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The reaction of β-enaminoesters with organolithium reagents: a convenient method for the regioselective synthesis of enaminoketones

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Abstract—A simple and practical method for the regioselective preparation of β-enaminoketones is described. The method relies on the reaction of β-enaminoesters with organolithium reagents, and allows the preparation of a range of unusual β-enaminoketones.

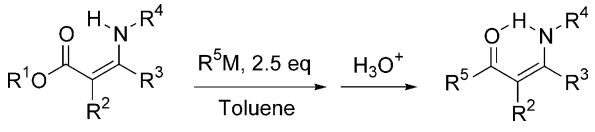
Enaminoketones are versatile building blocks that have been studied extensively for their properties[1] and as precursors of several interesting classes of compounds.[2] They can also be used as starting materials for the stereoselective preparation of γ-aminoalcohols (by reduction).[3] Moreover, several synthetic methodologies (affording many different classes of compounds[4]) based on the reaction of dianions of N-monoalkylated-β-enaminoketones with various electrophiles were developed.

β-Enaminoketones can be prepared in several ways: the direct condensation, either under homogeneous or heterogeneous conditions,[5] of the appropriate amine with symmetrical β-dicarbonyl compounds affords the simplest one, while the acylation of lithium imines with esters represents another way for their regioselective preparation.[6]

In this paper a simple and direct procedure for the regioselective preparation of β-enaminoketones by reaction of organolithium reagents with β-enaminoesters is reported. Although the reaction of β-enaminoesters with organolithium reagents has been studied previously,[7] clean synthesis of β-enaminoketones has never been achieved. Nevertheless β-enaminoesters represent a practical class of starting materials, for the preparation of β-enaminoketones, because easily obtainable by simple condensation of amines with β-ketoesters.[8] They are easily accessible more conveniently also by acylation of lithium imines with diethyl carbonate or benzyl chloroformate.[9]

When N-monoalkyl-β-enaminoester (**1**) was treated with 2.5 equiv of an organolithium reagent in toluene, the corresponding N-monoalkyl-β-enaminoketone (**2**) was obtained in moderate to good yields. The reaction is quite general: methyllithium, *n*-butyllithium, *tert*-butyllithium and phenyllithium all react with the starting β-enaminoesters (**1**). The procedure is simple and does not request dangerous or expensive chemicals, although one has to take into account the normal precautions for the use of organolithium reagents. In all the reactions, β-enaminoketones (**2**) were the only products obtained. The resulting product from addition to the second electrophilic centre, (i.e., C-3 α to the nitrogen atom) was never observed.

The reaction is depicted in Scheme 1; the yields and the products obtained are reported in Table 1.



1 **2**

Scheme 1.

Keywords: β-Enaminoesters; β-Enaminoketones; Organolithiums; Regioselective synthesis.
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Table 1. Yields and products of the addition of organolithium reagents to enaminoesters **1**

Entry	1	R^1	R^2	R^3	R^4	2[a]	R^5M	Yield (%)[b]
1	**1a**[10]	Et	H	Ph	Bn	**2aa**[13]	MeLi	51
2	**1a**[10]	Et	H	Ph	Bn	**2ab**	Bu^nLi	72
3	**1a**[10]	Et	H	Ph	Bn	**2ad**[14]	PhLi	84
4	**1b**[11]	Et	H	Ph	Ph	**2bb**	Bu^nLi	17
5	**1b**[11]	Et	H	Ph	Ph	**2bc**	Bu^tLi	85
6	**1b**[11]	Et	H	Ph	Ph	**2bd**[15]	PhLi	80
7	**1c**	Bn	H	Me	Bn	**2cb**	Bu^nLi	46
8	**1d**[12]	Et	$-(CH_2)_3-$		Bn	**2db**	Bu^nLi	30
9	**1e**[10]	Et	H	Ph	Me	**2eb**	Bu^nLi	43

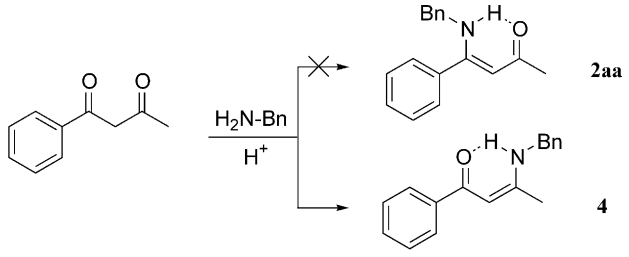
[a] All products were fully characterized by ^1H NMR, ^{13}C NMR, IR and mass spectroscopy.
[b] Pure isolated compounds and unoptimized yields.

A hypothesis concerning the mechanism is reported in Scheme 2.

