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α-OXIDATION OF KETONES USING N-CATION RADICALS

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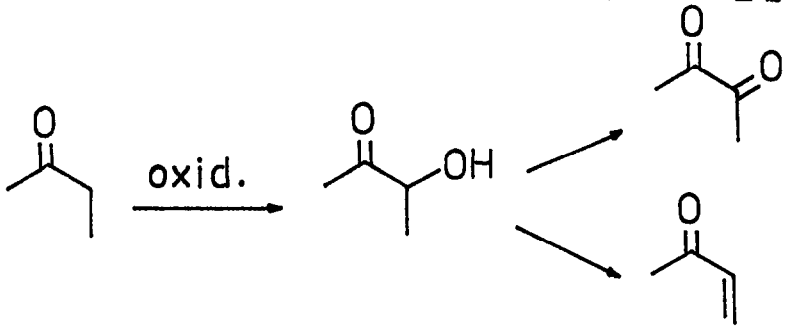
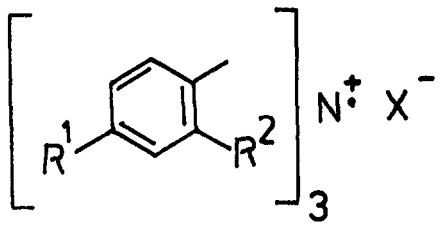
Abstract: Six-membered ring ketones and acyclic ketones were oxidized by stable triarylamminium radical cations in moist acetonitrile at room temperature in the presence of a base to α-hydroxy ketones in good yield. Five-membered ring ketones gave the corresponding α,ß-unsaturated compounds.

α-Hydroxylation of carbonyl compounds such as esters, ketones and 1,3-dicarbonyl compounds is an important operation in organic synthesis because the α-hydroxylated derivatives are useful synthons for further syntheses.[1] α-Hydroxy carbonyl compounds can be obtained from the starting carbonyl compounds by different oxidation methods. Recently new oxygen transfer reagents were used for this transformation. Enolates of ketones and esters were oxidized with MoO_5·pyridine·HMPT,[2] 2-sulfonyl-oxaziridines [3] or $PhI(OAc)_2$ [4] to the corresponding α-hydroxy compounds. Silyl enol ethers and silyl ketene acetals could be transformed into the α-hydroxy carbonyl compounds by oxidation with m-chloroperoxybenzoic acid, [5] $PhIO/BF_3 \cdot Et_2O/H_2O$, [6] singlet oxygen [7] or $Pb(OAc)_4$. [8]

In this paper we report the results obtained from the oxidation of ketones to α-hydroxy ketones, to α-diketo compounds or to α,ß-unsaturated ketones with stable radical cation salts of triarylamines 1-3. [9, 10]



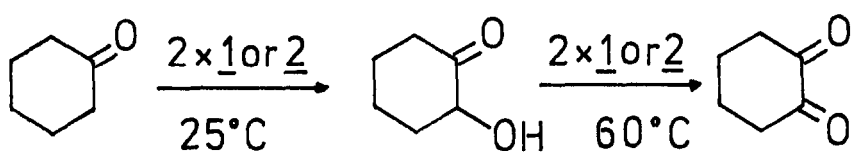
Radical cation salts 1 and 3 were used by Steckhan and co-workers for the oxidative cleavage of benzylic ethers and esters under mild conditions. [11, 12]



1: R^1=Br, R^2=H, X= $SbCl_6$
2: R^1=R^2=H , X= BF_4
3: R^1=R^2=Br, a: X= ClO_4
b: X= $SbCl_6$

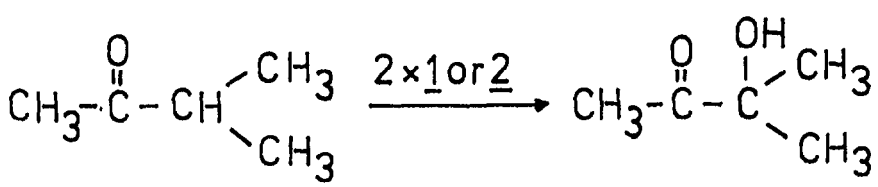
We treated some ketones, dissolved in acetonitrile (containing small amounts of water), with the radical cation salts 1-3 in the presence of a base at predominantly room temperature. The radical cations were used as their stable salts (1, 2, 3b) or generated in situ electrochemically from the corresponding amine 3a . The experimental conditions and the results of the reaction of radicals 1-3 with different ketones are given in Table 1.

