Preparation of 1,1-Dialkoxy-2-alkanones

R. VERHÉ, D. COURTHEYN[1], N. DE KIMPE[2], L. DE BUYCK, N. SCHAMP

Laboratory of Organic Chemistry, Faculty of Agricultural Sciences, State University of Gent, Coupure 535, B-9000 Gent, Belgium

α-Ketoacetals are key synthons in organic synthesis[3-8], but they are not general available by specific acetalization of the aldehyde function in α-ketoaldehydes, except for *t*-butyl- and arylglyoxals[9,10,11]. Nevertheless, various procedures are available for the regioselective synthesis of α-ketoacetals, but most approaches are lacking generality and often are time-consuming and low-yielding.

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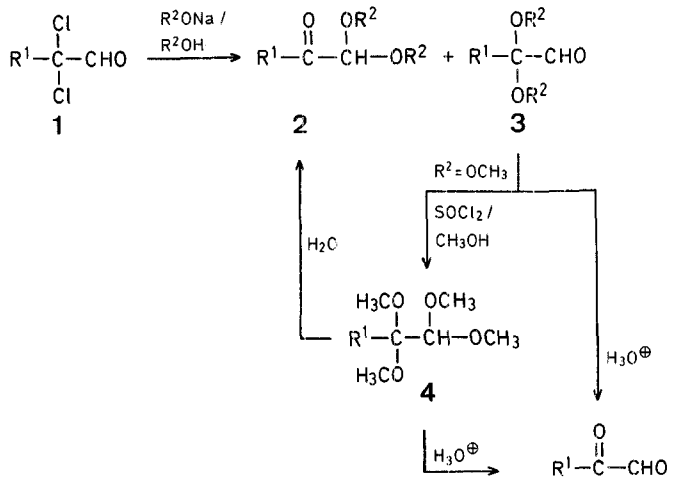
1,1-Dialkoxy-2-alkanones **2** have been prepared by selective hydrolysis of bis-acetals of α-ketoaldehydes[12], acidic hydrolyses of *N*-2-(1,1-dimethoxyalkylidene)-amines[13,14] and *gem*-dimorpholino compounds[15], and acidic alcoholyses of α,α'-dihydroxy ketones[16], nitrosoketones[17], and 4-(halomethylene)-1,3-dioxolanes[18]. Other methods involved the action of hypochlorites on diazoketones[19], the reaction of Grignard reagents on dialkoxyacetates[20], acetonitriles[21], and acetamides[22], the hydroxide-induced cleavage of γ,γ-dialkoxy-α-alkylacetoacetates[23] and by treatment of β-oxosulfides with thallium triacetate in alcohols[24].

In the course of our studies on the reactivity of α,α-dihalo aldehydes[25,26], it was found that reaction of α,α-dichloro aldehydes **1** (readily prepared by chlorination with chlorine in dimethylformamide of the parent aldehydes or alcohols[27]) with alkoxides generally provided an unseparable mixture of α,α-dialkoxy ketones **2** and α,α-dialkoxy aldehydes **3**[25,26,28]. The ratio between **2** and **3** is strongly dependent upon the substrate, alkoxide, and reaction conditions, e.g. reaction of α,α-dichlorobutanal with 2 normal sodium methoxide in methanol (2.5 equiv) at room temperature for 12 h gave 70% **2** and 30% **3**, while the action of sodium isopropoxide in isopropanol furnished pure **2**.



1 **2** **3** **4** **5**

Our one-pot procedure for the preparation of the α-ketoacetals **2** consists of the reaction of α,α-dichloro aldehydes **1** with 2.5 equiv. of sodium alkoxide in the corresponding alcohol (2 normal solution) for 12 h at room temperature (Table 1).

