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A novel CAN-mediated oxidative rearrangement of monoterpenes†

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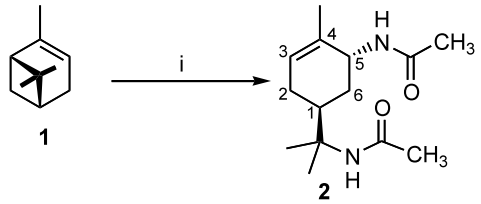
Abstract—A facile CAN-mediated oxidative rearrangement of monoterpenes of the pinene family to afford bisamides and ether derivatives is described. © 2002 Elsevier Science Ltd. All rights reserved.

As a consequence of the ever increasing applications of radical methodology in organic synthesis, one electron oxidants such as cerium(IV) ammonium nitrate (CAN) have attracted considerable attention.[1] Our investigations have uncovered a number of novel carbon–carbon and carbon–heteroatom bond forming reactions mediated by CAN.[2] In this context, we were interested in probing the reactivity of CAN towards monoterpenes such as the pinenes. Although the chemistry of pinenes is well studied,[3] work still continues in this area because of their propensity to undergo skeletal rearrangements via multiple pathways.[4] These rearrangements deliver menthane, bornane or fenchane derivatives of value depending on the conditions employed for the reaction.[5]

Our studies commenced by exposing (+)-α-pinene **1** to a solution of CAN in acetonitrile; a remarkable transformation occurred culminating in the bisamide **2** in 72% yield (Scheme 1).[6]



Scheme 1. *Reagents and conditions*: (i) CAN (2.3 equiv.), CH_3CN, rt, 3 h, 72%.

The bisamide **2** was characterized on the basis of spectroscopic data. In its ^1H NMR spectrum, the five methyl groups gave sharp singlets at δ 1.16, 1.29, 1.68, 1.90 and 1.97, the latter two corresponding to the acetyl groups. The olefinic proton was discernible as a broad singlet at δ 5.56. The -NH proton attached to the quaternary carbon C-7 resonated as a broad singlet at δ 5.35, while the -NH proton attached to C-5 resonated as a doublet at δ 5.77, supporting the strong IR absorption at 3285 cm^{-1}. In the ^{13}C NMR spectrum, the two amide carbonyls were seen at δ 169.29 and 169.71, respectively. The relative disposition of the substituents at C-1 and C-5 was confirmed to be *trans* from the NOESY spectrum of **2**. It is also noteworthy that the bisamide **2**, on base catalyzed hydrolysis, affords the corresponding amine which is useful in the preparation of linear polymers and whose derivatives as Schiff's bases are unusually stable.[7] It may be mentioned that the bisamide **2** has been prepared earlier by the Ritter reaction of *trans*-sobrerol and α-pinene oxide in the presence of conc. H_2SO_4.[8]

The facility with which **1** underwent the transformation leading to **2** prompted us to examine its reactivity along with that of related strained monoterpene derivatives towards CAN in different solvents and our results are summarized in Table 1.

A tentative mechanistic rationale for the formation of the different products from (+)-α-pinene **1** is presented in Scheme 2.

It is conceivable that the initial event involves the single electron oxidation of (+)-α-pinene **1** to furnish a radical cation II which presumably transforms to its distonic

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† This paper is dedicated with best wishes to Professor Dr Weldemar Adam on the occasion of his 65th birthday.

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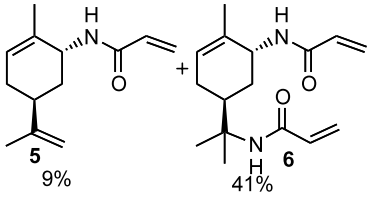
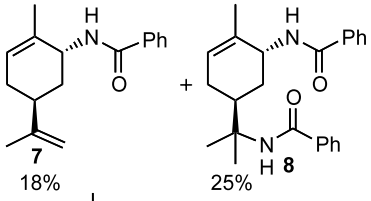
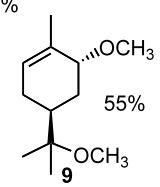
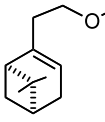
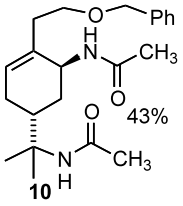
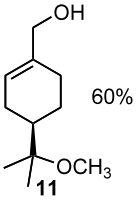
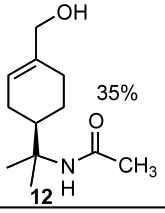
Table 1. Oxidative rearrangements of monoterpenes induced by CAN

Entry	Substrate	Conditions	Products/Yield (%)
1	 **1**	acrylonitrile RT, 3 h	 **5** 9% + **6** 41%
2	 **1**	CAN, C_6H_5CN RT, 24 h	 **7** 18% + **8** 25%
3	 **1**	CAN, CH_3OH 60 °C, 5h	 **9** 55%
4	 **3**	CAN, CH_3CN RT, 5h	 **10** 43%
5	 **4**	cat.CAN, CH_3OH RT, 5h	 **11** 60%
6	 **4**	cat.CAN, CH_3CN RT, 5h	 **12** 35%