Oxidation of cyclohexanone 4 at room temperature gave 2-hydroxycyclohexanone 5 in good yield (70-90%) with high conversion of 4. At higher temperatures (60 °C) only the higheroxidation product 6 is formed.



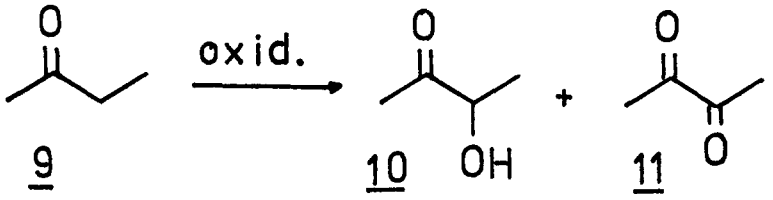
4 5 6

Isopropylmethylketone 7 was converted under the same conditions to 2-hydroxy-2-methylbutan-3-one 8 (50-70%).

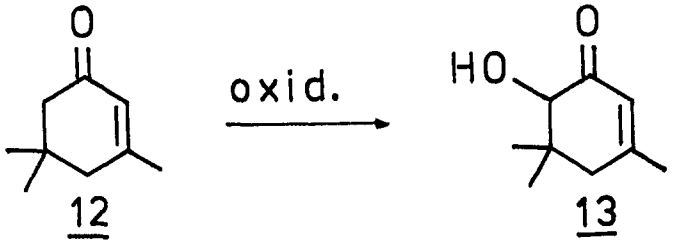


7 8

In the case of ethylmethylketone 9 a mixture of the α-hydroxy ketone 10 and butane-2,3-dione(11) is produced. The proportionsof 10 and 11 in this reaction depend upon the molar ratios of the starting ketone and the radical cation.



The synthetic value of this oxidation method is demonstrated by the "one pot conversion" of isophorone 12 to α-hydroxyisophorone (13). This method provides a good alternative process for the synthesis of 13.



Further, the yield of 13 is higher than in the case when $Pb(OAc)_4$ is used as oxidant [13] and comparable with the m-chloroperoxybenzoic acid procedure. [5] Overoxidation of 13 can be reduced when an excess of starting material 12 is employed.

In contrast to the oxidation of 12, hydroxy compounds 15 and 16 could not be obtained by the reaction of cyclohexenone (14) with cation radicals, and hydroquinone (17) and catechol (18) were always isolated as the major products. In this case the overoxidation of 14 is favoured by the formation of a stable aromatic system.

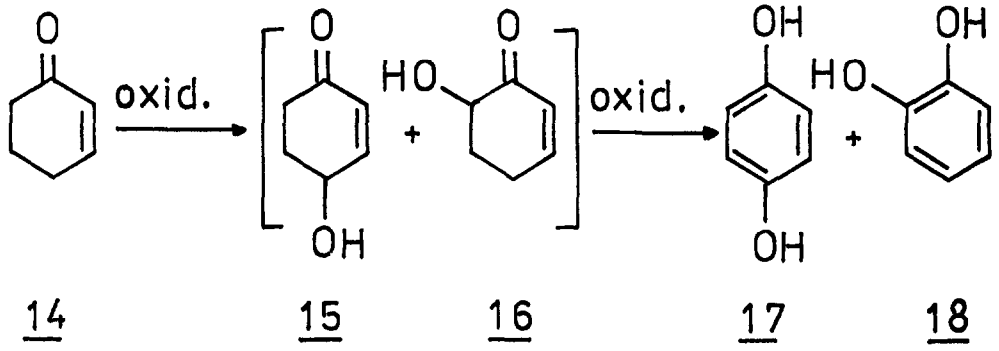


Table 1: Conversion of ketones using cation radicals 1-3, reaction conditions and yields

