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COPPER-CATALYZED CONJUGATE ADDITION OF AN ACETAL-CONTAINING GRIGNARD REAGENT. A METHOD FOR CYCLOPENTENE ANNULATION.

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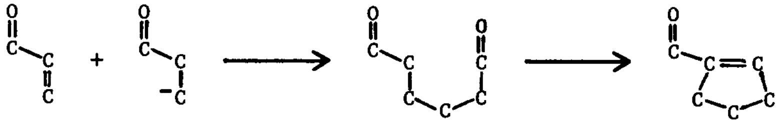
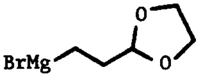
Methods for the annulation of five-membered rings onto pre-existing carbon skeletons are valuable in the synthesis of several classes of natural products.[1,2] In this communication we wish to report a method based upon the general concept illustrated in equation 1. This approach is based upon the conjugate addition of a synthon for the β-oxocarbanion, 1, to afford 1,6-dicarbonyl compounds; intramolecular condensation would then give the desired annulation products. The newly generated enone functionality of these products would be very useful in subsequent transformations.



1

(1)

As a synthon for 1 and as a part of our continuing program of study of functionalized organometallic intermediates,[3] we chose to investigate the use of the acetal-containing Grignard reagent, 2. This and related ones[4] have had several synthetic applications includ-

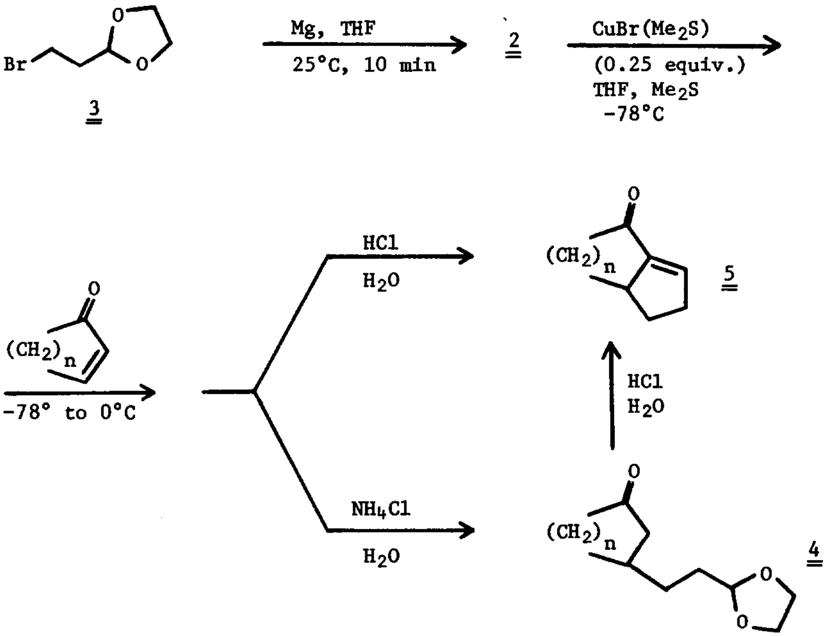


2

ing the synthesis of maytansinoids,[5] caparradiols and -triols,[6] histrionicotoxin precursors,[7] various steroids,[8] porantherine,[9] nuciferal,[10] γ-ketoaldehydes,[11] naphthalenes,[12] γ-lactones,[13] benzothiophenes,[14] and benzimidazoles.[15] The only report of the use of one of these Grignard reagents in conjugate additions and subsequent cyclizations (according to eq. 1) was in an attempted synthesis of dendrobine which was abandoned because of difficulties with later steps; no further investigation of this annulation procedure was pursued.[16] We are now pleased to report that the use of 2 as a synthon for 1 provides a very convenient method for cyclopentene annulation. This work complements Posner's route to cyclic compounds which involves conjugate addition of organocopper complexes to α,β-unsaturated carbonyl compounds bearing acetal-containing appendages.[17]

