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A One-Pot Synthesis of Functionalized 2,2-Disubstituted 2*H*-1-Benzopyrans

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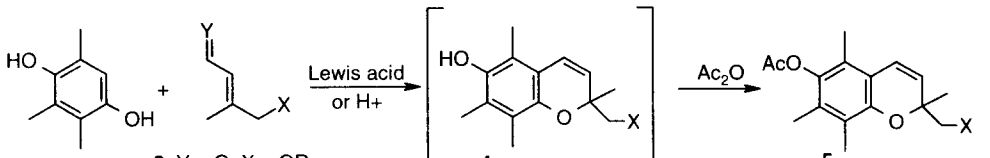
Abstract: The synthesis of functionalized 2,2-disubstituted 2*H*-1-benzopyrans was achieved by condensing 2,3,5-trimethylhydroquinone (TMHQ) with α,β-unsaturated aldehydes or α,β-unsaturated acetals under acidic conditions.

Keywords: benzopyrans, aldehydes, acetals, cyclization.

Many biologically active compounds contain the 3,4-dihydro-2*H*-1-benzopyran or 2*H*-1-benzopyran nucleus. Several syntheses of 2*H*-1-benzopyrans based on the Claisen rearrangement of propargyl ethers have been documented [1]-[9]. However, in the case of aryl propargyl ethers derived from phenols having electron-withdrawing groups, the method gives low yields by using this rearrangement [10]. Condensation of electron-rich phenols with α,β-unsaturated aldehydes [11]-[13] or their acetal equivalents [14]-[16] generate 2*H*-1-benzopyrans in modest yields, except when pyridine or 3-picoline-catalyst is present [17]-[18]. Implementation of these latter conditions for the preparation of **5** from **1**, **2** or **3** failed in our hands. Herein, we report an efficient one-pot synthesis of 2*H*-1-benzopyrans of type **5** via the acetylation of unstable compounds of type **4**. The latter were obtained by condensing 2,3,5-trimethylhydroquinone (TMHQ) **1** with α,β-unsaturated aldehyde **2** or α,β-unsaturated acetals of type **3** under acidic conditions.



1 **2**: Y = O, X = OR; **3**: Y = $(OR)_2$, X = OR or halide **4** **5**

Acetal **3a** {X = O-C_6H_4-NO_2, Y = $(OMe)_2$} is obtained by condensing *p*-nitrophenol **6** with the unsaturated chloroacetal **3c** {X = Cl, Y = $(OMe)_2$} under basic conditions (K_2CO_3)

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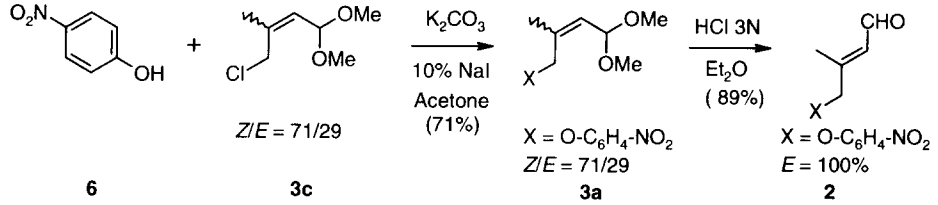
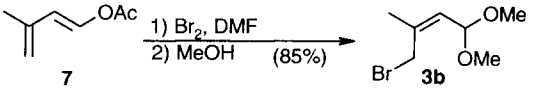
and in the presence of a catalytic amount of NaI (10%) [19]. It is obtained as a 71/29 mixture of the *Z* and *E* isomers. This ratio is representative of the isomeric ratio of the starting chloroacetal **3c**. When **3a** was hydrolyzed (HCl 3N, Et_2O), (*E*)-aldehyde **2** was the only product isolated.



6 **3c** **3a** **2**

Acetal **3b** {X = Br, Y = $(OMe)_2$} was prepared with 85% yield by bromination of the dienyl acetate **7** [20] followed by treatment with methanol.



7 **3b**

When acetal **3a** was condensed with TMHQ **1** in the presence of an acid such as $BF_3.Et_2O$, $BiCl_3$, $ZnBr_2$ or *p*-toluenesulfonic acid, the unstable product **4a** {X = O-C_6H_4-NO_2} was obtained. This compound was purified by flash chromatography on silica gel and immediately acetylated with acetic anhydride to give compound **5a**. The highest overall yield in **5a** [21] (52%) was obtained when $ZnBr_2$ was used as catalyst. The condensation of TMHQ **1** was achieved with α,β-unsaturated aldehyde **2** {X = O-C_6H_4-NO_2, Y = O} in the presence of $ZnBr_2$, and led to a low yield in compound **5a** (10%).