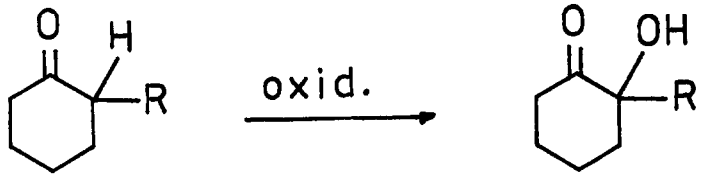
Ketone	Molar ratio [a]	Reaction conditions [b]	Products (Yield %) [c] [Conversion] [d]
4	1:2:1	1; A; X; 25 °C; 10 h	5 (88[g], 70[e]) [90]
4	1:2:1	2; A; X; 25 °C; 10 h	5 (71[e])
4	1:2:1	1; B; X; 25 °C; 10 h	5 (91[g], 75[e]) [90]
4	1:2:1	2; B; X; 25 °C; 10 h	5 (73[e])
4	1:4:2	1; A; X; 60 °C; 17 h	6 (72[f])
4	1:4:2	1; B; X; 60 °C; 17 h	6 (79[f])
7	1:2:2	1; B; X; 25 °C; 8 h	8 (70[f])
7	1:2:1	2; A; X; 25 °C; 8 h	8 (51[e])
7	1:2:1	2; B; X; 25 °C; 8 h	8 (63[e])
9	1:2:2	1; A; X; 25 °C; 9 h	10 (40[f]) 11 (45[f])
9	1:3:1	1; B; X; 25 °C; 10 h	10 (18[f]) 11 (68[f])
9	1:3:1	2; A; X; 25 °C; 10 h	10 (33[e]) 11 (48[e])
9	1:4:1	2; B; X; 25 °C; 12 h	10 (10[f]) 11 (75[f])
12	1:2:1	1; A; X; 25 °C; 12 h	13 (30[f])
12	1:2:1	1[i]; A; Y; 25 °C; 13 h	13 (25[f])
12	1:3:1	1; A; X; 25 °C; 15 h	13 (<10[f])
12	10:2:1	1; A; X; 25 °C; 5 h	13 (50[e]) [10]
12	5:2:1	1; A; X; 25 °C; 7 h	13 (89[f]) [20]
12	2:2:1	1; A; X; 25 °C; 9 h	13 (82[f], 70[e]) [50]
12	1:2:1	3b; A; X; 25 °C; 3 h	13 (40[f])
12	1:1:1	3b; A; X; 25 °C; 2 h	13 (56[f]) [50]
14	1:3:1	1; A; X; 25 °C; 10 h	17 (25[e]) 18 (30[e])
14	1:3:1	2; A; X; 25 °C; 10 h	17 (30[e]) 18 (37[e])
14	1:3:1	2; B; X; 25 °C; 10 h	17 (41[e]) 18 (27[e])
19a	1:2:2	1; A; X; 25 °C; 12 h	20a (30[f]) [75]
19a	1:2:2	1; D; X; 25 °C; 15 h	20a (55[e]) [65]
19a	1:2.2[l]:2	3a[h]; A; X; 25 °C; 70 h	20a (47[f]) [20]

Ketone	Molar ratio [a]	Reaction conditions [b]	Products (Yield %) [c] [Conversion] [d]
19b	1:2:2	1; A; X; 25 °C; 12 h	20b (65[f]) [85]
19b	1:2:2	1; C; X; 25 °C; 17 h	20b (45[e]) [98]
19b	1:2:2	1; D; X; 25 °C; 17 h	20b (55[e])
19b	1:2.2[l]:2	3a[h]; A; X; 25 °C; 70 h	20b (46[f]) [80]
19b	1:2:2	1; D; Z; 25 °C; 4 h	20b (15[e]) 25 (15[e])
19b	1:2:2	1; E; Z; 25 °C; 6 h	26[k] (20[f])
19b	1:2:2	1; A; Z; 25 °C; 11 h	20b (7[f]) 25 (25[f]) 26[k] (3[f]) [97]
21a	1:2:2	1; A; X; 25 °C; 10 h	22a (50[e]) [76]
21a	1:2.2[l]:2	3a[h]; A; X; 25 °C; 70 h	22a (53[f]) [62]
21a	1:2:2	1; D; X; 25 °C; 17 h	22a (80[f]) [63]
21b	1:2:2	1; A; X; 25 °C; 12 h	22b[j] (40[f]) [65]
21b	1:2.2[l]:2	3a[h]; A; X; 25 °C; 60 h	22b (30[f]) [60]
23	1:2:2	1; A; X; 25 °C; 10 h	24 (40[e])

