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Versatile Synthesis of Benzopyrans via Ortho-Claisen Rearrangement of Allyl Ethers

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Abstract: *Benzopyrans can be efficiently synthesized by reacting a phenol and an allylic alcohol in a trifluoroacetic acid / water mixture under argon at room temperature. The procedure is widely applicable and allows benzopyrans to be synthesized rapidly.*

Classical syntheses of benzopyran and benzofuran heterocycles consist of an acid catalysed condensation of an allylic alcohol with a suitable hydroquinone [1]. For example, all rac-α-tocopherol can be synthesized by the condensation of trimethylhydroquinone with isophytol [1], yielding a racemic mixture of two enantiomers (denoted RRR and RRS) - the so called "2-ambo-α-tocopherol" [2]. With the advent of sophisticated chromatographic techniques and high resolution NMR, it has become evident that the classical acid condensation procedures of Karrer *et al.* and Smith *et al.* introduce a number of metallic impurities [3]. It was therefore desirable to devise a versatile procedure for synthesizing benzopyrans which avoids the use of catalysts such as $ZnCl_2$ [3], BF_3 or $AlCl_3$ [4]. In the present instance, the ideal solvent for the reactants should be the catalyst for both the cyclization and subsequent condensation reaction (Figure 1) [5] (the threshold of acidity (H_o) required for pyran formation is approximately -3.0 [6]).

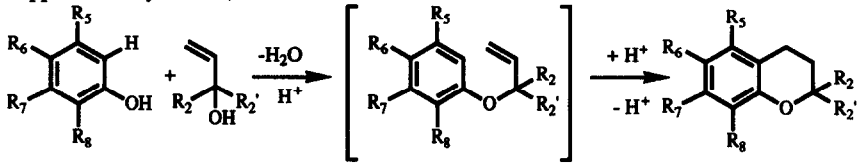

Figure 1

It should be also insensitive to traces of moisture and sufficiently volatile to facilitate subsequent work-ups. Trifluoroacetic acid (TFA; H_o = -3.0 [6,7], bp = 72.4 °C) fulfils the aforementioned criteria and can be readily used to synthesize efficiently a variety of racemic benzopyrans (see table 1, figure 1). Provided that oxygen is rigourously excluded, stirring a solution of phenol and allyl alcohol (1:1 mole ratio dissolved in the minimum quantity of TFA) at room temperature can be used to drive the reactions to completion (monitored by TLC) cleanly and efficiently within 15 to 30 minutes, depending on the nature of the reactants. The reactions were worked up using following procedure: TFA was evaporated from the reaction mixtures (at reduced pressure) to yield oils which were dissolved in hexane. After neutralisation with bicarbonate, and drying (brine wash, $MgSO_4$), the residues were purified using flash chromatography under argon (silica gel, pet. ether (30/60 °C)/diethyl ether 9:1 or petroleum ether (30/60 °C)/ethyl acetate 9:1) [3c,8].

If required, the reactions can be accelerated by refluxing provided that oxygen is again rigourously excluded. Surprisingly, the presence of water (up to 10% v/v), which was not tolerated by conventional procedures [3-6], actually enhanced the rate of benzopyran formation (approximately) twenty fold. Similar phenomena have been reported in the literature [2-4], where ortho-Claisen rearrangement of allyl ethers in trifluoroacetic acid/water have been used to synthesize o-allyl-p-cresol from allyl p-tolyl ether. The mechanism of rearrangement is thought to involve a highly polar transition state [9] with the degree of proton transfer depending

on the exact conditions. In analogous work, phenols and propargyl alcohols when heated together can directly yield 2,2-dimethylchromenes, as in the Späth synthesis of the natural product seselin [10].

The trifluoroacetic acid/water catalysed cyclization was found to be widely applicable and over 40 benzopyrans have been made using the method. These include tocopherols [10, 11], as well as tocopheramine [12], tocol [11,13] and napthopyrans [14] (see table 1 for a selection of compounds). Compounds were authenticated by comparing their spectral and chromatographic properties with those obtained of authentic compounds.

Table1: Benzopyrans Prepared from the Corresponding Phenol and Allyl Alcohol.

R_2	$R_{2'}$	R_5	R_6	R_7	R_8	%Yield*	Lit
CH_3	CH_3	H	HO	H	H	33%	13
CH_3	CH_3	CH_3	HO	CH_3	CH_3	63%	15
CH_3	CH_3	CH_3	HO	H	CH_3	48%	16
CH_3	phytyl	CH_3	HO	CH_3	CH_3	70%	11
CH_3	CH_3	CH_3	H	CH_3	CH_3	48%	11
CH_3	phytyl	CH_3	HO	-CH=CH-		42%	14
CH_3	phytyl	CH_3	H_2N	CH_3	CH_3[a]	60%	15, 17

* Reported yields are not optimised.

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