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α DIKETONE - MONOKETALS AND - MONOTHIOKETALS

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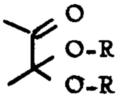
α-ketoketals 1 and α-ketothioketals 2 have recently become key intermediates in organic synthesis (see, for instance, (1,2,3) and references cited therein). But very often they are not avalaible, for instance, by selective blocking of one carbonyl group of a disymmetrical α-diketone.



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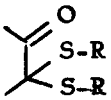

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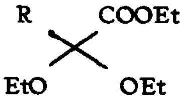
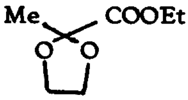
One α-ketoketal : $Et-C(OEt)_2-CO-Me$ can be obtained by reaction of Me_2CuLi (4) or Me-MgI (5) with the following ester : $Et-C(OEt)_2-CO_2Et$. On the other hand, Me-MgBr gives a tertiary alcohol (4). But these reactions have not been generalized.

α-ketothioketals 2 have mainly been prepared either by acylation of substituted or unsubstituted 2-lithio-1,3 dithianes (1,6) or by hydroxymethylenation (2,7) or enamine formation (8) of the parent monoketone followed by treatement with 1,3-propanedithiol ditosylate. In the particular case of the synthesis of α-thioketal cyclobutanones a convenient [2 + 2] cycloaddition has been described (9).

We report a simple route to compounds such as 1 and 2 from α,α-dialkoxy, α-ethylen-ketal and α-ethylen-thioketal esters, for example 3, 4 and 5 respectively, all of which are easily prepared from α-keto esters (10) or α-keto acids (11).



3a R = Me
3b R = Et



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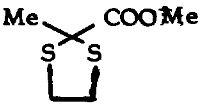

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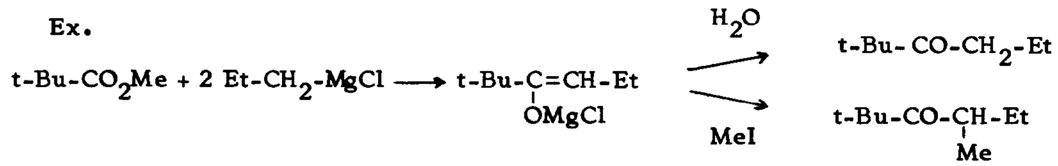
[*] Equipe de Recherche Associée au C.N.R.S.

Previously we showed that the reaction of Grignard reagents in HMPT with aliphatic saturated esters leads predominantly to ketones enolates (12).



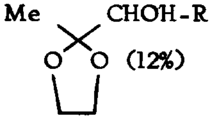
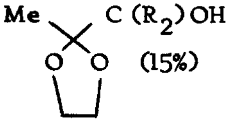
Ex.

$$t\text{-Bu-CO}_2\text{Me} + 2\ \text{Et-CH}_2\text{-MgCl} \longrightarrow t\text{-Bu-}\underset{\text{OMgCl}}{\text{C}}\text{=CH-Et} \quad \xrightarrow{H_2O} t\text{-Bu-CO-CH}_2\text{-Et} \quad \xrightarrow[\text{MeI}]{} t\text{-Bu-CO-}\underset{\text{Me}}{\text{CH}}\text{-Et}$$

When applied to ketal and thioketal esters 3-5, the reaction of Grignard reagents in HMPT, followed by hydrolysis (Table 1) led directly, with satisfactory yields, to the corresponding α-diketone-monoketals and -monothioketals 6-12.

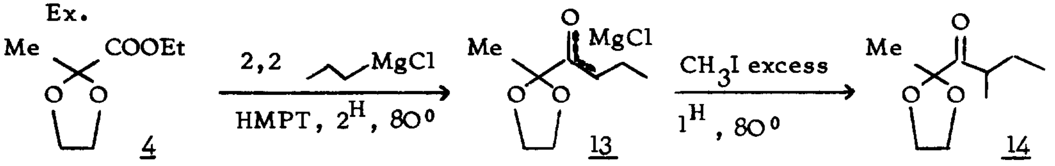
The isolation technique used depends on the nature and relative amounts of the by-products obtained.

