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Zirconium tetrachloride catalysed synthesis of symmetric and unsymmetric ethers from secondary benzylic alcohols†

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Secondary benzylic alcohols are coupled in the presence of zirconium tetrachloride to afford the corresponding symmetrical ethers in good yields. Unsymmetric ethers are obtained with good selectivity by condensation of two different secondary benzylic alcohols under the action of the same catalyst.

Keywords: symmetric ethers, unsymmetric ethers, $ZrCl_4$, secondary benzylic alcohol

Etherification by direct coupling of alcohols is a useful method in organic synthesis.[1] The reaction is generally carried out by using a small amount of an inorganic or organic acid. The Williamson ether synthesis,[2] one of the most commonly used methods, requires the conversion of alcohols to halides or tosylates. Various Lewis acids such as $FeCl_3$,[3] $BiBr_3$,[4] $ZnCl_2$,[6] $GaCl_3$,[6] methylrhenium trioxide[7] and rare earth metal triflates[8] can also catalyse the etherification. However, many of these methods suffer from drawbacks such as the use of expensive reagent or stiochiometric amount of catalyst, harsh reaction conditions, longer reaction times, high temperature and low yields.

In continuation of our synthetic work,[9] we have discovered a suitable method for the direct preparation of symmetric and unsymmetric ethers by using a catalytic amount of $ZrCl_4$ under reflux. Various secondary benzylic alcohols having electron-donating groups underwent the reaction smoothly to furnish the ethers in good yields (Scheme 1) while the substrates having electron withdrawing groups afforded the products with lower yields.

The reaction was complete within 1–3 h (Table 1). Unsymmetrical ethers were also formed with good selectivity by coupling of two different benzylic alcohols in the presence of the catalyst (Table 2). However, in the case of cyclic benzylic alcohols, olefins are produced in high yields at room temperature (Scheme 2, Table 3). The structures of the products were determined from their spectral (^{1}H NMR and MS) data.

Recently, $ZrCl_4$ has been used in various chemical transformations as it possesses an interesting reactivity, is less costly and is less toxic than some alternatives.[10] The reagent has been employed in the synthesis of nitriles,[11] oxidation of alcohols,[12] selective tosylation of alcohols,[13] tetrahydropyranylation and detetrahydropyranylation of alcohols and phenols.[14] Here we describe the catalytic activity of $ZrCl_4$ in the etherification of secondary benzylic alcohols.

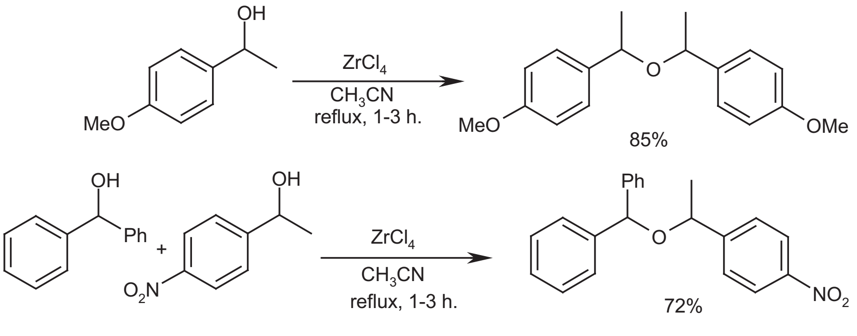
We have developed a mild and efficient method for direct preparation of symmetrical and unsymmetrical ethers using catalytic amount of zirconium tetrachloride. The major advantages of this protocol include short reaction times, availability of the catalyst, high yields, good selectivity and simple experimental procedure.

