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Oxidative cyclisation of cinnamyl ethers mediated by CAN: a stereoselective synthesis of 3,4-*trans* disubstituted tetrahydrofuran derivatives

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Received (in Cambridge, UK) 5th April 2001, Accepted 6th July 2001
First published as an Advance Article on the web 16th August 2001

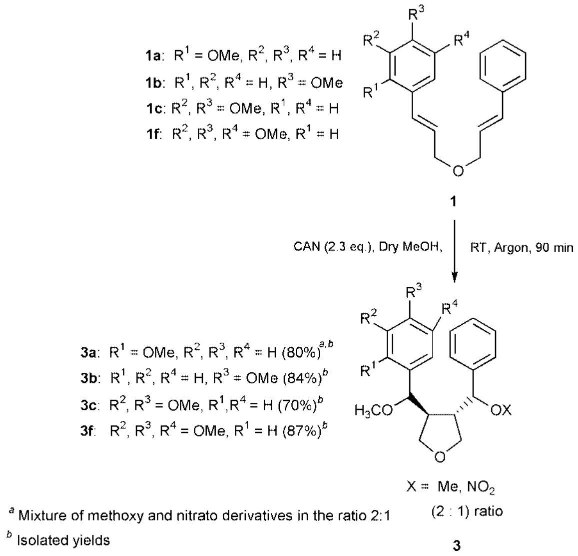
The oxidative cyclisation of cinnamyl ethers mediated by cerium(IV) ammonium nitrate results in the stereospecific formation of 3,4-*trans* disubstituted tetrahydrofuran derivatives in moderate to good yields.

Cerium(IV) ammonium nitrate (CAN) has been found to be a very efficient reagent for carbon–carbon bond formation especially in reactions involving the oxidative addition of 1,3-dicarbonyl compounds to alkenes.[1a,b] In spite of its success in this and a variety of other highly efficient intermolecular reactions of value in organic synthesis,[1] CAN has found very little use in intramolecular C–C bond formation;[2] this is in contrast to the general acceptance of Mn(III) in intramolecular cyclisations.[3] In view of this and prompted by our recent observation of CAN induced dimerisation of alkoxy styrenes,[4] we surmised that appropriately tethered alkoxy cinnamyl ethers would undergo CAN mediated cyclisation leading to tetrahydrofuran derivatives. It is noteworthy that a chemical electron transfer mediated intramolecular cyclobutanation of dicinnamyl ethers using triarylaminium salts has been reported by Bauld *et al.*[5]

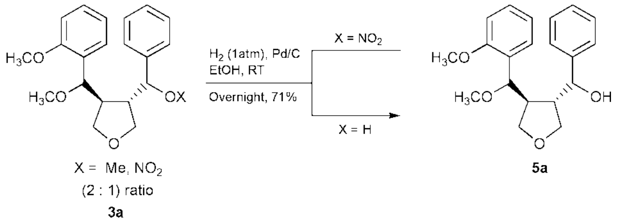
Our studies were initiated by the reaction of 2-methoxycinnamyl cinnamyl ether **1a** with CAN in methanol under an oxygen atmosphere. In the event, the reaction afforded a tetrahydrofuran derivative **2a**, in moderate yield. The reaction was found to be general and applicable to similar substrates (Scheme 1).

Interestingly, when the reaction of **1a** with CAN was carried out under argon atmosphere, instead of the ketone, a mixture of the methoxy and nitrato derivatives **3a**, in the ratio 2:1, was obtained in high yield. Similar results were obtained with other substrates (Scheme 2).

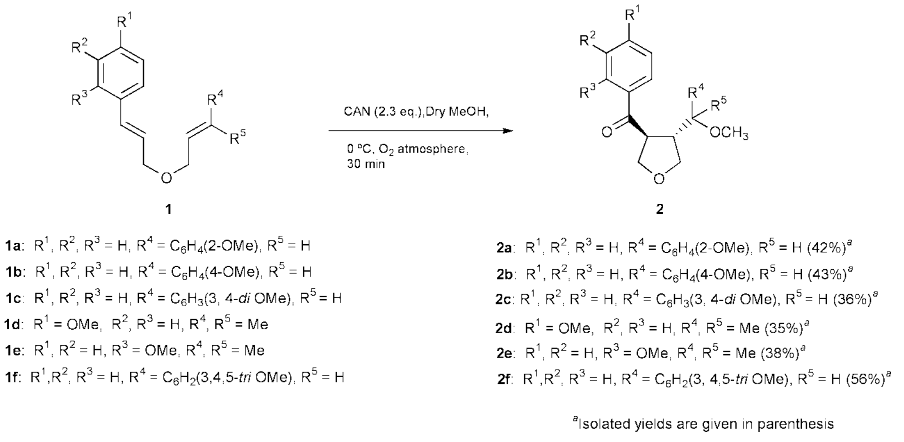
Catalytic hydrogenation of the mixture of methoxy and nitrato derivatives **3a** effected the selective conversion of the latter to the corresponding alcohol **5a** (Scheme 3).



