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Bismuth (III) bromide, catalyzed synthesis of new benzoin ethers

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Abstract: Etherification reaction between benzoin derivatives and aliphatic alcohols catalyzed by Bi (III) bromide 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

Owing to the prevalence of carbon–oxygen (C–O) bonds in organic compounds being relevant in biological, pharmaceutical, and material sciences, the development of environmentally friendly, safe and reliable transition metal-catalysed methods for their construction constitutes a major goal of high practical value for modern chemistry and chemical industry [1-2]. Ethers are fundamental compounds used as precursors for pharmaceuticals, fragrance precursors, [3] and reformulated gasoline [4]. 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 [5- 6].

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 have showed high activity towards inhibiting some receptor related to diseases such as diabetes, obesity, hyperlipidaemia, hyperglycaemia, hyperinsulidemia, hypertens, and also glaucoma, osteoporosis, tuberculosis, dementia, cognitive disorders and depression [7]. 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 respect, Bismuth is an ideal transition metal, given its low price, non-toxicity and environmentally benign character, which often offers notable advantages in terms of sustainable chemistry and represents hence an attractive alternative to other commonly used transition metals.

Herein we report a facile catalytic protocol for the synthesis of unsymmetrical ethers from aromatic α-hydroxy ketones and alkyl alcohols.

Results and discussion

Synthesis of starting materials:

All benzoins were prepared according to standard procedures by reacting the aldehydes in the presence of catalytic amounts of sodium cyanide [8-9].

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 Pd (II) and Mn (II) [10] that have been reported in the etherification of benzylic alcohols were found to be unreactive. Brönstedt acid such as PTSA was also examined and was found uneffective.

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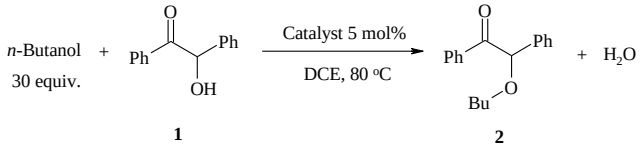
At the end of the reactions, samples were taken out regularly for ^{1}H-NMR spectroscopic analysis. The samples were filtered through silica to remove the catalyst and the solvent was evaporated *in vacuo*. To the samples a ferrocene as standard was added and quantification of the products was performed by comparing signals. The results of these experiments are shown in Table **1.**

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



1 **2**

Entry	Catalyst	Conversion (%)	Yield of 2
1	$PdCl_2$	0	0
2	Pd (acac)	10	0
3	Cu $(OAc)_2$	0	0
4	$CuSo_4$	0	0
5	$CuCl_2$	5	3
6	CuO	0	0
7	Co $(OAc)_2$	0	0
8	$Mn(OAc)_2$	5	0
9	$BiBr_3$	48	40
10	AgI	0	0
11	$MgSO_4$	0	0
12	I_2	0	0
13	PTSA	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 ºC.

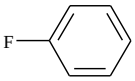
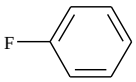
Lewis acids vs. Brønsted acids as catalyst:

To compare the Lewis acid catalysts used in this work with the efficiency of Brønsted acid, a reaction using 4-toluenesulfonic acid was preformed. Although Brønsted acids seem to function as efficient catalyst for this type of reactions, many desired substrates may be acid sensitive and metal based acids are preferred. This metal based catalyst may also have greater potential, because Brønsted acids are limited by the fact that they only protonate the substrate, while the specific interaction between metal based catalysts can be developed further [11-12].

Expansion of derivatives:

We use the optimization condition of previous published paper [13] in this work, too.

Table 2: Substituent effect in the etherification of different benzoins.

Entry	Ar	Ar'	R-OH	Product	Time (h)	Yield (%)
1			*n*-Bu	2a	11	85
2			*n*-Bu	2b	14	55
3			*n*-Bu	2c	15	63
4			*n*-Bu	2d	19	68
5			*n*-Bu	2e	18	66

The reactions were run using 1 mmol of benzoin, 30 mmol of aliphatic alcohol, and 25 mol% of $BiBr_3$ in 3.2 mL of dichloroethane for 11- 19 hours. Reaction time was monitored by ^{1}H NMR spectroscopy using ferrocene as internal standard.

Conclusion

A mild etherification procedure of aromatic α-keto benzylic alcohols has been developed. Of the different catalysts screened, only Bi (III) bromide 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 Bi (III) and independent on the concentration of 1.

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 $BiBr_3$ (0.11 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 **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-Butoxy-1,2-di(furyl)-1-ethanone (2b):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 3068, 1668, 1595, 1506, 1450, 1232, 1205, 1153, 876, 848, 755, 714. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (3 H, t, $^3J_{HH}$ = 7.4 Hz, CH_3), 1.61-1.63 (2 H, m, CH_2), 1.64-1.66 (2 H, m, CH_2), 3.60 (2 H, t, $^3J_{HH}$ = 6.9 Hz, O-CH_2), 5.62 (1 H, s, CH), 6.35 (1 H, dd, $^3J_{HH}$ = 4.1, 1.8, CH), 6.40 (1 H, d, $^3J_{HH}$ = 2.7 Hz, CH), 7.29-7.44 (3 H, m, 3 CH), 7.56 (1 H, d, $^3J_{HH}$ = 2.7 Hz, CH), 8.0 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 18.4 (CH_2), 30.9 (CH_2), 71.0 (O-CH_2), 80.3 (CH), 109.3 (CH), 112.0 (CH), 114.7 (CH), 118.3 (CH), 143.6 (CH), 145.1 (C), 146.3 (C), 190.1 (C=O). Anal. Calcd. for $C_{14}H_{14}O_4$ (248.28): C, 67.73; H, 6.50. Found: C, 67.53; H, 6.65.