a) Amount of ketone: radical: base; b) base: A - sym. collidine, B-Na_2CO_3, 10 H_2O, C - Li_2CO_3, D - K_2CO_3, E - $NaOCH_3$, solvent: X - $MeCN/H_2O$, Y - CH_2Cl_2/H_2O, Z = MeCN/MeOH; c) yield based on conversion; d) conversion based on the ketone introduced, no data given- conv. = 100 %; e) isolated product; f) yield based on gas chromatography data; g) yield (GC) after reduction to cyclohexane-1,2-diol by $LiAlH_4$; h) electrochemical oxidation with tris-(2,4-dibromophenyl)amine as mediator; i) 1 dissolved in CH_2Cl_2; j) characterization of the product after preparative GC; k) only identified by GC/MS; l) amount of charge.

Regioselectivity of the reaction:

Oxidation of ketones 7 and 9 shows, that the hydroxylation reaction occurs on the more substituted side of the carbonyl group. In order to prove this observation we oxidized the substituted cyclohexanone derivatives 19a,b under various conditions (Table 1). In all cases we found only the α-hydroxy compounds 20a,b, the corresponding isomers were not detected, whereas the Moriarty oxidation of 19a gave a 6:1 mixture of 20a and the isomeric 2-hydroxy-6-methylcyclohexanone.[4]



19a,b

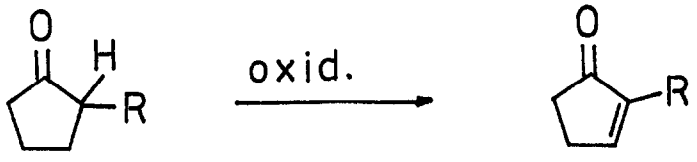
a: R= CH_3
b: R= C_6H_5

20a,b

a: R= CH_3
b: R= C_6H_5

The MoO_5 oxidation of 19b in the presence of LDA led to the isomeric 2-hydroxy-6-phenylcyclohexanone (62% yield).[2] In MoO_5 oxidation of 19b with KH as a base, a mixture of isomeric hydroxy ketones containing 30% of 20b was formed.[2]

Oxidation of the substituted cyclopentanone derivatives 21a,b using cation radicals 1 or 3a led to the α,ß-unsaturated ketones 22a,b.



21a,b

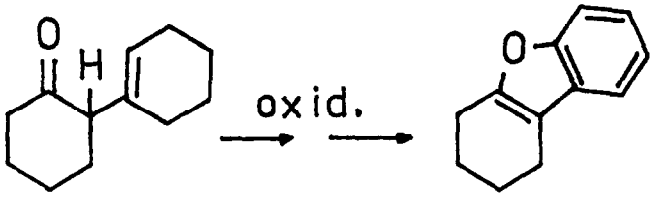
a: R= CH_3
b: R= tert-C_4H_9

22a,b

a: R= CH_3
b: R= tert-C_4H_9

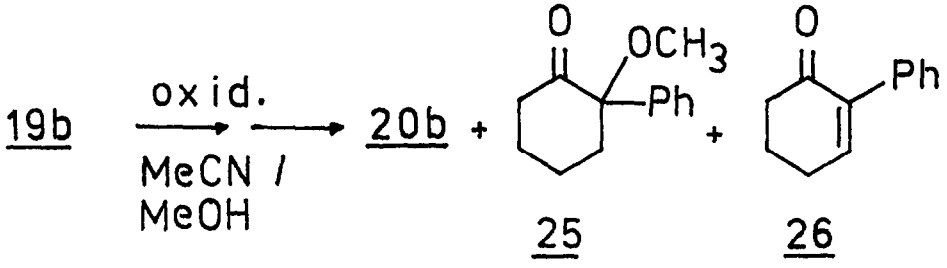
Alternative methods for the preparation of 22b involve a 5-step synthesis[14] and with an overall yield of about 10%. On the other hand, dehydrogenation of substituted cyclic ketones by Pd catalyst yields α,ß-unsaturated ketones with the double bond on the less sterically hindered side of the carbonyl group.[15]

The mechanism of the hydroxylation reaction is not yet clear. It seems likely that the reaction proceeds via enols which are responsible for facile electron transfer to the cation radicals. The oxidation of 2-(cyclohexen-1-yl)cyclohexanone (23) with 1 in the presence of sym. collidine to the cyclic ether 24 indicates that a cationic intermediate, which is formed from a radical intermediate, must play a role during the oxidation of ketones by cation radicals 1 - 3 .



