A Three-component Reaction of Phenol, Aldehyde, and Active Methylene Substrate under Lewis acid Catalysis: Successful Trapping of *o*-Quinone Methide to Afford Benzopyran Systems

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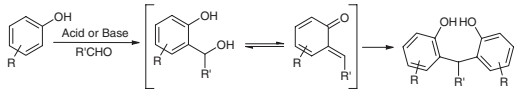
A three-component condensation involving reactive phenols, aldehydes, and active methylene substrates is described under $BF_3.Et_2O$ catalysis to afford benzopyranyl products in satisfactory yields.

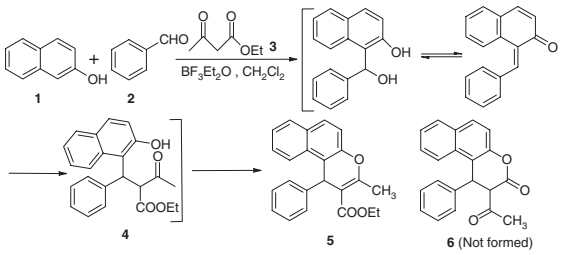
During last two decades, multi-component reactions (MCR) have proven remarkably successful in generating molecular complexities in a single synthetic operations.[1] In context to MCR, *ortho*-quinone methides (*o*-QMs) have also been utilized in many elegant tandem processes.[2] However, a majority of reactions of *o*-QMs are restricted to cycloadditions with reactive olefins[3,4] while only a limited work has appeared with carbon nucleophiles.[5] Difficulty in formulating proper reaction conditions compatible with the simultaneous generation of both *o*-QM and the carbanions seems to hamper the fuller exploitation of *o*-QMs in organic synthesis.[2]

Though, *o*-QMs are believed to be involved in 2:1 condensation of phenols with aldehydes under acid or base catalysis[6] (Scheme 1), surprisingly to our knowledge the trapping of *o*-QMs with nucleophilic reagents other than phenols has never been reported under these conditions.



Scheme 1.

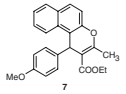
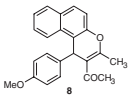
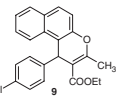
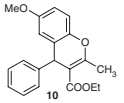
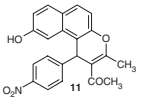
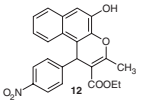
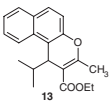
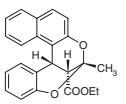
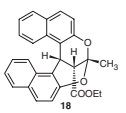
Our goal was to develop a tandem process that would allow in-situ trapping of *o*-QM with suitable carbon nucleophiles other than phenols to provide a rapid access to novel heterocyclic products. Towards this end, we choosed active methylene substrates as precursors of carbon centered nucleophiles and Lewis acid to promote the generation of *o*-QM as well as to effect enolisation of active methylene substrates. A test reaction using an equivalent amount of 2-naphthol **1** and benzaldehyde **2** and an excess of ethyl acetoacetate **3** was carried out under $BF_3.Et_2O$ catalysis as depicted in the Scheme 2.



Scheme 2.

We anticipated that the Michael product **4** formed via the trapping of the *o*-QM by the enol might undergo ring closure by the participation of phenolic OH either at the keto or the ester function to form benzopyran **5** or benzo-fused lactone **6**. In the event, the reaction (0 °C → RT, 8 h and then under reflux, 4 h) provided a colourless solid (59% yield, mp 118–120 °C) identified on the basis of analysis and spectral data[7] as benzo-fused pyran **5**. It is noteworthy that none of the lactone product **6** was detected presumably due to the preferred attack of the phenolic OH at the softer keto group, being further activated by Lewis acid complexation.[8,9] The present procedure has been successfully extended to different combinations of phenols, alde-

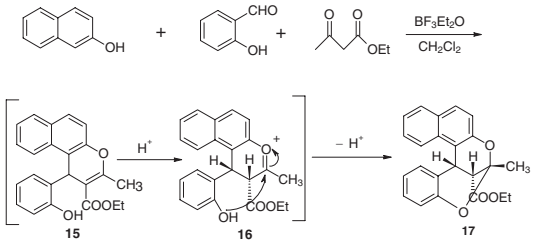
Table 1. 3 Component condensations between reactive phenols, aldehydes, and active methylene substrates[7,10]

Sr. No.	Reactants	Product	Yield %	mp / °C
1	β-naphthol, *p*-anisaldehyde, Ethyl acetoacetate	 7	57	117–19
2	β-naphthol, *p*-anisaldehyde, Acetylacetone	 8	60	156–57
3	β-naphthol, *p*-cholobenzaldehyde, Ethyl acetoacetate	 9	50	130–32
4	4-methoxyphenol, benzaldehyde, Ethyl acetoacetate	 10	48	140–43
5	2,7-dihydroxynaphthalene, *p*-nitrobenzaldehyde, Acetyl acetone	 11	30	232–34
6	2,3-dihydroxynaphthalene, *p*-nitrobenzaldehyde, Ethyl acetoacetate	 12	41	215–17
7	β-naphthol, isobutyraldehyde, Ethyl acetoacetate	 13	30	oil
8	β-naphthol, salicylaldehyde, Ethyl acetoacetate	 17	61	200–02
9	β-naphthol, 2-hydroxynaphthaldehyde, Ethyl acetoacetate	 18	35	180–82

hydes, and active methylene substrates under $BF_3.Et_2O$ catalysis and the results are cited in the Table 1.[10]

Attempts to effect the reaction with Brønstedt acids failed, whereas other Lewis acids examined i.e. $SnCl_4$, $AlCl_3$, and $TiCl_4$ produced complex mixtures; only $ZnCl_2$ worked, though in the test reaction, **5** was obtained in a low yield of 27%. Thus, by using an excess of active methylene substrate and $BF_3.Et_2O$ as the catalyst of choice, we have been successful in effectively trapping the *o*-QM intermediate to offer a convenient 3-component process towards the synthesis of benzo-fused pyrans.

