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Screening of Lewis acids catalyzed cross etherification of α-hydroxy ketones by aliphatic alcohols

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Abstract: Etherification reaction between benzoin derivatives and aliphatic alcohols catalyzed by Fe (III) proceeds in moderate to good yields. Other metal complexes showed either low reactivity or low chemo selectivity where oxidation of benzoin to benzil was a competing reaction.

Keywords: Lewis acids, α-Hydroxy ketones, Aliphatic alcohols, Ethers, Catalytic etherification.

Introduction

The search for low-waste technologies and multifunctional processes in organic synthesis is becoming more and more pressing for both economical and environmental concerns [1-8]. Ethers are fundamental compounds used as precursors for pharmaceuticals, fragrance precursors, [9] and reformulated gasoline [10]. Even though the preparation of unsymmetrical ethers is a well known transformation in organic synthesis with a wide range of procedures, they all suffer from limitations. The Williamson ether synthesis represents the most widely used method [11]. However, it involves manipulation of the hydroxyl group into a halide or tosylate in the presence of a base in a separate step, and thereby requires stoichiometric amount of reagents and generates waste. Furthermore, the reaction work efficiently only for primary alcohols, but gives lower conversions for secondary and tertiary alcohols. Alternative routes to synthesize unsymmetrical ethers include Brönstedt acid catalysis which are usually performed under harsh reaction conditions and give low chemoselectivity due to competing elimination reaction [12].

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In this regard, catalysis based on a variety of transition metals has been reported for the etherification to produce unsymmetrical ethers. Furthermore, alkyl ethers of benzoin-like compounds (Figure **1**) have showed high activity towards inhibiting the 11βHSD1 receptor related to diseases such as diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulidemia, hypertens, and also glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders and depression [13]. Considering the above facts, development of a facile and straight forward methodology for the synthesis of alkyl ethers of benzoin-like compounds is quite essential. In this connection we herein report a facile catalytic protocol for the synthesis of unsymmetrical ethers from aromatic α-hydroxy ketones and alkyl alcohols.

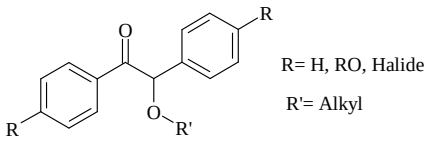


Figure 1: Biologically active alkyl ether of benzoin.

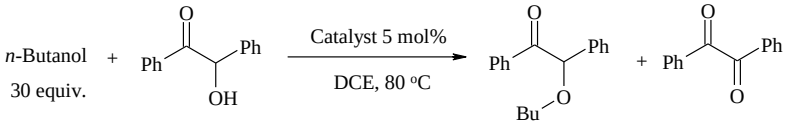
Results and discussion

*Synthesis of starting material***:** Symmetrical benzoins were prepared according to standard

procedures by reacting the aldehyde in the presence of catalytic amounts of sodium cyanide [14-15].

Choice of catalyst: In the initial stage of our study, we screened a number of catalysts to study their activities in the reaction between benzoin (**1**) and *n*-butanol. In contrast to other facile etherifications of benzylic alcohols the α-keto substituent proved more difficult. Catalysts based on Re (I), Gold (III) [16] and In(III) [17] that have been reported in the etherification of benzylic alcohols were found to be unreactive (Table **1**). Brönstedt acid such as *p*-toluene sulfonic acid (PTS) was also examined. Considering all, anhydrous $FeCl_3$ was found to be the best choice for this reaction.

Table 1: Catalyst screening in the etherification of benzoin by butanol.



