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SYNTHESIS OF 3,4-DIHYDRO-2*H*-BENZOPYRANS FROM PHENOLS AND α,β-UNSATURATED CARBONYL COMPOUNDS

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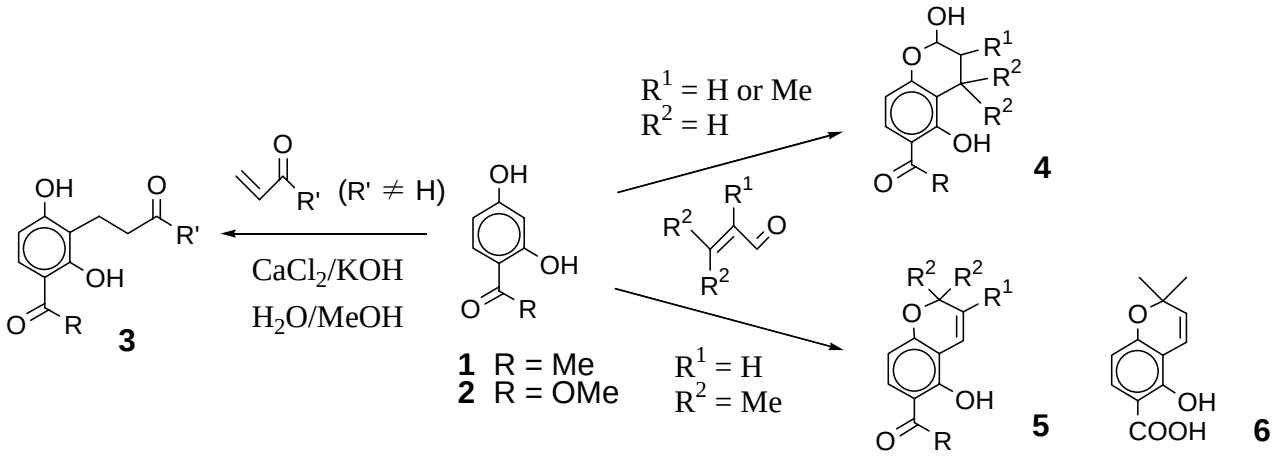
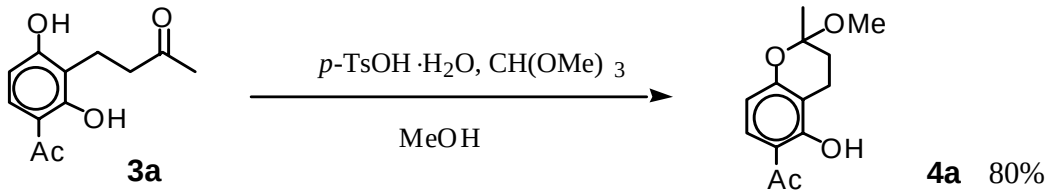
Abstract - The reaction between 2',4'-dihydroxyacetophenone and methyl vinyl ketone catalyzed by $CaCl_2$/KOH in aqueous methanol yielded a 1,4-adduct, which was cyclized to 3,4-dihydro-2*H*-benzopyran (**4**) by acidic treatment. Analogous reaction using α,β-unsaturated aldehydes afforded benzopyrans (**4**) or (**5**) in a one-pot reaction. This method was successfully applied to the synthesis of β-tubaic acid (**6**), an antimicrobial 2*H*-1-benzopyran-6-carboxylic acid.

Organic syntheses in aqueous media, by eliminating the constraints of inert atmosphere and anhydrous conditions, have become an important topic of current interest.[1-4] Based on the findings that $CaCl_2$ / KOH can catalyze aldol-type reactions of some enolates in H_2O / MeOH,[5-7] herein we report on the reaction between phenolic enolates and α,β-unsaturated aldehydes or ketones, mediated by the calcium reagent. We found that the reaction of 2,4-dihydroxybenzenecarbonyl compounds (**1**) and (**2**) with vinyl ketones in H_2O / MeOH yielded the corresponding 1,4-adducts (**3**), and that the same reaction with α,β-unsaturated aldehydes afforded benzopyrane (**4**) or (**5**) in a one-pot reaction (Scheme 1). This synthetic sequence was applied towards the formal synthesis of β-tubaic acid (**6**), an antimicrobial natural product isolated from derris roots.[8] Because we could not convert **2** to desired methyl ester (**5f**) by conventional[9] and recently described[10] methods, which were carried out in pyridine, the present method



