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A Diastereoselective Synthesis of Benzopyrans using a Novel Intramolecular Nicholas Reaction in the Key Cyclisation Step

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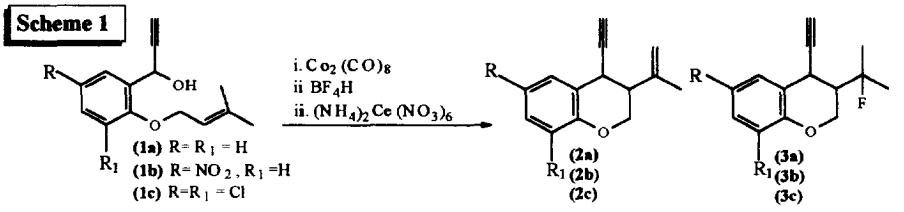
Abstract: A novel intramolecular cyclisation reaction between an organocobalt stabilised cation and a trisubstituted alkene was accomplished to afford a new family of benzopyran derivatives.

Although a variety of activated carbon nucleophiles have been used to quench a dicobalt hexacarbonyl stabilised cation in the Nicholas reaction [1] the use of unactivated alkenes have received little or no attention in the chemistry literature.[2] In an effort to redress this imbalance we have recently embarked upon a series of intramolecular cyclisation reactions in which the key cyclisation step involved the attack of a dicobalt hexacarbonyl complexed propargyl cation with a trisubstituted alkene. We now wish to report the preliminary results obtained from these investigations.

The treatment of **1a** [3] (Scheme 1) with dicobalt octacarbonyl led to quantitative conversion to the dicobalt hexacarbonyl complex which was then cyclised, by reaction with tetrafluoroboric acid, followed by decomplexation of dicobalt hexacarbonyl using ceric ammonium nitrate (CAN). This novel procedure led to the synthesis of the benzopyrans **2a** and **3a**, [4] in a 1:1 ratio, in 35% yield from **1a** as single diastereoisomers. In our endeavours to improve the efficiency of this cyclisation strategy we have now been able to effect the

Scheme 1



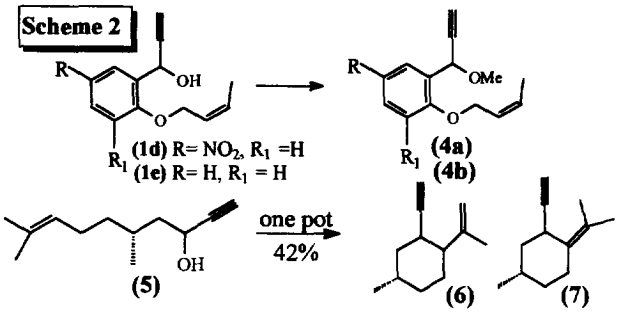
key cyclisation step (complexation, cyclisation and decomplexation) in a one pot procedure.[5]

The stereochemical relationship of the ring methine protons in compound **2a** and **3a**[6] was determined by extensive ^{1}H nmr experiments and shown by the magnitude of the coupling constants to be *trans*.[7] The generality of both the cyclisation reaction and the one pot procedure was then extended with the propargyl alcohols **1b** and **1c**. Using the one pot procedure compound **1b** cyclised to afford **3b** exclusively in 65% yield and **1c** cyclised to afford **3c** in 55% yield, none of the corresponding *iso*propenyl derivatives **2b** or **2c** were isolated, again, both compounds exhibited a *trans*-stereochemistry.

We then focused upon the origins of the 2 benzopyrans **2a** and **3a** i.e. did **3a** arise from an *in situ* addition of HF to **2a** or did **2a** originate from the elimination of HF from **3a**.[8] A clue to the origin of **2a** was obtained during the nmr investigations when it was observed that for stored samples of **3b** additional

resonances attributed to the *iso*propenyl derivative **2b** began to appear on the nmr spectrum, and furthermore the intensity of the resonances increased with time suggesting that **2a** may in fact be derived from **3a** *via* the elimination of HF. In order to test this we repeated the cyclisation of **1b** and left it for a longer time period[9] whereupon we found that not only had the reaction mixture ungone an *in situ* decomplexation of dicobalt hexacarbonyl but the non-fluorinated compound **2b** was isolated in 55% yield, as the only product, suggesting that the origins of compound **2a, b** and **c** may well be compounds **3a, b** and **c** respectively.

Scheme 2



Attempts to effect the cyclisation of **1d** and **1e** (Scheme 2), analogues of **1a-c**, failed affording only the propargyl ethers **4a** and **4b**. Thus although the cobalt stabilised propargyl cations were formed (suggested by the methanol quench upon decomplexation) a disubstituted alkene appears insufficiently nucleophilic to effect the subsequent cyclisation reaction suggesting that the trisubstituted alkene may be a minimum requirement for a successful cyclisation reaction.

This methodology is not limited to aromatic systems thus cyclisation of the citronellal derivative **5** was effected in a one pot procedure to afford the cyclohexane derivatives **6** and **7** as a 1:1 mixture in 42% yield with compound **6** exhibiting *trans*-stereochemistry.

In summary, we have effected a hitherto unrecorded variation of the Nicholas reaction between a dicobalt hexacarbonyl stabilised cation and a trisubstituted alkene, in a one pot procedure, to afford a range of novel benzopyrans. In addition we have attempted to establish the minimum requirements in the alkene to effect this reaction. The diastereoselective reaction initially appears to afford the fluorinated compound but in time this undergoes an unusual HF elimination to give the the alkenyl derivative with *trans*-stereochemistry.

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References and notes:

1. Nicholas, K.M. *Acc. Chem. Res.*, **1987**, 20, 207.
2. A recent intermolecular reaction: Kraft, M.E.; Cheung, Y.Y.; Wright, C.; Cali, R. *J.Org. Chem.* **1996**, 61, 3912.
3. Synthesised in 2 steps from the corresponding salicylaldehyde derivatives in overall 80%-90% yields.
4. Recently reviewed: Roxburgh, C.J. *Synthesis*, **1996**, 3, 307.
5. This gives between 5%-25% higher yields over the alternative 3-step procedure.
6. The ^{19}F nmr spectrum of **3b** consisted of a multiplet (14 peaks) centred at δ -59.0414 ppm.
7. The magnitude of the coupling constants for the methine protons in compounds **2a** and **3a** was found to be 12 and 4.8 Hz respectively, nOe studies of the methine protons in **3a** showed no enhancement in the signal when the benzylic proton was irradiated.
8. Alternatively **3a** and analogues could arise from an *intra*molecular ene-type reaction.
9. The one pot procedure can be monitored by tlc and in most instances is complete within 30 minutes, this reaction was left for 48 hours.

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