Pergamon

Tetrahedron 54 (1998) 593–598

TETRAHEDRON

Comparative Autoxidation of 3-Carene and α-Pinene: Factors Governing Regioselective Hydrogen Abstraction Reactions.

Gadi Rothenberg, Yael Yatziv and Yoel Sasson*

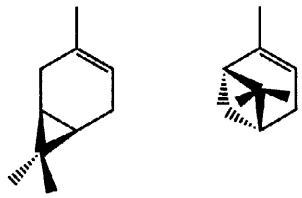
Casali Institute of Applied Chemistry, Hebrew University of Jerusalem, Jerusalem 91904, Israel.
e-mail: ysasson@vms.huji.ac.il

Received 29 September 1997; revised 31 October 1997; accepted 6 November 1997

Abstract: Autoxidation reactions of 3-Carene **1** and α-Pinene **2** were performed using various homogeneous catalysts. Different product and regio-selectivities were observed. The factors that promote hydrogen abstraction (HA) reactions in both molecules are discussed, and it is proposed that the difference in the product selectivities is due to the lack of "cyclic activation" in **2**. Oxidation of **1** produced mainly 3-carene-5-one **3**, while **2** yielded 2,3-epoxypinane **6** as the major product.

INTRODUCTION

In the course of our studies of allylic oxidations, we investigated the reactions of 3,7,7-trimethylbicyclo[4.1.0]hept-3-ene (3-Carene, **1**) and 2,7,7-trimethylbicyclo[3.1.1]hept-2-ene (α-Pinene, **2**) with molecular oxygen. Generally, autoxidation of olefins is not valued as a synthetic tool, because of the plethora of peroxidic products obtained.[1,2] However, this subject is still studied extensively, owing to the merits of O_2 as a "green" oxidant.[3-10] The specific interest in oxygenation products of terpenes arises due to their importance in natural product synthesis.[11,12] Bicyclic terpenes such as **1** and **2** are often grouped together, as they are structural isomers that often appear together in natural products and oils. Nevertheless, these compounds differ in their ring structure, and exhibit diverse chemical behavior.[13]



1 **2**

Autoxidations of olefins can be simply divided into epoxidations and allylic oxidations. The mechanistic outlines are well-known.[14,15] The first step in epoxidations involves an attack on the double bond, while allylic oxidations begin with the abstraction of an allylic hydrogen. Both reactions involve free-radical intermediates, and understanding the factors that promote either path is of interest.

In papers dealing with hydrogen abstraction (HA) processes, the lability of allylic hydrogens in unconjugated olefins towards HA is found to be 3°>2°>1°. Furthermore, the ratio of abstraction depends on the relative position of methyl groups, (CH_2 *trans* to Me):(CH_2 *gem* to Me):Me being 3:1:<0.1.[16] A study of 3-methyl-1-cyclohexene revealed unusual activity for 3° hydrogens vs 2° ones, when calculated *per atom.*[17] It was proposed that, in certain cases, only the pseudo-axial hydrogen is available for HA. Notwithstanding these considerations, an enhanced reactivity of cyclic allylic hydrogens compared to acyclic ones is reported.[18] This "cyclic activation" factor is common to several HA systems, regardless of the abstracting species, and is not observed in the corresponding saturated compounds (table 1). Terse qualitative explanations[19-22] of this have attributed a smaller entropy loss to the cyclic molecule in the formation of the transition state.

0040-4020/98/$19.00
PII: S0040-4020(97)10319-2

Table 1: Relative Reactivities[a] of C-H Bonds Towards HA.

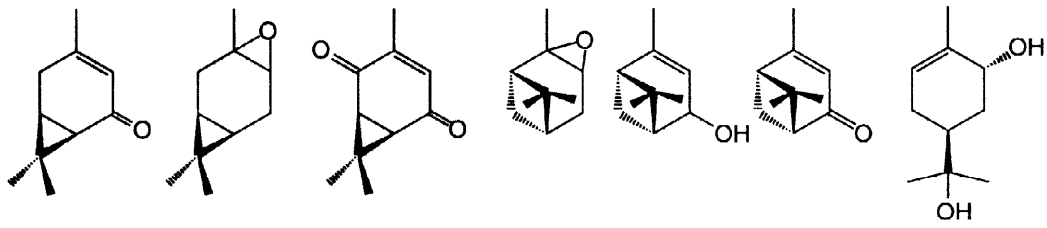
Entry	Hydrocarbon	ROO· 30 °C[b]	*t*-BuO· 40 °C[c]	C_6H_5· 65 °C[d]	Br· 40 °C[e]	NBS 80 °C[f]
1	2° acyclic aliphatic	-	0.8-1.2	1.01	<0.01	0.0054
3	cyclopentane	-	1.38	1.15	-	-
4	cyclohexane	-	1.50	1.00	0.004	0.0028
2	2° acyclic allylic	6.3	6-9	3.3	35-40	35
5	cyclopentene	21	38	9.7	100-600	99 ± 15
6	cyclohexene	18	37	11.2	160	129 ± 22

