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# CAN mediated cyclization of epoxypropyl cinnamyl ethers: a facile stereoselective synthesis of tetrahydropyran derivatives

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Dedicated with best wishes to Professor Goverdhan Mehta on the occasion of his 60th birthday

**Abstract**—Cerium(IV) ammonium nitrate in substoichiometric amounts, promotes the intramolecular cyclization of epoxypropyl cinnamyl ethers to the corresponding 3,4,5-trisubstituted tetrahydropyran derivatives in moderate to good yields.


The general acceptance of radical methodology in organic synthesis has contributed to the development of a number of single electron oxidants.[1] Of these, cerium(IV) ammonium nitrate (CAN) has emerged as an important reagent and numerous examples, which illustrate the potential of CAN in intermolecular carbon–carbon and carbon–heteroatom bond forming reactions are known.[2–4] In spite of the demonstrated versatility of CAN, barring a few examples, most notably that of Snider, intramolecular reactions mediated by CAN have received only meagre attention.[5] In addition, CAN mediated reactions, in general, require the use of excess of the reagent, and this has been a deterrent in its use in large scale reactions.

We have been concerned about these two issues and recently we devised an intramolecular reaction mediated by CAN, which involved the oxidation of an alkoxystyrene moiety and the capture of the radical cation thus generated, by a styrenyl tether resulting in a stereoselective synthesis of 3,4-*trans* disubstituted tetrahydrofuran derivatives.[6–8] We surmised that an analogous intramolecular capture of a radical cation generated from epoxides by CAN, by a suitable tether indicated the possibility of a catalytic process.[7] The catalytic use of CAN in the opening of epoxides by nucleophiles reported by Iranpoor lends credence to our rationale.[7] Takemoto et al. have reported the generation of radical cations from arylcyclopropyl sulfides and their intramolecular capture to afford furan and pyran derivatives using large excess of CAN.[9] Herein we report the results of our experiments designed using the rationale outlined above, constituting a stereoselective synthesis of 3,4,5-trisubstituted tetrahydropyran derivatives.[10]

Our studies commenced with the reaction of 3-phenyl-2,3-epoxypropyl cinnamyl ether **1** with a catalytic amount of CAN in methanol. Contrary to our expectations, no intramolecular reaction occurred. Only solvolytic opening of the epoxide leading to the product **2** in 64% yield was observed. A similar reaction was found to occur in ethanol also (Scheme 1).

It is apparent that in the above reactions the facile quenching of the intermediate cationic species by the nucleophilic solvent precludes the possibility of intramolecular participation by the styrene moiety. Naturally, this implies that a relatively less nucleophilic solvent might facilitate the desired intramolecular reaction. Interestingly, in acetonitrile the reaction of **1** afforded the tetrahydropyran derivative **4** along with small amounts of the nitrato derivative **5** as a mixture of *syn* and *anti* isomers (Scheme 2).

The IR spectrum of **4** displayed characteristic –NH and –OH vibrations at 3306 and 3539 $cm^{-1}$, respectively. In

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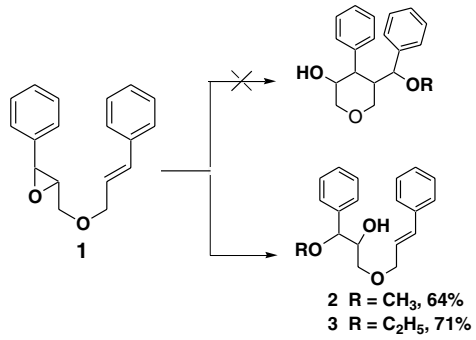
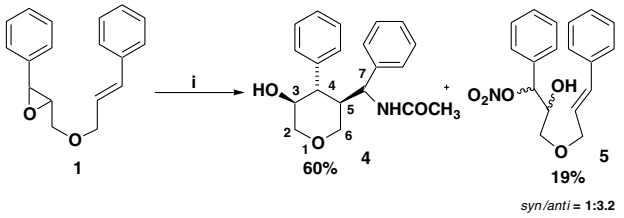



**Scheme 1.** Reagents and conditions: (i) CAN (0.5 equiv), ROH, argon, rt, 1 h.




**Scheme 2.** Reagents and conditions: (i) CAN (0.5 equiv), dry $CH_3CN$, argon, rt, 16 h.

the $^1H$ NMR spectrum, a sharp singlet at $\delta$ 1.87 is characteristic of the acetamido-methyl protons. The proton on C-7 resonated as a doublet at $\delta$ 4.88 ($J = 8.8$ Hz) and the proton on C-3 was visible as a multiplet centered at $\delta$ 3.81. The C-4 and C-5 protons resonated together as a multiplet centered at $\delta$ 2.56. In the $^{13}C$ NMR spectrum, the characteristic amide carbonyl resonance was observed at $\delta$ 168.32. All other signals were in agreement with the assigned structure. Final proof of the structure and stereochemistry of **4** was obtained by single crystal X-ray analysis (Fig. 1).