1 **2**

Entry	Catalyst	Conversion (%)	Yield of 2
1	CrF_2	0	0
2	$ReMe(CO)_5$	0	0
3	$InCl_3$	0	0
4	$ZnBr_2$	0	0
5	$ZnCl_2$	0	0
6	ZnI_2	5	2
7	TiF_3	0	0
8	$TiCl_3$	0	0
9	$TiBr_3$	0	0
10	$NaAuCl_4$	20	4
11	$FeSO_4$	5	Trace
12	$FeCl_3.6H_2O$	35	3
13	$Fe(ClO_4)_3.H_2O$	48	28
14	$FeCl_3$	47	41
15	PTS	31	10

The reactions were run using 1 mmol of 1, 30 mmol of butanol, and 5 mol% of [Catalyst] in 3.2 mL of dichloroethane at 80 °C. Reactions were monitored by ^{1}H NMR spectroscopy using ferrocene as internal standard

Catalyst loading: After successfully choosing $FeCl_3$ as active catalyst, we made an attempt to evaluate the optimum amount of catalyst required for this transformation. Dry benzoin (**1**) (1 mmol) and dry butanol (30 mmol) were added to a Schlenk-flask with $FeCl_3$ (x mol%, see Figure **1**) in DCE (3.2 mL) under an atmosphere of nitrogen (Figure **2**).

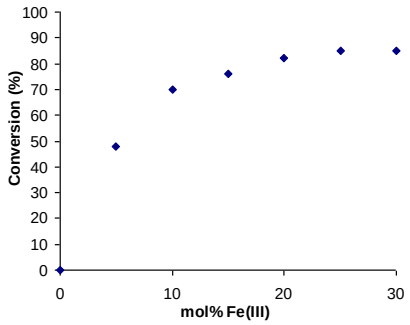


Figure 2: Dependence of Fe(III) in the etherification of **1** by *n*-butanol.

The reactions were run for 24 hours at 80 °C and monitored by ^{1}H NMR spectroscopy using ferrocene as internal standard.

Effect of solvent: After optimization of the catalyst loading of $FeCl_3$ required for the etherification, a number of dried solvents were examined. The results clearly showed that DCE is the best solvent for this kind of reactions (Table **2**).

Table 2: Solvent effect in the etherification of benzoin by butanol.

Entry	Solvent	Temp. °C	Conversion %	Yield %
1	DCE	80	100	85
2	Toluene	95	100	36
3	Acetonitril	80	80	60
4	THF	66	40	14
5	*n*-pentane	36	45	13
6	DCM	30	20	6
7	Solvent Free	80	100	51

The reactions were run using 1 mmol of **1**, 30 mmol of butanol, and 25 mol% of $FeCl_3$ in 3.2 mL of solvent for 24 hours. Reactions were monitored by ^{1}H NMR spectroscopy using ferrocene as internal standard.

Effect of alcohol: in another attempt we tried to optimize the amount of alcohol. When the amount of nucleophile was increased higher yield of the products

was observed. But above 30 equivalents of *n*-butanol, further improvement in generating **2a** was not observed (Figure **3**).

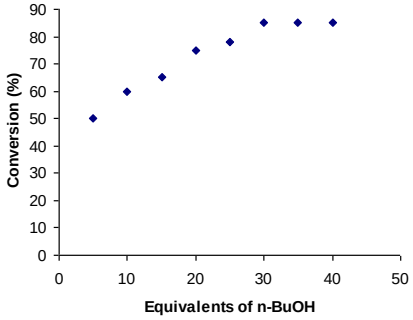


Figure 3: Dependence on *n*-butanol in the etherification of **1**.

Reaction time: The conversion of **1** to **2a** followed a linear correlation to reaction time. After running the reaction for 11 hours, no unreacted starting materials were recoverd while the yield of **2a** was 85% and the remaining 15% corresponded to the oxidized benzil **3** (Figure **4**).