[a] per H atom; Toluene=1. [b] ref. 19. [c] ref. 20. [d] ref. 18. [e] ref. 23. [f] ref. 24.

In this work we present our findings regarding the catalytic autoxidation of **1** and **2**, proposing that the susceptibility of different hydrogen atoms towards HA can account for the difference in the product selectivities between the two substrates. Furthermore, we show that ring flexibility is of paramount importance for the so-called "cyclic activation" of allylic hydrogens in these substrates.

RESULTS

In a typical experiment, dioxygen was bubbled through a stirred mixture of the olefin and the catalyst. Hydroperoxide formation was monitored by iodometric titration, and reactant conversion was monitored by GC. Product analysis evidenced epoxidation and allylic oxidation products (table 2). Different product and regio-selectivities were observed. Oxidation of **1** produced predominantly 3-carene-5-one **3**, together with some 3,4-epoxycarane **4** and 3-carene-2,5-dione **5**, while **2** yielded 2,3-epoxypinane **6** as the main product, together with verbenol **7** and verbenone **8**.[25]



3 **4** **5** **6** **7** **8** **9**

The formation of the epoxide **6** is incompatible with findings published previously.[26] This product, however, was isolated and identified by us, both as the epoxide and as its rearranged hydrolysis product *trans-p*-menth-6-ene-2,8-diol (*trans*-sobrerol) **9**.

We have employed a wide spectrum of homogeneous catalysts, ranging from metal-oxo types (e.g. Cr^{VI}) to known electron-transfer ones (e.g. Co^{II}, Cu^{I}, Cu^{II}). The simple metal salts as well as the pyridine, 4-picoline, and bipyridine complexes were studied. Complexes were prepared both *in situ* and as isolated compounds. Earlier studies, utilizing peresters or *t*-butyl hydroperoxide (TBHP) as oxidants, have reported mechanistic dissimilitudes between chelating pyridine ligands and monodentate pyridines.[27, 17] Conversely, using dioxygen we observed a similar reaction for both ligand types.

Generally, reactions were performed at ambient temperatures to avoid polymerization, although the reaction was slower. **1** polymerized considerably above 40 °C, while **2** showed only little polymerization below 100 °C (at <50% conversion). Conversions were much lower when air was used instead of oxygen, or when organic solvents (C_6H_6, CH_2Cl_2, C_6H_5Cl) were added. These results indicate that once the concentration of oxygen dissolved in the reaction mixture reaches a certain level, the reaction is chemically controlled.

Several reactions were carried out in the presence of catalytic amounts of TBHP, reasoning that the presence of additional free-radicals from its decomposition would accelerate the reaction, but the changes were insignificant.[27]

Table 2: Autoxidation[a] of **1** and **2**.

Entry	Substrate	Catalyst (mol%)	Temp °C	Conversion %	Time h	Prods. (% Selectivity)[c]
1	**1**	$Co(4\text{-picoline})_2Cl_2$ (1)	20	38	6	**3**(35) **4**(19) **5**(6)
2	**1**	$CoCl_2$ (1)	20	79	9	**3**(46) **4**(18) **5**(5)
3	**1**	none	20	26	20	**3**(40) **4**(20) **5**(12)
4	**1**	$CoCl_2$ (1) + pyridine (1)	20	36	20	**3**(36) **4**(15) **5**(13)
5	**1**	CrO_3 (1) + pyridine (5)	25	70	22	**3**(60) **4**(25) **5**(9)
6	**1**	CrO_3 (1) + pyridine (1)	25	66	18	**3**(64) **4**(22) **5**(8)
7	**2**	$Co(bipy)Cl_2$ (1)[b]	90	15	2	**6**(46) **7**(27) **8**(16)
8	**2**	$Cu(bipy)Br_2$ (1)[b]	90	18	1.5	**6**(39) **7**(22) **8**(25)
9	**2**	Cu-Phthalocyanin(1)	90	12	2	**6**(40) **7**(27) **8**(19)
10	**2**	CrO_3(bipy) (1) +TBHP[b]	90	40	2.5	**6**(39) **7**(20) **8**(29)
11	**2**	CrO_3(bipy) (1)[b]	90	23	1	**6**(49) **7**(17) **8**(23)
12	**2**	$Cu(pyridine)_2Cl_2$ (1)	90	20	2	**6**(54) **7**(17) **8**(27)
13	**2**	$Co(4\text{-picoline})_2Cl_2$ (1)	65	53	4	**6**(50) **7**(19) **8**(23)