23 24

Other experimental observations are in accord with this thesis. Oxidation of 19b with 1 in the presence of methanol (instead of water) affords a mixture of both α-hydroxy compound 20b and α-methoxy compound 25. Using sodium methanolate as a base the oxidation of 19b by 1 resulted in the α,ß-unsaturated ketone 26 as a main product. The formation of the hydroxy compound 20b may result via the ring opening an intermediate epoxide.[16]



EXPERIMENTAL

Melting points were determined using a Boetius melting point apparatus and are uncorrected. IR spectra were obtained using Specord 71/IR (VEB Carl Zeiss Jena) spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were recorded with a Bruker HX 90R spectrometer using hexamethyldisiloxane (HMDS) as an internal standard. Mass spectra were obtained using Hewlett Packard GC/MS 5992B apparatus at 70 eV. For GC analysis a Giede gaschromatograph 18.3 (VEB Chromatron Berlin) was used.

Starting material: ketones 4, 7, 9 and 12 were commercially available from VEB Laborchemie Apolda. Cyclohexenone 14 was prepared by oxidation of cyclohexene with CrO_3.[17] 2-Methylcyclohexanone 19a was available from 2-methylcyclohexanol by oxidation with the same reagent.[18] 2-Phenylcyclohexanone 19b was obtained from the reaction of 2-chlorocyclohexanone with phenylmagnesium bromide.[19]

Ketone 23 was prepared by the base catalyzed autocondensation of cyclohexanone.[20] 2-Methylcyclopentanone 21a was obtained by methylation of cyclopentanone according to the procedure of Stork.[21] 2-tert-Butylcyclopentanone 21b was prepared from cyclopentanone via the corresponding trimethylsilylenol ether by alkylation with tert-BuCl/$TiCl_4$.[22] The cation radical salts 1-3 were available by known methods.[10-12]

General procedure: a) 5-10 mmol of the ketones 4, 7, 9, 12, 14, 19a,b, 21a,b and 23 were dissolved in 50 ml pure acetonitrile containing 2 ml of water or methanol. The mixture was treated with 5-20 mmol of base (see Table 1) and stirred at room temperature. The cation radical salt was added to the mixture in 1-1.5 g portions. After the blue or green colour of 1-3 had disappeared (4-20 h), the reaction mixture was filtered and the filtrate was poured into 300 ml of water and the resulting mixture neutralized with $NaHCO_3$. The products were isolated by steam distillation followed by saturation of the distillate with NaCl, extraction with ether, drying over $MgSO_4$ and evaporation of the solvent in vacuo. Liquid products were analyzed by GC, GC/MS and NMR spectra or were distilled and compared with authentic samples by GC. Solid products were identified by their mixed melting point with authentic samples.

b) 10 mmol of the ketone was dissolved in a solution of $Et_4N^+ClO_4^-$ (10^{-1} mol · l^{-1}) in 120 ml of electrochemically pure acetonitrile and 2 ml of water. The resulting mixture was poured into a divided glass cell containing a platinium anode, a graphite cathode and a standard calomel electrode. The mixture was stirred and degassed with argon and 20 mmol of the base and 1 mmol of tris-(2,4-dibromophenyl)amine were added to the mixture. The electrochemical oxidation was carried out at a potential of 1.7 V versus s.c.e. up to 2000 C. The isolation process was the same as described under a).

Analytical data of the isolated products:

α-Hydroxycyclohexanone (5): 5 was isolated by using a continous extraction apparatus, the crude product was crystallized from MeOH/H_2O, m.p. 90 °C, m.p [23] 90 °C (no depression of mixed melting point with an authentic sample. IR(KBr): 3350 (OH), 2980 (CH), 1000 (CO) cm^{-1}.

Cyclohexane-1,2-dione (6): comparison with an authentic sample [24] by GC (3 m silicon rubber, 80-120 °C, 6 °C/min).

2-Hydroxy-2-methylbutan-3-one (8): purified by distillation b.p. 140-142°C, identical with an authentic sample [25] (b.p. 141 °C) - GC: 5 m Apiezon (basic) 60-150 °C (6 °C/min).

2-Hydroxybutan-3-one (10): purified by distillation b.p. 143-144 °C, identical with an authentic sample [26] (b.p. 144 °C) - GC: 5 m Apiezon (basic) 60-150 °C (6 °C/min).