It is very important to carefully control the amount of organometallic reagent used. Reactions that were performed with more than 2.5 equiv of organolithium reagent gave decreased yields, (although the starting β-enaminoester was totally consumed) and complex mixtures of products were obtained. These results may be accounted for by assuming that a double addition of organometallic reagent on the carbonyl group takes place, followed by retro-aldol decomposition of the intermediate hydroxyimine **3**, as depicted in Scheme 3. It is known from the literature[16] that hydroxyimines **3** are very unstable compounds that rapidly decompose.

The regioselective synthesis of β-enaminoketones by reaction of organolithium reagents with β-enaminoesters is complementary to the methods present in the literature. For example, product **2aa** cannot be prepared by direct condensation of benzoylacetone with the appropriate amine, because of the poor reactivity of the benzoyl group towards nucleophiles. In this case, the only product obtained is enaminoketone **4** (Scheme 4) (alternatively product **2aa** can be obtained by more complex procedures[17]).

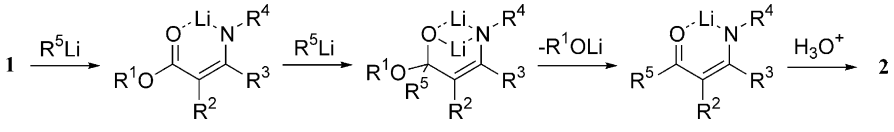
On the other hand, it is known[18] that the condensation of 1,3-diphenylpropan-1,3-dione with amines is difficult, and affords products like **2ad** after long reaction times only: enaminoketones derived from 1,3-diphenylpropan-1,3-dione in fact are obtained by alternative reactions.[19] The reaction of β-enaminoketones with organolithium reagents represents a more practical and direct method to obtain these particular derivatives. Finally, the preparation of product **2cb** by acylation of lithium imines with butanoic esters involves the preparation of aliphatic imines, which are quite unstable and therefore difficult to purify. These and related problems can easily be avoided by using the method described in this paper.



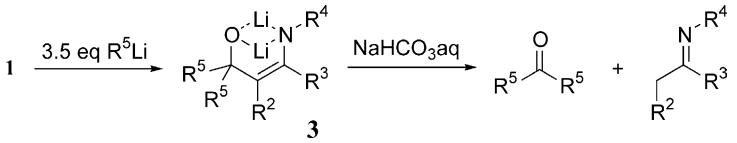
Scheme 4.

In summary, the reaction of N-monoalkyl-β-enaminoesters with organolithium reagents represents a practical and cheap method for the regioselective preparation of N-monoalkyl-β-enaminoketones (**2**). The reaction is general, simple, efficient and nicely complements the existing methodology.

General procedure for the preparation of β-enaminoketones (**2**). β-Enaminoester **1** (1 mmol) was dissolved in dry toluene (3 mL) under a nitrogen atmosphere, at



Scheme 2.



Scheme 3.

0 °C. Then organolithium reagent (2.5 mmol) was added to the solution and the reaction monitored by TLC (*n*-hexane/ethyle acetate: 80/20) until the starting material was consumed or the conversion remained unaltered for 1 h. The reaction mixture was quenched with NH_4Cl aqueous saturated solution and extracted with CH_2Cl_2 (2×10 mL). The organic layers were dried and the solvent evaporated under reduced pressure. The crude oil obtained was purified by column chromatography or crystallized.[20]

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Supplementary data

Experimental procedures and spectroscopic characterization (^{1}H NMR, ^{13}C NMR, IR, HRMS) of all new compounds are available in the supporting informations. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.027.

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20. Spectroscopic data of compound **2ab**: (*Z*)-1-(benzylamino)-1-phenylhept-1-en-3-one: Yellow oil; ν_{max} (liquid film) 2956, 1607, 1568, 1481, 1328, 1134, 1075, 755, 698 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.93 (t, 3 H, J = 7.1 Hz), 1.25–1.72 (m, 4 H), 2.36 (t, 2H, J = 7.7 Hz), 4.34 (d, 2H, J = 6.6 Hz), 5.14 (s, 1H), 7.15–7.45 (m, 10 H), 11.20 (b s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.2, 22.9, 28.4, 42.4, 48.4, 97.1, 127.1, 128.0, 128.3, 128.6, 128.9, 129.6, 135.5, 138.9, 165.2, 199.7. Anal. Calcd for $C_{20}H_{23}NO$, *m/z* (EI) 293 (M^+, 18), 236 (51), 208 (31), 104 (18), 91 (100); MW 293.40: C, 81.87; H, 7.90; N, 4.77%. Found: C, 81.54; H, 8.02; N, 4.58%.