Subsequent treatment, without work-up of the reaction mixture, with 1.5 equiv. of thionyl chloride, generating hydrogen chloride and dimethyl sulfite, affords the tetraalkoxy compounds **4** (Table 2) which can be regioselectively hydrolyzed in the presence of water (Method A). Only 1,1,2,2-tetramethoxypropane (**4**; $R^1=R^2=CH_3$) resisted hydrolysis to 1,1-dimethoxy-2-propanone under these circumstances. Bis-acetals of methylglyoxal have been prepared by the reaction of propargyl aldehyde with alcohols in acidic media in the presence of mercury(II) salts or the action of methyl nitrate on acetone in acidic media[17,30].

The α-ketoacetals **2** can also be prepared in lower yield by selective hydrolysis of the mixture **2** and **3** with 10% phosphoric acid as the acetals **3** are hydrolyzed faster then **2** (Method B) circumventing in this way the hydrolysis of **4**.

It is obvious that the acidic hydrolysis of the reaction mixture **2** and **3** provides an elegant and fast method for the preparation of the difficultly accessible aliphatic α-ketoaldehydes **5**, in moderate yields (40–60%). The method cannot be employed when $R^1=H$ as the reaction of dichloroacetaldehyde with sodium methoxide gave a complex reaction mixture which was not further investigated.

2-Ketoacetals 2; General Procedures:

Method A: To a solution of α,α-dichloroaldehyde **1** (0.1 mol) in the appropriate alcohol (10 ml) is added slowly a 2 normal solution of sodium alkoxide (0.25 mol) in the corresponding alcohol at room temperature and the reaction mixture is stirred for 12 h. The resulting mixture of the acetals **2** and **3** is treated with water (3 equiv.) and thionyl chloride (1.5 equiv.) at room temperature during 6 h (except for **2b** where 10 equiv. of water and a temperature of 40 °C are necessary). Afterwards, the mixture is made alkaline by adding potassium carbonate, followed by addition of brine (500 ml), and extraction with dichlo-

Table 1. α-Ketoacetals **2a–k**

Product[a] No.	R^1	R^2	Method	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported	I.R. (NaCl) ν [cm⁻¹]	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. *m/e* (rel. intens. %)
2a	CH_3	CH_3	B	44	34–36°/13	141°/760[23]	1735	2.07 (s, 3H); 3.37 (s, 6H); 4.17 (s, 1H)	no $M^{\oplus}$; 87 (4); 75 (100); 71 (2); 59 (5); 47 (9); 43 (5)
2b	C_2H_5	CH_3	A	73	47–48°/12	49°/13[23]	1730	1.00 (t, 3H, *J*=7.2 Hz); 2.48 (q, 2H, *J*=7.2 Hz); 3.35 (s, 6H); 4.24 (s, 1H)	no $M^{\oplus}$; 75 (100); 57 (6); 47 (21); 45 (10); 41 (6); 40 (9)
2c	*n*-C_3H_7	CH_3	B	47	63–65°/13	66°/14[23]	1735	0.91 (t, 3H, *J*=6.4 Hz); 1.6 (m, 2H); 2.43 (t, 2H, *J*=7.0 Hz); 3.35 (s, 6H); 4.21 (s, 1H)	146 (M^+, 0.04); 115 (10); 75 (100); 71 (11); 47 (10); 43 (6)
2d	*i*-C_3H_7	CH_3	A	78	51°/11	—[b]	1730	1.03 (d, 6H, *J*=6.9 Hz); 2.94 (sept, 1H, *J*=6.9 Hz); 3.34 (s, 6H); 4.33 (s, 1H)	no $M^{\oplus}$, 75 (100); 55 (5); 47 (14); 44 (5); 43 (8); 41 (7); 40 (9)
2e	*n*-C_4H_9	CH_3	B	55	78–83°/13	73°/10[23]	1730	0.91 (t, 3H, *J*=6.5 Hz); 1.2–2.0 (m, 4H); 2.49 (t, 2H, *J*=7.0 Hz); 3.38 (s, 6H); 4.35 (s, 1H)	no $M^{\oplus}$; 85 (4); 75 (100); 71 (3); 57 (4); 47 (6); 43 (3); 41 (2)
3f	*t*-C_4H_9	CH_3	A	80	61–62°/13	68–70°/13[13]	1730	1.15 (s, 9H); 3.34 (s, 6H); 4.70 (s, 1H)	no $M^{\oplus}$; 75 (100); 57 (12); 47 (12); 44 (8); 41 (8); 40 (19)

