TRANSITION METAL SALTS MEDIATED OXIDATIVE RADICAL ADDITION OF ETHYL ACETOACETATE TO LIMONENE

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Abstract: transition metal salts mediated oxidative radical addition of ethyl acetoacetate to limonene produced chemo- and regiospecificaly (1'R,5RS)-3-carboethoxy-2,5-dimethyl-5-(4'-methylcyclohexen-3'-enyl)-4,5-dihydrofuran as a 1:1 mixture of diastereoisomers. The best yield (72 % isolated) was obtained using limonene (1 mol equiv.), ethyl acetoacetate (1 mol equiv.) and $Mn(OAc)_3 \cdot 2H_2O$ (2 mol equiv.) in acetic acid at 70°C. The utilisation of cerium(IV) ammonium nitrate (CAN) or $Co(OAc)_2$ instead of Mn(III) led to lower yields of the dihydrofurans along with diethyl 2,3-diacetylsuccinate. Fe(III) salts gave a complex mixture of products and using $CuCl_2$ there was no reaction.

Introduction

The addition of organic free radicals to alkenes is a powerful methodology for construction of C-C bonds (1). In this category, the so-called "oxidative free radical addition" mediated by transition metal salts has enormously increased in the last 30 years (2). Since the initial works on this area (3), a variety of transition metal salts and oxides has being used to mediate the reaction and among them, Mn(III), Ce(IV), Co(II), and Fe(III) salts are the most widely explored (2). Both inter- and intramolecular versions of the oxidative radical addition methodology are known (4) and the reactions are widely used for the preparation of natural and unnatural products (5).

The oxidative radical addition of carboxylic acids to limonene 1 mediated by CAN [cerium(IV) ammonium nitrate] produces chemo- and regiospecifically the γ-butyrolactones 2 in good yields (6). Furthermore, similar reaction using β-diketones (dimedone or acetylacetone) produces the 2,3-dihydrofurans 3 in moderate yield (7) (Scheme 1).

Continuing our interest in chemo- and regiospecific functionalization of the acyclic double bond of limonene (8), we communicate here the results on the reaction of limonene with ethyl acetoacetate mediated by diverse transition metal salts.

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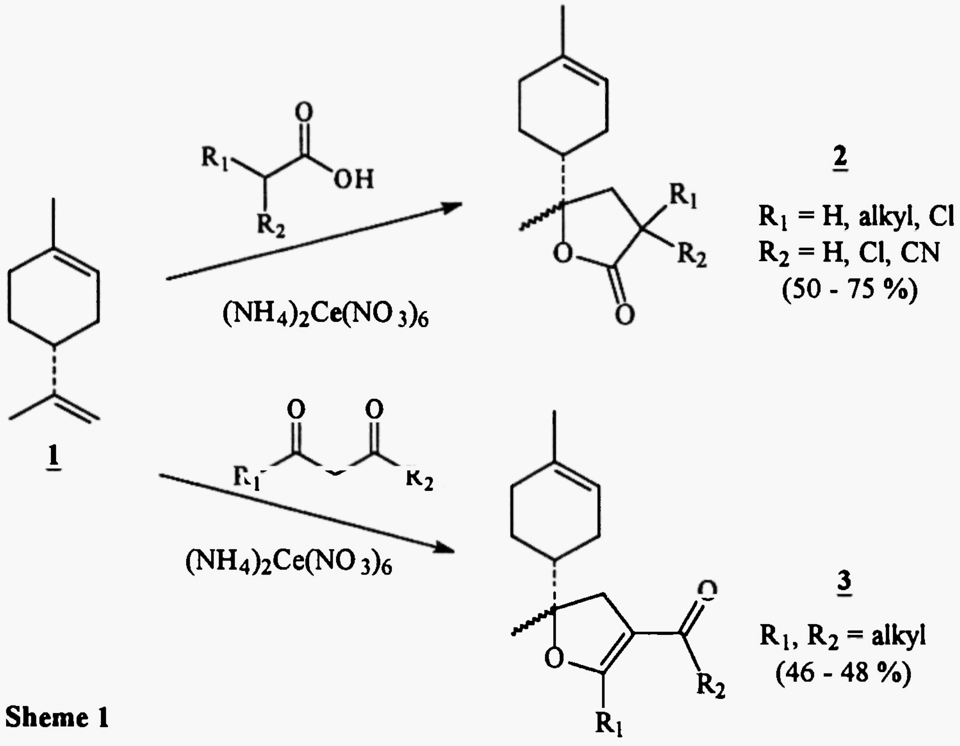
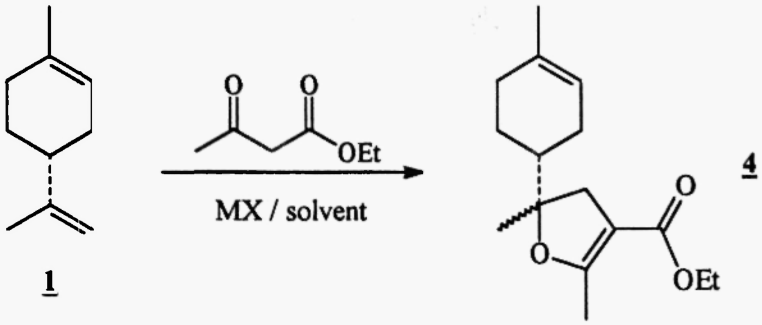