Experimental

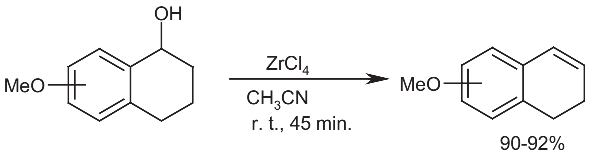
The spectra were determined with the following instruments: Melting points were measured on a Büchi 510 instrument and are uncorrected. IR, Perkin Elmer spectrophotometer; NMR, Varian Gemini 200 MHz and MS: Micromass VG 7070 H (70 eV), Column chromatography was performed over silica gel (BDH, 100–200 mesh) and TLC with silica gel GF_{254}.

General procedure for the synthesis of symmetric and unsummetric ethers

To a mixture of a secondary benzylic alcohol (1 mmol) (or two different secondary benzylic alcohols [0.5 mmol each]) in acetonitrile (5 ml), $ZrCl_4$ (0.2 mmol) was added. The mixture was stirred at reflux and the reaction was monitored by TLC. After completion,



Scheme 1



Scheme 2

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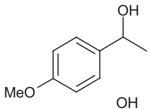
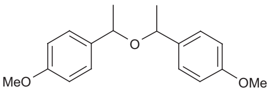
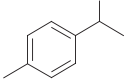
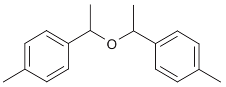
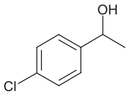
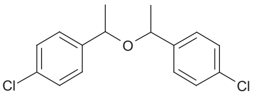
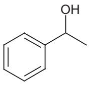
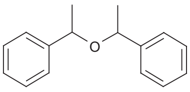
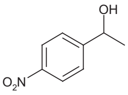
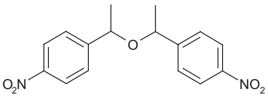
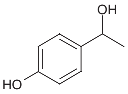
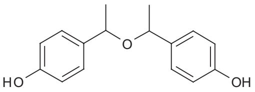
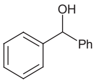
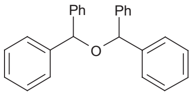
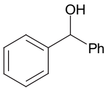
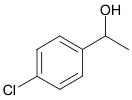
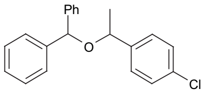
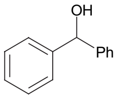
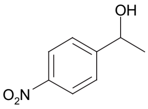
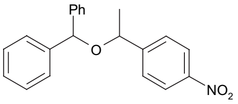
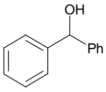
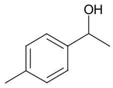
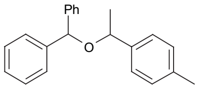
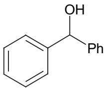
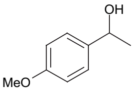
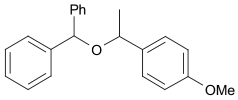
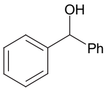
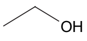
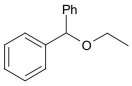
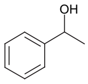
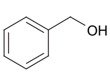
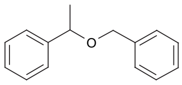
† Part 155 in the series, "Studies on novel synthetic methodologies".

Table 1 Formation of symmetric ethers from sec-benzylic alcohols catalysed by $ZrCl_4$[a]

Entry	Substrate	Product	Time/h	Isolated yield/%	M. p./°C (reported)[lit]
1			1	85	Liquid
2			1.5	80	Liquid
3			1.5	85	Liquid
4			2	86	Liquid (liquid)[6]
5			3	55	146–148
6			2	78	92–94
7			1	95	90–92 (89–91)[6]

[a]All the products were characterised from spectral (^{1}H NMR and MS) data.

Table 2 Formation of unsymmetric ethers by coupling of different alcohols catalysed by $ZrCl_4$[a]

Entry	Alcohol A	Alcohol B	Product	Time/h	Isolated yield/%[b]	M. p./°C (reported)[lit]
8				1.5	74[b]	Liquid
9				2	72[b]	117–119
10				2.5	70[b]	Liquid
11				2	75[b]	Liquid
12				3	76	Liquid
13				3	64	Liquid (liquid)[6]

[a]All the products were characterised from spectral (^{1}H NMR and MS) data.
[b]Symmetric bis (diphenyl)methyl ether was formed in small quantity (7–10%) as determined by ^{1}H NMR spectrum of the crude product.