Table: Synthesis of compounds of type **4** and **5**.

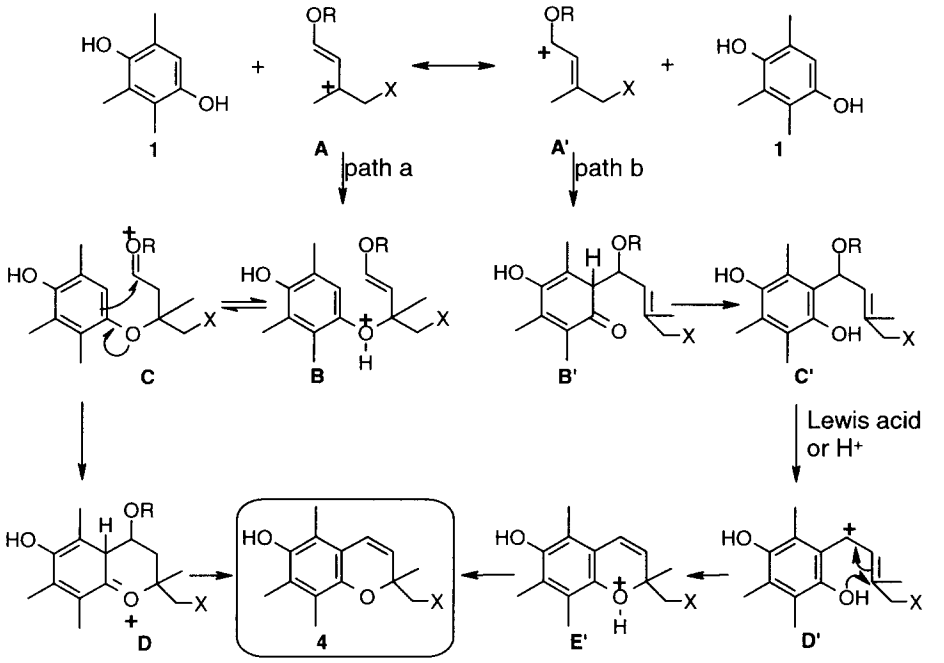
2-3	catalyst or promoter	**4**	**5** (yield)
2: X = O-C_6H_4-NO_2, Y = O	$ZnBr_2$ (3 eq.)	**4a**	**5a** (10%)
3a: X = O-C_6H_4-NO_2, Y = $(OMe)_2$	H_2SO_4 (cat.)	-	-
	PTSA (cat.)	**4a**	**5a** (20%)
	$BF_3.Et_2O$ (1 or 3 eq.)	**4a**	**5a** (15%)
	$BiCl_3$ (3 eq.)	**4a**	**5a** (21%)
	$ZnBr_2$ (3 eq.)	**4a**	**5a** (52%)
3b: X = Br, Y = $(OMe)_2$	H_2SO_4 (cat.)	-	-
	$ZnBr_2$ (3 eq.)	**4b**	**5b** (35%)
3c: X = Cl, Y = $(OMe)_2$	H_2SO_4 (cat.)	**4c**	**5c** (40%)
	$ZnBr_2$ (3 eq.)	**4d**	**5c** (45%)

In the case of the α,β-unsaturated acetal **3b**, compound **4b** {X = Br} was not formed when a protic acid, such as H_2SO_4, was used as catalyst. Fortunately, the use of $ZnBr_2$ (3 equiv.) allowed one to obtain **4b** which was acetylated into **5b** {X = Br} in 35% yield.

The condensation of TMHQ **1** with acetal **3c**, in the presence of $ZnBr_2$ (3 equiv.) or a catalytic amount of H_2SO_4 gave, after acetylation with acetic anhydride, compound **5c** {X = Cl} in similar yields (40-45%). The results are summarized in the Table.

To explain the formation of **4**, we suggest that either carbocation **A**↔**A'** reacts with **1**. In the case of path a, the carbocation **A** is attacked by the hydroxy group α to the less hindered carbon of TMHQ **1** to give intermediate **B**. After prototropy, cation **C** can be attacked intramolecularly by the aromatic ring to induce the formation of **D** which is the precursor of compound **4**. A second pathway (path b) can be envisaged from carbocation **A'**. This carbocation can be attacked by the less hindered carbon of TMHQ **1** to produce intermediate **B'** which can lead to **C'**. A second molecule of acid can complex the allylic ether of type **C'** to induce the formation of a secondary carbocation **D'** which can lead to intermediate **E'**, precursor of **4**, after losing a proton.

Scheme: Mechanisms for the formation of compounds of type **4**.