[a] all reactions were carried out under 1 atm. of O_2. [b] bipy=2,2'-bipyridine. [c] Polymers and peroxidic products account for 5-30% of the mass-balance.

DISCUSSION

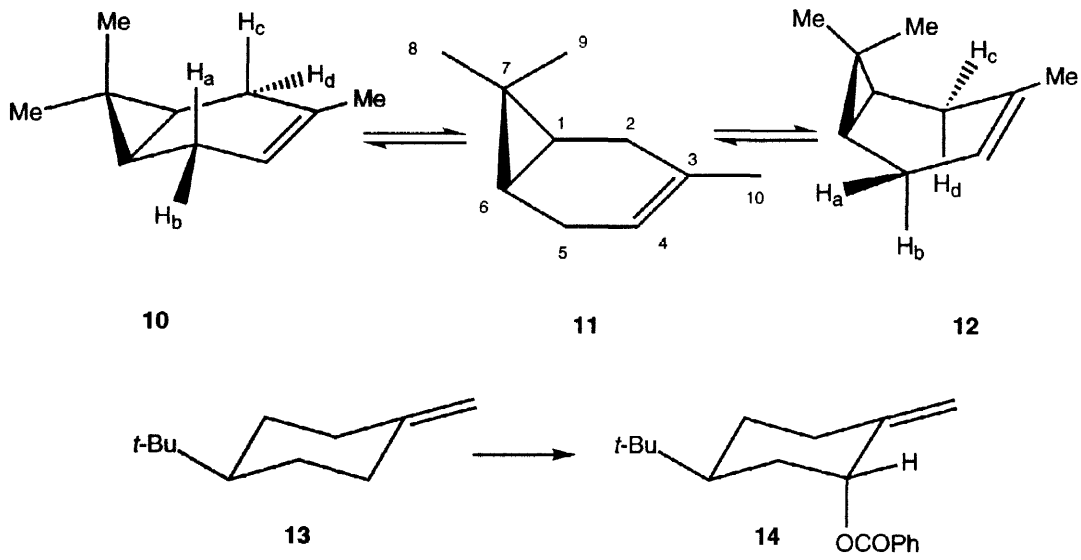
Allylic oxidation vs. double-bond epoxidation

Previous studies have shown that 1-methylcyclohexene, a monocyclic, unhindered analogue of **1** and **2**, exhibits a strong preference for allylic oxidation over epoxidation (85:15 ratio) under autoxidative conditions.[28] Under the same conditions, **2** would be expected to yield less epoxide than **1**, as the bicyclic structure in **2** forces the attack on the double bond from the *trans* position.[29] Conversely, our observation that **2** yields *more* epoxide than **1** suggests that when labile hydrogen atoms are available, HA takes precedence over the attack on the double bond, leading to a higher ratio of allylic oxidation products over epoxides.

Factors that promote regioselective HA from 1 and 2

Regardless of the abstracting radical, the 2° cyclic allylic hydrogens would be expected to undergo HA easily. Due to the bicyclic structure two factors should be considered: the rigidity of the 6-membered ring, and the stereoelectronic effects of the smaller ring.

The 6-membered ring in **1** is flexible, and its preferred conformation has been shown to be almost planar (structure **11**).[30, 31] A conformational change is necessary in order to enable overlapping between the olefinic π-orbital and the developing p-orbital containing the unpaired electron in the transition state.[32, 33] Such overlapping would occur in one of the boat conformations **10** or **12**. Conformer **10**, where the hindering disubstituted cyclopropyl ring is at an equatorial position, is probably the more stable of the two, promoting regioselective abstraction of H_a and H_c. A similar explanation was proposed for the formation of 1-methylene-4-*t*-butyl-cyclohexyl-*trans*-2-benzoate **14** *via* perester oxidation of **13**.[34]



Regarding the effects of the 3-membered ring, it was argued that a conjugative interaction with an adjacent cyclopropyl ring can facilitate HA from the cyclopropylcarbinyl site.[35] As the *trans* radical is more stable, abstraction at C_5 would be preferred over that at C_2. Upon combining the above considerations, H_a is the best candidate for HA from **1**. The selective formation of **3** supports these arguments.

