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Cerium(IV) ammonium nitrate-mediated oxidative rearrangement of cyclobutanes and oxetanes

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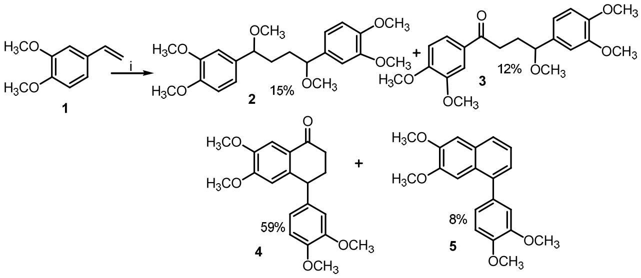
This paper is dedicated with best wishes to Professor Dr. H. M. R. Hoffmann

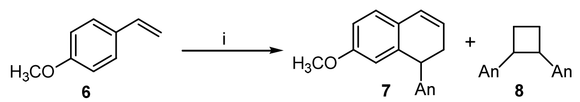
Abstract—A facile CAN-mediated oxidative rearrangement of alkoxyaryl cyclobutanes and oxetanes is described. © 2003 Elsevier Science Ltd. All rights reserved.

As a consequence of the enormous growth in radical methodology during the last two decades, there has been considerable interest in the application of one electron oxidants such as cerium(IV) ammonium nitrate (CAN) in organic synthesis.[1,2] In the course of our investigations on carbon–carbon bond forming reactions mediated by CAN, we discovered a facile cyclodimerization of alkoxystyrenes leading to aryltetralin derivatives (Scheme 1).[3]



Scheme 1. (i) CAN, CH_3OH, 0°C, 30 min.

In addition to the synthetic potential of the reaction, vested in the close relationship of the aryltetralins to naturally occurring bioactive lignans, we were intrigued by the mechanistic implications of the cyclodimerization. By analogy with PET-mediated cyclodimerization of alkoxystyrenes (Scheme 2),[4] we invoked a mechanism akin to that proposed by Bauld et al. essentially involving the formation of a long-bond cyclobutane radical cation.[5]



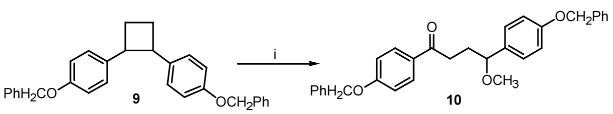
An = 4-methoxyphenyl

Scheme 2. (i) *hν*, chloranil.

We reasoned that if the formation of the long-bond cyclobutane radical cation was involved, then the corresponding reaction of alkoxyaryl cyclobutanes with CAN should afford products similar to those obtained in the CAN-mediated dimerization of alkoxystyrenes. Thus, it was obligatory to investigate the reaction of alkoxyaryl cyclobutanes with CAN and our results validating the above assumption are discussed below.

Our studies were initiated with the reaction of cyclobutane **9**, prepared by the photochemical [2+2] cycloaddition of 4-benzyloxystyrene, with a methanolic solution of CAN under an atmosphere of oxygen. The reaction furnished the keto-methoxybutane derivative **10** in 73% yield (Scheme 3).[6]

The reaction under absolutely oxygen free conditions afforded the corresponding dimethoxybutane derivative **11** (Table 1). Similar results were obtained with the



Scheme 3. (i) CAN (2.5 equiv.), dry CH_3OH, oxygen, rt, 2 h, 73%.

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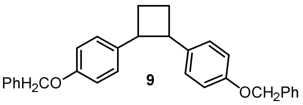
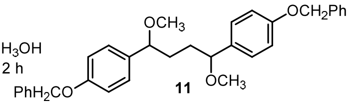
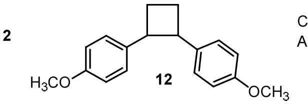
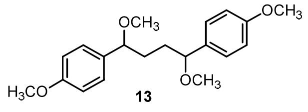
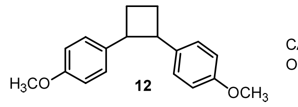
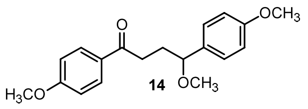
Table 1.

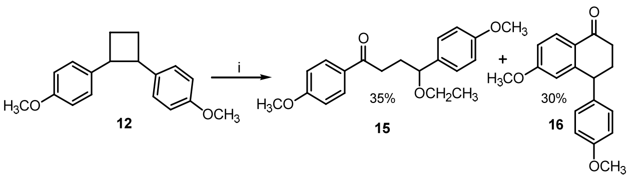
Entry	Substrate	Reaction Conditions	Product	Yield (%)*
1	 **9**	CAN, dry CH_3OH Argon, RT, 2 h	 **11**	69[a]
2	 **12**	CAN, dry CH_3OH Argon, RT, 1 h	 **13**	62[a]
3	 **12**	CAN, dry CH_3OH Oxygen, RT, 1 h	 **14**	52

