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The CAN-Mediated Chemo- and Regio-Specific Radical Addition of Carboxylic Acid to Limonene: Synthesis of Norbisabolide and Other γ-Butyrolactones[1]

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A adição de ácidos carboxílicos (acético, butírico, dicloro-acético e ciano-acético) ao limoneno em presença de CAN (2 mol. equiv.) leva à formação químio e regioespecífica de γ-butirolactonas em 50-75% de rendimento isolado.

The addition of carboxylic acids (acetic, butyric, dichloroacetic and cyanoacetic) to limonene mediated by CAN (2 mol. equiv.) gives chemo- and regio-specific γ-butyrolactones in 50-75% isolated yields.

Keywords: *limonene, CAN, γ-butyrolactone, norbisabolide*

Introduction

Norbisabolide (**3a**) is a norsesquiterpenoid γ-butyrolactone isolated by Shringapure and Sabata from the root bark of *Atlantia monophylla*[2] and some syntheses of it are described in the literature, principally from limonene (**1**) and derivatives[3]. Among these, Gardrat[3a] prepared **3a** in a 50% total yield by the reaction of limonene with $Mn(OAc)_3$ in acetic acid, followed by formic acid-promoted lactonization of the γ,δ-unsaturated acid **2** (Fig. 1).

Since the publications by Bush and Finkbeiner[4] and Heiba[5] describing the formation of γ-butyrolactones in the reaction of carboxylic acids with alkenes in the presence of $Mn(OAc)_3$, transition metal salts mediated free radical addition of carbonyl compounds to alkenes has increased enormously[6,7]. The roles of the transition metal in these reactions are (i) one electron oxidation of the α-carbon of the carboxylic acid generating an eletrophilic α-carboxyalkyl radical which adds to the alkene forming a γ-carboxy-

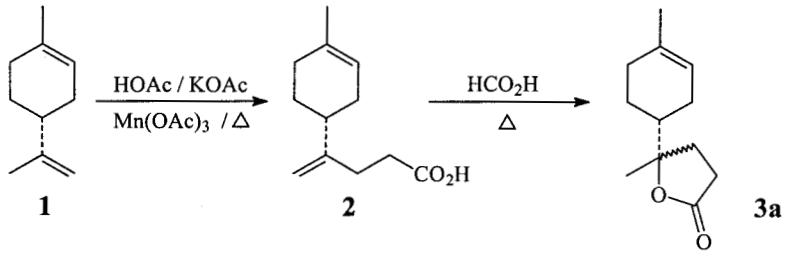

Figure 1. Synthesis of norbisabolide according to Gardrat[3a].

alkyl radical and (ii) oxidation of this new radical to produce a carbenium ion that frequently cyclizes[6]. Among the various transition metals, manganese(III) salts are the most commonly employed[6]. Although the expensive $Mn(OAc)_3$ can be prepared by permanganate oxidation of $Mn(OAc)_2$ in acetic acid[8], it can suitably be substituted by the inexpensive and readily available CAN [cerium(IV) ammonium nitrate][9].

Continuing our interest in chemo- and regio-specific functionalization of the acyclic double bond of limonene[10], we describe here our preliminary results on the preparation of γ-butyrolactones by the reaction of limonene with carboxylic acids in the presence of CAN.

Results and Conclusions

The CAN mediated reaction of limonene with acetic acid was carried out by stirring together a suspension of 1 mol. equiv. of limonene, 2 mol. equiv. of CAN and 0.3 mol. equiv. of sodium acetate in acetic acid (solvent) under reflux which led to **3a** in a 60% isolated yield (superior to that described by Gardrat in his two-step synthesis[3a]) as a *ca.* 1:1 mixture of diasteromers (determined by HRGC - high-resolution gas chromatography). No significant amount of the γ,δ-unsaturated acid **2** was detected in the crude product, and **3a** was characterized by comparing its spectral data with those previously reported[3a].

Based on the above result, it was decided to demonstrate the generality and utility of this simple methodology to prepare diverse γ-butyrolactones **3** from limonene and carboxylic acids (dichloroacetic, butyric and cyanoacetic), the results are summarized in Fig. 2 and Table 1.

In conclusion, the chemo- and regio-specific preparation of γ-butyrolactones **3** is effective in the presence of 2 mol. equiv. of the inexpensive and commercially available CAN. This simple methodology ("radical route") is com-

Table 1. Yields of 3 obtained according to Fig. 2.