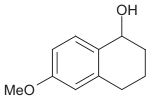
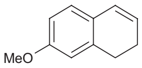
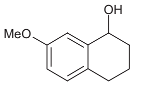
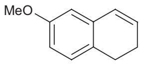
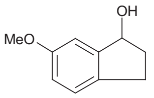
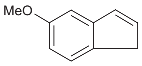
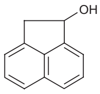
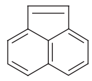
the mixture was diluted with EtOAc (10 ml) and washed with brine (20 ml) and water (2 × 10 ml). The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (silica gel, hexane: EtOAc) to afford the pure ether.

The spectral data of some of the representative ethers (Table 1–3) are given below.

(**1**): Colourless liquid IR (KBr): 2926, 1602, 1258, 1046 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.27–7.10 (m, 2H), 6.82–6.65 (m, 6H), 4.46 (q, J = 6.7 Hz, 1H), 4.18 (q, J = 6.7 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 3H), 1.44 (d, J = 6.7 Hz, 3H), 1.34 (d, J = 6.7 Hz, 3H); FABMS: m/z 309 $[M + Na]^+$; Anal. Calc. for $C_{18}H_{22}O_3$: C, 75.5; H, 7.7%. Found: C, 75.5; H, 7.5%.

(**2**): Colourless liquid IR (KBr): 3021, 1486, 1350, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): 7.15–699 (m, 8H), 4.41 (q, J = 6.5 Hz, 1H), 4.13 (q, J = 6.5 Hz, 1H), 2.23 (s, 3H), 2.16 (s, 3H), 1.35 (d,

Table 3 Formation of alkenes from cyclic benzylic alcohols catalysed by $ZrCl_4$[a]

Entry	Substrate	Product	Time/min	Isolated yield/%[b]	M. p. (°C) (reported)[lit]
14			45	92(5)	Liquid
15			45	90(6)	Liquid (liquid)[8]
16			70	73(10)	Liquid (liquid)[8]
17			40	89	80–82 (79–81)[8]

[a]All the products were characterised from spectral (^1H NMR and MS) data.
[b]Yield reported in parentheses is for corresponding symmetrical ether.

J = 6.4 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H); FABMS: m/z 277 [M + Na]$^+$; Anal. Calc. for $C_{18}H_{22}O$: C, 85.0; H, 8.7%. Found: C, 85.1; H, 8.6%.

Compound (**3**): Colourless liquid IR (KBr): 3061, 1496, 1450, 1090 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.35–7.12 (m, 8H), 4.40 (q, J = 6.5 Hz, 1H), 4.12 (q, J = 6.5 Hz, 1H), 1.40 (d, J = 6.8 Hz, 3H), 1.32 (d, J = 6.8 Hz, 3H); FABMS: m/z 317, 319, 321 [M + Na]$^+$; Anal. Calc. for $C_{16}H_{16}Cl_2O$: C, 64.9; H, 5.4%. Found: C, 64.8; H, 5.3%.

(**5**): White solid; m. p. 146-148°C; IR (KBr): 2925, 2854, 1522, 1347, 1236, 1066 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 8.21 (m, 4H), 7.55 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 8.2 Hz, 2H), 5.86 (q, J = 6.5 Hz, 1H), 4.25 (q, J = 6.5 Hz, 1H), 1.58 (d, J = 6.4 Hz, 3H), 1.42 (d, J = 6.4 Hz, 3H); FABMS: m/z 339 [M + Na]$^+$; Anal. Calc. for $C_{16}H_{16}N_2O_5$: C, 60.7; H, 5.1; N, 8.86%. Found: C, 60.8; H, 5.1; N, 8.8%.