* isolated yield

[a] 50:50 mixture of diastereomers

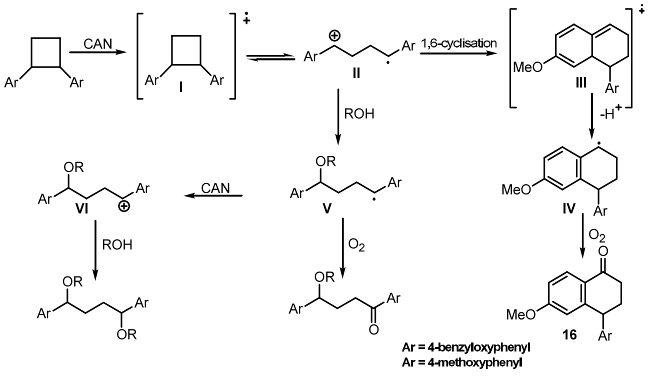
cyclobutane **12** obtained from the [2+2] photochemical reaction of 4-methoxy styrene and the results are summarized in Table 1.

The reaction of cyclobutane **12** with a solution of CAN in ethanol under an atmosphere of oxygen afforded the products **15** and **16** in 35 and 30% yields, respectively (Scheme 4).



Scheme 4. (i) CAN (2.5 equiv.), CH_3CH_2OH, oxygen, rt, 1 h.

A tentative mechanistic rationale for the formation of the above products is depicted in Scheme 5.



Scheme 5.

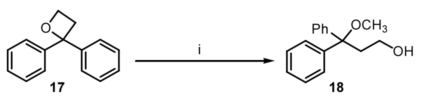
Conceivably, the cyclobutane undergoes oxidative electron transfer in the presence of Ce(IV) to furnish the radical cation[7] **I** which will exist in equilibrium with **II**. Nucleophilic solvents like methanol can quench the cationic site of the radical cation **II** to generate the radical intermediate **V**. The radical center in **V** is intercepted by oxygen to afford the keto-methoxy products.[8] Alternatively, the radical intermediate **V** on further oxidation by Ce(IV) generates the cationic intermediate **VI** which is eventually quenched by methanol to afford the dimethoxy products.

The distonic radical cation **II** can also undergo 1,6-cyclization to give a substituted hexatriene radical cation **III**. The latter on losing a proton gives the radical intermediate **IV** which is intercepted by oxygen to give the tetralone **16**, via the intermediacy of a peroxy radical.[8]

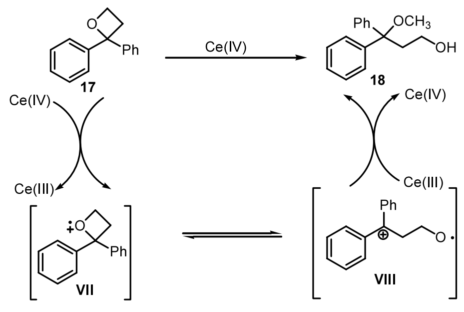
As a logical extension to the CAN-mediated reactions of aryl cyclobutanes, it was of interest to explore such chemistry with oxetanes. In this context it may be recalled that the oxidative protocol for the ring opening of epoxides has received considerable attention. In particular, the study of CAN-mediated oxidative transformations of epoxides in the presence of different nucleophiles has been pursued in detail.[9] An intriguing aspect of mechanistic importance evolves from the fact that all these reactions are autocatalytic in nature whereas the vast majority of CAN-mediated oxidations require stoichiometric or super stoichiometric quantities of the oxidant. A survey of the literature reveals that even though the ring expansion as well as ring cleavage reactions of oxetanes have been studied in detail,[10] their reactivity with CAN remains hitherto unexplored.

In a pilot experiment, when the oxetane **17** was treated with a catalytic amount of CAN in methanol at room temperature it underwent facile ring opening to afford the product **18** in 90% yield (Scheme 6).[11,12]

A tentative mechanistic rationale for the formation of the product **18** is depicted in the following scheme (Scheme 7).



Scheme 6. (i) CAN (0.5 equiv.), CH_3OH, rt.

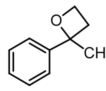
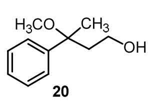
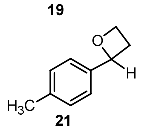
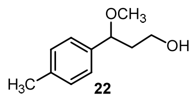
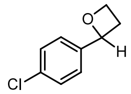
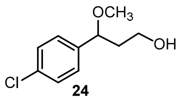
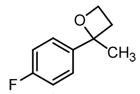
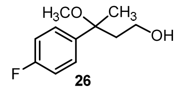
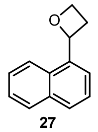
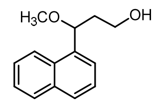


Scheme 7.

The oxetane **17** is initially oxidized by Ce(IV) to the radical cation **VII** which presumably exists in equilibrium with its distonic version **VIII**. The alkoxy radical in **VIII** is reduced to the anion with the concomitant re-oxidation of Ce(III) to Ce(IV), making the cycle catalytic. The cationic center in **VIII** is quenched by methanol affording the final product. The probability of CAN functioning as a Lewis acid in these reactions is minimal since in independent experiments using Ce(III), which has comparable Lewis acidity, the oxetane remained unchanged.