Table 1. (Continued)

Product[a] No.	R^1	R^2	Method	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported	I.R. (NaCl) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. *m/e* (rel. intens. %)
3g	n-C_5H_{11}	CH_3	B	43	93–95°/13	98°/5[23]	1730	0.89 (t, 3H, J=6.5 Hz); 1.1–1.7 (m, 6H); 2.45 (t, 2H, J=6.8 Hz); 3.36 (s, 3H); 4.22 (s, 1H)	no $M^{\oplus}$; 99 (5); 75 (100); 71 (3); 59 (4); 55 (4); 47 (7); 43 (3)
3h	C_6H_5	CH_3	A	75	115°/12	87–88°/1[29]	1730	3.45 (s, 6H); 4.85 (s, 1H); 7.3–7.5 (m, 3H); 7.9–8.1 (m, 2H)	no $M^{\oplus}$; 121 (2); 105 (6); 77 (10); 75 (100); 51 (6); 47 (13)
3i	C_2H_5	C_2H_5	A	80	64–65°/11	98–100°/55[21]	1725	0.97 (t, 3H, J=7.1 Hz); 1.17 (t, 6H, J=6.8 Hz); 2.51 (q, 2H, J=7.1 Hz); 3.3–3.8 (m, 4H); 4.32 (s, 1H)	no $M^{\oplus}$; 115 (1); 103 (13); 97 (5); 75 (24); 59 (6); 57 (9); 47 (100); 41 (10)
3j	i-C_3H_7	C_2H_5	A	82	70–71°/11	103–104°/45[11]	1730	1.03 (d, 6H, J=7.0 Hz); 1.21 (t, 6H, J=6.8 Hz); 3.03 (sept, 1H, J=7.0 Hz); 3.2–4.0 (m, 4H); 4.51 (s, 1H)	no $M^{\oplus}$; 103 (46); 75 (43); 55 (10); 47 (100); 43 (23); 40 (10)
3k	i-C_3H_7	i-C_3H_7	A	84	80°/10	—[c]	1730	1.03 (d, 6H, J=7.0 Hz); 1.13 (d, 6H, J=6.1 Hz); 1.19 (d, 6H, J=6.1 Hz); 3.06 (sept, 1H, J=7.0 Hz); 3.81 (sept, 2H, J=6.1 Hz); 4.51 (s, 1H)	no $M^{\oplus}$; 89 (42); 47 (10); 45 (7); 43 (100); 41 (11); 40 (10)

[a] Purity >97% as checked by ^{1}H-N.M.R. and G.L.C. (conditions: SE 30 5%; Chrom W; 3 m)

[b] $C_7H_{14}O_3$ (146.2) calc. C 57.51 H 9.65 found 57.43 9.72

[c] $C_{11}H_{12}O_3$ (202.3) calc. C 65.31 H 10.96 found 65.44 10.84

Table 2. Bis-acetals **4** prepared

Product R^1	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported	^{1}H-N.M.R. (CCl_4) δ [ppm]	M.S. *m/e* (rel. intens. %)
CH_3	84	56–57°/12	70°/22[30]	1.12 (s, 3H); 3.14 (s, 6H); 3.38 (s, 6H); 4.00 (s, 1H)	no $M^{\oplus}$; 133 (18); 89 (84); 75 (80); 59 (38); 47 (45); 43 (100)
C_2H_5	89	63°/10	—[a]	0.83 (t, 3H, J=7.1 Hz); 1.60 (q, 2H, J=7.1 Hz); 3.16 (s, 6H); 3.37 (s, 6H); 4.06 (s, 1H)	no $M^{\oplus}$; 147 (14); 103 (100); 75 (85); 57 (48); 47 (18); 41 (20); 70 (18)
i-C_3H_7	87	68°/10	—[b]	0.93 (d, 6H, J=6.9 Hz); 1.98 (sept, 1H, J=6.9 Hz); 3.18 (s, 6H); 3.37 (s, 6H); 4.06 (s, 1H)	no $M^{\oplus}$; 117 (74); 75 (100); 55 (21); 53 (20); 43 (38); 41 (17)