α-Hydroxyisophorone (13): excess of starting material 12 was removed by distillation in vacuo (b.p. 100 °C/20 mm) and the residue crystallized from n-hexane m. p. 43 °C (no depression of mixed melting point with an authentic sample [13] m. p. 44 °C). - GC 3 m Apiezon, 160 °C.

Oxidation of 14 to 17 and 18: the oxidation mixture from 14 was directly extracted with ether after quenching with water/$NaHCO_3$ without steam distillation. Crude 17 was obtained by treating the residue with benzene and purified by crystallization from light petroleum m. p. 170 °C (no depression of mixed melting point with an authentic sample from VEB Laborchemie Apolda), 18 was obtained from the mother liquid by treating with light petroleum and was purified by crystallization from light petroleum m. p. 105 °C (no depression of mixed melting point with an authentic sample from VEB Laborchemie Apolda).

2-Hydroxy-2-methylcyclohexanone (20a): the mixture of 20a and starting material 19a was directly analyzed by GC (Carbowax 2000, 80 °C) GC/MS and ^{13}C NMR. GC/MS: m/e 128 (M^+); ^{13}C NMR ($CDCl_3$): δ 213.5 (s in off resonance), 76.0 (s), 42.0 (t), 37.95 (t), 27.82 (t), 25.39 (q), 22.96 (t) ppm.

2-Hydroxy-2-phenylcyclohexanone (20b): light yellow oil; GC-purity: > 95% (Carbowax 2000, 180 °C); GC/MS: m/e 190 (M^+); ^{13}C NMR ($CDCl_3$): δ 213.2 (s), 140.51 (s), 129.31 (d), 128.53 (d), 126.73 (d), 80.41 (s), 39.30 (t), 28.52 (t), 23.52 (t) ppm.

2-Methylcyclopent-2-en-1-one (22a): the resulting mixture of starting material 21a and 22a was analyzed directly by GC (Carbowax 2000, 80 °C), GC/MS and ^{13}C NMR. GC/MS: m/e 96 (M^+); ^{13}C NMR ($CDCl_3$): δ 210.14 (s), 158.01 (d), 142.01 (s), 34.21 (t), 26.36 (t), 10.12 (q) ppm: identical with the reported ^{13}C NMR data.[27]

2-tert-Butylcyclopent-2-en-1-one (22b): Carbowax 2000, 90 °C; GC/MS: m/e 138 (M^+); ^1H NMR characterization of 22b after preparative GC - ^1H NMR (CCl_4): δ 1.07 (s,9H,$3CH_3$); 2.04-2.42 (m,4H,$2CH_2$), 6.79 (t,1H,olefinic CH) ppm (reported data see [15]).

8,9,10,11-Tetrahydro-dibenzofuran (24): light yellow oil after distillation of impurities in vacuo (50 °C, 20 mm); GC-purity: > 95% (Carbowax 2000, 150 °C); GC/MS: m/e 172 (M^+); ^{13}C NMR ($CDCl_3$): δ 154.33 (s), 153.91 (s), 128.80 (s), 122.87 (d), 122.03 (d), 118.25 (d), 112.74 (s), 110.70 (d), 23.40 (t), 22.92 (t), 22.68 (t), 20.40 (t) ppm; identical to the

^{13}C-NMR-spectrum of an authentic sample (b. p. 138 °C/15 mm) prepared by the method of Ebel [28] from 2-chlorocyclohexanone and sodium phenolate.

2-Methoxy-2-phenylcyclohexanone (25): the reaction mixture of 20b and 25 was analyzed directly by GC/MS and NMR spectroscopy. GC/MS: m/e 204 (M^+); ^{1}H NMR ($CDCl_3$): δ 0.51-2.48 (m,8H,4CH_2), 2.89 (s,3H,OCH_3), 6.93 (m,5H, aromatic protons); ^{13}C NMR ($CDCl_3$): δ 209.4 (s), 137.3 (s), 128.38, 127.96, 127.72, 85.36 (s), 51.20 (q), 40.23 (t), 37.48 (t), 22.71 (t), 21.96 (t).

REFERENCES AND NOTES

This paper is dedicated to Professor Dr. Ch. Rüchardt, Albert-Ludwigs-University of Freiburg (Breisgau) on the occasion of his 60th birthday.

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