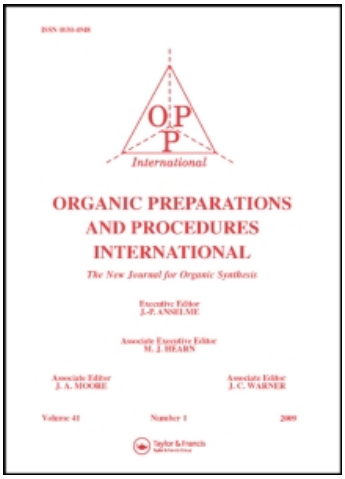

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PREPARATION OF α,α-DIALKYL-β-HALOKETONES

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PREPARATION OF α,α-DIALKYL-β-HALOKETONES

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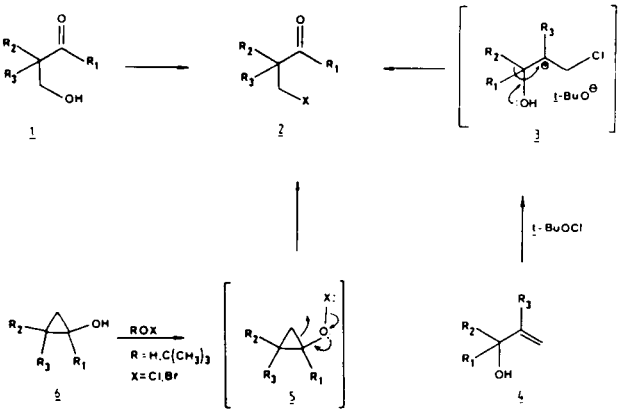
β-Haloketones are a class of bifunctional compounds, the synthesis of which has already been described in a number of publications.[1-24] They can be prepared from β-hydroxyketones 1 by substitution of the hydroxyl group by a halogen atom,[1-13] or from cyclopropanols 6 and allylic alcohols 4 by reaction with hypochlorites or hypobromites.[14-24] For the preparation of large quantities of β-haloketones 2 with two substituents in the α-position (R_2 = R_3 = alkyl) the transformation of β-hydro-

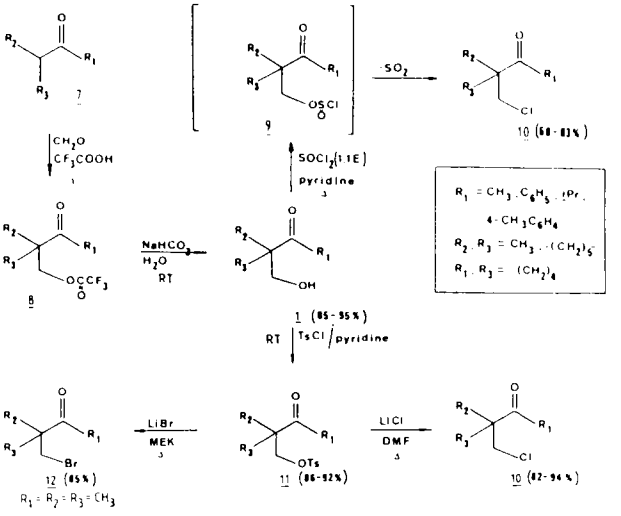


SCHEME I

xyketones 1 to β-haloketones 2 seems to be the most straigth-forward method. Recently we required substantial amounts of

β-halogenated ketones. The synthetic methods described in the literature raised several problems. This article describes an alternative method for the preparation of α,α-dialkyl-β-haloketones free of side-reactions. The synthesis of compounds 2 is divided into two parts, namely the formation of β-hydroxyketones 1 and the transformation of β-hydroxyketones into the corresponding β-haloketones.

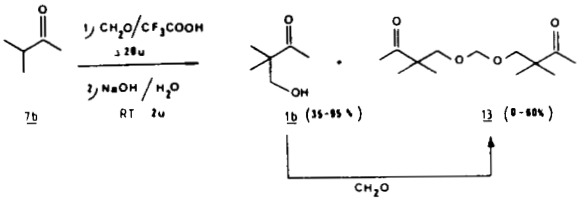
The formation of β-hydroxyketones 1 via acid catalyzed reaction of ketones with formaldehyde, according to a literature method[7], was less attractive for large-scale preparations due to the formation of numerous side-products depending upon the



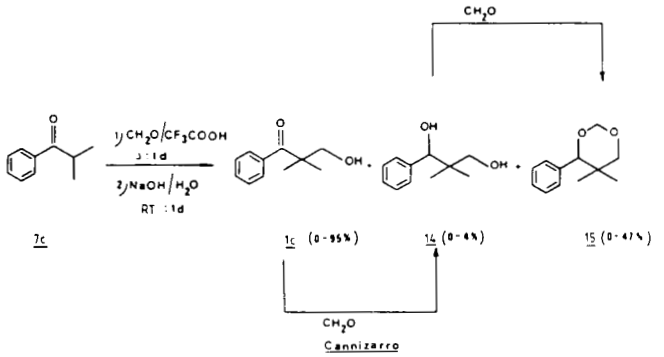
SCHEME II

reaction conditions. However, this method was taken as a basis for further improvements of the preparation of β-hydroxyketones. The first part of this method, namely the reaction of ketone 7 with paraformaldehyde in trifluoroacetic acid with the formation of trifluoroacetate 8, was easily performed at reflux temperature and the transformation could be followed by ^{1}H-NMR.