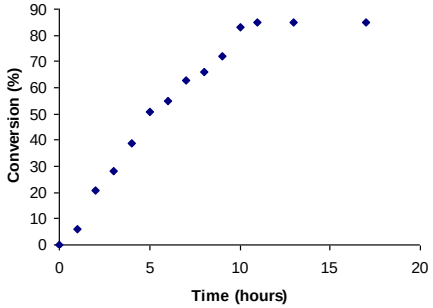
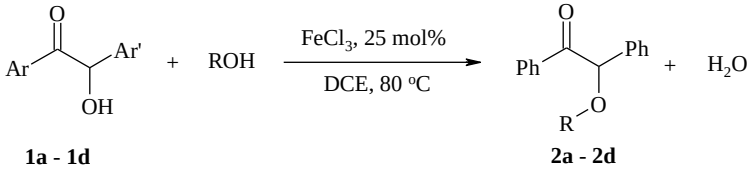


Figure 4: Reaction profile in the Fe(III) catalyzed etherification of **1**.

Expansion of derivatives: The optimized reaction conditions with 30 equivalents of *n*-butanol in DCE were employed in the catalytic nucleophilic substitutions of various aromatic benzoins and alcohols (Table **3**).

Table 3. Substituent effect in the etherification of different benzoins.



1a - 1d **2a - 2d**

Entry	Ar	Ar'	R-OH	Product	Time (h)	Yield (%)
1			*n*-Bu	2a	11	85
2			*n*-Pr	2b	12	75
3	4-OMe-Ph	4-OMe-Ph	*n*-Bu	2c	2	58
4	4-F-Ph	4-F-Ph	*n*-Bu	2d	18	70

The reactions were run using 1 mmol of benozoin, 30 mmol of aliphatic alcohol, and 25 mol% of $FeCl_3$ in 3.2 mL of dichloroethane for 11-18 hours. Reaction was monitored by ^1H NMR spectroscopy using ferrocene as internal standard.

Substitution effect: Substitution of the phenyl ring in the *para*-position with an electron-donating methoxy substituent gave a remarkable effect in efficiency. The electron-donating methoxy substituent is known to promote oxidation in which Fe(III) is reduced [18]. This experiment also shows that the electron-donating substituent promotes the reversible reaction between etherification product and pseudo carbocation intermediate or the alcohol (Figure **5**). Substituention in *para*-position with electron-withdrawing fluorine atom did not influence the reaction outcome significantly.

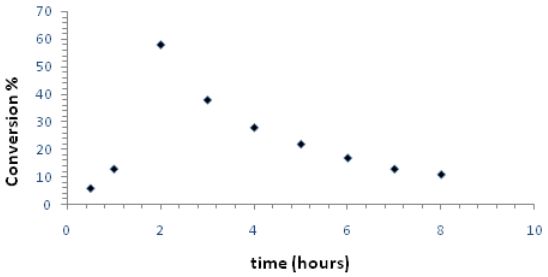


Figure 5: Effect of paramethoxy group on the reaction time and product

Proposed mechanism: The reaction outcome was dependent on both the concentration of alkyl alcohol and Fe(III) and independent on the concentration of **1**. The electronic substituent of the benzoin proved to be important. Electron-donating substituents led to a competing oxidation to the corresponding benzil after prolonged reaction time.

Conclusion

A mild etherification procedure of aromatic α-keto benzylic alcohols has been developed. Of the different catalysts screened, only Fe (III)-based catalysts showed high reactivity and selectivity toward etherification product. Other metal complexes were either unreactive or showed low chemoselectivity where the corresponding benzil was a major side-product. The reaction outcome was dependent on both the concentration of alkyl alcohol and Fe(III) and independent on the concentration of **1**. The electronic substituent of the benzoin proved to be important. Electron-donating substituents led to a competing oxidation to the corresponding benzil after prolonged reaction time. Electron-withdrawing substituents led to predominat formation of desired ether.