Scheme 1.

in aqueous media provides a convenient one-pot procedure for the synthesis of these types of compounds. As shown in Entries 1, 2, and 3 of Table 1, treatment of 2',4'-dihydroxyacetophenone (**1**) and methyl vinyl ketone (**7**) with $CaCl_2$/KOH afforded the 1,4-adduct (**3a**)[11] in a good yield (72%), whereas the reactions in the presence of either KOH or $CaCl_2$ resulted in lower or no yields, respectively. The transformation of 1,4-adduct (**3a**) to benzopyran derivative (**4a**) (80% yield) was carried out in methanol in the presence of *p*-TsOH·H_2O and $CH(OMe)_3$ at room temperature (Scheme 2).



Scheme 2.

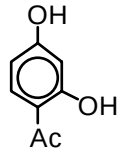
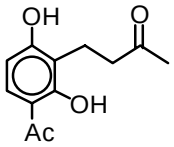
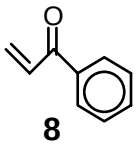
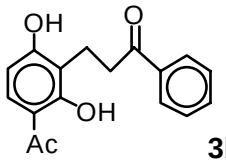
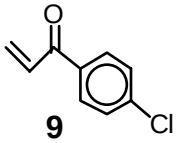
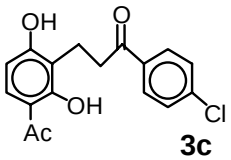
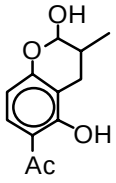
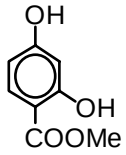
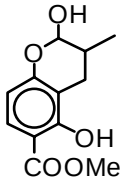
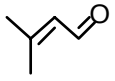
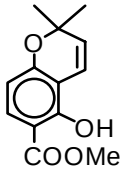
The reaction of phenyl vinyl ketone (**8**) with phenol (**1**) were carried out in the presence of $CaCl_2$/KOH to yield 1,4-adduct (**3b**) (Entry 4). A methanol solution of (**8**) was prepared from 3-chloropropiophenone and potassium acetate, and used without further purification and isolation of (**8**).[12] As a note, simultaneous mixing of 3-chloropropiophenone and potassium acetate with (**1**) and $CaCl_2$/KOH did not yield adduct (**3b**). Analogously, a methanol solution of 1-(4-chlorophenyl)-2-propen-1-one (**9**), prepared by the reaction of the corresponding 3-chloropropiophenone with potassium acetate as mentioned above, was subjected to the coupling reaction with **1** to afford **3c** in Entry 5. In contrast, the reaction of an α,β-unsaturated ester, methyl acrylate, with phenol (**1**) did not proceed (100% recovery of **1**, data not shown).

The reaction between phenol (**1**) and methacrolein (**10**) yielded benzopyran derivative (**4d**) (Entry 6) in a one-pot reaction, which is attributable to the 1,4-addition of the phenolic enolate followed by the hemiacetal formation. The reaction of methyl 2,4-dihydroxybenzoate (**2**) with **10** also yielded benzopyran derivative (**4e**) (Entry 7). In contrast to the reaction of resorcinol with enones under acidic conditions,[13] a C-C bond formation was regioselectively performed at the C(3) position of substrates (**1**) and (**2**).

A typical procedure is as follow: a mixture of **1** (91 mg, 0.60 mmol), methacrolein (51 mg, 0.72 mmol), and $CaCl_2 \cdot 2H_2O$ (147 mg, 1.0 mmol) was stirred in 0.4 M KOH in methanol (5 mL) at 25 ˚C for 30 h. After acidification using aqueous 1 M HCl, extractive workup followed by preparative TLC (chloroform / ethyl acetate = 5 : 1) afforded benzopyran (**4d**)[14] (69 mg, 52% yield) along with recovered **1** (17 mg, 19%). Using ^{1}H NMR spectral analysis, the diastereomeric ratio of **4d** was determined to be approximately 1 : 1.