It was found that the quantity of the expensive solvent (i.e. TFA) used to perform this transformation could be reduced to two molar equivalents in comparison with the original report.[7] The second part of the formation of β-hydroxyketones 1, namely the transformation of β-trifluoroacetoxyketones 8 to the corresponding β-hydroxyketones 1, gave problems (Table 1, entries 1-15). The literature procedure[7], namely the transformation of



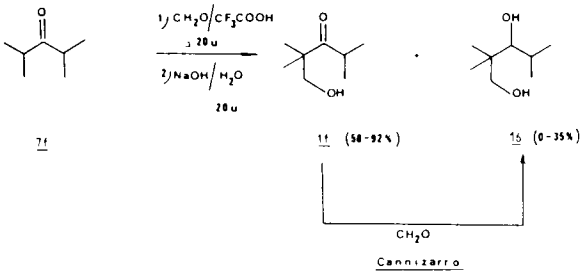
SCHEME III



SCHEME IV

of 8 to 1 using an aqueous sodium hydroxide solution, gave, depending upon the reaction conditions and especially the molar quantities, many side-products. The aqueous workup of the trifluoroacetate derived from the reaction of 3-methyl-2-butanone 7b ($R_1 = R_2 = R_3 = CH_3$) with paraformaldehyde in trifluoroacetic acid afforded, with the expected 4-hydroxy-3,3-dimethyl-2-butanone 1b, also variable amounts (up to 60%) of the acetal 13 (Table 1, entry 4). The reaction of isobutyrophenone 7c

(R_1 = Ph,R_2 = R_3 = Me) with paraformaldehyde in trifluoroacetic acid, followed by workup of the reaction mixture with an aqueous sodium hydroxide solution afforded three reaction products, namely the expected ketone 1c, 1-phenyl-2,2-dimethyl-1,3-propanediol 14 and 4-phenyl-5,5-dimethyl-1,3-dioxane 15 (Table 1, entries 7 and 8). The reaction of diisopropyl ketone 7f (R_1 = i-Pr,R_2 = R_3 = Me) with the same reagents gave, in addition to β-hydroxyketone 1f, diol 16 in variable amounts (0-35%) (Table 1 : entry 13). Compounds 14 and 16 were formed during the workup by the Cannizarro reaction from the excess formaldehyde present in the medium through reaction with β-hydroxy-



SCHEME V

ketones 1c and 1f. Dioxane 15 was formed from formaldehyde and propanediol 14, while dione 13 resulted from reaction of formaldehyde with two molecules of β-hydroxyketone 1b. In order to avoid all these side reactions the original literature procedure[7] was modified. Instead of using an aqueous sodium hydroxide solution, an aqueous sodium bicarbonate or aqueous potassium carbonate solution was used. When this adapted method was applied no side products were found and β-hydroxyketones 1 were isolated as the sole compounds in high yields (85-95%). The reaction conditions and the spectral data of β-hydroxyketones 1 are compiled in Tables 1, 2 and 3.

2. TRANSFORMATION OF β-HYDROXYKETONES INTO β-HALOKETONES

The transformation of β-hydroxyketones 1 into β-haloketones 2 was performed according to known principles from the literature. By reaction of β-hydroxyketones 1 with p-toluenesulfonyl chloride in pyridine at room temperature, β-tosyloxyketones 11 were formed in nearly quantitative yields (Table 1, entries 16-21). On reaction of compounds 11 with lithium chloride in dimethylformamide, β-chloroketones 10 were produced while on reaction of 11 with lithium bromide in 2-butanone (MEK) β-bromoketone 12 was the only product isolated (Table 1, entries 27-34). An alternative method for the preparation of β-hydroxyketones consisted of the reaction of β-hydroxyketones 10 with thionyl chloride in pyridine (Table 1; entries 23 and 24). It was somehow surprising that, when this reaction was performed at 0°C it was not possible to isolate compound 10 from the reaction mixture. The isolated compound was a product with an AB-system (^{1}H-NMR) in the region of 4 ppm and structure 9 was proposed for the isolated compound. On the other hand, β-chloroketones 10 were the only isolated products when the reaction of β-hydroxyketones 1 was performed with thionyl chloride in pyridine at higher temperature or when the reaction mixture obtained at 0°C was warmed up. The latter alternative method was hardly used for the preparation of β-chloroketones 10, because via this method the yield of the compound 10 was lower than through transformation of 1 into ketone 10 via tosylate 11. The spectral data of β-haloketones 10 and 12 and β-tosyloxyketones 11 are given in Tables 2 and 3.

In conclusion it can be stressed that an improved method for

Table 1. Preparation of β-Hydroxyketones 1, β-Tosyloxyketones 11 and β-Haloketones 10 and 12.