Ketones 6 and 7 are easily isolated by distillation. 8 is isolated by column chromatography on silicagel (CC), to eliminate a small amount of unreacted ester 3b.

Ketones 9 and 10 are obtained either by CC, which removes the reduction alcohol  (12%) and the addition alcohol  (15%) or by distillation after oxidation (CrO_3, Pyridine, CH_2Cl_2 (13) of the crude product transform the reduction alcohol into ketone). Ketone 11 is obtained in satisfactory yield (45%) if the reduction alcohol is oxidized in the same way. Otherwise the yield is only 10%. Ketone 12, formed along with many by-products may easily be isolated by CC.

It should be recalled that in the ketones preparations described above, the reaction proceeds via an enolate ion. By reacting the esters with a primary Grignard reagent, the intermediate enolate (e.g 13) may be alkylated (12,14) in situ in reasonable yield (with secondary Grignard reagents the yields, in first steps, are considerably lower).

Ex.



37% isolated by CC

The α-diketone monothioketals are particularely attractive for organic synthesis as either carbonyl group may be protected (15). For example, ketalization of 12 gives the diketal 15 which may then be converted to 16 (isolated by CC) in the overall yield of 60%.

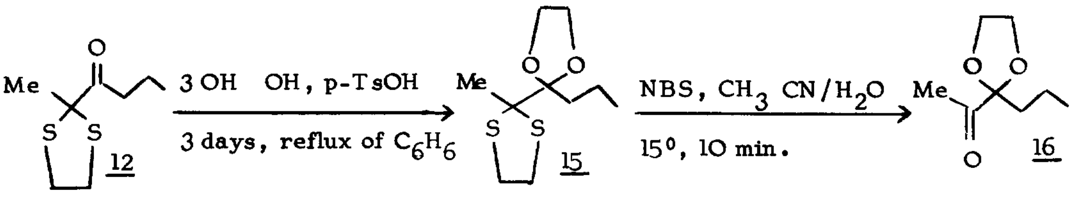
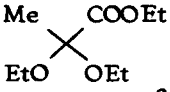
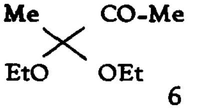
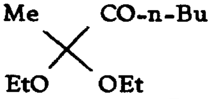
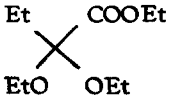
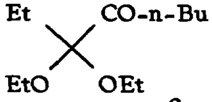
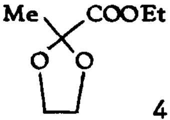
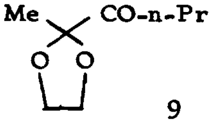
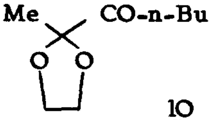
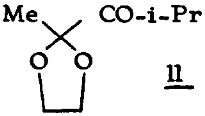
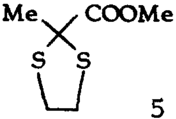
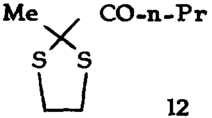


Table 1 - Reactions of R-MgX/HMPT with ketal and thioketal esters

Esters	Reaction conditions	Ketones obtained	Yields[a]
 3a	2,5 Me-MgCl, 3^{H}, 80°	 6	70% D
"	2,5 n-Bu-MgBr, 27^{H}, 78°	 7	77% D
 3b	2,5 n-Bu-MgBr, 45^{H}, 80°	 8	54% CC
 4	3 n-Pr-MgCl, 3^{H}, 75°	 9	50% CC
"	2,5 n-Bu-MgBr, 1,3^{H}, 80°	 10	61%[b] D
"	3 i-Pr-MgCl, 16^{H}, 80°	 11	45%[b] CC
 5	3 n-Pr-MgCl, 1,5^{H}, 60°	 12	40% CC

a) Ketones are isolated by column chromatography on silicagel (CC) or distillation (D)

b) After oxidation of crude product (cf. text)

We also obtained α-diketones from α-ketoketals and α-ketothioketals using previously described conditions(15).

The investigation described above shows new examples of the reaction of esters with the R-MgX/HMPT system. The products, α-diketone -monoketals and -monothioketals have been shown to be versatile compounds in preparative organic chemistry and other synthetic applications for these products are presently under investigation.

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