In the cases of the α,β-unsaturated aldehyde possessing substituents at the β-position, such as **11** (Entry 8), 1,2-addition-cyclization product (**5f**)[15] and a diaryl derivative (**12**) were produced in low yields. Since benzopyran (**5f**)[8,16] is an important precursor in the synthesis of a naturally occurring benzopyran, β-tubaic acid (**6**), the reaction was repeated under various conditions, and as shown in Entry 9, the optimum yield was achieved by using $CaCl_2$ / Et_3N. The regioselective incorporation of the *p*-hydroxy group of

Table 1. Reaction of Phenolic Enolates with α,β-Unsaturated Compounds[a]

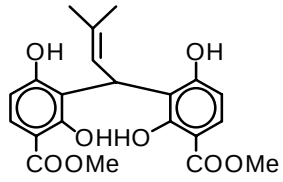
Entry	Phenolic substrate	Electrophile	Reagent (mol/l)	H_2O/MeOH (v/v)	Temp (˚C)	Time (h)	Product (%)	
1	 **1**	 **7**	$CaCl_2$/KOH 0.2/0.4	9/1	65	3		**3a** 72
2	**1**	**7**	$CaCl_2$ 0.2	9/1	65	3		**3a** 0
3	**1**	**7**	KOH 0.4	9/1	65	3		**3a** 50
4	**1**	 **8**	$CaCl_2$/KOH 0.2/0.4	1/1	65	1		**3b** 77
5	**1**	 **9**	0.2/0.4	1/1	65	1		**3c** 70
6	**1**	 **10**	0.2/0.4	1/100	25	30		**4d** 52
7	 **2**	**10**	0.2/0.4	1/100[b]	25	4		**4e** 51
8	**2**	 **11**	0.2/0.4	1/100[b]	0 - 10	68		**5f** 10[c]
9	**2**	**11**	$CaCl_2$/Et_3N 0.2/0.8	1/100[b]	50	21		**5f** 37[d]

[a] Substrate, 0.60 mmol; electrophile, 0.60 - 0.72 mmol; solvent, 5 mL.

[b] Solvent, 2 mL.

[c] A diaryl derivative (**12**) (14% yield) was produced as a by-product.

[d] By-product (**12**), 22% yield.



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substrates (**1**) and (**2**) into the newly formed pyran ring of products (**4**) and (**5**) was confirmed by ^{1}H NMR spectral analysis, in which a singlet peak corresponding to the unreacted *o*-hydroxy proton was observed at 11 - 13 ppm.

ACKOWLEDGMENTS

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11. **3a**: ^{1}H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.54 (s, 3H), 2.79 – 2.86 (m, 2H), 2.92 – 3.00 (m, 2H), 6.49 (d, *J* = 8.8 Hz, 1H, H-5), 7.53 (d, *J* = 8.8 Hz, 1H, H-6), 9.10 (br s, 1H, 4-OH), 13.04 (s, 1H, 2-OH); MS *m/z* (%) 222 (M^+, 15), 179 (45), 43 (100). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.57; H, 6.33.
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14. **4d**: ^{1}H NMR ($CDCl_3$) δ 1.06 (d, *J* = 7.0 Hz, 1.5H), 1.17 (d, *J* = 7.0 Hz, 1.5H), 2.0 –2.2 (m, 1H, H-3), 2.37 – 2.5 (m, 1H, H-4), 2.80 (dd, *J* = 5.2, 17.0 Hz, 0.5H, H-4), 2.91 (dd, *J* = 5.9, 17.0 Hz, 0.5H, H-4), 3.11 (d, *J* = 4.6 Hz, 0.5H, 2-OH), 3.27 (d, *J* = 5.9 Hz, 0.5H, 2-OH), 5.22 (t, *J* = 5.1 Hz, 0.5H, H-2), 5.4 – 5.5 (m, 0.5H, H-2), 6.39 (d, *J* = 9.2 Hz, 1H, H-8), 7.52 (d, *J* = 9.2 Hz, 1H, H-7), 12.99 (s, 0.5H, 5-OH), 13.01 (s, 0.5H, 5-OH); MS *m/z* (%) 222 (M^+, 47), 194 (59), 165 (100). Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.59; H, 6.48.
15. **5f**: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 6H), 3.90 (s, 3H), 5.60 (d, *J* = 10.1 Hz, 1H, H-3), 6.32 (d, *J* = 8.5 Hz, 1H, H-8), 6.70 (d, *J* = 10.1 Hz, 1H, H-4), 7.60 (d, *J* = 8.5 Hz, 1H, H-7), 11.15 (s, 1H, 5-OH).
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