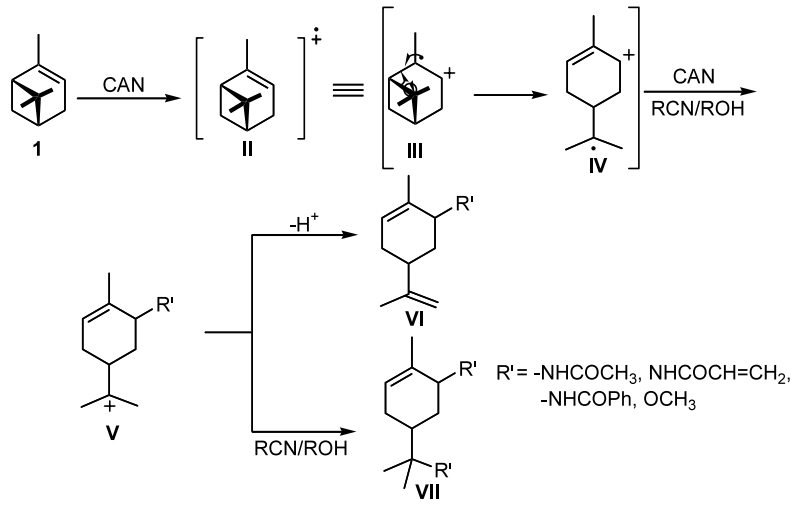
acyclic version IV. The cationic center in IV is quenched by the solvent while the radical center is further oxidized by CAN to afford the cation V which is then neutralized by the solvent to afford the final product VII. Alternatively, the cationic intermediate V loses a proton affording the product VI.

The formation of products **11** and **12** from β-pinene oxide was found to occur with equal ease in the presence of Lewis acids such as $BF_3{\cdot}OEt_2$. Hence the possibility of CAN acting as a Lewis acid in this case cannot be ruled out.

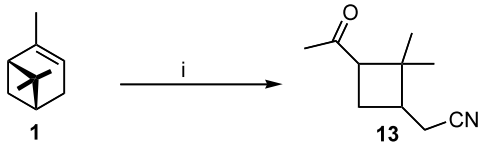
Interestingly, when (+)-α-pinene **1** was treated with NaN_3 and CAN in methanol, it afforded the product **13** in which the cyclobutane ring was left intact (Scheme 3).

The preparation of **13** from α-pinene has been previously reported by its reaction with iodosobenzenediacetate and trimethylsilylazide,[9] and also by a multistep process involving an oximation and Beckmann rearrangement.[10]

In conclusion, we have uncovered some novel and useful CAN-mediated reactions of monoterpenes of the pinene family which are of interest both from the mechanistic and synthetic standpoints. It is worthy of note that in view of the experimental simplicity and mild reaction conditions, the present method offers a



Scheme 2.



Scheme 3. *Reagents and conditions*: (i) NaN_3, CAN (2.3 equiv.), CH_3OH, 0°C, 61%.

convenient alternative to the existing methods for the preparation of mono- and bisamides of monoterpenes. Since the products are important intermediates for a variety of compounds, it is conceivable that these reactions will find practical applications.

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6. Typical experimental procedure: A solution of CAN (1.37 g, 2.5 mmol) in acetonitrile (10 mL) was added dropwise to a solution of 1*R*-(+)-α-pinene **1** (136 mg, 1 mmol) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred at room temperature for 3 h. On complete consumption of the starting material, the reaction mixture was diluted with water (10 mL) and extracted with chloroform (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. Elution using a chloroform–methanol mixture (98:2) afforded **2** as a white crystalline solid (181 mg, 72%). Mp: 214°C (lit.[8a] mp: 212–213°C). **IR (KBr)** ν_{max}: 3285, 3076, 2975, 2935, 2840, 1640, 1546, 1438, 1371, 1297, 1196, 1094, 1040, 933, 811, 730 cm^{-1}. **^{1}H NMR**: δ 1.16 (s, 3H, C$\underline{H}_3$), 1.29 (s, 3H, C$\underline{H}_3$), 1.33–1.37 (m, 1H, C$\underline{H}_2$), 1.68 (s, 3H, C$\underline{H}_3$), 1.69–1.83 (m, 2H, C$\underline{H}_2$), 1.90 (s, 3H, NHCOC$\underline{H}_3$), 1.97 (s, 3H, NHCOC$\underline{H}_3$), 1.99–2.05 (m, 1H, C$\underline{H}_2$), 2.56–2.63 (m, 1H, C$\underline{H}$), 4.35 (br s, 1H, C$\underline{H}$NHCOCH$_3$), 5.35 (br s, 1H, N$\underline{H}$COCH$_3$), 5.56 (br s, 1H, olefinic), 5.77 (d, 1H, J=7.5,

NHCOCH$_3$). ^{13}**C NMR**: δ 20.85, 23.39, 23.84, 24.43, 24.66, 27.02, 30.58, 34.17, 48.39, 56.11, 125.89, 132.99, 169.29, 169.71. **HRMS** calcd for $C_{14}H_{24}N_2O_2$: 252.1838. Found: 252.1849.

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