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THE SYNTHESIS OF MANNICH BASES FROM KETONES AND ESTERS VIA ENAMINONES.

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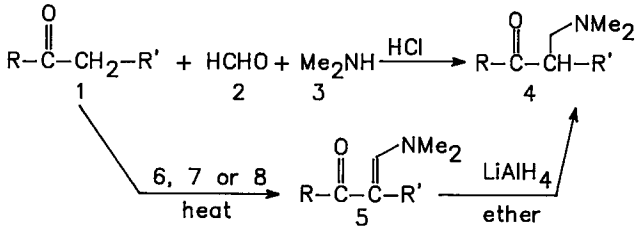
Abstract: The reactions of a series of activated methylene compounds with amide acetals to form high yields of enaminones is described. Further conversion to the Mannich Bases via reduction with lithium aluminum hydride is also covered.

The reaction of active methylene compounds **1** with formaldehyde **2** (or an equivalent) and a secondary amine **3** in the presence of a strong acid (the Mannich reaction) forms the Mannich Base **4** in one step (**SCHEME I**).[4] This intermediate has been frequently used as a masked α-methylene carbonyl source via base catalyzed β-elimination of the derived methiodide salt,[5] thermal elimination of the N-oxide,[6] or a decarboxylative elimination process.[7]

SCHEME I

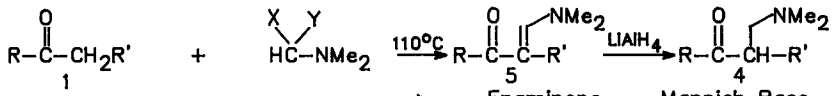


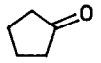
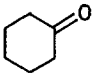
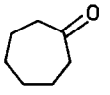
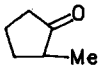
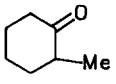
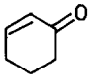
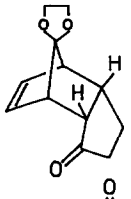
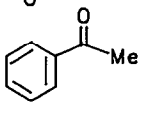
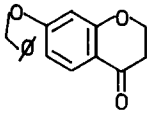
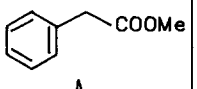
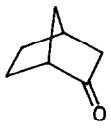
For several applications in our laboratories, we required a method for the introduction of the α-methylene unit that would: (a) not have a strong acid present at any stage and, (b) introduce the β-dimethyaminomethylene unit regioselectively at the least substituted side of an unsymmetrical ketone. Generally, the Mannich reaction is done in the presence of a strong aqueous acid (eg. HCl),[8] and the reaction on an unsymmetrical ketone gives predominantly reaction at the most substituted site.[9]

Abdulla[10] has shown that ketones react rapidly and efficiently with amide acetals and derivatives[11] to afford the vinylogous amides (aka enaminones) at the least substituted site. Furthermore, Martin[12] and other workers[13] have demonstrated in a limited number of cases that enaminones are regiospecifically reduced at the 4-position with little or no competitive or subsequent carbonyl reduction. In view of these results, we envisioned a two-step process shown in **SCHEME I**, that would lead to the Mannich Base **4**, keeping in mind our requirements of no acidic conditions in the reactions and regioselectivity.

We examined a series of activated methylene compounds in order to determine the scope and limitations of the two-step sequence. The results of these studies are shown in **TABLE I.**

TABLE I



Entry	Compound	Amide Acetal *	Enaminone % Yield	Mannich Base % Yield
1		6	86	88
2		6	47	98
3		6	66	83
4		6 7	52 76	82 81
5		6 7	44 99	81 81
6		6	61	52
7		6	75	98
8		6	61	72
9		6	92	96
10		6	97	84
11		6 7	0 91	– 99