3	R_1	R_2	Yield (%)
a	H	H	60
b	Cl	Cl	50
c	Et	H	58
d	CN	H	75

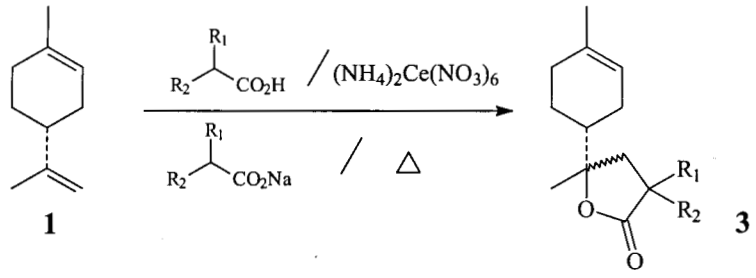

Figure 2. The CAN-mediated addition of carboxylic acids to limonene.

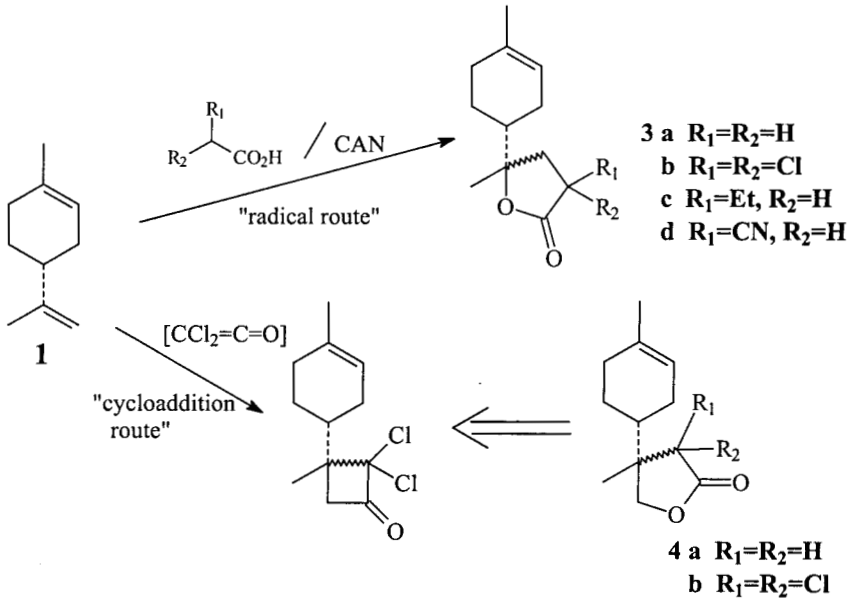

Figure 3. The formation of regioisomeric γ-butyrolactones.

plementary to the "cycloaddition route", where the regioisomeric γ-butyrolactones **4** were prepared by dichloroketene cycloaddition to limonene followed by regiospecific Baeyer-Villiger oxidation[10b] (Fig. 3).

Experimental

Typical procedure for the CAN-mediated addition of carboxylic acid to limonene; synthesis of norbisabolide (**3a**)[11]

To a suspension of glacial acetic acid (100 mL) and sodium acetate (21.5 g, 30.6 mmol), limonene (1.36 g, 10 mmol) was added, followed by CAN (11.8 g, 20 mmol). After 30 min. reflux under a stream of dry N_2, the brownish solution was cooled and extracted with ether (3 x 50 mL). The ether solution was thoroughly washed with water (*ca.* 500 mL) and then with 5% $NaHCO_3$ (3 x 50 mL). After drying (Na_2SO_4), the organic layer was filtered, the solvent evaporated in a rotary evaporator at reduced pressure and the residue purified on a Chromatotron (eluent: CCl_4) to give 1.16 g (60%) of pure norbisabolide (**3a**).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.42 (s_{br}, 1H), 2.60-2.30 (m, 2H), 2.25-1.70 (m, 9H), 1.67 (s_{br}, 3H), 1.30 (s, 3H) ppm.

IR (neat): ν 2950, 2910, 1770, 1450, 1400, 1020, 800 cm^{-1}.

MS (70 eV, %): m/z: 194 (26), 134 (10), 121 (44), 99 (100).

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11. For the preparation of **3b** and **3c**, the corresponding carboxylic acid (solvent) and sodium carboxylate were used. For the preparation of **3d**, a suspension of cyanoacetic acid (2.5 g) and sodium acetate (1.5 g) in acetic acid (100 mL) was used. (Under these conditions, HRGC analysis did not show the formation of **3a**.)