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A CONVENIENT METHOD FOR THE SYNTHESIS OF α,β-UNSATURATED CARBONYL COMPOUNDS

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A variety of α,β-unsaturated ketones are conveniently synthesized from enaminoketones and organolithium compounds especially when the reaction is carried out in *petroleum ether;* this reaction provides a facile method for the synthesis of α,β,γ-trisubstituted 2-cyclopentenones in combination with the regioselective alkylation of enaminoketones.

Enamines are versatile synthetic intermediates in organic synthesis, and there are some reports[1-6)] on the reaction of enaminoketones with organometallic reagents in which amino groups are directly replaced by alkyl groups originated from alkyllithium in low yields. Almost all of these reactions are limited to the enaminoketones with no active hydrogen. In fact, complex products were obtained when 5-pyrrolidino-4-hepten-3-one was treated with Grignard reagent in ether, and most of the starting material was recovered unchanged when it was treated with *n*-butyllithium in tetrahydrofuran (THF). Based on these results, we have studied these reactions in detail in order to increase the chemical yields of α,β-unsaturated ketones.

After examination of reaction conditions, it was found that the reactivity of organolithium compounds as nucleophiles toward enaminoketones is greatly influenced by solvents. To our surprise, organolithium compounds reacted quite smoothly with enaminoketones in *hydrocarbon solvent* such as petroleum ether and *n*-hexane to give α,β-unsaturated ketones in fairly good yields.

There are two possible pathways (Path A and Path B) for the present reaction as shown in Scheme 1. In Path A, α,β-unsaturated ketone is formed with loss of pyrrolidinolithium from an intermediate, the Michael addition product of enaminoketone and alkyllithium. In Path B, enaminoketone is deprotonated to give a diolefinic lithium enolate which regenerates the starting material on hydrolysis. The hydrocarbon solvent plays an important role on increasing the nucleophilicity and decreasing the basicity of organolithium compounds, and makes Path A much more favourable than Path B.

The reactions of acyclic enaminoketones with some organolithium compounds proceeded very smoothly at low temperature and, as is shown in Table 1, vinyl- and ethynyllithium gave better results than alkyllithium probably due to their decreased basicity.

Scheme 1.

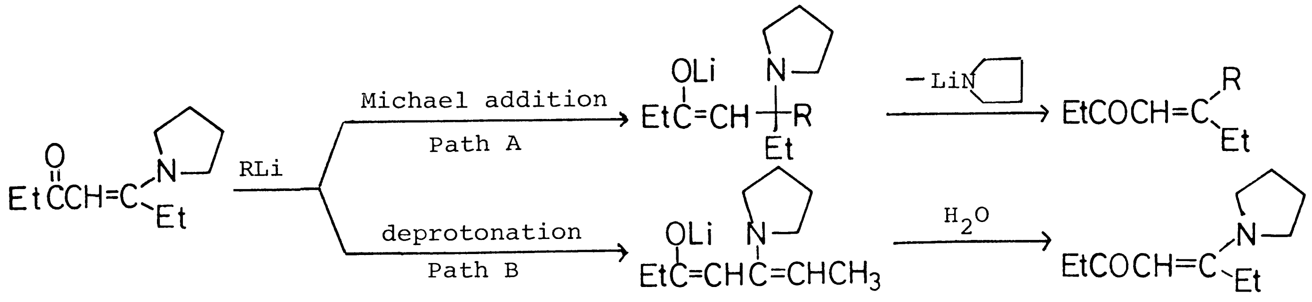
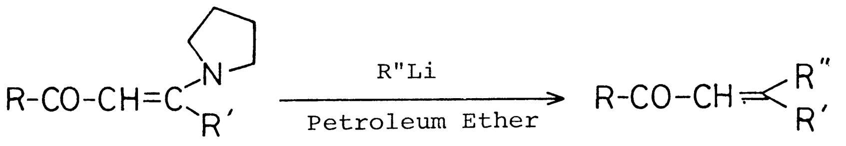


Table 1. Preparation of α,β-Unsaturated Acyclic Ketones[a]

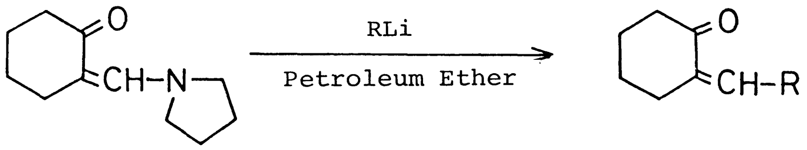


R	R'	R"[b]	Reaction Conditions		Yield(%)[c]
			Temp (°C)	Time (h)	
Et	Et	$CH_3CH=CH-$	-40	2	81
Et	Et	Bu	-40	2	67
t-Bu	Et	Me	-40	2	68
t-Bu	Et	Bu	-40	2	65
t-Bu	Pr	$CH_3CH=CH-$	-40	2	84
t-Bu	$PhCH_2CH_2-$	Bu	-40	2	68
t-Bu	Me	$C_6H_{13}C{\equiv}C-$[d]	-20	2	47
Et	Et	$C_6H_{13}C{\equiv}C-$[d]	-30	2	73

a) All the products were fully characterized by NMR and IR spectra.
b) In all experiments, 1.1 equiv of organolithium compounds were used.
c) Yields of isolated product.
d) 1-Octynyllithium was prepared by adding equimolar of butyllithium to 1-octyne in petroleum ether, and the alkylation was carried out by adding enaminoketone to the resulting suspension.