* 6 X=Y=OMe; 7 X=NMe_2 Y=OtBu; 8 X=Y=NMe_2

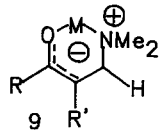
The carbonyl compounds **1** were reacted with the amide acetals (**6**, **7**, or **8**) as shown, in an oil bath at 110°C to afford the enaminones **5** in generally good to excellent yields. This reaction is usually very clean and the product easily purified by vacuum distillation if necessary. The amide acetals used were dimethylformamide dimethyl acetal (DMF-DMA) (**6**),[14] bis-dimethyamino-t-butoxymethane (Bredereck's Reagent) (**7**)[15] and tris-dimethylaminomethane (TRIS-DMAM) (**8**).[16] In general, DMF-dimethyl acetal (**6**) is the reagent of choice because it is commercially available at a very reasonable price. The other derivatives (**7** and **8**), although usually more reactive, must be synthesized. In general, the enaminone formation reaction was first attempted using DMF-DMA (**6**). If this failed to react, Bredereck's Reagent (**7**) was tried next. Finally, TRIS-DMAM (**8**) was used as a last resort.

It should be noted that entries 4, 5, and 7 in TABLE I show that the condition of regiospecificity of the reaction has been fulfilled. It is also noted (entry 6) that 2-cyclohexene-1-one reacts only at the α'-position. Additionally, no products resulting from enaminone olefin isomerization into the ring to afford the aromatic product was detected. Finally, the amide acetals react well with activated esters (eg. methyl phenylacetate; entry 10) and vinylogous esters (eg. benzyloxychromanone; entry 9) to give the vinylogous urethanes.

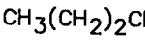
The reduction of enaminones with lithium aluminum hydride has been studied in a very limited number of cases.[12,13] The enaminones **5** in **TABLE I** were all reduced using the conditions reported by Martin and co-workers.[12] A solution of enaminone derivative **5** in ether was added rapidly (ca. 5-10 min) to a rapidly stirred, cold (0-5°C) suspension of lithium aluminum hydride (2.8 hydride equivalents) in ether. The mixtures were generally stirred for 10 min, then quenched with ethyl acetate and aqueous sodium hydroxide. The salts were filtered off and the volatiles evaporated to afford the Mannich bases **4** in very good to excellent yields.[17] The amine products were usually pure as isolated from the reaction mixtures, as determined by NMR analysis.

In all the cases examined, only 1,4-reduction of the enaminone moiety was realized. No reduction of the carbonyl in either the ketones or esters, or 1,4-reduction of the enone olefin in 2-cyclohexene-1-one (entry 6) was observed. This is presumably due to the formation of the unreactive cyclic complex **9** as proposed by Martin,[12] and Walker.[13a]

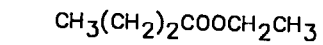
Several compounds that were subjected to the enaminone formation reaction failed to react productively with any of the amide acetals (**6,7,8**). Butyraldehyde (**10**) underwent extensive decomposition, and ethyl butyrate (**11**) gave no reaction under the standard reaction conditions. Thus, it appears that unactivated aldehydes and esters are not susceptible to this reaction sequence. Also, norbornenone (**12**) failed to react under the reaction conditions. This was somewhat of a surprise since the dihydro derivative (norbornanone; entry 11) reacted smoothly and in high yield with Bredereck's Reagent (**7**) to give the enaminone. However, the Mannich base for this compound was able to be synthesized directly as shown in **SCHEME II**, by formation of the lithium enolate, followed by the addition of Eschenmoser's Salt (dimethyl(methylene)ammonium iodide).[18]



9



10



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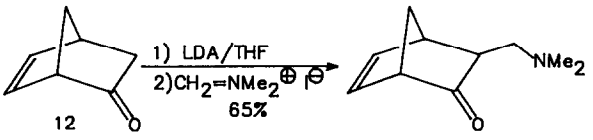
SCHEME II



The use of the Mannich bases formed by this sequence for the synthesis of natural products,[19] as well as other uses for these products will be described in further communications on this subject.

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