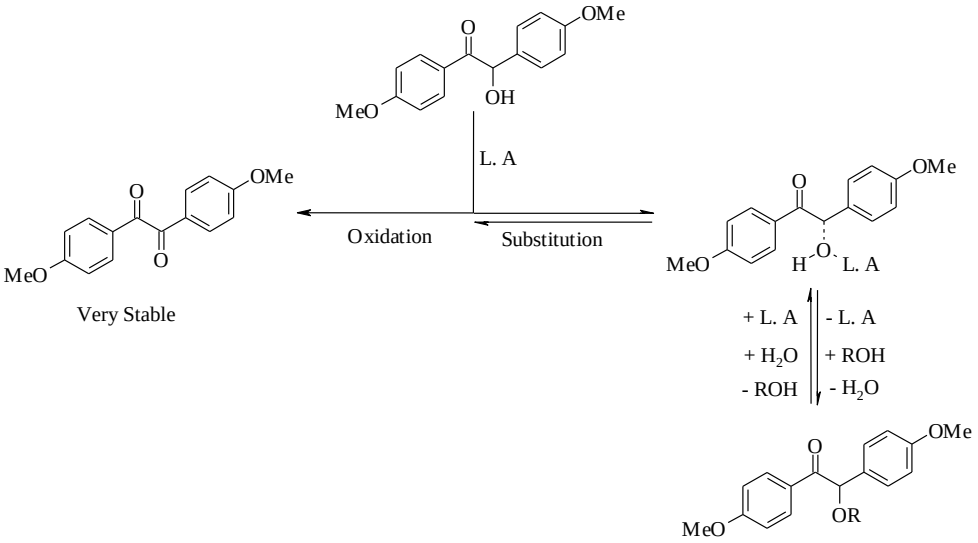


Figure 6: proposed mechanism **(**a Competition between oxidation and substitution reactions).

Experimental

Typical procedure for the synthesis of ethers: 2-Butoxy-1,2-diphenyl-1-ethanone (2a):

Freshly distilled *n*-butanol (2.22 g, 2.70 ml, 30 mmol) was added to a mixture of benzoin **1** (0.212 g, 1 mmol) and $FeCl_3$ (0.040 g, 25 mol%) in dry DCE (3.2 mL), in a oven-dried Schlenk-flask under an atmosphere of N_2 and the reaction mixture was degassed for 5 minutes. A reflux condenser was added to the Schlenk-flask and the reaction was refluxed for 11 h. The yield was determined by comparing signal of ferrocene (δ = 4.18 ppm) and the benzilic C-H (δ = 5.55 ppm). The solution was cooled to room temperature and the solvents were evaporated under vacuum. The crude product was purified by column chromatography on silica gel (hexanes:EtOAc = 30:1) to afford 0.23 g (85%) **2a** as white crystals**.** IR (KBr) (ν_{max}/cm^{-1}): 2953, 1718, 1694, 1677, 1597, 1448, 1106, 1027, 757. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.36-1.44 (2 H, m, CH_2), 1.62-1.68 (2 H, m, CH_2), 3.57 (2 H, t, $^3J_{HH}$ = 6.6 Hz, O-CH_2), 5.55 (1 H, s, CH), 7.31-7.40 (6 H, m, 6 CH), 7.50 (2 H, d, $^3J_{HH}$ = 8.4 Hz, 2 CH), 8.06 (2 H, d, $^3J_{HH}$ = 8.4 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 19.5 (CH_2), 32.0 (CH_2), 70.2 (O-CH_2), 85.9 (CH), 127.4 (2 CH), 128.4 (CH), 128.6 (2 CH), 129.0

(2 CH), 129.4 (2 CH), 133.4 (CH), 135.3 (C), 137.0 (C), 198.2 (C=O). Anal. Calcd. for $C_{18}H_{20}O_2$ (268.36): C, 80.56; H, 7.51. Found: C, 80.85; H, 7.45.