Entry	Starting Compound	R_1	R_3	R_2	Reaction Conditions[a]		Yield (%)[b]	bp./mp.
1	7a	Me	$-(CH_2)_5-$		CH_2O/CF_3COOH (1.1E/2E) Δ 8h	$NaOH/H_2O$ (2N/5E) RT 10h	1a : 95%	bp. 131-133°C/ 10mm Hg
2	7a	Me	$-(CH_2)_5-$		CH_2O/CF_3COOH (1.1E/2E) Δ 8h	K_2CO_3/H_2O (10E/10%) RT 4d	1a : 100%	bp. 131-133°C/ 10mm Hg
3	7b	Me	Me	Me	CH_2O/CF_3COOH (1.3E/5E) 24h 60°C	$NaOH/H_2O$ (2N/2E) RT 2h	1b : 92%[c]	bp. 85-90°C/ 18mm Hg
4	7b	Me	Me	Me	CH_2O/CF_3COOH (1.5E/2E) Δ 20h	$NaOH/H_2O$ (2N/5E) RT 2h	1b : 35%[d]	bp. 45-48°C/ 0.05mm Hg
5	7b	Me	Me	Me	CH_2O/CF_3COOH (1E/2E) Δ 7h	$NaHCO_3/H_2O$ (10E/10%) RT : 1d	1b : 95%	bp. 85-90°C/ 18mm Hg
6	7b	Me	Me	Me	CH_2O/CF_3COOH (1E/2E) Δ 7h	K_2CO_3/H_2O (10E/10%) RT 4d	1b : 92%	bp. 85-90°C/ 18mm Hg
7	7c	C_6H_5	Me	Me	CH_2O/CF_3COOH (1E/2E) Δ 12h	$NaOH/H_2O$ (2N/5E) RT 1d	1c : 79%[e,f]	bp. 100-104°C/ 0.2mm Hg
8	7c	C_6H_5	Me	Me	CH_2O/CF_3COOH (1E/2E) Δ 2d	$NaOH/H_2O$ (2N/5E) RT 1d	1c : 0%[g]	-
9	7c	C_6H_5	Me	Me	CH_2O/CF_3COOH (2E/2E) Δ 22h	K_2CO_3/H_2O (10E/10%) RT 4d	1c : 90%	bp. 100-104°C/ 0.2mm Hg
10	7d	$-(CH_2)_4-$		Me	CH_2O/CF_3COOH (1.1E/2E) Δ 2h	$NaHCO_3/H_2O$ (10E/10%) RT 3d	1d : 90%	bp. 95-100°C/ 8mm Hg or 80°C/0.1mm Hg
11	7e	$4\text{-}MeC_6H_4$	Me	Me	CH_2O/CF_3COOH (1.1E/2E) Δ 8h	$NaHCO_3/H_2O$ (10E/10%) RT 3d	1e : 85%[h]	-
12	7f	i-Pr	Me	Me	CH_2O/CF_3COOH (1E/2E) Δ 20h	$NaOH/H_2O$ (2N/5E) RT 2h	1f : 85%[i,j]	bp. 87-90°C/ 13mm Hg
13	7f	i-Pr	Me	Me	CH_2O/CF_3COOH (2E/2E) Δ 20h	$NaOH/H_2O$ (10E/2N) RT 20h	1f : 58%[k]	bp. 87-90°C/ 13mm Hg
14	7f	i-Pr	Me	Me	CH_2O/CF_3COOH (2E/2E) Δ 20h	$NaHCO_3/H_2O$ (10E/10%) RT 2d	1f : 92%	bp. 87-90°C/ 13mm Hg
15	7f	i-Pr	Me	Me	CH_2O/CF_3COOH (2E/2E) Δ 20h	K_2CO_3/H_2O (10E/10%) RT 2d	1f : 90%	bp. 87-90°C/ 13mm Hg
16	1a	Me	$-(CH_2)_5-$		TsCl/pyridine (1.1E/10%) RT 10h		11a : 87-92%	mp. 46°C
17	1b	Me	Me	Me	TsCl/pyridine (1.2E/10%) RT 20h		11b : 91%[l]	mp. 56°C

