January 1979 Communications 33

Preparation of Acetals of Substituted Glyoxylic Esters (Methyl 2,2-Dimethoxyalkanoates)

F. HUET, M. PELLET, J. M. CONIA

Laboratoire des Carbocycles*, Université de Paris-Sud, Bâtiment 420, F-91 405 Orsay, France

Acetals of α -oxoesters (2,2-dialkoxyalkanoic esters, A) are interesting intermediates in organic synthesis, for example, in the preparation of lactones and α -methylenelactones¹ and in steroid chemistry². They may be prepared by esterification and acetalization of α -oxoacids³, by alkylation of tetramethoxyethylene⁴, or by α -functionalization of alkanoic esters via a multistep reaction sequence⁵.

$$R^{2}O$$
 R^{3} $R^{2}S$ R^{3} $R^{2}S$ R^{3} $R^{2}S$ R^{3}

Compounds A are useful starting materials for the synthesis of monoacetals of vic-diketones (by reaction with Grignard reagents in HMPT⁶), α -methyleneacetals⁷ and α -cyclopropylideneacetals⁸ (by carbonyl olefination with alkylidene- or cyclopropylidenephosphoranes), and corresponding carbonyl compounds^{7,8,9} (by acetal cleavage). The readily available S,S-acetals $B^{10,11}$ cannot be used for these purposes because their conversion to the S,S-acetals of monothiovic-diketones (α , α -dialkylthioketones) can only be achieved with poor yield and acetal cleavage of the α -methylene-S,S-acetals or α -cyclopropylidene-S,S-acetals obtained by carbonyl olefination with phosphoranes is difficult^{7,8}.

$$\begin{array}{c} \text{H}_{3}\text{CO} \\ \text{H}_{3}\text{CO} \\ \text{I} \\ \\ \text{H}_{3}\text{CO} \\ \text{O} \\ \text{CH-COOCH}_{3} \\ \\ \text{I} \\ \\ \text{H}_{3}\text{CO} \\ \text{COOCH}_{3} \\ \\ \text{COOCH}_{3} \\ \\ \\ \text{COOCH}_{3} \\ \\ \text{COOCH}_{4} \\ \\ \text{COOCH}_{3} \\ \\ \text{COOCH}_{4} \\ \\ \text{COOCH}_{5} \\ \\ \\ \text{COOCH}_{5} \\ \\ \text{COOCH}_{5} \\ \\ \\ \text{COOCH}_{5} \\ \\ \\ \text{COOCH}_{5} \\ \\ \text$$

Table. Methyl 2,2-Dimethoxyalkanoates (4)

In the present communication, we show that methyl 2,2-dimethoxyalkanoates (acetals of α -oxoesters, 4) are readily obtained by reaction of the lithio derivative of methyl dimethoxyacetate (2) with alkyl halides (3) in tetrahydrofuran.

By-products such as N,N-diisopropyldimethoxyacetamide (5) can be easily removed (except in the case of 4g) by column chromatography of the product over silica gel using ether/pentane as eluent.

$$H_3CO$$
 O $CH-C$ $N(C_3H_7-i)_2$ **5**

The lithio derivative **2** has previously been used to prepare alkyl 2,2-dimethoxyalkanoates of the type **4** by reaction with enolizable aldehydes or ketones followed by dehydration and hydrogenation².

Whereas disulfurated carbanions are frequently used in organic synthesis (see, for example, Ref. ^{12,13}), their oxygen analogs (e.g. 2) which are less stable have rarely been used except in the conjugate addition to butenolides¹ and in the reaction with carbonyl compounds².

Methyl 2,2-Dimethoxyalkanoates (4); General Procedure:

A solution of lithium diisopropylamide (5 mmol) is prepared by adding dropwise diisopropylamine (459 mg, 5 mmol) to a stirred solution of methyllithium (5 mmol of a \sim 2 molar solution in ether) in anhydrous tetrahydrofuran (6 ml) under an argon atmosphere at -5° . After 15 min, the mixture is cooled to -70° and a solution of methyl dimethoxyacetate¹⁶ (1; 670 mg, 5 mmol) in tetrahydrofuran (6 ml) is added dropwise with stirring. The mixture is stirred for a further 15 min at -70° whereupon a solution of the alkyl halide (3; 5 mmol) in tetrahydrofuran (6 ml) is added dropwise over a 15 min period with stirring at -70° . After a further 20 min, the mixture is gradually warmed $(-70^{\circ} \rightarrow -10^{\circ})$ within 40 min), allowed to stand at -10° for 20 min, and quickly poured into water (5 ml). The resultant mixture is stirred for 5 min, the organic phase isolated, and the aqueous phase extracted with 1:1 ethyl acetate/ether $(4 \times 15 \,\mathrm{ml})$. The organic phases are combined, washed with 10 % hydrochloric acid (15 ml) and with