2-Propoxy-1,2-diphenyl-1-ethanone (2b):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 2962, 1693, 1676, 1597, 1579, 1448, 1105, 1075, 719. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.65-1.70 (2 H, m, CH_2), 3.53 (2 H, t, $^3J_{HH}$ = 7.1 Hz, O-CH_2), 5.56 (1 H, s, CH), 7.32-7.51 (6 H, m, 6 CH), 7.51 (2 H, d, $^3J_{HH}$ = 7.8 Hz, 2 CH), 8.04 (2 H, d, $^3J_{HH}$ = 7.8 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.8 (CH_3), 23.2 (CH_2), 72.0 (O-CH_2), 85.0 (CH), 127.4 (2 CH), 128.5 (CH), 128.6 (2 CH), 128.9 (2 CH), 129.5 (2 CH), 133.4 (CH), 135.2 (C), 136.9 (C), 198.2 (C=O). Anal. Calcd. for $C_{17}H_{18}O_2$ (254.33): C, 80.28; H, 7.13. Found: C, 80.54; H, 7.34.

2-Butoxy-1,2-bis(4-methoxyphenyl)-1-ethanone (2c):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 2933, 1682, 1679, 1600, 1573, 1462, 1305, 1250, 1167, 1100, 1028, 834, 790. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.38-1.42 (2 H, m, CH_2), 1.60-1.66 (2 H, m, CH_2), 3.55 (2 H, t, $^3J_{HH}$ = 6.9 Hz, O-CH_2), 3.78 (3 H, s, OMe), 3.84 (3 H, s, OMe), 5.47 (1 H, s, CH), 6.84 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 6.88 (2 H, d, $^3J_{HH}$ = 7.2 Hz, 2 CH), 7.39 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH), 8.04 (2 H, d, $^3J_{HH}$ = 8.7 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.5 (CH_3), 19.5 (CH_2), 32.1 (CH_2), 55.5 (O-Me), 55.6 (O-Me), 69.9 (O-CH_2), 85.3 (CH), 113.8 (2 CH), 114.3 (2 CH), 128.7 (2 CH), 129.4 (C), 129.4 (2 CH), 132.6 (C), 159.7 (C), 163.6 (C), 198.0 (C=O). Anal. Calcd. for $C_{20}H_{24}O_4$ (328.41): C, 73.15; H, 7.37. Found: C, 73.45; H, 7.40.

2-Butoxy-1,2-bis(4-flurophenyl)-1-ethanone (2d):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 2959, 1694, 1678, 1597, 1500, 1410, 1224, 1154, 1092, 1014, 833, 800.. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, $^3J_{HH}$ = 7.2 Hz, CH_3), 1.35-1.42 (2 H, m, CH_2), 1.62-1.66 (2 H, m, CH_2), 3.56 (2 H, t, $^3J_{HH}$ = 6.8 Hz, O-CH_2), 5.43 (1 H, s, CH), 7.02-7.11 (4 H, m, 4 CH), 7.45 (2 H, dd, $^3J_{HH}$ = 8.9, $^4J_{HF}$ = 5.7 Hz, 2 CH), 8.08 (2 H, dd, $^3J_{HH}$ = 9.0, $^4J_{HF}$ = 5.7 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.5 (CH_2), 32.0 (CH_2), 70.3 (O-CH_2), 85.7 (CH), 115.7 (d, $^2J_{CF}$ = 21.6 Hz, 2 CH), 116.0 (d, $^2J_{CF}$ = 21.6 Hz, 2 CH), 128.8 (d, $^3J_{CF}$ = 7.9 Hz, 2 CH), 131.2 (d, $^4J_{CF}$ = 2.9 Hz, C), 132.3 (d, $^3J_{CF}$ = 9.0 Hz, 2 CH), 132.7 (d, $^4J_{CF}$ = 3.1 Hz, C), 162.5 (d, $^1J_{CF}$ = 228.0 Hz, C), 165.5 (d, $^1J_{CF}$ = 236.0 Hz, C), 196.7 (C=O). Anal. Calcd. for $C_{18}H_{18}F_2O_2$ (304.34): C, 71.04; H, 5.96. Found: C, 71.24; H, 6.15.

Acknowledgements

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