18	1c	C_6H_5	Me	Me	TsCl/pyridine (1.1E/10%) RT 18h	11c : 86%[m]	mp. 71°C
19	1d	$-(CH_2)_4-$	Me	Me	TsCl/pyridine (1.1E/10%) RT 2d	11d : 90%	mp. 56°C
20	1d	4-MeC_6H_4	Me	Me	TsCl/pyridine (1.1E/10%) RT 4d	11e : 83%[n]	mp. 59°C
21	1f	i-Pr	Me	Me	TsCl/pyridine (1.1E/10%) RT 2d	11f : 92%[o,p]	-
22	1b	Me	Me	Me	HCl (conc.) (10E) RT 20h	10b : 0%	-
23	1b	Me	Me	Me	$SOCl_2$/pyridine (1E/10%) 0° 2h	9 : 83%[q]	-
24	1b	Me	Me	Me	$SOCl_2$/pyridine (1E/10%) Δ 1h	10b : 68%[r]	bp. 60-65°C/ 15mm Hg
25	11b	Me	Me	Me	HCl (10E) RT 20h	10b : 0%	-
26	11b	Me	Me	Me	HCl (10E) Δ 48h	10b : 0%	-
27	11b	Me	Me	Me	LiCl/MEK (2E/10%) Δ 48h	10b : 0%[s]	-
28	11b	Me	Me	Me	LiCl/DMF (2E/10%) Δ 3d	10b : 82%[r]	bp. 60-65°C/ 15mm Hg
29	11b	Me	Me	Me	LiBr/acetone (2E/10%) Δ 2d	12 : 85%[t]	-
30	11a	Me	$-(CH_2)_5-$		LiCl/DMF (2E/10%) Δ 10h	10a : 90%	bp. 110-112°C/ 10mm Hg
31	11c	C_6H_5	Me	Me	LiCl/DMF (2E/10%) Δ 24h	10c : 85%[u]	bp. 82-86°C/ 0.1mm Hg
32	11d	$-(CH_2)_4-$	Me	Me	LiCl/DMF (2E/10%) Δ 8h	10d : 94%	bp. 102-109°C/ 12mm Hg
33	11e	4-MeC_6H_4	Me	Me	LiCl/DMF (1.5E/10%) Δ 1d	10e : 88%[v]	bp. 105-112°C/ 0.1mm Hg
34	11f	i-Pr	Me	Me	LiCl/DMF (2E/10%) Δ 3d	10f : 90%[p]	bp. 75-78°C/ 13mm Hg

a) E = molar equivalents; Δ = reflux; h = hours; RT = room temperature; N = normal; conc = concentrated. b) Compounds 1a, 1d, 10a, 10d, 11a, 11d, 13, 14, 15 and 16 gave correct elemental analyses. c) Lit.[25] bp. 78-79°C/14mm Hg. d) 60% 5,7-dioxa-3,3,9,9-tetramethyl-2,10-undecanedione 13; bp. 98-102°C/0.02mm Hg or 115°C/0.8mm Hg; mp. 50°C. e) Lit.[9] bp. 152-153°C/12mm Hg. f) 4% 1-phenyl-2,2-dimethyl-1,3-propanediol 14; bp. 120-125°C/0.01mm Hg; mp. 78°C; 16% starting material. g) 47% 4-phenyl-5,5-dimethyl-1,3-dioxane 15; 53% starting material. h) This compound was not purified, but immediately transformed into the corresponding tosylate (crude yield given). i) Lit.[26-27] bp. 88°C/12mm Hg. j) Also 8% starting material. k) 35% 2,2,4-Trimethyl-1,3-pentanediol 16. l) Lit.[6] mp. 55.5-56°C; Lit.[28] mp. 55°C. m) Lit.[28] mp. 69-70°C; Lit.[29] mp. 72°C. n) Lit.[30]. o) The tosylate was not isolated, but immediately transformed into the corresponding β-chloroketone. p) Lit.[31]. q) Decomposition at room temperature.[14] r) Lit.[23] bp. 37-40°C/4mm Hg. s) No reaction observed. t) 4-Hydroxy-4-methyl-2-pentanone was also formed by aldol condensation of acetone. u) Lit.[32]. v) Lit.[33].

Table 2. Spectral Data of β-Hydroxyketones 1, β-Tosyloxyketones 11 and β-Haloketones 10 and 12.