2-Butoxy-2-(2-furyl)-1-phenyl-1-ethanone (2c):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 2940, 1668, 1595, 1506, 1232, 1205, 1153, 876, 848, 755, 715. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.60-1.62 (2 H, m, CH_2), 1.64-1.66 (2 H, m, CH_2), 3.56 (2 H, t, $^3J_{HH}$ = 6.8 Hz, O-CH_2), 5.66 (1 H, s, CH), 6.35 (1 H, dd, $^3J_{HH}$ = 4.1, 1.8, CH), 6.40 (1 H, d, $^3J_{HH}$ = 2.7 Hz, CH), 7.29-7.44 (3 H, m, 3 CH), 7.56 (1 H, d, $^3J_{HH}$ = 2.7 Hz, CH), 8.0 (2 H, d, $^3J_{HH}$ = 7.5 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 19.4 (CH_2), 29.9 (CH_2), 70.0 (O-CH_2), 79.0 (CH), 110.3 (CH), 111.0 (CH), 128.7 (2 CH), 129.3 (2 CH), 133.6 (CH), 135.1 (C), 135.3 (C), 143.5 (CH), 150.1 (C), 195.1 (C=O). Anal. Calcd. for $C_{16}H_{18}O_3$ (258.32): C, 74.40; H, 7.02. Found: C, 75.1; H, 7.12.

2-Butoxy-1-(4-flurophenyl)-2-phenyl-1-ethanone (2d):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 2940, 1668, 1593, 1507, 1452, 1227, 1205, 1153, 846, 757, 714. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.41-1.46 (2 H, m, CH_2), 1.63-1.68 (2 H, m, CH_2), 3.56 (2 H, t, $^3J_{HH}$ = 6.6 Hz, O-CH_2), 5.46 (1 H, s, CH), 7.06 (2 H, dd, $^3J_{HH}$ = 8.9, $^3J_{HF}$ = 8.4 Hz, 2 CH), 7.30-7.50 (5 H, m, 5 CH), 8. 1 (2 H, dd, $^3J_{HH}$ = 9.0, $^3J_{HF}$ = 5.4 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), 86.4 (CH), 115.7 (d, $^2J_{CF}$ = 21.6 Hz, 2 CH), 127.0 (2 CH), 128.5 (CH), 129.0 (2 CH), 131.3 (d, $^4J_{CF}$ = 3.1 Hz, C), 132.4 (d, $^3J_{CF}$ = 9.3 Hz, 2 CH), 136.8 (C), 165.9 (d, $^1J_{CF}$ = 253.8 Hz, C), 196.8 (C=O). Anal. Calcd. for $C_{18}H_{19}FO_2$ (286.35): C, 75.59; H, 6.69. Found: C, 76.7; H, 6.80.

2-Butoxy-2-(4-flurophenyl)-1-phenyl-1-ethanone (2e):

Prepared according to the general procedure. IR (KBr) (ν_{max}/cm^{-1}): 2895, 1668, 1595, 1411, 1238, 1203, 1153, 878, 844, 714. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.90 (3 H, t, $^3J_{HH}$ = 7.5 Hz, CH_3), 1.33-1.45 (2 H, m, CH_2), 1.60-1.67 (2 H, m, CH_2), 3.54 (2 H, t, $^3J_{HH}$ = 6.9 Hz, O-CH_2), 5.52 (1 H, s, CH), 7.05 (2 H, dd, $^3J_{HH}$ = 8.9, $^3J_{HF}$ = 8.4 Hz, 2 CH), 7.38-7.54 (5H, m, 5 CH), 8.01 (2 H, d, $^3J_{HH}$ = 8.5 Hz, 2 CH). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1 (CH_3), 19.5 (CH_2), 32.1 (CH_2), 70.2 (O-CH_2), 85.1 (CH), 115.4 (d, $^2J_{CF}$ = 21.3 Hz, 2 CH), 128.7 (2 CH), 129.1 (d, $^3J_{CF}$ = 8.2 Hz, 2 CH), 129.4 (2CH), 132.7 (d, $^4J_{CF}$ = 3.1 Hz, C), 133.5 (CH), 135.0 (C), 162.8 (d, $^1J_{CF}$ = 245.5 Hz, C), 198.0 (C=O). Anal. Calcd. for $C_{18}H_{19}FO_2$ (286.35): C, 75.59; H, 6.69. Found: C, 76.4; H, 6.51.

Acknowledgments

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