(**6**): White solid; m.p. 92–94 °C; IR (KBr); 3246, 1630, 1520, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.21–7.12 (m, 2H), 6.65–6.75 (m, 6H), 4.46 (q, J = 6.5 Hz, 1H), 4.12 (q, J = 6.5 Hz, 1H), 1.43 (d, J = 6.5 Hz, 3H) 1.32 (d, J = 6.5 Hz, 3H); FABMS: m/z 281 [M + Na]$^+$; Anal. Calc. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0%. Found: C, 74.3; H, 6.8%.

(**8**). Colourless liquid; IR (KBr); 3028, 1600, 1492, 1450, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.38–7.12 (m, 14H), 5.15 (s, 1H), 4.39 (q, J = 6.0 Hz, 1H), 1.45 (d, J = 6.0 Hz, 3H); FABMS: m/z 345, 347 [M + Na]$^+$; Anal. Calc. for $C_{21}H_{19}ClO$: C, 78.0; H, 5.9%. Found: C, 77.7; H, 5.9%.

(**9**): **L**ight yellow solid; m.p. 117–119°C; IR (KBr); 2923, 2852, 1514, 1343, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 8.20 (d, J = 8.0 Hz, 2H), 7.48 (d, J = 8.0 Hz, 2H), 7.34–7.12 (m, 10H), 5.17 (s, 1H), 4.51 (q, J = 6.3 Hz, 1H), 1.50 (d, J = 6.3, Hz 3H); FABMS: m/z 356 [M + Na]$^+$; Anal. Calc. for $C_{21}H_{19}O_3N$: C, 75.67; H, 5.70; N, 4.20%. Found: C, 75.54; H, 5.66; N, 4.10%.

(**10**): Colourless liquid; IR (KBr); 2932, 1532, 1436, 1085 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.31–7.06 (m, 14H), 5.16 (s, 1H), 4.30 (q, J = 6.5, Hz 1H), 2.35 (s, 3H), 1.45 (d, J = 6.5 Hz, 3H); FABMS: m/z 325 [M + Na]$^+$; Anal. Calc. for $C_{22}H_{22}O$: C, 87.41; H, 7.28%. Found: C, 87.58; H, 7.36%.

(**11**): Colourless liquid; IR (KBr); 3028, 1601, 1489, 1258, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.40–7.15 (m, 12H), 6.80 (d, J = 8.2 Hz, 2H), 5.2 (s, 1H), 4.40 (q, J = 6.4 Hz, 1H), 3.72 (s, 3H), 1.45 (d, J = 6.8 Hz, 3H); FABMS: m/z 341 [M + Na]$^+$; Anal. Calc. for $C_{22}H_{22}O_2$: C, 83.01; H, 6.91%. Found: C, 83.24; H, 6.98%.

(**12**): Colourless liquid; IR (KBr); 2974, 2866, 1453, 1493, 1096 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 7.35–7.14 (m, 10H), 5.38 (s, 1H), 3.45 (q, J = 7.2 Hz, 2H), 1,25 (t, J = 7.2 Hz, 3H); FABMS: m/z 235 [M + Na]$^+$; Anal. Calc. for $C_{15}H_{15}O$: C, 85.30; H, 7.10%. Found: C, 85.22; H, 7.24%.

(**14**): Colourless liquid; IR (KBr); 3032, 2996, 1480, 1453, 1245, cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): 6.90 (d, J = 8.0, 1H), 6.66–6.57 (m, 2H), 6.35 (d, J = 9.0, 1H), 5.85 (m, 1H), 3.75 (s, 3H), 2.76 (t, J = 7.0, 2H), 2.31–2.20 (m, 2H); FABMS: m/z 183 [M + Na]$^+$; Anal. Calc. for $C_{11}H_{12}O$: C, 82.50; H, 7.50%. Found: C, 82.46; H, 7.61%.

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