Compound	IR (cm^{-1})	^{1}H-NMR
8b	-	δ(CF_3COOH) : 1.21 (6H,s,$(CH_3)_2$); 2.23 (3H,s,CH_3C=O); 4.41 (2H,s,CH_2).
8c	-	δ(CF_3COOH) : 1.51 (6H,s,$(CH_3)_2$); 4.62 (2H,s,CH_2); 7.20-7.80 (5H,m,C_6H_5).
8d	-	δ($CDCl_3$) : 1.23 (3H,s,CH_3); 1.00-3.00 (8H,m,$(CH_2)_4$); 4.34 and 4.48 (2H,2xd,AB, CH_2O).
8f	-	δ(CF_3COOH) : 1.16 (6H,d,J=6.8Hz,$CH(CH_3)_2$); 1.37 (6H,s,$(CH_3)_2$); 3.30 (1H,septet,J=6.8Hz,$CH(CH_3)_2$); 4.50 (2H,s,CH_2).
1a	$\nu_{C=O}$: 1705 ν_{OH} : 3445	δ(CCl_4) : 1.00-2.40 (10H,m,$(CH_2)_5$); 2.21 (3H,s,CH_3C=O); 3.63 (2H,s,CH_2OH); 3.40-3.80 (1H,s,br,OH).
1b	$\nu_{C=O}$: 1710 ν_{OH} : 3450	δ(CCl_4) : 1.08 (6H,s,$(CH_3)_2$); 2.09 (3H,s,CH_3C=O); 3.44 (2H,s,CH_2); 2.80 (1H,s, br,OH).
1c	$\nu_{C=O}$: 1676 ν_{OH} : 3460	δ($CDCl_3$) : 1.37 (6H,s,$(CH_3)_2$); 3.48 (1H,s,br,OH); 3.73 (2H,s,CH_2); 7.20-8.00 (5H,m,C_6H_5).
1d	$\nu_{C=O}$: 1702 ν_{OH} : 3450	δ($CDCl_3$) : 1.10 (3H,s,CH_3); 1.40-2.10 (6H,m,$(CH_2)_3$); 2.20-2.60 (2H,m,CH_2C=O); 3.53 (2H,s,CH_2OH); 3.40-3.50 (1H,s,br,OH).
1f	$\nu_{C=O}$: 1702 ν_{OH} : 3480	δ($CDCl_3$) : 1.06 (6H,d,J=6.2Hz,$CH(CH_3)_2$); 1.20 (6H,s,$(CH_3)_2$); 3.11 (1H,septet, J=6.2Hz,$CH(CH_3)_2$); 3.56 (2H,s,br,CH_2); 2.62 (1H,s,br,OH).
13	$\nu_{C=O}$: 1718	δ($CDCl_3$) : 1.10 (12H,s,2x$(CH_3)_2$); 2.11 (6H,s,2xCH_3C=O); 3.45 (4H,s,2xCH_2O); 4.55 (2H,s,O-CH_2O).
14	ν_{OH} : 3300	δ($CDCl_3$) : 0.81 (3H,s,CH_3); 0.85 (3H,s,CH_3); 3.52 (2H,s,CH_2); 3.51 (1H,s,br, OH); 3.89 (1H,d,J=3.2Hz,OH); 4.61 (1H,d,J=3.2Hz,CH-OH); 7.33 (5H,s,C_6H_5).
15	-	δ($CDCl_3$) : 0.69 (3H,s,CH_3); 0.95 (3H,s,CH_3); 3.49 and 3.67 (2H,2xd,AB,J=11Hz, CH_2); 4.33 (1H,s,CH-O); 4.78 and 5.22 (2H,2xd,AB,J=6Hz,O-CH_2-O); 7.27 (5H,s, C_6H_5).
16	ν_{OH} : 3370	δ($CDCl_3$); 0.92 (6H,s,$(CH_3)_2$); 0.95 and 0.99 (6H,2xd,J=6.4Hz,$CH(CH_3)_2$); 3.27 (2H,s,CH_2); 3.20-3.70 (3H,m,OH+CHOH); 1.40-2.20 (1H,m,$CH(CH_3)_2$).
11a	$\nu_{C=O}$: 1717	δ($CDCl_3$) : 1.20-2.00 (10H,m,$(CH_2)_5$); 2.10 (3H,s,CH_3C=O); 2.45 (3H,s,$CH_3C_6H_4$); 4.07 (2H,s,CH_2); 7.38 and 7.80 (4H,2xd,AB,J=8Hz,C_6H_4).
11b	$\nu_{C=O}$: 1715	δ($CDCl_3$) : 1.14 (6H,s,$(CH_3)_2$); 2.12 (3H,s,CH_3C=O); 2.46 (3H,s,$CH_3C_6H_4$); 4.05 (2H,s,CH_2); 7.40 and 7.82 (4H,2xd,AB,J=8.2Hz,C_6H_4).
11c	$\nu_{C=O}$: 1691	δ($CDCl_3$) : 1.32 (6H,s,$(CH_3)_2$); 2.37 (3H,s,$CH_3C_6H_4$); 4.09 (2H,s,CH_2); 7.00-7.80 (9H,m,C_6H_5 and C_6H_4).
11d	$\nu_{C=O}$: 1718	δ($CDCl_3$) : 1.13 (3H,s,CH_3); 1.40-2.00 (6H,m,$(CH_2)_3$); 2.00-3.60 (2H,m,CH_2C=O); 2.41 (3H,s,$CH_3C_6H_4$); 4.03 (2H,s,CH_2); 7.33 and 7.73 (4H,2xd,AB,J=8.4Hz,C_6H_4).

