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REACTIVITY OF ORGANO LITHIUM REAGENTS ON DIMETHYL SQUARATE : A 1,2-ADDITION PROCESS LEADING TO NEW 2-HYDROXY-3,4 DIMETHOXY 3-CYCLOBUTENONE

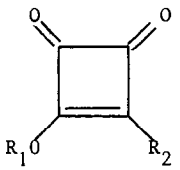
Jean Louis KRAUS

Laboratoire de Chimie Organique Biologique, Faculté des Sciences, 33, rue Louis Pasteur
84000 AVIGNON. FRANCE

ABSTRACT :

Lithium reagents react with dimethylsquarate at the carbonyl group according to a 1,2-addition process, leading to new 2-hydroxy-3,4 dimethoxy-3 cyclobutenone.

Moniliformin 1 a and related analogs 1 b,c,d,e, have been reported[1] as potent inhibitors of thiamine-dependent enzymes. Recently, it has been pointed out that specific ene-diols[2] are possible transition-state inhibitors of glyoxalase, and could be used to retard tumor growth, possibly through the effect of methylglyoxal on new protein synthesis[3]. In a program for the synthesis of new glyoxalase inhibitors, designed on a transition-state analogy as an approach to potential antileukemic agents, we have investigated the reaction of various lithium reagents with dimethyl squarate 1e.



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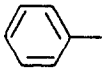
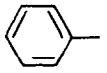
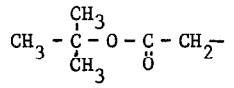
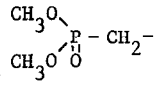
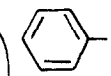
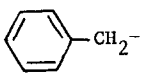
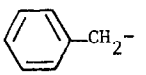
1 a $R_1 = R_2 = H$ (Moniliformin)
1 b $R_1 = H$ $R_2 = CH_3$
1 c $R_1 = H$ R_2 = Phenyl
1 d $R_1 = H$ $R_2 = OH$ (squaric acid)
1 e $R_1 = CH_3$ $R_2 = OCH_3$ (dimethylsquarate)

Previous studies[4] on the reaction of Grignard reagents with dimethyl squarate resulted in the isolation of mono- or dialkyl-cyclobutenedione derivatives, according to a 1,4-addition process. Surprisingly, we discovered that lithium reagents reacted with dimethyl squarate at the carbonyl group according to a 1,2-addition process, leading to new 2-hydroxy-3, 4-dimethoxy 3-cyclobutenones of the general formula 2a. In this paper we wish to report the reactivities of organolithium nucleophiles and Grignard nucleophiles on dimethyl squarate 1e.

Table I

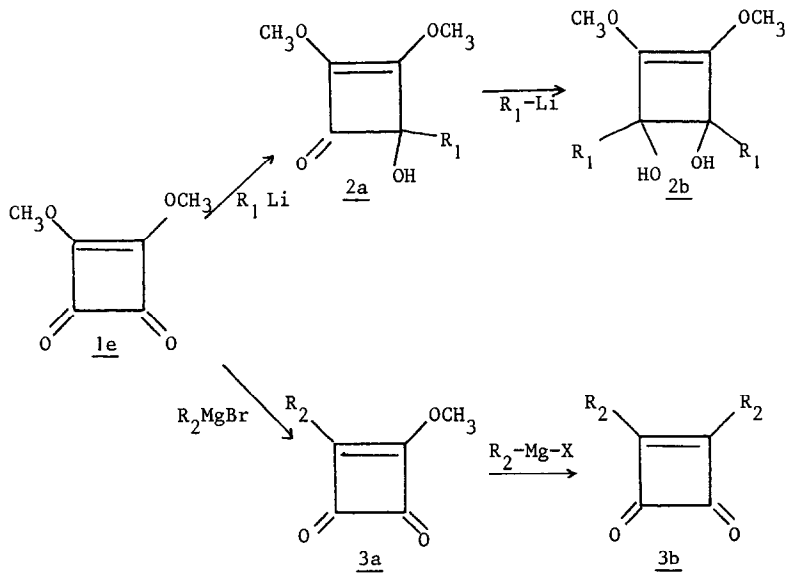
	Equivalents of Organo-metallic	Compound a* % yield isolated**	Compound b* % yield isolated**
R_1Li: CH_3^-	1.1	2a (55)	2b (9)
R_1Li: CH_3^-	2.2	2a (8)	2b (75)
R_1Li: 	1.1	2a (58)	2b (11)
R_1Li: 	2.2	2a (5)	2b (90)
R_1Li: 	1.1	2a (62)	no isolated compound
R_1Li: 	1.1	2a (55)	no isolated compound
$Br\text{-}Mg\text{-}R_2$: CH_3^-	1.1	3a (44)	no isolated compound
$Br\text{-}Mg\text{-}R_2$: CH_3^-	2.2	3a (7)	3b[7] (72)
$Br\text{-}Mg\text{-}R_2$: 	1.1	3a[8] (48)	no reaction product
$Br\text{-}Mg\text{-}R_2$: 	1.1	3a (65)	3b (20)
$Br\text{-}Mg\text{-}R_2$: 	2.2	3a (5)	3b (90)

* : All new compounds gave satisfactory high field ^1H NMR, and IR spectra. High resolution mass spectral data are in accord with the structures given.

** : All yields recorded here are based upon material isolated after flash chromatography.

Moreover it is interesting to note that the use of excess organolithium reagent leads to dihydroxy dimethoxy dialkyl cyclobutenones 2b, while the use of excess Grignard reagent leads to the dialkylcyclobutenones 3b.

Finally, the reaction of organolithium on dimethylsquarate 1e provides a simple route to hydroxy alkyl dimethoxycyclobutenones or to the dihydroxy dialkyl dimethoxycyclobutenones



The results summarized in table I, were obtained using the following general procedure : the organometallic reagent was added to a solution of dimethylsquarate (2 mM) in dry THF (10 ml) at - 78° C under nitrogen. After stirring 3 h at - 78° C and additional 2 h at room temperature, the reaction mixture was poured into water (7 ml) and quickly extracted with methylene chloride or ethylacetate. The organic extracts were dried ($MgSO_4$), filtered and evaporated. Flash chromatography afforded the pure compounds listed in table I.

From the results listed in table I, it appears that lithium reagents attack dimethyl-squarate exclusively at the ketone function, while Grignard reagents favor conjugate addition selectively. When there is a competition between direct attack on a ketone function (1,2-addition) and conjugate addition on an α, β-unsaturated ketone substrate, the less stable carbanions favor 1,2-addition while the more resonance stabilized carbanions favor conjugate addition[9]. But in the specific case of dimethyl squarate as substrate, resonance stabilization of the attacking carbanion is obviously not the factor which directs the attack. During the course of irreversible additions leading to 1,4-addition a concurrent transfer of the metal cation may be required in aprotic solvents and the metal transfer may be facilitated by the nature of the coordination of the metal with the nucleophile. The major factor in the direction of the attack seems to be the nature of the counter ion ; lithium favors 1,2-addition while Grignard reagent promotes conjugate addition.

selectively.

Due to the high reactivity of the carbons attached to the methoxy-groups towards nucleophiles[5] and to their high tendency towards hydrolysis, these new intermediates appear to be promising for further reactivity and enzymology studies.

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