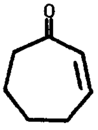
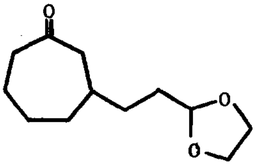
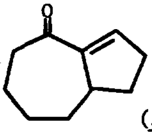
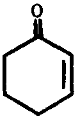
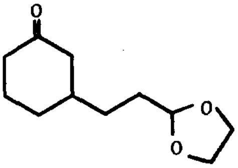
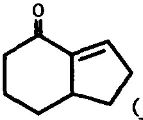
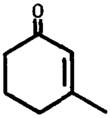
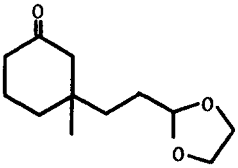
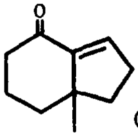
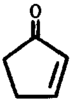
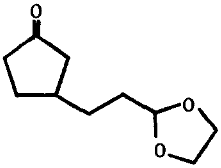
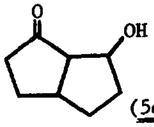
We find that the Grignard reagent, 2, is more efficiently and more rapidly generated from the bromoacetal, 3,[10] through use of a suspension of magnesium powder[18] in tetrahydrofuran (THF) rather than the usual magnesium turnings. As shown in Scheme I, conjugate addition to various α,β-unsaturated ketones is promoted by a catalytic amount of a cuprous salt; we generally employ the dimethyl sulfide complex of cuprous bromide because of its favorable solubility properties and the high state of purity in which it may be obtained.[19] Quenching of the reaction mixtures with aqueous ammonium chloride permits isolation of the conjugate addition products (4) which may subsequently be treated with hydrochloric acid to give the annulation products (5). Alternatively, the reaction mixtures resulting from the conjugate addition may be treated with hydrochloric acid to give 5 directly in a "one-flask" experiment. Typical results are given in Table I. We wish to emphasize that the yields reported here have not been optimized. The results appear to be largely independent of the period of time over which the bromide (3) is added to the suspension of magnesium; small amounts (*ca.* 5%) of the Wurtz-type coupling product are formed whether the addition is done over a period of a few minutes or several hours. A sample procedure follows.

Scheme I



Bicyclo[4.3.0]non-9-en-2-one (5b). Magnesium powder was generated under nitrogen from anhydrous magnesium dichloride (0.68 g, 7.14 mmol) and potassium (0.5 g, 13 mmol) in THF (10 ml) according to the published procedure.[18] To the suspension at 25°C was added the neat bromoacetal (3; 1.14 g, 6.3 mmol) over a period of 2 min. After 10 min., the mixture was cooled to -78°C, a solution of the cuprous bromide-dimethyl sulfide complex[19] (0.33 g, 1.6 mmol) in dimethyl sulfide (3 ml) was added over a period of 3 min, the mixture was stirred at -78°C for 1 hr, a solution of 2-cyclohexenone (0.48 g, 5.0 mmol) in ether (6 ml) was added over a period of 4 hr, and the mixture was stirred at -78°C for 10 hr and then allowed to warm up to 0°C over a period of 6 hr. Quenching of the mixture with a solution of saturated aq. ammonium chloride (adjusted to pH 8 with aq. ammonia) gave the ketoacetal (85% yield by GLPC with *n*-hexadecane as an internal standard). Hydrolysis of this product

Table I. Formation of Annulation Products

Enone	Ketoacetal	Yield(%)	Annulation Product	Yield(%)	One-flask[a] Yield(%)
		87[b]	 (5a)	80[c]	
		85[b]	 (5b)	89[c]	62[c]
		74[b]	 (5c)	77[c]	48[c]
		77[b,d]	 (5d)	54[c,e]	

[a] Reaction mixtures treated with aq. HCl; ketoacetal not isolated. [b] Yield determined by GLPC using an internal standard. [c] Isolated yield. [d] Two equivalents of 2 employed. [e] No enone was formed under the usual conditions.

at 25°C for 72 hr with aq. THF containing HCl (1.3%) afforded 5b which was isolated in 89% yield by column chromatography (silica gel, 2% acetone/methylene chloride): ir (neat film) 1685 and 1615 cm^{-1}; nmr ($CDCl_3$) 6.70 (dd, J = 5.5, 2.5 Hz, 1 H) and 0.67–3.33 (m, 11 H); ms (70 eV) m/e 136.0880 (M^+; calcd. for $C_9H_{12}O$, 136.0885). Alternatively, quenching of the reaction mixture with aq. THF containing HCl instead of aq. NH_4Cl after the conjugate addition followed by stirring at 25°C for 72 hr gave 5b directly in an isolated yield of 62%.

In summary, the reactions reported here provide a convenient method of annulation which promises to have many applications in synthesis. The formation of the hydrazulenone (5a) in one of the examples is especially promising as an approach to the pseudoguaianolides.[20] Because the annulation products are themselves α,β-unsaturated carbonyl compounds, this method should, in principle, be iterative and therefore allow the construction of complex, polycyclic systems. Also, we are currently studying the extension of the method to the annulation of rings of other sizes.

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