11e	$\nu_{C=O}$: 1676	δ($CDCl_3$) : 1.35 (6H,s,($C\underline{H}_3$)$_2$); 2.39 (3H,s,$C\underline{H}_3C_6H_5$); 2.45 (3H,s,$C\underline{H}_3C_6H_5$); 4.19 (2H,s,$C\underline{H}_2$); 7.00-7.90 (8H,m,2x$C_6\underline{H}_4$).
9[b]	$\nu_{C=O}$: 1710	δ(CCl_4) : 1.15 (6H,s,($C\underline{H}_3$)$_2$); 2.13 (3H,s,$C\underline{H}_3C$=O); 3.85 and 3.99 (2H,2xd,AB, J=10.2Hz,$C\underline{H}_2$).
12	$\nu_{C=O}$: 1718	δ(CCl_4) : 1.24 (6H,s,($C\underline{H}_3$)$_2$); 2.16 (3H,s,$C\underline{H}_3C$=O); 3.48 (2H,s,$C\underline{H}_2$).
10a	$\nu_{C=O}$: 1713	δ(CCl_4) : 1.00-2.30 (10H,m,($C\underline{H}_2$)$_5$); 2.12 (3H,s,$C\underline{H}_3C$=O); 3.57 (2H,s,$C\underline{H}_2Cl$).
10b	$\nu_{C=O}$: 1715	δ(CCl_4) : 1.22 (6H,s,($C\underline{H}_3$)$_2$); 2.17 (3H,s,$C\underline{H}_3C$=O); 3.63 (2H,s,$C\underline{H}_2$).
10c	$\nu_{C=O}$: 1683	δ($CDCl_3$) : 1.40 (6H,s,($C\underline{H}_3$)$_2$); 3.77 (2H,s,$C\underline{H}_2$); 7.20-7.80 (5H,m,$C_6\underline{H}_5$).
10d	$\nu_{C=O}$: 1712	δ($CDCl_3$) : 1.21 (3H,s,$C\underline{H}_3$); 1.60-2.10 (6H,m,($C\underline{H}_2$)$_3$); 2.10-2.60 (2H,m,$C\underline{H}_2C$=O); 3.67 (2H,s,$C\underline{H}_2$).
10e	$\nu_{C=O}$: 1675	δ(CCl_4) : 1.42 (6H,s,($C\underline{H}_3$)$_2$); 2.39 (3H,s,$C\underline{H}_3C_6H_4$); 3.73 (2H,s,$C\underline{H}_2$); 7.14 and 7.56 (4H,2xd,AB,J=8.2Hz,$C_6\underline{H}_4$).
10f	$\nu_{C=O}$: 1712	δ($CDCl_3$) : 1.09 (6H,d,J=6.6Hz,CH($C\underline{H}_3$)$_2$); 1.28 (6H,s,($C\underline{H}_3$)$_2$); 3.17 (1H,septet, J=6.6Hz,$C\underline{H}$(CH_3)$_2$); 3.70 (2H,s,$C\underline{H}_2$).

a) The substitution pattern is given in Table 1 or in the schemes. b) R_1=R_2=R_3=Me.

Table 3. ^{13}C-NMR Spectral Data (δ, $CDCl_3$) of β-Hydroxyketones 1, β-Tosyloxyketones 11 and β-Haloketones 10 and 12.

Compound[a]	C=O (s)	CH_3C=O (q)	R_2=R_3=CH_3 $C(\underline{C}H_3)_2$ (q)	$\underline{C}R_2R_3$ (s)	$CR_2R_3\underline{C}H_2$ (t)	Co, Cm (q)	Cq (s)	Cp	$\underline{C}H_3C_6H_4SO_2$ (q)	Others
1a	214.5	26.1	-	53.9	67.7	-	-	-	-	29.9; 25.9 and 22.4 (3xt, ($\underline{C}H_2$)$_5$).
1b	214.2	25.7	21.6	49.6	69.4	-	-	-	-	-
1c	209.4	-	22.8	49.2	70.3	131.1[c] 128.1[c]	138.2	127.7[c] (d)	-	
1d	217.8	-	-	50.2	68.9	-	-	-	-	39.0; 35.6; 27.3 and 20.8 (4xt,($\underline{C}H_2$)$_4$); 20.2 (q, $\underline{C}H_3$).
1f	220.9	-	21.2[a]	49.8	69.3	-	-	-	-	19.9[a] (q,CH($\underline{C}H_3$)$_2$); 34.5 (d,$\underline{C}H$).
13	212.0	25.7	21.9	48.3	74.8	-	-	-	-	95.9 (t,O-$\underline{C}H_2$-O).
14	-	-	22.8 19.0	38.9	71.9	127.7[c] 127.4[c]	141.5	127.7[c] (d)	-	82.0 (d,$\underline{C}H$).
15	-	-	22.1 18.6	34.7	78.4	127.5[c] 127.4[c]	137.9	127.2[c] (d)	-	94.6 (t,O-$\underline{C}H_2$-O); 87.2 (d,$\underline{C}H$).

16	-	-	23.3[a]	39.2	73.4	-	-	-	-	83.3 (d,CH); 29.2 (d,CH $(CH_3)_2$); 19.7[a] and 16.7[a] (2xq,C$(CH_3)_2$).
11a	209.9	26.0	-	51.4	73.5	129.9 127.9	145.0	132.6 (s)	21.6	22.0; 25.5 and 29.8 (2xt, -$(CH_2)_5$-).
11b	210.0	25.3	21.4	47.6	75.0	129.9 127.9	145.0	132.6 (s)	21.6	-
11c	205.3	-	22.8	47.6	75.7	129.8 127.8 128.2[c] 127.5[c]	144.8 137.6	132.8 131.3[c] (d+s)	21.5	-
11d	211.9	-	-	48.4	74.5	129.8 127.9	144.8	132.6 (s)	21.5	20.0 (q,CH_3); 20.5; 26.7; 35.4 and 38.4 (4xt, $(CH_2)_4$).
11e	204.5	-	23.0	47.5	75.9	129.8 128.0 128.9 128.0	144.8 142.1	132.7 (s) 134.6 (s)	21.6	21.4 (q,$CH_3C_6H_4$).
9[b]	210.8	25.6	21.8	47.9	67.4	-	-	-	-	-
12	209.7	25.2	23.5	48.5	41.0	-	-	-	-	-
10a[d]	208.1	25.9	-	52.8	50.1	-	-	-	-	31.3; 25.3 and 22.5 (3xt, -$(CH_2)_5$-).
10b	210.0	25.4	22.7	49.2	51.7	-	-	-	-	-
10c	206.2	-	24.1	49.3	52.5	131.0[c] 128.2[c]	138.4	127.3[c] (d)	-	-
10d	212.6	-	-	49.8	51.3	-	-	-	-	38.8; 36.4; 27.0 and 21.0 (4xt,-$(CH_2)_4$-); 21.3 (q, CH_3).
10e	205.2	-	24.2	49.1	52.8	128.9 127.8	141.7	135.3 (s)	-	21.3 (q,$CH_3C_6H_4$).
10f	216.6	-	22.8	49.9	52.1	-	-	-	-	34.8 (d,CH); 20.2 (q, $CH(CH_3)_2$).