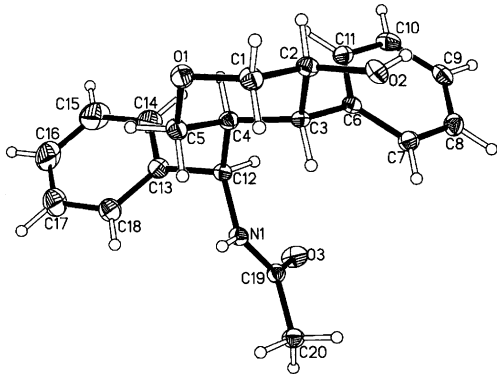


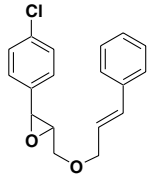
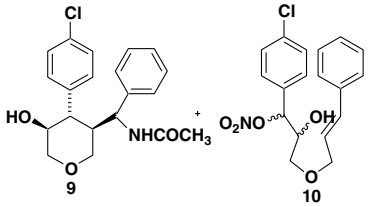
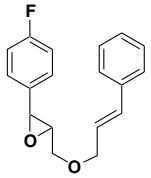
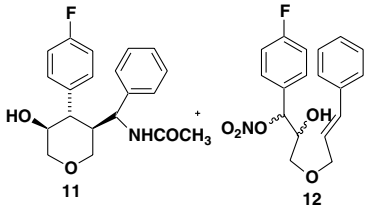
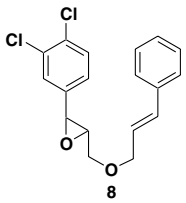
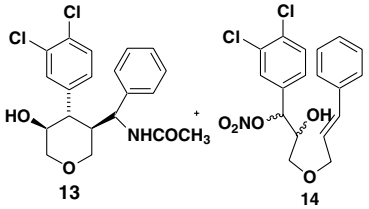

**Figure 1.** ORTEP diagram of **4**.

It is remarkable that the compound **4** was obtained stereoselectively; it has four contiguous stereocenters and has some resemblance to the naturally occurring bioactive norlignans called sequirins.[11,12]

Similar results obtained with epoxy cinnamyl ethers **6**–**8**[13,14] are shown in Table 1.

In the next phase, we used *tert*-butanol as the reaction medium. The reaction of **1** afforded the expected product, the tetrahydropyran derivative **15** along with the nitrato derivative **5** as the *syn* isomer. The consumption of 1 equiv of CAN here vis a vis the reaction in aceto-

**Table 1**

| Entry | Substrate | Products | Yield |
|---|---|---|---|
| 1 |  |  | **9** = 71%<br>**10** = 14% |
| 2 |  |  | **11** = 62%<br>**12** = 12% |
| 3 |  |  | **13** = 59%<br>**14** = 13% |

Reaction conditions: CAN (0.5 equiv), dry $CH_3CN$, Argon, 16 h.

nitrile may be attributed to the slow oxidation of *tert*-butanol by CAN (Scheme 3).

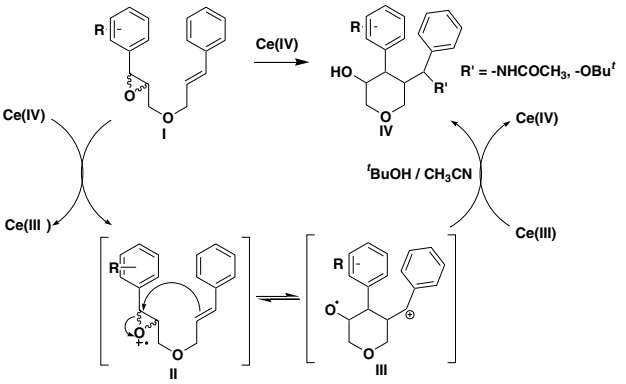
Similar results obtained with epoxy cinnamyl ethers **6–8** are shown in Table 2.

