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Mild and efficient synthesis of 3-acyl-5-hydroxybenzofurans via bismuth chloride-catalyzed cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds

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ABSTRACT

A method to prepare a variety of substituted 3-acyl-5-hydroxybenzofurans efficiently that relies on bismuth chloride-catalyzed cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds is reported. The reaction was shown to be operationally straightforward and proceeds expediently under mild conditions to give the corresponding products in good to excellent yields (up to 95%) and with complete regioselectivity.

Key words: $BiCl_3$, cycloadiition, 1,4-benzoquinones, 1,3-dicarbonyl.

INTRODUCTION

Benzofurans are found in a wide variety of bioactive natural products and compounds of current therapeutic interest[1,2]. However, while this has led to a myriad of methods for benzofuran synthesis under strongly acidic and basic conditions, examples of the analogous reactions catalyzed by a Lewis acid have received less attention[1,3]. To our knowledge, approaches to benzofurans that explore the use of ecologically benign Lewis acid catalysts in combination with low cost and readily available substrates under mild conditions are limited to only three reported

Methods [4,5]. The first two reported the 1,4-conjugate addition/cyclization of 1,4-benzoquinones with 1,3-dicarbonyl compounds in the presence of a stoichiometric amount of $ZnCl_2$ as a catalyst that was achieved in low to moderate product yields [4]. More recently, De Kimpe and co-workers showed that $Yb(OTf)_3$ mediated the cycloaddition of activated 1,4-naphthoquinones with 1,3- dicarbonyl compounds and provided the corresponding 3-acyl-5-hydroxynaphtho[1,2-b]furans in good to excellent yields and regioselectivity [5]. As part of an ongoing programme on developing new Lewis acid-catalyzed reactions [6]. In continuation to our effort of exploring the applicability of bismuth chloride ($BiCl_3$)[7] as mild Lewis acid in various organic synthesis, here in we report the use of $BiCl_3$ as a catalyst for the cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds (Scheme 1).

EXPERIMENTAL

Initially, we found that treating 2,5-dimethylcyclohexa-2,5-diene-1,4-dione 1a (1 equiv) with dibenzoylmethane 2a (2 equiv) and 5 mol % of $BiCl_3$ in toluene at reflux for 10 h gave the best result. Under these conditions, (5-hydroxy-4,7-dimethyl-2-phenyl benzofuran-3-yl)(phenyl)methanone **3a** was furnished in 95% yield, and was comparable to the analogous $Yb(OTf)_3$-catalyzed cycloaddition of 1,4-naphthoquinones with 1,3-dicarbonyl compounds [5]. The structure of the benzofuran product was confirmed by ^1H NMR analysis. To define the scope of the present procedure, we examined the reactions of a variety of unactivated 1,4-benzoquinones and 1,3-dicarbonyl compounds

(Table 1). Experiments revealed that with $BiCl_3$ as the catalyst, 1,4-benzoquinones 1a–c and 1,3-dicarbonyl compounds 2a–e underwent the cycloaddition process and gave the corresponding benzofuran products in good to excellent yields (entries 1–11). Notably, this included the cycloaddition of 1a–c with the less acidic β-ketoester 2d which gave the corresponding adducts 3d, 3i and 3l in good to excellent yields (entries 3 and 8). Moreover, in instances where it was envisaged that reactions with 1,3-dicarbonyl compounds containing two different aryl substituents as in 2g–e would lead to a mixture of isomers, only one regioisomer was obtained. Similarly, the analogous cycloadditions of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds bearing both an aryl and alkyl group as in 2c and 2e were found to provide the corresponding 3-acyl-5-hydroxybenzofurans. With the cycloaddition process proceeding at either the more electropositive or less sterically hindered carbonyl carbon centre of the 1,3-dicarbonyl compound under our conditions, this suggested that the present procedure was regioselective.

Typical experimental procedure

To a suspension of 2 (0.72 mmol) and $BiCl_3$ (5 mol %) in toluene (2 mL) under a nitrogen atmosphere was added drop wise a solution of 1 (0.36 mmol) dissolved in toluene (1 mL). The reaction mixture was stirred at reflux for 8 h and monitored by TLC analysis using a 4:1 n-hexane/EtOAc solvent system. Upon completion, the reaction mixture was quenched with 10 mL of saturated NH_4Cl solution and extracted with EtOAc (3 10 mL).The combined organic layers were washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated under reduced pressure and purified by flash silica gel column chromatography (n-hexane/EtOAc as eluent) to give the title compound **3**.

RESULTS AND DISCUSSION

This could involve initial activation of both 1 and 2 through coordination with the metal catalyst in a manner similar to that proposed by De Kimpe

Table 1 : Bismuth Chloride - catalyzed cycloaddition of unactivated 1,4-benzoquinones 1a-d with 1,3-dicarbonyl compounds 2a-ea

Entry	Substrates	Product	Yieldb (%)
1		1a + 2b	
		3b, R4 = R5=Me	60
2	1a + 2c	3c, R4 = Ph, R5 =Me	87
3	1a + 2d	3d, R4 = Ph, R5 = OEt	90
4	1a + 2g	3e	86
5	1b + 2a	3f, R4 = R5 = Ph	91
6	1b + 2b	3g, R4 = 5=Me	65
7	1b + 2c	3h, R4 = Ph, R5=Me	93
8	1b + 2d	3i, R4= Ph, R5 = OEt	95
9	1c + 2a	3j, R4 = R5 = Ph	81
10	1c + 2c	3n, R4 = Ph, R5 = Me	77
11	1c + 2d	3l, R4 = Ph, R5 = OEt	79

[a]All reactions were performed at reflux temperature for 8 h in PhMe with a ratio of catalyst/1/2 = 1:20:40.