a) The substitution pattern is given in Table 1 or in the schemes. b) R_1=R_2=R_3=Me. c) Or vice versa. d) The ^{13}C-NMR spectrum was recorded in C_6D_6 in order to avoid overlapping of the CH_3C=O and the CH_2 signals.

the preparation of large quantities of β-haloketones with two substituents in the α-position was developed starting from ketones via acid-catalyzed hydroxymethylation and substitution of the hydroxyl group by chlorine or bromine.

EXPERIMENTAL SECTION

^{1}H-NMR spectra were measured with a Varian T-60 NMR spectrometer, while ^{13}C NMR spectra were obtained with a Varian FT 80 NMR spectrometer. IR spectra were performed with a Perkin-Elmer model 1310 spectrophotometer and mass spectra were measured with a Varian-Mat model 112 mass spectrometer. Satisfactory elemental analyses were performed for all new compounds. Elemental analyses were performed by the Laboratory of Soil Physics and the Laboratory of Agrochemistry (University of Gent).

Preparation of β-Hydroxyketones 1. General Procedure.- A mixture of 0.1 mol of ketone 7, 0.2 mol of trifluoroacetic acid and 0.1-0.2 mol of paraformaldehyde was stirred under reflux during several hours (Table 1, entries 1-15). When the reaction was complete (control ^{1}H-NMR), the mixture was poured carefully into a saturated sodium bicarbonate solution (100 ml). The mixture was stirred overnight (14-20 hrs) and afterwards extracted four times with each 100 ml of dichloromethane. The combined extracts were dried ($MgSO_4$) and, after removal of the solvent under vacuo, the residual reaction mixture was distilled in vacuo to give pure β-hydroxyketones 1 in good yields. The spectral data of β-hydroxyketones 1 are given in Tables 2 and 3.

Preparation of β-Tosyloxyketones 11. General Procedure.- To a solution of 0.1 mol of β-hydroxyketone 1 in pyridine (10% solution), 0.11 mol p-toluenesulfonyl chloride was added under vigorous stirring and under cooling with a waterbath. After stirring at room temperature during several hours (Table 1, entries 16-21), the reaction mixture was poured into 1 liter of 10 N

hydrochloric acid. The acidic solution was extracted with carbon tetrachloride (4 x 150 ml). After drying of the combined extracts ($MgSO_4$) and after removal of the solvent, the residue was treated with 100 ml ether. The solution was cooled to -30°C in the refrigerator during several hours and the solid β-tosyloxyketones 11 were isolated in high yields by filtration. The spectral data of β-tosyloxyketones 11 are presented in Tables 2 and 3.

Preparation of β-Chloroketones 10. General Procedure.- To a solution of 0.1 mol of β-tosyloxyketone 11 in dimethylformamide (DMF) (10 % solution), two equivalents of lithium chloride were added. After reflux during several hours (Table 1, entries 27, 28,30-34), the reaction mixture was poured into 1 liter of 10 N hydrochloric acid. The acidic solution was extracted with carbon tetrachloride (5 x 150 ml), and the combined extracts were dried ($MgSO_4$). After evaporation of the solvent, the reaction mixture was distilled under vacuo to afford β-chloroketones 10. The spectral data of β-chloroketones 10 are reported in Tables 2 and 3.

Preparation of β-Bromoketone 12. General Procedure.- To a solution of 0.1 mol of β-tosyloxyketone 11b in 100 ml 2-butanone, two equivalents of lithium bromide were added. After reflux during several hours (Table 1; entry 29) the reaction mixture was poured into 1 liter of water. After extraction with dichloromethane (4 x 100 ml), the combined extracts were dried ($MgSO_4$) and the solvent was evaporated. The reaction mixture containing ketone 12 was not distilled because this compound decomposes partially during distillation. The compound was of sufficient

purity (≥ 97 %; checked by ^{1}H-NMR) for further elaboration.

The spectral data of β-bromoketone 12 are reported in Tables 2 and 3.