In summary, our results demonstrate that 2,2-disubstituted 2*H*-1-benzopyrans are obtained easily by condensing 2,3,5-trimethylhydroquinone (TMHQ) with α,β-unsaturated acetals under acidic conditions.

Acknowledgment:

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19. Acetal **3c** was furnished by Rhône-Poulenc Industrialisation.
20. Dienyl acetate **7** was furnished by Rhône-Poulenc Industrialisation.
21. Preparation of 6-acetoxy-2,5,7,8-tetramethyl-2-[(4-nitrophenoxy)methyl]-2*H*-1-benzopyran (**5a**):
    To a degassed solution of 2,3,5-trimethylhydroquinone (TMHQ) (0.46 g, 3.02 mmol) and $ZnBr_2$ (2 g, 8.88 mmol) in CH_2Cl_2 (8 mL) was added dropwise at 25 °C, under an inert atmosphere, over a period of 2h, a solution of 1,1-dimethoxy-3-methyl-4-(4-nitrophenoxy)but-2-ene **3a** (1 g, 3.74 mmol) in CH_2Cl_2 (10 mL). After 2h at room temperature, ethyl acetate (30 mL) and an aqueous solution of hydrochloric acid 1N (10 mL) were added to the reaction mixture. The organic phase was separated, dried over $MgSO_4$, filtered and the solvent was removed in *vacuo*. The residue was purified by flash chromatography on silica gel by using petroleum ether/ethyl acetate (80/20). The 2,5,7,8-tetramethyl-2-[(4-nitrophenoxy)methyl]-2*H*-1-benzopyran-6-ol **4a** was isolated and used directly in the following step.
    ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (d, J = 9.2 Hz, 2H, **H**C_{Ar}=C-NO_2), 6.93 (d, J = 9.2 Hz, 2H, **H**C_{Ar}=C-O), 6.69 (d, J = 9.9 Hz, 1H, C(4)-H), 5.70 (d, J = 9.9 Hz, 1H, C(3)-H), 4.39 (s, 1H, OH), 4.05 (m, 2H, CH_2-OAr), 2.18, 2.12, 2.04 (3s, 9H, 3 CH_3-Ar), 1.56 (s, 3H, CH_3-C(2)).
    The previously obtained benzopyran-6-ol **4a** was immediately diluted in CH_2Cl_2 (10 mL) and acetic anhydride (3 mL, 31.8 mmol) and *N,N*-dimethylaminopyridine (0.03 g, 0.24 mmol) were added to the solution. After stirring for 1h at room temperature, methanol (2 mL) was added to the reaction mixture. After 15 mn, a saturated aqueous solution of $NaHCO_3$ (3mL) was added. The reaction mixture was extracted with CH_2Cl_2 (20 mL), the organic layer was separated, dried over $MgSO_4$, filtered and the solvant was removed in *vacuo*. 6-Acetoxy-2,5,7,8-tetramethyl-2-[(4-nitrophenoxy)methyl]-2*H*-1-benzopyran **5a** (0.62 g) was isolated (yield 52% from TMHQ).
    IR: 2920, 1755, 1600, 1510, 1350, 1270, 1210 cm^{-1}.
    ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (d, J = 9.3 Hz, 2H, **H**C_{Ar}=C-NO_2), 6.89 (d, J = 9.3 Hz, 2H, **H**C_{Ar}=C-O), 6.62 (d, J = 10.0 Hz, 1H, C(4)-H), 5.65 (d, J = 10.0 Hz, 1H, C(3)-H), 4.03 (m, 2H, CH_2-OAr), 2.29 (s, 3H, CH_3-COO), 2.02, 2.00, 1.96 (3s, 9H, 3 CH_3-Ar), 1.53 (s, 3H, CH_3-C(2)).
    ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.3 (s, COO), 163.7 (s, C_{Ar}-O), 147.6 (s, C_{Ar}-NO_2), 141.7, 141.5 (2s, C(6), C(10)), 129.7 (s), 125.7 (d, 2 **H**C_{Ar}=C-NO_2), 125.2 (d, C(4)), 122.8 (s), 122.2 (d, C(3)), 117.3 (s), 114.6 (d, 2 **H**C_{Ar}=C-O), 75.9 (s, C(2)), 72.5 (t, CH_2-OAr), 23.2 (q, **C**H_3-C(2)), 20.6 (q, **C**H_3-COO), 13.1 (q, CH_3-Ar), 11.4 (2q, CH_3-Ar).
    MS (EI, 70eV): *m/z* 245 (100), 204 (12), 203 (87), 202 (16), 173 (9), 159 (10).