A tentative mechanistic rationale for the formation of the different products may be along the following lines (Scheme 4). The epoxide moiety of the ether **I** is initially oxidized to the radical cation **II**. In less nucleophilic solvents, **II** exists in equilibrium with its distonic cyclic version **III**, whereas in nucleophilic solvents, solvolytic opening of **II** precludes cyclization. The incipient alkoxy radical in **III** gets reduced to the anion with concomitant re-oxidation of Ce(III) to Ce(IV). The cationic center is then quenched by the solvent affording the final product.

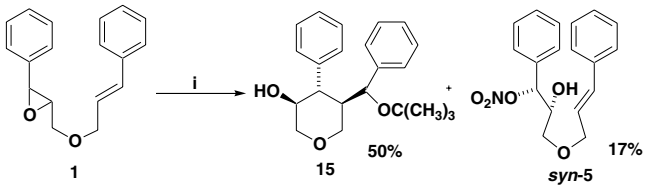
Although this scheme involves a catalytic role for CAN, its requirement of 0.5 and 1 equiv in acetonitrile and *tert*-butanol, respectively, may be attributed to the slow oxidation of the solvent by this reagent.

The probability that the present reaction is not an oxidative radical mediated process but simply an acid catalyzed cyclization with CAN serving as a Lewis acid or a proton source, can be discounted by the failure of experiments using acids such as $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $CeCl_3$, and TFA in effecting cyclization of **1** to deliver the corresponding tetrahydropyran derivative. It is also noteworthy that when CAN mediated cyclization of **1** was monitored by cyclic voltametry both Ce(III) and Ce(IV) species were detected, thus clearly showing that the reaction involves an oxidative process. Convincing evidence for the intermediacy of a radical was provided by the formation of polyacrylamide in large quantities when the CAN mediated cyclization of **1** was carried out in the presence of acrylamide.[7] A decrease in the reaction rate in this case as well as in the experiment performed under an oxygen atmosphere is also diagnostic of the involvement of a radical mechanism.

In conclusion, the CAN mediated oxidative cyclization of cinnamyl substituted epoxyethers constitutes an

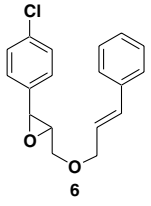
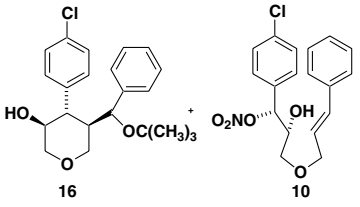
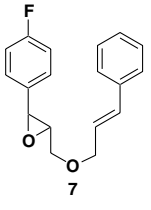
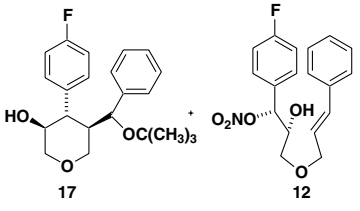
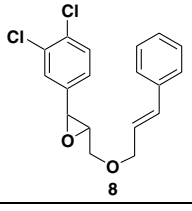
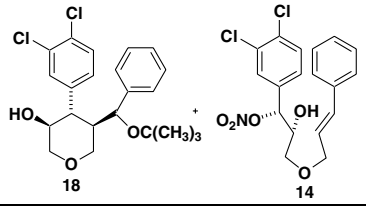



**Scheme 4.**




**Scheme 3.** Reagents and conditions: (i) CAN (1 equiv), $^t$BuOH, argon, rt, 16 h.

**Table 2**

| Entry | Substrate | Products | Yield |
|---|---|---|---|
| 1 |  |  | **16** = 59%<br>**10** = 21% |
| 2 |  |  | **17** = 67%<br>**12** = 15% |
| 3 |  |  | **18** = 66%<br>**14** = 14% |

Reaction conditions: CAN (0.5 equiv), $^t$BuOH, Argon, 16 h.

efficient and facile route for the stereoselective construction of tetrahydropyran derivatives with four contiguous stereocenters. It is conceivable that the methodology uncovered will find application in the synthesis of natural products such as lignans, which possess substituted tetrahydropyran frameworks.