REFERENCES

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1. W. Kraemer, H. L. Elbe, K. H. Buechel and M. Plempel (Bayer A.-G.), Ger. Offfen. DE 3.021. 581 (Cl. A61K31/41), Dec. 1981, Appl. Jun. 1980; Chem. Abstr., 96, 181291w (1982).
2. E. Regel, K. H. Buechel, K. Luerssen, P. E. Frohberger and W. Brandes (Bayer A.-G.), Eur. Pat. Appl. EP 44,425 (Cl. C07D249/08), Jan. 1982, DE Appl. 3,025,242, Jul. 1980; Chem. Abstr., 96, 181293y (1982).
3. E. Regel, K. H. Buechel, K. Luerssen, P. E. Frohberger and W. Brandes (Bayer A.-G.), Ger. Offen. DE 3,025,242 (Cl. C07D249/08), Jan. 1982, Appl. Jul. 1980; Chem. Abstr., 96, 142865s (1982).
4. W. Kraemer, H. L. Elbe, K. H. Buechel, W. Brandes and P. E. Frohberger (Bayer A.-G.) Ger. Offen. DE 3,021,551 (Cl. C07F249/08), Dec. 1981, Appl. Jun. 1980; Chem. Abstr., 96, 122806v (1982).
5. W. Kraemer, K. H. Buechel, M. Plempel and I. Haller (Bayer A.-G.), Ger. Offen. 2,811,916 (Cl. A61K31/415), Sep. 1979, Appl. Mar. 1978; Chem. Abstr., 92, 111018f (1980).
6. L. Fitjer and W. Lüttke, Chem. Ber., 105, 907 (1972).
7. W. C. Lumma, Jr. and O. H. Ma, J. Org. Chem., 35, 2391 (1970).
8. E. Cros, I. Elphimoff-Felkin and P. Sarda, C. R. Acad. Sci. Paris (C), 286, 261 (1978).
9. R. C. Fuson, W. E. Ross and C. H. McKeever, J. Am. Chem. Soc., 60, 2935 (1938).
10. N. H. Cromwell, D. S. Soriano and E. Doomes, J. Org. Chem., 45, 4983 (1980).
11. D. Barlocco and G. Gignarella, Synthesis, 876 (1985).
12. G. A. Odoeva, T. P. Memekh, G. L. Epstein and E. G. Sotchilin, Zh. Org. Khim., 4, 1684 (1968); Chem. Abstr., 69, 106122 (1968).
13. O.C. Dermer and J. Newcombe, J. Am. Chem. Soc., 74, 3417 (1952).

14. C. H. De Puy, W. C. Arney, Jr. and D. H. Gibson, ibid., 90, 1830 (1968).

15. J. W. Wilt and J. W. Hill, J. Org. Chem., 26, 3523 (1961).

16. C. H. De Puy and R. J. Van Lanen, ibid., 39, 6360 (1974).

17. C. R. Johnson and R. W. Herr, ibid., 38, 3153 (1973).

18. C. R. Johnson, C. J. Cheer and D. J. Goldsmith, ibid., 29, 3320 (1964).

19. H. H. Wasserman, M. J. Hearn and R. E. Cochoy, ibid., 45, 2874 (1980).

20. S. Julia and C. Gueremy, Bull. Soc. Chim. Fr., 2994 (1965).

21. V. R. Kartashov, V. P. Pushkarev, I. V. Bodrikov and K. N. Tishkov, Zh. Org. Khim., 7, 1570 (1971); Chem. Abstr., 75, 151146b (1971).

22. I. V. Bodrikov, V. R. Kartashov and T. I. Temnikova, ibid., 3, 669 (1967); Chem. Abstr., 67, 43500p (1967).

23. V. R. Kartashov and I. V. Bodrikov, ibid., 2, 1120 (1966); Chem. Abstr., 65, 15218 (1966).

24. V. R. Kartashov, V. P. Pushkarev and I. V. Bodrikov, ibid., 7, 1574 (1971).

25. C. L. Karl, E. J. Maas and W. Reusch, J. Org. Chem., 37, 2834 (1972).

26. Y. Ishii, K. Yamawaki, T. Yoshida, T. Ura and M. Ogawa, J. Org. Chem., 52, 1868 (1987).

27. U. Schwenk and A. Becker, Justus Liebigs Ann. Chem., 706, 95 (1967).

28. P. K. G. Hodgson and S. Warren, J. Chem. Soc. Perkin Trans. 2, 372 (1975).

29. K. Lucas, P. Weyerstahl, H. Marschall and F. Nerdel, Chem. Ber., 104, 3607 (1971).

30. T. I. Temnikova, N. A. Venediktova and V. S. Karavan, Zh. Org. Khim 8, 1214 (1972); Chem. Abstr. 77, 113653y (1972).

31. A. G. Robinson and A. W. McCollum, U.S. US 3692801, 19 Sep 1972, Appl. or Pr. 72, 839, 16 Sep 1970; Chem. Abstr. 78, 44203h (1973).

32. K. Soai; S. Niwa, T. Yamanoi, H. Hikima and M. Ishizaki, J. Chem. Soc., Chem. Commun. 1018 (1986).

33. E. Blume and E. Granzer, (Hoechst A.-G.), Ger. Offen. DE 3235589 A1, 29 Mar 1984, Appl. 3235589, 25 Sep 1982; Chem. Abstr., 101, 90904d (1984).

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