On the other hand, **2** is a rigid structure, and orbital overlapping cannot promote HA.[34] Indeed, H_c is orthogonal to the p-orbital, and H_a and H_b are at an approximate 45° angle to it (Fig 1.). The so-called "cyclic activation" factor, resulting from an initial arrangement of the molecule that is similar to the transition state during HA, does not apply in this case. Thus, double-bond attack leading to epoxidation becomes the major route.

Even when HA does occur, H_c, despite being a 3° allylic hydrogen, is not preferentially abstracted from **2**. Besides its unfavorable positioning for p-π interaction, the allylic radical formed by its abstraction is *cis* with the Me group.[20] When comparing H_a and H_b, it is reasonable that the approach of the abstracting radical to H_a would be encumbered by the adjacent methyl group, which could lead to a lower pre-exponential factor.[36] It follows that H_b is the foremost candidate for HA from **2**.

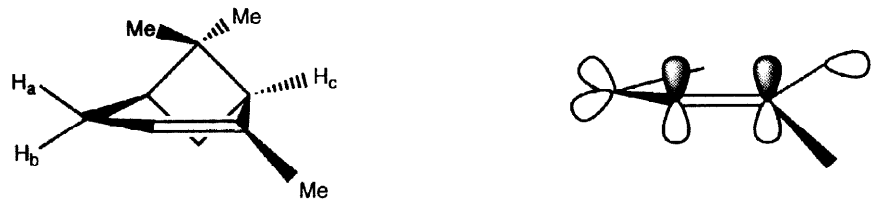


Fig. 1. Orbital interactions of allylic hydrogens in α-pinene

CONCLUSIONS

Skeletal Molecular flexibility is essential, in this case, for the "cyclic activation" of allylic hydrogens. It may be assumed that the primary parameter pertaining to this activation is the ability of the substrate molecule to align the allylic hydrogen and the double bond on the same plane. The degree of conformational change required for the formation of the transition state is consequently reduced. Regioselective HA reactions can thus account for the disparate results obtained from the autoxidation of **1** and **2**.

EXPERIMENTAL SECTION

General. ^{1}HNMR and ^{13}CNMR spectra were measured on a Bruker 300MHz instrument. δ shift values are reported in ppm relative to TMS. GC analysis was performed on a HP-5890 with a semi-polar packed column and FID.

Materials and product identification. Pyridine and bipyridine complexes of transition metals were synthesized by adaptation of the literary procedure.[37] Commercial samples of compounds **6**,**7** and **8** were purchased from Aldrich and were used as calibrating standards. **3**, **4**, **5** and **9** were isolated and identified by their spectral properties. Unequivocal proof that **6** is a precursor to **9** was obtained by a separate synthesis of **9** from a commercial sample of **6**.

Transition-metal complexes: Specific example: $CoCl_2$(4-picoline)$_2$. $CoCl_2$ (50ml of 1M soln. in EtOH) and 4-picoline (50 ml of 2.5M soln. in EtOH) were warmed to 60 °C, mixed and cooled slowly to 20 °C. Filtration and recrystallizing from EtOH afforded 14.1 gr (ca. 90%) of pink-purple complex, which remained stable under vacuum at ambient temperature. Other complexes used were analogously prepared.