3	Prod- uct	Yield ^a [%]	b.p./torr ^b	b.p./torr reported	¹H-N.M.R. (CCl₄) δ [ppm]
H ₃ C J	4a	50	70°/13	59.5°/11 ¹⁴	1.4 (s, 3 H); 3.2 (s, 6 H); 3.7 (s, 3 H)
C_2H_5 —J	4 b	50	87°/13	77°/16 ¹⁵	0.78 (t, 3H); 1.82 (q, 2H); 3.2 (s, 6H); 3.7 (s, 3H)
n-C ₃ H ₇ —Br	4c	55°	98°/13	40 65°/12 ⁵	0.95 (t, 3H); 1.27 (m, 2H); 1.77 (t, 2H); 3.2 (s, 6H); 3.7 (s, 3H)
<i>i</i> -C ₃ H ₇ J	4 d	30°	97°/13	d	0.88 (d, 6H); 2.05 (m, 1H); 3.2 (s, 6H); 3.7 (s, 3H)
$H_2C = CH - CH_2 - Br$	4e	50	102°/13	e	2.55 (d, 2H); 3.2 (s, 6H); 3.68 (s, 3H); 4.82-6.02
C_6H_5 — CH_2 — Br	4f	70	172°/13	95-105°/0.14	(m, 3H) 3.09 (s, 2H); 3.28 (s, 6H); 3.48 (s. 3H); 7.15 (s, 5H)
H ₃ C-O-CH ₂ -Cl	4g	65°		56°/0.14	3.22 (s, 6H); 3.31 (s, 3H); 3.55 (s, 2H); 3.73 (s, 3H)

^a Yields of the pure isolated products except for 4g which was not separated from the amide 5.

The reaction was carried out in the presence of HMPT (1 equiv) to improve the yield.

d C ₈ H ₁₆ O ₄	calc.	C 54.53	H 9.15
(176.2)	found	54.08	9.28
° C ₈ H ₁₄ O ₄	calc.	C 55.16	H 8.10
(174.2)	found	55.31	8.26

^b Measured by bulb-to-bulb distillation.

water (15 ml), and dried with magnesium sulfate. The solvent is evaporated and the crude product chromatographed on a silicagel column (20 g/g; silica gel 60 Merck, for column chromatography, 70–230 mesh) using ether/pentane (20:80) as eluent. Product 4 is eluted first (except in the case of 4 g which is eluted together with 5).

The general procedure is used for the synthesis of **4a**, **b**, **e**, **f**. In the synthesis of **4c**, **d**, **g**, HMPT (895 mg, 5 mmol) is added to the lithium diisopropylamide solution at -20° prior to the addition of methyl dimethoxyacetate at -70° . The general procedure is then followed except that at the end of the reaction the mixture is warmed to $+10^{\circ}$ and held at this temperature for $60 \, \text{min}$.

Received: July 24, 1978

^{*} Équipe de Recherche Associée au C.N.R.S.

¹ R. E. Damon, R. H. Schlessinger, Tetrahedron Lett. 1975, 4551.

² G. Neef, U. Eder, Tetrahedron Lett. 1977, 2825.

³ C. G. Wermuth, H. Marx, Bull. Soc. Chim. Fr. 1964, 732.

⁴ R. W. Hoffmann, J. Schneider, Chem. Ber. 99, 1899 (1966).

⁵ B. M. Trost, G. S. Massiot, J. Am. Chem. Soc. **99**, 4405 (1977).

⁶ F. Huet, M. Pellet, J. M. Conia, Tetrahedron Lett. 1976, 3579.

⁷ F. Huet, M. Pellet, J. M. Conia, Tetrahedron Lett. 1977, 3505.

⁸ F. Huet, A. Lechevallier, J. M. Conia, Tetrahedron Lett. 1977, 2521.

⁹ F. Huet, A. Lechevallier, M. Pellet, J. M. Conia, *Synthesis* 1978, 63.

¹⁰ E. L. Eliel, A. A. Hartmann, J. Org. Chem. 37, 505 (1972).

¹¹ L. M. Lerner, J. Org. Chem. 41, 2228 (1976).

¹² B. T. Gröbel, D. Seebach, Synthesis 1977, 357.

¹³ O. W. Lever, Tetrahedron 32, 1943 (1976).

¹⁴ J. W. Baker, J. Chem. Soc. 1942, 520.

¹⁵ L. N. Owen, J. Chem. Soc. 1945, 385.

¹⁶ H. Gross, J. Freiberg, DDR Patent (East Germany) 52360 (1966); C. A. 67, 2773 (1967).

E. Bisagni, J. P. Marquet, J. Andre-Louisfert, Bull. Soc. Chim. Fr. 1968, 637.