

A NEW GENERAL METHOD FOR CARBON-CARBON CONDENSATION
OF CONJUGATED ENAMINOKETONES AT THE γ -POSITION

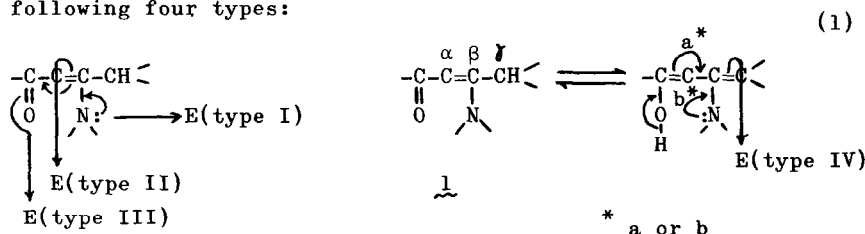
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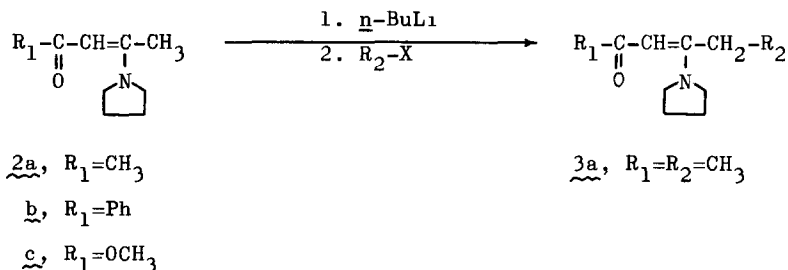
The nucleophilic reactions of conjugated enaminoketones 1 are classified into the following four types:



E: electrophile

While type I,² II,^{2,3} and III^{2,3} reactions are well known, the type IV reaction proceeds in special cases.⁴ We now wish to report a new general method for this type IV reaction, i.e. carbon-carbon condensation of enaminoketones at the γ -position.

Addition of n-butyllithium to an equimolecular amount of 4-pyrrolidino-3-penten-2-one (2a) in tetrahydrofuran at -60° gave a homogeneous solution which was then treated with methyl iodide to afford 4-pyrrolidino-3-hexen-2-one (3a), mp $35-36^{\circ}$ in 76% yield after recrystallization. The site of methylation was unambiguously established by examining the nmr spectrum of 3a: $(\text{CCl}_4) \delta$ 1.07 (t, 3H, $J=7.5$ Hz, $-\text{CH}_2\text{CH}_3$), 2.90 (q, 2H, $J=7.5$ Hz, $-\text{CH}_2\text{CH}_3$), 1.82-2.15 (m, 4H, pyrrolidine β -hydrogens), 1.90 (s, 3H, CH_3CO), 3.15-3.55 (m, 4H, pyrrolidine α -hydrogens), and 4.75 (s, 1H, $-\text{CH}=\text{C}$). It should be stressed that no α - or O-alkylated product was formed by this procedure i.e. the crude reaction product was practically pure as



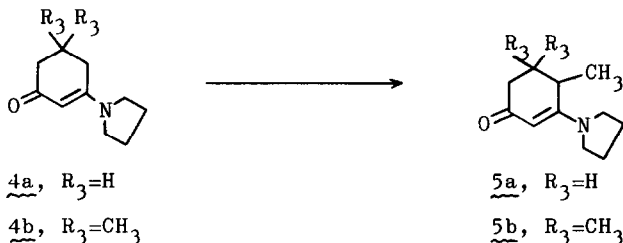
far as nmr spectrum was concerned. Analogously pyrrolidine enamine of benzoyl-acetone 2b and methyl acetoacetate 2c were alkylated with alkyl halides at the γ -position through lithium derivatives in good yields. These results are summarized in Table I.

Table I. Alkylation of Enaminoketones at the γ -position

Enamino-ketone	R ₁	R ₂ -X	yield of <u>3</u> , ^{a, b} %	mp or bp of <u>3</u> , °C (P, mm)
<u>2a</u>	CH ₃	CH ₃ I	76	mp 35-36
<u>2a</u>	CH ₃	H ₂ C=CH-CH ₂ Br	89	bp 125-130 ^c (0.001)
<u>2a</u>	CH ₃	BrCH ₂ COOEt	53	bp 150-155 ^c (0.01)
<u>2b</u>	Ph	CH ₃ I	79	mp 119-121
<u>2b</u>	Ph	CH ₃ CH ₂ CH ₂ I	84	bp 170-175 ^c (0.001)
<u>2c</u>	CH ₃ O	CH ₃ I	81	bp 115-120 ^c (0.001)
<u>2c</u>	CH ₃ O	PhCH ₂ Cl	73	mp 81-83

^a All products exhibited analytical and spectral data in accord with assigned structures. ^b Yields refer to distilled or recrystallized products. ^c Bath temperature.