[b]Isolated yield.

and co-workers for the $Yb(OTf)_3$-catalyzed cycloaddition of activated 1,4-naphthoquinones with 1,3- dicarbonyl compounds [5].

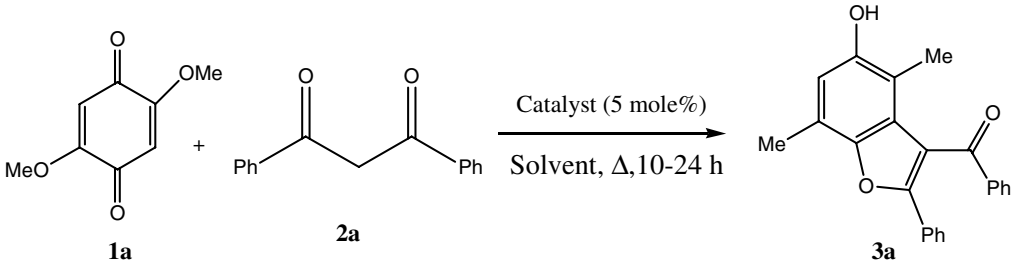
Compound 3a

Pale yellow solid; mp 114–116 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.95 (d, 2H, J = 7.5 Hz), 7.67 (d, 2H, J = 6.7), 7.54 (t, 1H, J = 7.2 Hz), 7.41–7.25 (m, 5H), 6.68 (s, 1H), 4.55 (s, 1H), 2.53 (s, 3H), 1.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 195.3, 153.4, 149.5, 147.8, 37.8, 133.9, 129.9, 129.8, 129.0, 128.8, 128.6, 128.0, 126.9, 119.3, 116.9, 115.2, 112.7, 14.8, 12.0; IR (neat, cm^{-1}): 3018, 1215, 767; HRMS (ESI): calcd for $C_{23}H_{19}O_3$ $[M+H]^+$ 343.1334, found 343.1328.

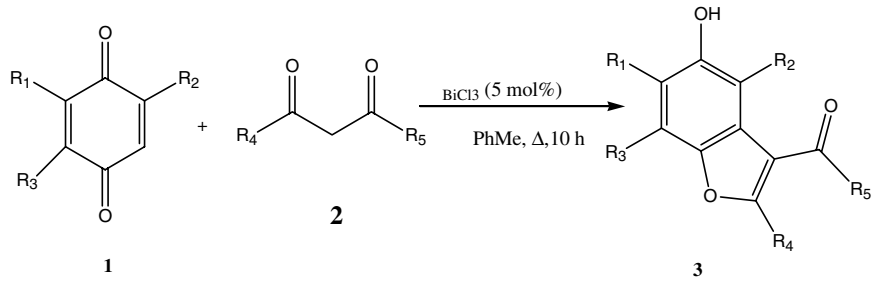
Compound 3d

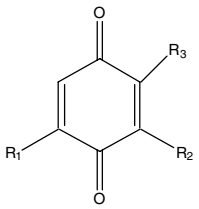
Pale yellow solid; mp 133–135 ^{0}C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.81 (d, 2H, J = 7.5 Hz), 7.47–7.40 (m, 3H), 6.65 (s, 1H), 4.76 (s, 1H), 4.40 (q, 2H, J = 7.1 Hz), 2.45 (s, 3H), 2.37 (s, 3H), 1.32 (t, 3H, J = 7.1 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4, 155.8, 149.6, 147.9, 130.0, 129.4, 128.4, 127.6, 126.2, 119.3,114.9, 112.6, 111.1, 61.5,14.7,13.9,11.6; IR (neat, cm^{-1}) :3018, 1215, 756; HRMS (ESI): calcd for $C_{19}H_{19}O_4$ $[M+H]^+$ 311.1283, found 311.1286.

In summary, an efficient and regioselective indium-catalyzed synthetic route to 3-acyl-5-hydroxybenzofurans based on cycloaddition of unactivated 1,4-benzoquinones with 1,3-dicarbonyl compounds has been reported. These results show that the reaction tolerates a structurally diverse set of substrates and complements earlier work with activated 1,4-naphthoquinones and 1,3-dicarbonyl

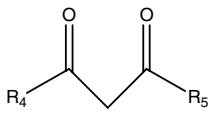


Scheme 1: In(OTf)$_3$- 3-acyl-5-hydroxybenzofurans from unactivated 1,4-benzoquinones and 1,3-dicarbonyl compounds

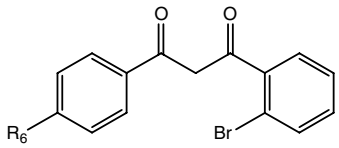




1b, $R_1 = R_2 = R_3 = H$
1c, $R_1 = Me$, $R_2 = R_3 = OMe$



2b, $R_4 = R_5 = Me$
2c, $R_4 = Ph$, $R_5 = Me$
2d, $R_4 = Ph$, $R_5 = OEt$



2e, $R_6 = OMe$

compounds mediated by $Yb(OTf)_3$ [5]**.** In addition, the present method was shown to be practical and operationally straight forward and gives good product yields.

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