, 31.8, 33.5, 74.0, 74,6, 126.1, 129.0, 137.0, 142.1; M^+ : 218; For $C_{15}H_{22}O$: Calcd C, 82.52; H, 10.16. Found: C, 82.46; H, 10.11%.

(1-Cyclohexyloxy-ethyl)-benzene 3o: Colourless oil, IR (neat): 3028, 2931, 2858, 1491, 1449, 1363, 1094, 1028, 759,700 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.10-1.22 (3H, m), 1.24-1.38 (2H, m), 1.42

(3H, d, J = 7.9Hz), 1.46-1.55 (1H,m), 1.65-1.79 (3H, m), 1.96-2.02 (1H, m), 3.12-3.2 (1H, m), 4.60 (1H, quartet, J = 7.9Hz), 7.24-7.38 (5H, m); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 23.0, 24.9, 31.8, 33.4, 74.2, 74.8, 126.1, 127.1, 128.2, 145.1; M^+ : 204; For $C_{14}H_{20}O$: Calcd C, 82.30; H, 9.87. Found: C, 82.23; H, 9.81%.

Conclusion

An efficient method is developed for the synthesis of benzyl ethers by direct coupling of benzyl alcohols with various alcohols in the presence of catalytic amount of indium trichloride, under solvent free condition at 80°C.

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