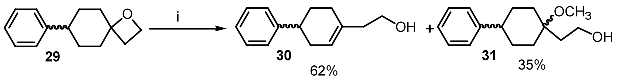
Similar results were obtained with a number of other oxetanes and the results are shown in Table 2.

Table 2.

Entry	Oxetane	Product	Yield (%)
1	 **19**	 **20**	70
2	 **21**	 **22**	82
3	 **23**	 **24**	91
4	 **25**	 **26**	91
5	 **27**	 **28**	87

Reaction Conditions: cat. CAN, CH_3OH, RT

Interestingly, the reaction of the oxetane **29** with a catalytic amount of CAN in methanol at room temperature afforded two products, the cyclohexenyl derivative **30** in 62% yield and the product **31** as a 3:1 mixture of diastereoisomers in 35% yield (Scheme 8).



Scheme 8. (i) CAN (0.5 equiv.), CH_3OH, rt.

In conclusion, the reaction of cyclobutanes with CAN affords products identical to those obtained by the CAN-mediated dimerization of alkoxystyrenes. This observation strongly supports our assumption of the formation of a long-bond cyclobutane radical cation in the CAN-mediated dimerization of alkoxy styrenes. The regiospecific ring opening of oxetanes with catalytic amounts of CAN leading to functionalized alcohols has also been achieved. It is anticipated that in addition to the mechanistic implications, these reactions will find use in organic synthesis.

Acknowledgements

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6. *Typical experimental procedure and spectral data for compound* ***10***: A solution of CAN (329 mg, 0.60 mmol) in dry methanol (10 mL), saturated with oxygen was added dropwise to an oxygenated solution of the cyclobutane **9** (100 mg, 0.24 mmol) in dry methanol (5 mL). The

reaction mixture was stirred at ambient temperature for 2 h. On complete consumption of the starting material the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (5×20 mL). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulfate. After the removal of the solvent on a rotary evaporator, the residue was subjected to column chromatography on silica gel using 90:10 hexane–ethyl acetate mixture to afford **10** as a white crystalline solid (82 mg, 73%). Mp 161°C. IR (KBr) ν_{max}: 2928, 2881, 2827, 1681, 1593, 1512, 1458, 1249, 1169, 1013 cm^{-1}. ^{1}H NMR: δ 2.04–2.15 (m, 2H, C$\underline{H}_2$), 2.96 (t, 2H, $J=7.1$, C$\underline{H}_2$), 3.17 (s, 3H, OC$\underline{H}_3$), 4.13–4.17 (m, 1H, C$\underline{H}$), 5.05 (s, 2H, OC$\underline{H}_2$Ph), 5.11 (s, 2H, OC$\underline{H}_2$Ph), 6.95 (t, 4H, $J=8.8$, Ar$\underline{H}$), 7.19–7.40 (m, 12H, Ar$\underline{H}$), 7.90 (d, 2H, $J=8.7$, Ar$\underline{H}$). ^{13}C NMR: δ 32.66, 34.28, 56.48, 70.00, 70.07, 82.47, 114.50, 114.77, 127.42, 127.45, 127.82, 127.95, 128.22, 128.58, 128.69, 130.33, 130.40, 134.21, 136.23, 154.77, 158.38, 162.45, 198.26. HRMS calcd for $C_{31}H_{30}O_4$: 466.2144. Found: 466.2137.

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11. *Typical experimental procedure and spectral data for compound **18***: A solution of CAN (274 mg, 0.50 mmol) in methanol (10 mL) was added dropwise to a solution of the oxetane **17** (230 mg, 1.10 mmol) in methanol (5 mL). The reaction mixture was stirred at room temperature for 30 min. On complete consumption of the starting material the reaction mixture was diluted with water (10 mL) and extracted with dichloromethane (5×20 mL). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulfate. After the removal of the solvent on a rotary evaporator, the residue was subjected to column chromatography on silica gel using 80:20 hexane–ethyl acetate solvent mixture to afford pure **18**[13] as a colorless viscous liquid (240 mg, 90%). IR (film) ν_{max}: 3341, 3059, 2946, 2893, 2827, 1598, 1490, 1446, 1190, 1100, 1059, 1036 cm^{-1}. ^{1}H NMR: δ 2.50 (br s, 1H, O$\underline{H}$), 2.58 (t, 2H, $J=6.2$, C$\underline{H}_2$), 3.08 (s, 3H, OC$\underline{H}_3$), 3.52 (t, 2H, $J=6.1$, C$\underline{H}_2$OH), 7.18–7.33 (m, 10H, Ar$\underline{H}$). ^{13}C NMR: δ 37.24, 50.78, 59.28, 83.24, 126.96, 127.06, 128.13, 144.46.
12. For the prepapration of oxetanes, see: Okuma, K.; Tanaka, Y.; Kaji, S.; Ohta, H. *J. Org. Chem.* **1983**, *48*, 5133–5134.
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