## Acknowledgements

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13. Experimental procedure for the preparation of epoxypropyl alkenyl ethers: Epoxy alcohols were prepared by a routine procedure involving the *m*-CPBA oxidation of cinnamyl alcohols. A solution of epoxyalcohol (1 mmol) in dry THF was added to a suspension of NaH (2.5 mmol) in dry THF maintained at 5 °C. When the evolution of hydrogen was complete, a solution of alkenyl bromide (1.2 mmol) in dry THF was added to it and the reaction mixture was gradually brought to room temperature and stirred overnight. The solvent was evaporated and the crude residue diluted with water (25 mL), and extracted with dichloromethane (3×15 mL). The combined extracts were washed with water, brine and dried over anhydrous sodium sulfate. The pure compound was obtained by chromatography on a silica gel column.
14. All new compounds were fully characterized. *Typical experimental procedure and data for compounds* **4** *and* **5**: A deoxygenated solution of CAN (104 mg, 0.19 mmol) in dry acetonitrile (15 mL) was added dropwise to a deoxygenated solution of **1** (100 mg, 0.38 mmol) in dry acetonitrile (10 mL). The reaction mixture was stirred under argon atmosphere at room temperature for 16 h. On complete consumption of the starting material the solvent was evaporated. The residue was diluted with water (25 mL) and extracted with dichloromethane (3×15 mL). The combined extract was washed with water, brine and dried over anhydrous sodium sulfate. The residue obtained was subjected to silica gel column chromatography using hexane–ethyl acetate (90:10) to afford **5** (yellow oily liquid, 24 mg, 19%) as a mixture of *syn* and *anti* isomers in the ratio 1:3.2. Further elution using chloroform–methanol (90:10) furnished pure **4** as a colorless crystalline solid (70 mg, 60%). Data for compound **4**: mp 249–250 °C. IR (KBr): 3539, 3306, 2955, 2914, 2847, 1650, 1546, 1494, 1454, 1383, 1281, 1204, 1139, 1092, 1068. $^1$H NMR: (300 MHz, $CDCl_3$–$CCl_4$, 7:3 v/v): $\delta$ 7.42–6.99 (m, 10H), 5.47 (s, 1H, exchangeable with $D_2O$), 4.88 (d, $J = 8.8$ Hz, 1H), 4.06 (dd, $J_1 = 4.9$ Hz, $J_2 = 10.9$ Hz, 1H), 3.92 (d, $J = 10.9$ Hz, 1H), 3.82–3.80 (m, 1H), 3.20 (t, $J = 10.9$ Hz, 1H), 3.12 (t, $J = 10.6$ Hz, 1H), 2.56 (m, 2H), 1.87 (s, 3H), 1.47 (br s, 1H, exchangeable with $D_2O$); $^{13}$C NMR: $\delta$ 168.32, 140.71, 139.86, 127.52, 127.26, 126.97, 125.51, 124.62, 71.54, 69.19, 65.83, 51.35, 50.116, 45.67, 21.58; Anal. Calcd for $C_{20}H_{23}NO_3$: C, 73.82, H, 7.12, N, 4.30. Found: C, 73.79, H, 7.09, N, 4.27.
Data for compound **5** (mixture of *syn* and *anti* isomers): IR (thin film): 3389, 3051, 3028, 2901, 1638, 1461, 1256, 1134 cm$^{-1}$. $^1$H NMR: $\delta$ 7.36–7.23 (m, 10H), 6.51 (d, $J = 16.0$ Hz, 1H), 6.23–6.14 (m, 1H), 5.94 (d, $J = 8.0$ Hz, 0.76H), 5.90 (d, $J = 6.1$ Hz, 0.24H), 4.18–4.01 (m, 3H), 3.62–3.50 (m, 0.48H), 3.43 (dd, $J_1 = 3.2$ Hz, $J_2 = 9.9$ Hz, 0.76H), 3.20 (dd, $J_1 = 4.5$ Hz, $J_2 = 9.8$ Hz, 0.76H), 2.78 (br s, 1H, exchangeable with $D_2O$). $^{13}$C NMR: $\delta$ 136.33, 134.90, 133.31, 129.38, 129.20, 128.90, 128.74, 128.60, 127.94, 127.46, 127.29, 126.55, 125.06, 125.02, 85.85, 84.02, 72.11, 71.98, 70.96, 69.72, 69.61.