In the case of the reaction of the enamines having no hydrogen atom adjacent to pyrrolidino group with organolithium compounds, it can be expected that Path A becomes a main route for the reaction because deprotonation in Path B is deleted. Expectedly, the reaction of 2-(pyrrolidinomethylidene)cyclohexanone with organolithium compounds gave the desired products in nearly the same yields irrespective of their structures. Thus present procedure provides an excellent method for the syntheses of α-alkylidene-, α-alkenylidene-, and α-alkynylidenecyclohexanones (Table 2).

Table 2. Preparation of α-Alkylidenecyclohexanones[a)]

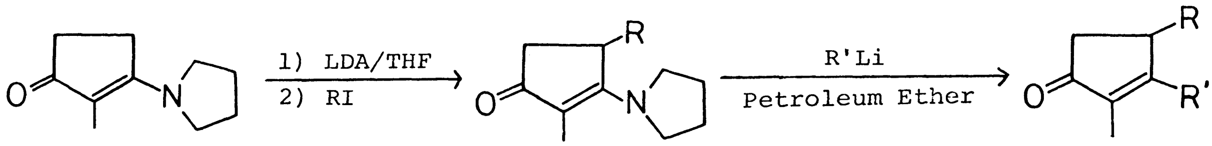


$R^{b)}$	Reaction Conditions Temp (°C)	 Time (h)	Yield(%)[c)]
Bu	-40	2	83
Me	-40	2	81
$CH_3CH{=}CH-$	-30	2	78
$C_6H_{13}C{\equiv}C-^{d)}$	-30	2	80

a - d) Same as noted in Table 1.

The reaction was further successfully applied to the syntheses of α,β-disubstituted and α,β,γ-trisubstituted cyclopentenones. The treatment of 2-methyl-3-pyrrolidino-2-cyclopentenone with alkyllithium gave β-substituted 2-methyl-2-cyclopentenones in fairly good yields and α,β,γ-trisubstituted 2-cyclopentenones were also obtained in combination with the selective alkylation[7)] of 2-methyl-3-pyrrolidino-2-cyclopentenone at γ-position (Table 3).

Table 3. Preparation of α,β,γ-Trisubstituted 2-Cyclopentenones[a)]



R	R'[b)]	Reaction Conditions Temp (°C)	 Time (h)	Yield(%)[c)]
–	Bu	0	2	61
–	Et	0	2	57
Me	Bu[d)]	0	2	53
Et	Bu[d)]	0	2	56

a - c) Same as noted in Table 1.
d) The alkylation of the enamine was carried out in accordance with the typical experimental procedures.

Typical experimental procedures are given below: The preparation of 5-ethyl-4,6-octadiene-3-one (1). To a stirred suspension of 5-pyrrolidino-4-hepten-3-one (250 mg, 1.38 mmol) in petroleum ether (3 ml) was added an ether solution of 1-propenyllithium (1.52 mmol) at -40°C under an argon atmosphere, and stirring was continued for 2 h at the same temperature. The reaction mixture was quenched with water and then extracted with ether. The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was chromatographed on silica gel to give 1 (168 mg, 81%). The preparation of 2,4-dimethyl-3-butyl-2-cyclopentenone (2). To a stirred solution of diisopropylamine (220 mg, 2.18 mmol) in THF (3 ml) was added a hexane solution of butyllithium (2.09 mmol) at -78°C under an argon atmosphere. Stirring was continued for 30 min, and a solution of 2-methyl-3-pyrrolidino-2-cyclopentenone (300 mg, 1.82 mmol) in THF (2 ml) was added at the same temperature. After 2 h, a THF solution of methyl iodide (300 mg, 2.10 mmol) was added, and the reaction mixture was gradually warmed to room temperature. The resulting solution was quenched with brine and then extracted with ethyl acetate. The combined extracts were dried over anhydrous sodium sulfate and concentrated to give 2,4-dimethyl-3-pyrrolidino-2-cyclopentenone (260 mg, 80%).

Enaminoketones thus obtained (180 mg, 1.01 mmol) were suspended in petroleum ether (4 ml), and then a hexan solution of butyllithium (1.11 mmol) was added with stirring at -20°C under an argon atmosphere. The reaction mixture was gradually warmed to 0°C and left at this temperature for 2 h. The resulting solution was quenched with brine and extracted with ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated. The residue was chromatographed on silica gel to give 2 (88 mg, 53%).

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