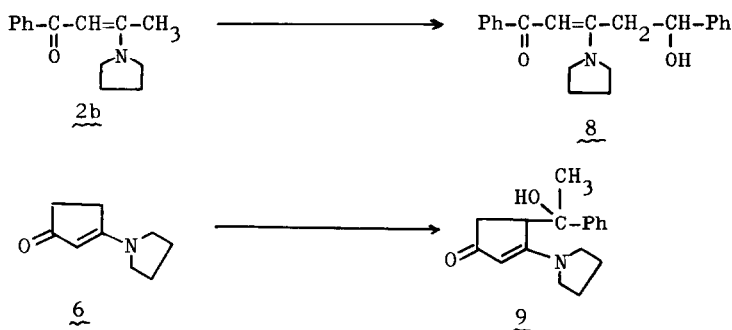
This method was successfully applied to cyclic enaminoketones. Thus, 3-pyrrolidino-2-cyclohexen-1-one (4a) was converted into 4-methyl-3-pyrrolidino-2-cyclohexen-1-one (5a), mp 82-83^o with *n*-butyllithium and methyl iodide. Even in a sterically hindered case the γ -alkylation took place in preference to α - or O-alkylation: the enamine of dimedone 4b was smoothly transformed into 5,5-dimethyl-4-methyl-3-pyrrolidino-2-cyclohexen-1-one (5b), mp 122-123^o in 62%



yield. Here the nmr spectrum of 5b also clearly indicated the position of methylation: (CDCl₃) δ 0.97 (s, 3H, CH₃), 1.10 (s, 3H, CH₃), 1.08 (d, 3H, $J=7.0$ Hz, CHCH₃) 1.85–2.20 (m, 5H, C₄-H and pyrrolidine β -hydrogens), 2.32 (s, 2H, CH₂CO), 3.15–3.60 (m, 4H, pyrrolidine α -hydrogens), and 4.98 (s, 1H, -CH=C). Analogously 3-pyrrolidino-2-cyclopenten-1-one (6) was selectively methylated at the 4 position to afford 4-methyl-3-pyrrolidino-2-cyclopenten-1-one (7), bp 156–162° (0.01 mm) in 55% yield. These selective alkylations at the γ -position are striking in connection with exclusive α -alkylation of enolates derived from α,β -unsaturated carbonyl systems.⁵

It is interesting that methylolithium and phenyllithium attack the carbonyl group of a conjugated enaminketone according to Meyers' report.⁶ Thus, the successful aspect of our alkylation method would be the temperature of the anion formation with *n*-butyllithium. An attempt to prepare the di-anion of 2a using 2 equivalents of *n*-butyllithium failed, judging from the fact that 3a was obtained in good yield after treatment with 2 equivalents of methyl iodide.

This alkylation method was extended to another nucleophilic reaction. Aldehydes and ketones also reacted with these anions at the γ -position to afford the corresponding alcohols. Thus, 1-phenyl-3-pyrrolidino-2-buten-1-one (2b) gave



1,5-diphenyl-5-hydroxy-3-pyrrolidino-2-penten-1-one (8), mp 152-153° on treatment with n-butyllithium and benzaldehyde in 52% yield. The cyclic enaminketone 6 was also converted into 9, mp 151-152° with acetophenone by the same procedure.

The following procedure is representative for alkylations. To a solution of 4-pyrrolidino-3-penten-2-one (2a) (50 mmol, 7.70 g) in dry THF (200 ml) was added 51 mmol of n-butyllithium in hexane at -60° under nitrogen. The mixture was stirred at -60° for 30 min, then a cooling bath was removed and stirring was continued for 1 hr. To the resulting homogeneous solution was added dropwise methyl iodide (60 mmol, 8.50 g) at -60°. The reaction mixture was stirred at that temperature for 30 min and at room temperature overnight. The solution was poured into saturated sodium chloride solution (100 ml) and extracted with ethyl acetate. The combined organic phase was washed with sodium chloride solution, dried over sodium sulfate and evaporated. Recrystallization of the crude product from n-heptane gave 4-pyrrolidino-3-hexen-2-on (3a) as prisms, mp 35-36° (6.42 g, 76% yield).

References

1. This form does not necessarily represent a true intermediate for a reaction. It is only for convenience in explanation.
2. For example see G.H. Alt in "Enamines: Synthesis, Structure, and Reactions; Electrophilic Substitutions and Additions to Enamines," A.G. Cook, Ed., Marcel Dekker, New York and London, 1969, Chapter 4, p 115.
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6. A.I. Meyers and S. Singh, Tetrahedron Lett., 5319 (1967).