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THE UNCATALYZED CONJUGATE ADDITION REACTION OF 2-(1,3-DIOXOLAN-2-YL)-ETHYLMAGNESIUM BROMIDE WITH CYCLIC α,β-ENONES

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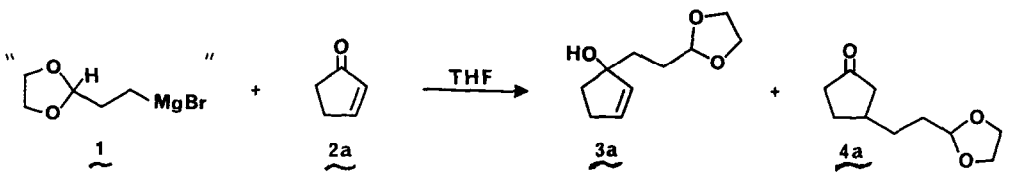
Summary: The in situ acetal-containing Grignard reagent 1 reacts with cyclic enones at -78°C to yield the product of conjugate addition in the absence of copper(I) salts.

To evaluate the influence of remote hydroxy substituents and their derivatives upon the intramolecular transacetalization reaction, we required the preparation of several precursors that contained a γ-hydroxyacetal moiety. A survey of the chemical literature clearly revealed that the most direct and well precedented approach involved the addition of an acetal containing Grignard reagent to a carbonyl.[1] Indeed, since the original report of Buchi in 1969,[2] acetal-containing Grignard reagents have been the subject of numerous investigations ranging from methodology development to applications in the area of natural products synthesis.[1,3,4] This communication describes the rather surprising result of preferential conjugate addition of "Buchi's Grignard reagent" to simple cyclic α,β-unsaturated carbonyls, and examines the influence of temperature upon the regioselectivity of the addition reaction.

Our actual entry into this study began with the remarkable results presented in equation 1. Following the general procedure reported by Rigby,[4] a solution of 2-(2-bromoethyl)-1,3-dioxolane in THF was added to magnesium turnings over a 1 hour period to generate Buchi's Grignard reagent 1. Subtle modifications included the use of ground magnesium turnings, continual addition of the alkyl halide-THF solution via a syringe pump, and stringent temperature control (22-24°C) during the addition period. After stirring at room temperature for 1 hour, the reaction mixture was cooled to 0°C and a solution



1 + 2a → 3a + 4a (eq.1)

Temp. =	3a	:	4a
0°	1	:	1
-78°	1	:	20

of 2-cyclopentenone (2a) in THF was slowly added via a syringe. The reaction mixture was quenched at 0°C and after a standard workup procedure we obtained an ~1:1 mixture of 1,2-addition product 3a[5] and 1,4-addition product 4a.[3,5] Reiteration of this reaction sequence with the only fundamental change being the addition of 2a and subsequent quenching of the reaction mixture at -78°C, unexpectedly provided the conjugate addition product 4a as the major isomer. This unexpected result coupled with the ability to completely reverse the regioselectivity to favor the 1,2-addition product 3a (vide infra), prompted us to more systematically investigate the reactivity of organomagnesium reagent 1 with α,β-unsaturated ketones. The results of this study are listed in Table I and Table II.

The experimental data summarized in the Tables was found to be independent of the commercial source of magnesium.[6] However, since we did not employ single crystal or ultrapure metal, details of the following mechanistic discussion will be presented within the framework of practical synthetic applications of adding *in situ* reagent 1 to α,β-unsaturated ketones.

The most striking conclusion from the tabulated data is that the active organomagnesium species at -78°C cannot be Grignard reagent 1 but must be dialkylmagnesium 8.[2,3] This tendency towards 8 in the Schlenk equilibrium occurs due to the internal coordination of the central metal by the flanking oxygens.[7] This intramolecular "solvolysis" of magnesium thus provides a softer carbon nucleophile which mimics the reactivity of organocopper reagents. This

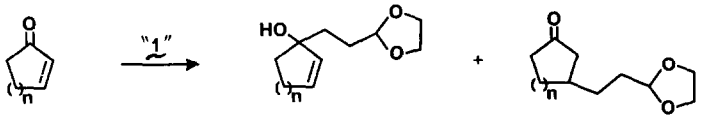


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Table I. Reaction of Cyclic Enones.