[a] $C_8H_{18}O_4$ (178.2) calc. C 53.91 H 10.18 found 53.78 10.29

[b] $C_9H_{20}O_4$ (192.3) calc. C 56.22 H 10.49 found 56.14 10.58

Table 3. α-Ketoaldehydes **5** prepared

Product R^1	Yield [%]	b.p. [°C]/torr found	b.p. [°C]/torr reported	^{1}H-N.M.R. (CCl_4) δ [ppm]
C_2H_5	47	88–91°/760	90°/760[23]	1.10 (t, 3H, J=6.9 Hz); 2.27 (q, 2H, J=6.9 Hz); 9.08 (s, 1H)
n-C_3H_7	34	110–112°/760	112°/760[23]	0.95 (t, 3H, J=7.4 Hz); 1.3–1.95 (m, 2H); 2.62 (t, 2H, J=7.7 Hz); 9.06 (s, 1H)
n-C_4H_9	43	50–53°/12	48°/12[23]	0.96 (t, 3H, J=7.0 Hz); 1.3–1.9 (m, 4H); 2.64 (t, 2H, J=7.2 Hz); 9.06 (s, 1H)
n-C_5H_{11}	55	62–64°/13	59°/10[23]	0.90 (dist. t, 3H); 1.2–1.8 (m, 6H); 2.6 (dist. t, 2H); 9.05 (s, 1H)
C_6H_5	72	84–89°/13	99–102°/20[23]	7.3–7.5 (m, 3H); 7.8–8.1 (m, 2H); 8.83 (s, 1H)

romethane (3 × 50 ml). The combined extracts are dried with potassium carbonate and the solvent is evaporated. Distillation of the residue gives the α-ketoacetals **2** (Table 1).

Method B: The reaction is carried out as in Method A except that the resulting mixture of the acetals **2** and **3** is poured into 10% phosphoric acid (100 ml) and the reaction mixture is stirred at room tem-

perature (during this period the dimethoxyaldehydes are completely hydrolyzed into the α-ketoaldehydes, leaving the dimethoxyketones **2** nearly unchanged). The reaction mixture is extracted with dichloromethane (3 × 100 ml), the combined extracts washed with brine, and water, and dried with magnesium sulfate. Evaporation of the solvent and distillation affords **2** (Table 1).

Bis-acetals 4; General Procedures:
A solution of the mixture of the acetals **2** and **3** (0.1 mol) in dry methanol is treated with thionyl chloride (1.2 equiv.) during 30 min (in the case of $R^2 = i\text{-}C_3H_7$, an additional 0.5 equivalents of thionyl chloride and 0.5 equivalents of methyl orthoformate are added). After neutralization with potassium carbonate, the mixture is stirred for 15 min with 2 normal aqueous potassium hydroxide (100 ml) in order to decompose the dimethyl sulfite. The mixture is poured into water and extracted with dichloromethane (3 × 50 ml). Work-up by Method A and distillation gives the bis-acetals **4** (Table 2).

α-Ketoaldehydes 5; General Procedure:
The mixture of the acetals **2** and **3** (0.1 mol) without work-up is poured into 10% phosphoric acid (100 ml) or 5% sulfuric acid (100 ml) and the reaction mixture is refluxed for 30 min. After cooling, the reaction mixture is extracted with dichloromethane (4 × 50 ml) and the combined extracts are successively washed with 5% sodium hydrogen carbonate solution (50 ml) and water (50 ml). Drying, evaporation of the solvent, and distillation furnishes **5** in moderate yields (Table 3).