trans-Sobrerol **9**. In a round-bottomed flask equipped with a condenser were placed, in this order, **6** (100 mmol, 15.22 gr, 1eq), $RuCl_3$ (0.1 mmol, 20.7 mg)[38] and H_2O (5 ml). The mixture was stirred mechanically for 5 min, (the reaction is exothermic and should be cooled if attempted on a large scale) and the crude solid product (16.1 gr, 94%) was dissolved in 500ml CH_2Cl_2 and filtered. The filtrate was concentrated to ca. 100 ml and left to crystallize for 2h at 20 °C. A portion of the white crystals was recrystallized from CH_2Cl_2. m.p. 131-132 °C. Anal. Calcd. for $C_{10}H_{18}O_2$: C 70.55%, H 10.65%, O 18.80%. Found: C 70.24%, H 10.49%, O 19.27%. ^{13}CNMR (gated-decoupling splitting): C_1=C 135.7 (s), C_6=C 126.4 (d); C_8-OH 73.0 (s), C_2-OH 69.5 (d); 40.0 (d); 34.5 (t); 28.4 (t); 27.4 (q); 27.3 (q); 21.5 (q). All values fit within ±1.0 ppm to published ones.[39] XRD (lit values[40]) monoclinic, *C2*, a = 18.96 (18.975, (5)), b =7.94 (7.939, (2)), c = 6.67 (6.680 (2)) Å, β = 96.12° (96.24 (3)).

Autoxidation of terpenes. **1** or **2** (100 mmol, 13.62 gr), together with C_6H_5Cl (3.0 gr, internal standard) were placed in a round-bottomed flask equipped with a mechanical stirrer, a condenser, a thermometer, and a gas inlet tube (glass, fused to the bottom of the flask). After the desired temperature was reached (oil bath), appropriate amounts of catalyst were added, and the mixture was stirred vigorously for 1 min, after which O_2 (99.9% pure) was bubbled through the mixture at ca. 20 ml/min. Periodically, samples were taken out and analyzed by GC. After the desired reaction time, 200 ml of 1:1 water:CH_2Cl_2 were added, the phases were separated and the aqueous phase was extracted (2 x 100 ml) with CH_2Cl_2. The organic solvent was evaporated *in vacuo* , and the residue was fractionally distilled and chromatographed on silica.[41] Selected ^{13}CNMR values (gated-decoupling splitting): **3**: C_5=O 195.15 (s); C_3=C 158.12 (s), C_4=C 125.22 (d). **4**: C_3-O 55.64 (s), C_4-O 58.0 (d). The diketone **5** was recrystallized from CH_2Cl_2 (yellow crystals, m.p. 80-82 °C), ^{1}HNMR (splitting): 1H, 2.30; 1H, 2.31; 1H, 6.48 (d); 3H, 1.95 (d); 3H, 1.30 (s); 3H, 1.30 (s). ^{13}CNMR (gated-decoupling splitting): C_5=O 194.90 (s), C_2=O 194.29 (s); C_3=C 149.92 (s), C_4=C137.60 (d); 3° C 39.77 (d), 38.93 (d); 4° C 33.46 (s); CH_3 15.38 (q), 29.02 (q), 16.13 (q). All values fit within ±1.0 ppm to published ones.[30]

REFERENCES AND NOTES

1. Courtneidge, J. L.; Bush, M., *J. Chem. Soc. Per. 1,* **1992**, 1531-1549.
2. Dimitrov, D.; Sirakova, V.; Stefanova, R., *Oxid. Commun.*, **1984**, 7 (3-4), 399-407.
3. Gomes, M. J. T.; Antunes, O. A. C., *J. Mol. Catal.*, **1997**, 121, 145-155.
4. Gusevskaya, E.; Gonsalves, J. A., *J. Mol. Catal.*, **1997**, 121, 131-137.