Sheme 1

Results

The results on the reaction of limonene (1 mol equiv.) with ethyl acetoacetate (1 mol equiv.) mediated by diverse transition metal salts (2 mol equiv.) at different conditions are shown in Scheme 2 and Table 1. The best result was obtained using $Mn(OAc)_3 \cdot 2H_2O$ which produced (1'R,5RS)-3-carboethoxy-2,5-dimethyl-5-(4'-methylcyclohexen-3'-enyl)-4,5-dihydrofuran 4 in 72% isolated yield as a *ca.* 1:1 mixture of diastereoisomers (9) - determined by high resolution gas chromatography. Changing the transition metal salt to $Co(OAc)_2$, 4 was formed in only 13 % yield. On the other hand, Fe(III) salts produced a complex mixture of products and with $CuCl_2$ there was no reaction after several hours.



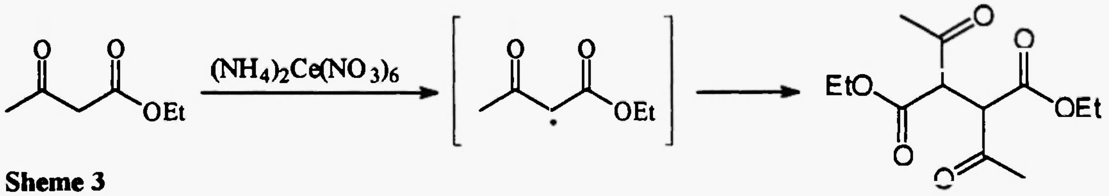
Sheme 2

MX	solvent	time (min)	Temp (°C)	Yield of 4 (%)^a
$Mn(OAc)_3 \cdot 2H_2O$	HOAc	90	70	72
CAN	HOAc	3	70	$7^{b,c}$
CAN	MeOH	20	5	35
CAN	MeCN	30	70	$-^c$
$K_3[Fe(CN)_6]$	HOAc	150	60	2^c
$K_3[Fe(CN)_6]$	MeCN	90	80	$-^c$
$Fe(ClO_4)_3$	HOAc	150	120	$-^c$
$Co(OAc)_2$	HOAc	60	75	13
$CuCl_2$	MeOH	960	rt	no reaction

[a]isolated yield. [b]chromatographic yield. [c]several unidentified products formed.

Table 1. Yield of 4 from the reaction of limonene and ethyl acetoacetate mediated by diverse transition metal salts.

Disappointing results were obtained with CAN at different conditions which produced 4 in very low yield along with diethyl 2,3-diacetylsuccinate 5, produced by dimerization of the radical formed by the reaction of ethyl acetoacetate with CAN (10) -Scheme 3. Several attempts to increase the formation of 4 changing solvent, reaction conditions (temperature, reactant ratios, etc) showed unsuccessful and even at low reaction times, 5 was produced in almost same proportion of 4.



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Sheme 3

In summary, in contrast with the literature information (5c, 7, 11), in our hands, $Mn(OAc)_3 \cdot 2H_2O$ was better than CAN to mediate the oxidative radical addition of ethyl acetoacetate to limonene. Furthermore the utilisation of the Mn(III) salt is also very convenient because it is a superior reagent in terms of atom economy (12) (its molecular weigh is *ca.* half of the CAN to produce the same effect, *ie.*, one electron transferring).

Acknowledgments

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(9) Selected analytical data for 4 (mixture of *ca.* 1:1 of diastereoisomers): **^{1}H NMR** (200 MHz, $CDCl_3$): δ 5.38 (brs, 1H, olefinic), 4.16 (q, 2H, J 7.1 Hz), 2.82 (d, 1H, J 14.4 Hz), 2.46 (dd, 1H, J 14.4 Hz), 2.17 (s, 3H), 1.98-1,73 (m, 7H), 1.65 (s, 3H), 1.30 (s, 3H), 1.29 (s, 3H) ppm. **^{13}C NMR** (75 MHz, $CDCl_3$): δ 167.2, 167.0 (C=O), 166.8 (q), 134.3, 134.1 (q), 120.3, 120.2 (CH), 101.2 (q), 90.8, 90.6 (q), 59.5 (CH_2), 43.3, 43.2 (CH), 39.2, 38.5 (CH_2), 30.7, 30.6 (CH_2), 29.9 (CH_2), 24.9, 24.5 (CH_3), 23.7 (CH_3), 14.7, 14.5 (CH_3) ppm. **MS** (70 eV, electron impact): m/z 264, 246, 219, 191, 172, 157, 134 (100 %), 119, 97, 79.

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