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[1] D. Courtheyn: "Aspirant" of the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek".
[2] N. De Kimpe: "Bevoegdverklaard Navorser" of the Belgian "Nationaal Fonds voor Wetenschappelijk Onderzoek".
[3] D. Seebach, E. J. Corey, *J. Org. Chem.* **40,** 231 (1975).
[4] J. A. Marshall, D. E. Seitz, *J. Org. Chem.* **39,** 1814 (1974).
[5] T. Severin, R. Adam, *Chem. Ber.* **108,** 88 (1975).
[6] A. I. Meyers, C.-C. Shaw, *Tetrahedron Lett.* **1974,** 717.
[7] M. Larcheveque, C. Lequet, A. De Bal, J. Y. Lallemand, *Tetrahedron Lett.* **22,** 1595 (1981).
[8] E. C. Taylor, D. J. Dumas, *J. Org. Chem.* **46,** 1394 (1981).
[9] W. Voss, *Justus Liebigs Ann. Chem.* **485,** 293 (1931).
[10] K. Schank, *Justus Liebigs Ann. Chem.* **716,** 87 (1968).
[11] K. Schank, A. Weber, *Chem. Ber.* **105,** 2188 (1972).
[12] J. Meisenheimer, *Ber. Dtsch. Chem. Ges.* **45,** 2637 (1912).
[13] N. De Kimpe, N. Schamp, *Bull. Soc. Chim. Belg.* **83,** 507 (1974).
[14] T. Cuvigny, H. Normant, *Synthesis* **1977,** 198.
[15] D. Papillon-Yegou, B. Bariou, N. Soyer, M. Kerfanto, *Bull. Soc. Chim. Fr.* **1977,** 977.
[16] S. K. Gupta, *J. Org. Chem.* **41,** 2642 (1976).
[17] *German Patent* 1252913 (1967), *C. A.* **68,** 49071 (1968).
[18] H. Meister, *Justus Liebigs Ann. Chem.* **724,** 128 (1969).
[19] *German Patent* 1254138 (1967); *C. A.* **68,** 49076 (1968).
[20] J. B. Wright, *J. Am. Chem. Soc.* **77,** 4883 (1955).
[21] R. Dulou, D. Savostianoff, *Compt. Rend. Acad. Sci. Ser. C* **262,** 564 (1968).
[22] R. Tiffany, J. Wright, R. Moffatt, R. Heinzelman, R. Strube, B. Aspergen, E. Lincoln, J. White, *J. Am. Chem. Soc.* **79,** 1682 (1957).
[23] E. E. Royals, A. G. Robinson, *J. Am. Chem. Soc.* **78,** 4161 (1956).
[24] Y. Nagao, M. Ochiai, K. Kaneko, A. Maeda, K. Watanabe, E. Fujita, *Tetrahedron Lett.* **1977,** 1345.
[25] R. Verhé, N. De Kimpe, L. De Buyck, C. Swyngedouw, N. Schamp; 1st European Symposium on Organic Chemistry, Cologne, W. Germany, August 1979, Abstr. p. 406.
[26] R. Verhé, L. De Buyck, N. De Kimpe, D. Courtheyn, N. Schamp; 5th Iupac Conference on Physical Organic Chemistry, Santa Cruz, California, U.S.A., August 1980, Abstr. p. 68.
[27] L. De Buyck, R. Verhé, N. De Kimpe, N. Schamp, *Bull. Soc. Chim. Belg.* **89,** 441 (1980).
[28] A. Fougerousse, J. J. Riehl, *Tetrahedron Lett.* **1973,** 3593.
[29] D. Papillon-Jegou, B. Bariou, M. Kerfanto, *Compt. Rend. Acad. Sci. Ser. C* **279,** 221 (1974).
[30] *German Patent* 1008216 (1957); *C. A.* **53,** 21613 (1959).

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