Entry	Enone	Equiv 1	Temp (°C)	Yield (%)[a]	Ratio (3:4)[a]
1	2a(n=1)	1	-78	39	5:95
2	2a	2	-78	73	5:95
3	2a	1	25	54	78:22[b]
4	2a	2	25	69	78:22[b]
5	2b(n=2)	1	-78	34	14:86
6	2b	2	-78	80	13:87
7	2b	1	25	76	88:12
8	2b	2	25	98	88:12

[a]The yields and ratios are based upon isolated material
[b]This ratio is unadjusted and represents the lower limit of 1,2-addition product 3a. Loss of material due to dehydration was unavoidable.

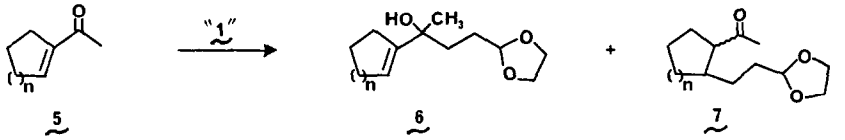
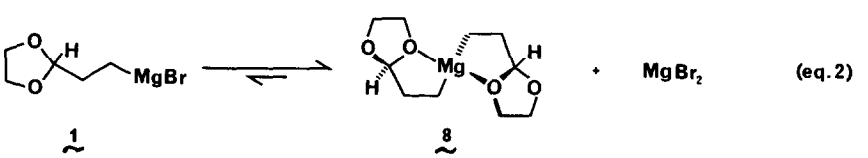


Table II. Reaction of Acyclic Enones.

Entry	Enone	Equiv 1	Temp (°C)	Isolated Yield (%)	Ratio (6:7)
1	5a(n=1)	1	-78	42	6a only
2	5a	2	-78	88	"
3	5a	1	25	67	"
4	5a	2	25	86	"
5	5b(n=2)	1	-78	30	6b only
6	5b	2	-78	82	"
7	5b	1	25	75	"
8	5b	2	25	93	"

premise is based upon the following experimental results and general observations: (a) all reactions conducted at -78°C required 2 equiv. of "Grignard reagent 1" per equiv. of carbonyl to obtain yields above 50%; (b) the strong preference of cyclic enones (Table I) versus acyclic enones (Table II) towards conjugate addition reactions follows the general reduction potential correlation pattern of organocopper reagents;[8] (c) the unprecedented result of reversing a kinetic ratio that favors conjugate addition at -78°C (Table I; entries 1,2,5,6) to a kinetic ratio that favors the 1,2-addition adduct at 25°C (Table I; entries 3,4,7,8). Experimentally this reversal was accomplished



by rapidly injecting the enone-THF solution into an unmoderated ambient temperature reaction mixture. The use of an external cooling bath, slow-controlled addition of the enone, or any attempt to regulate the vigorously refluxing reaction mixture yielded an inferior ratio of 1,2-to 1,4-adducts. Control experiments confirmed the irreversible character of these addition reactions.

Our results question an earlier study by Helquist in which *in situ* Grignard reagent **1** was reported to undergo $CuBr.Me_2S$-promoted conjugate addition to enones.[3] Since control 1,2-addition experiments were not cited, and the chromatographic purifications may have been required to remove unwanted 1,2-addition products that were obtained from the *cyclic enone* substrates, we conclude that the copper salt had no influence on the tendency of the *in situ* organomagnesium reagent **1** to add in a conjugate fashion.

The literature contains many inferences to the unique qualities of acetal-containing Grignard reagents. This study provides a reasonable explanation for the previously noted requirement of 2 equiv of reagent,[4] the ability to convert acid halides to ketones,[1,3] the lower reactivity of saturated ketones versus enones,[9] and the inability to effect 1,2 addition to an enone under "kinetic conditions".[10]

In summary, we have found that "Buchi's Grignard reagent" mimics an organocopper species *without any additive*. By intramolecular chelation the Schlenk equilibrium can be shifted to an *in situ* organomagnesium reagent with strong kinetic preference for 1,4-addition. This suggests that the influence of added chelating solvents[11] on *in situ* generated organometallic reagents may be responsible for conjugate addition and not the metal cation.

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