Scheme 2



Scheme 3



Scheme 1

DOI: 10.1039/b103111m

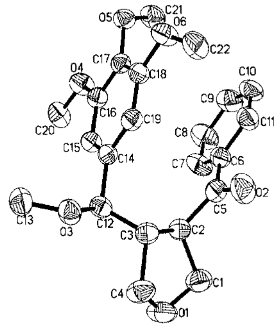
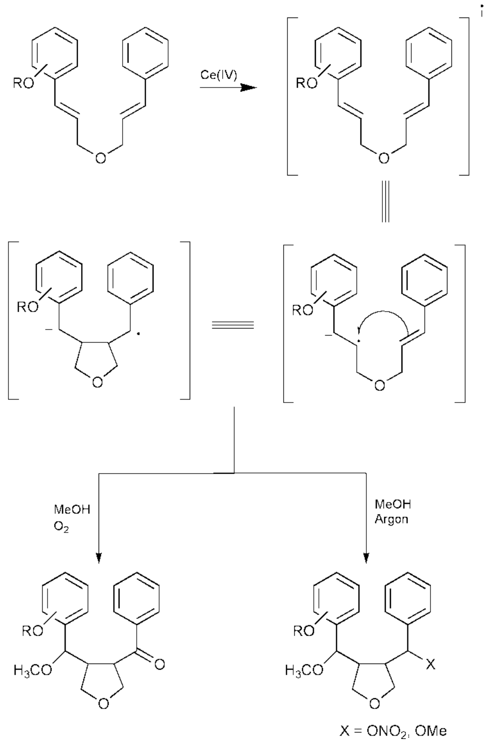


Fig. 1 X-Ray crystal structure of compound **2f**.

Relevant spectral data (IR, ^{1}H NMR, ^{13}C NMR, DEPT-135 NMR) of the products are in good agreement with structures assigned.† The stereochemistry of the 3,4-disubstituted-tetrahydrofuran derivative has been confirmed to be *trans* with the aid of single crystal X-ray analysis of compound **2f** (Fig. 1).‡

A mechanistic rationale for the formation of the product can be depicted along the following lines (Scheme 4).

A radical cation initially formed from the methoxy styrene unit of the substrate can add in an intramolecular fashion to the adjacent styrene moiety to form a distonic radical cation. The cationic center is quenched by methanol, whereas the radical center is prone to two different transformations.[1c,d] Under oxygen atmosphere, the radical site is quenched by molecular oxygen yielding the keto product *via* the initially formed peroxy radical. Under argon atmosphere, the radical site is quenched by nitrate by ligand transfer from CAN; alternatively, it can undergo oxidation by CAN to the benzylic cation with subsequent addition of methanol yielding the dimethoxy product.



Scheme 4

In conclusion, we have devised a novel and efficient route towards the stereospecific construction of 3,4-*trans* substituted tetrahydrofurans from relatively simple precursors, which assumes importance in view of the fact that substituted tetrahydrofurans feature in many natural products of biological importance,[6] especially lignans. Further studies are currently in progress.

L. B., V. S. and S. B. P. thank CSIR, New Delhi, for research fellowships. The authors also thank Ms Soumini Mathew for high-resolution NMR spectra and Mrs S. Viji for elemental analysis.

Notes and references

† Experimental procedure and selected data for **2f** : A solution of CAN (740 mg, 1.33 mmol) in dry methanol (15 ml) was added dropwise with stirring to a solution of **1f** (200 mg, 0.58 mmol) in dry methanol (10 ml) under oxygen atmosphere. After 30 minutes the reaction mixture was diluted with 50 ml water and extracted with DCM (3 × 25 ml). The combined organic extracts were washed with water, saturated brine and dried over sodium sulfate. After the removal of the solvent, chromatographic separation on silica gel using 80 : 20 hexane–ethyl acetate gave the THF derivative **2f** (128 mg) in 56% yield as a colorless crystalline solid. Mp: 115–117 °C (recrystallised from CH_2Cl_2–hexane). (Elemental analysis; Calcd for $C_{22}H_{26}O_6$ C, 68.38; H, 6.78. Found: C, 68.00; H, 6.75%) ν_{max}/cm^{-1} 2940, 2853, 1720, 1664, 1589, 1496, 1458, 1328, 1234, 1128, 1085, 1004. δ_H (300 MHz; $CDCl_3$) 7.54–7.46 (m, 3H, ArH), 7.35–7.30 (m, 2H, ArH), 6.42 (s, 2H, ArH), 4.23–4.17 (m, 1H), 4.09–3.92 (m, 3H), 3.84–3.72 (m, 11H, 3 × OCH_3 embedded in this multiplet), 3.19 (s, 3H, OCH_3), 3.1–3.06 (m, 1H); δ_C 198.96, 153.29, 136.47, 135.27, 133.02, 128.34, 127.90, 104.33, 85.36, 71.32, 71.27, 60.56, 56.70, 55.91, 50.67, 49.19; DEPT-135: (CH_2 negative) 71.32, 71.27. All new compounds were fully characterized.

‡ *Crystal data* for **2f**: $C_{22}H_{26}O_6$, FW 386.43, 0.30 × 0.20 × 0.14 mm, monoclinic, space group $P2_1/n$, unit cell dimensions: a = 10.8619(4) Å, α = 90°; b = 12.9527(4) Å, β= 99.570°; c = 14.2988(5) Å, γ = 90°. R indices (all data) $R1$ = 0.0656, $wR2$ = 0.1131. v = 1983.71(12) Å^3, Z = 4. D_{calc} = 1.294 Mg m^{-3}. $F(000)$ = 824. Absorption coefficient 0.094 mm^{-1}; reflections collected 42489 (G. M. Sheldrick, Siemens, Analytical X-ray Division, Madison, WI, USA, 1995). CCDC 163141. See http://www.rsc.org/suppdata/cc/b1/b103111m/ for crystallographic data in .cif or other electronic format.

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