We have also examined the 3-component reaction of salicylaldehyde with β-naphthol and an excess of ethyl acetoacetate under $BF_3.Et_2O$ catalysis. The reaction provided after SiO_2 column purification a novel bridged bichromans **17**[10] as a single diasteriomer in 61% yield (Entry 8). Mechanistically, the formation of **17** is proposed to proceed via the initially formed hydroxy-chromene product **15** in a manner similar to that shown in the Scheme 2. Subsequently, protonation on the enol ether from the side of the smaller benzylic hydrogen generates **16**. Finally, attack of phenolic OH on oxonium ion intermediate **16** completes the formation of **17** (Scheme 3). Low value of vicinal coupling constant ($J = 4$ Hz)[10] between the benzylic hydrogen and –C<u>H</u>CO_2Et supports cis-disposition of these protons as shown in the structure **17**.



Scheme 3.

Similar reaction was also found to occur with 2-hydroxynaphthaldehyde to provide the bridged bichroman **18** in moderate yield (Entry 9). The structure of **18** rests on spectral data[10] and a final confirmation is secured from its single crystal X-ray analysis[11] as depicted in the ORTEP plot (Figure 1).

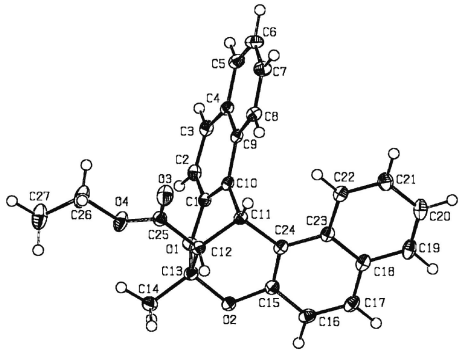


Figure 1. ORTEP plot of **18**.

In conclusion, we have reported an efficient 3-component methodology for a rapid construction of benzopyrans from easily available substrates.[12] Unlike the base-catalyzed additions of carbanions on *o*-QM which afford only open chain products,[5] the present procedure directly leads to cyclic benzo-fused pyran products. It is noteworthy that benzopyran structural motif is found in multitude of natural products,[13] many possessing significant biological activities.[14] In addition, the present methodology also offers an easy route towards the synthesis of novel bridged bichroman systems.

References and Notes

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7 Typical procedure: To a solution of ethyl acetoacetate (50 mmol, 6.5 g) in dry methylene chloride (50 mL) was added freshly distilled $BF_3.Et_2O$ (1.5 mL) and the reaction mixture cooled in ice-bath at 0–5 °C. To this stirred solution was added during 10 min a solution of 2-naphthol (10 mmol, 1.44 g) and benzaldehyde (10 mmol, 1.06 g) in CH_2Cl_2 (10 mL). The reaction mixture was allowed to stand at room temperture for 8 h and then gently refluxed for 4 h. The reaction was quenched by adding 1 N HCl and the organic layer was separated. The aqueous portion was extracted with CH_2Cl_2, and the combined organic extract was washed repeatedly with cold 10% NaOH, water and finally dried over anhyd Na_2SO_4. Crude solid obtained on solvent removal was chromatographed on SiO_2 column (elution 1:1 hexane-chloroform) to afford the product **5** as a colourless solid in (2.0 g) 59% yield.IR (KBr, ν cm^{-1}): 1710, 1603, 1506, 1210, 1170, 1070, 810. ^{1}H NMR: δ 1.3(3H, t, $J = 7.5$ Hz), 2.27(3H, s), 4.16(2H, q, $J = 7.5$ Hz), 5.5(1H, s), 6.7–7.5(11H, m); Anal calcd for $C_{23}H_{19}O_3$: C, 80.21; H, 5.85%. found: C, 80.36; H, 6.13%.

8 An alternate mechanism operating via the initially formed PhCH=C($COCH_3$)$CO_2C_2H_5$ was ruled out on the ground that an independently synthesized sample of this molecule [R. Wrigglesworth and R. Ferome, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 2645] failed to give **5** when treated with 2-naphthol under $BF_3.Et_2O$ catalysis.

9 According to a referee, regioselective formation of benzopyrans via 2 + 4 addition of *o*-QM with the enol of active methylene substrates, followed by dehydration is also possible.

10 Elemental analysis and spectral data for products cited in the Table 1 are given in the supplimentary information. In some cases (Entries 1–3), low polar product(s) formed in minor amounts have not been characterised.

11 The X-ray crystallographic data of **18** have been submitted to the Cambridge data-base as a file: CCDC 230653.

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