5. Alper, H.; Harustiak, M., *J. Mol. Catal.*, **1993**, 84, 87-92.
6. Ishii, Y.; Iwahama, T.; Sakaguchi, S.; Nakayama, K.; Nishiyama, Y., *J. Org. Chem.*, **1996**, 61, 4520-4526.
7. Drago, R. S.; Zuzich, A.; Nyberg, E. D., *J. Am. Chem. Soc.*, **1985**, 107, 2898-2903.
8. Morvillo, A.; Bressan, M., *J. Mol. Catal.*, **1986**, 37, 63-74.
9. Nam, W.; Kim, H. J.; Kim, S. H.; Ho, R. Y. N.; Valentine, J. S., *Inorg. Chem.*, **1995**, 35, 1045-1049.
10. Bystrom, S. E.; Larsson, E. M.; Akermark, B., *J. Org. Chem.*, **1990**, 55, 5674-5675.
11. Szmant, H. H., *Organic Building Blocks of the Chemical Industry.*, Wiley: New York, (**1989**), 386-391.
12. Mukesh, D.; Bhaduri, S.; Khanwalkar, V., *Chem. Eng. J.*, **1988**, 38, 153-160.
13. Reddy, M. M.; Punniyamurthy, T.; Iqbal, J., *Tetrahedron Lett.*, **1995**, 36(1), 159-162.
14. Sheldon, R. A.; Kochi, J. K. *Metal-catalyzed Oxidations of Organic Compounds;* Academic: New York, 84, 1981, pp. 25-26.
15. Drago, R. S., Activation of Molecular Oxygen by Transition Metal Complexes. In *Dioxygen Activation and Homogeneous Catalytic Oxidation*; Simandi, L. I., Ed.; Elsevier: Amsterdam, 1991; pp. 83-91.
16. Bolland, J. L., *Trans. Faraday Soc.*, **1950**, 46, 358-367.
17. Beckwith, A. L. J.; Phillipou, G., *Aust. J. Chem.*, **1976**, 29, 1277-1294.
18. Bridger, R. F.; Russell, G. A., *J. Am. Chem. Soc.*, **1963**, 85, 3754-3765.
19. Howard, J. A.; Ingold, K. U., *Can. J. Chem.*, **1967**, 45, 793-802.
20. Walling, C.; Thaler, W., *J. Am. Chem. Soc.*, **1961**, 83, 3877-3884.
21. Kooyman, E. C., *Disc. Faraday Soc.*, **1951**, 10, 163-174.
22. Ingold, K. U., *Intern. Symp. Free Radical Soln.*, Univ. of Michigan, Ann Arbor, Mich., **1966**, 49-67.
23. Russell, G .A.; De Boer, C., *J. Am. Chem. Soc.*, **1963**, 85, 3136.
24. Walling, C.; Rieger, A. L.; Tanner, D. D., *J. Am. Chem. Soc.*, **1963**, 85, 3129-3134.
25. We have not determined the exact stereochemical configuration of the oxirane ring in **4** and **6**, though GCMS analysis indicates two isomers for **4**, and only one for **6**. Similarly, we cannot say whether **7** is a mixture of two epimers or not.
26. Lajunen, M.; Koskinen, A. M. P., *Tetrahedron. Lett.*, **1994**, 35 (25), 4461-4464.
27. Rothenberg, G.; Wiener, H.; Sasson, Y., *J. Mol. Catal.*, submitted for publication, Sept. 1997.
28. Courtneidge, J. L.; Bush, M., *J. Chem. Soc. Chem. Commun.*, **1989**, 1227-1229.
29. Villenave, J. -J.; Francois, H.; Lalande, R., *Bull. Soc. Chim. Fr.*, **1970**, 599-601.
30. Kolehmainen, E.; Laihia, K.; Heinanen, M.; Rissanen, K.; Frolich, R.; Korvola, J.; Manttari, P.; Kauppinen, R., *J. Chem. Soc. Per. 1.*, **1993**, 641-648.
31. Abraham, R. J.; Cooper, M. A.; Whittaker, D., *Org. Magn. Reson.*, **1973**, 5 (11), 515-516.
32. Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A., *Conformational Analysis;* Interscience: New York, **1965**, pp. 109-111.
33. Frankel, E. N.; Garwood, R. F.; Vinson, J. R.; Weedon, B. C. L., *J. Chem. Soc. Per. 1*, **1982**, 2707-2713.
34. Cross, B.; Whitham, G. H., *J. Chem. Soc.*, **1961**, 1650-1654.
35. Detty, M. R.; Paquette, L. A., *J. Org. Chem.*, 43(6), **1978**, 1118-1121. Although this study concerns bishomocycloheptatrienes, where the allylic carbon is part of the cyclopropyl ring, we reason that a similar effect would ease HA from the methylenic positions in **1**.
36. Bunce, N. J.; Hadley, M., *J. Org. Chem.*, **1974**, 39(15), 2271-2276.
37. King, H. C. A.; Koros, E.; Nelson, S. M., *J. Chem . Soc.*, **1963**, 5449-5459.
38. This reaction can be performed with different catalysts (isolated yields 45-70% for CrO_3, $CuCl_2$) and also in the absence of catalyst (yield ca. 30 % after 25 min).
39. Bohlmann, F.; Zeisberg, R.; Klein, E., *Org. Magn. Reson.*, **1975**, 7, 426-432.
40. Giuseppetti, G.; Tadini, C.; Bettinetti, G. P., *Acta Cryst.*, **1992**, C 48, 148-150.
41. Baines, D. A.; Cocker, W., *J. Chem. Soc. Per. 1*, **1975**, 2232-2237.