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A Facile Preparation of α-Hydrazino-α,β-unsaturated Ketones *via* Aza-Baylis-Hillman Reaction

Akio Kamimura,*† Yoko Gunjigake†, Hiromasa Mitsudera† and Shuji Yokoyama††

†Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Ube 755-8611 JAPAN, and ††Ube Laboratory, Ube Industries Ltd., Ube 755-8633 JAPAN

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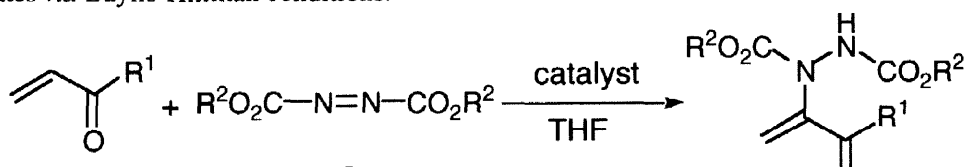
Abstract: α-(*N*,*N*'-Bisalkoxycarbonyl)hydrazino-α,β-unsaturated ketones are readily prepared *via* the aza-Baylis-Hillman reaction of alkyl vinyl ketones and azodicarboxylate esters.

Keywords: *Baylis-Hillman reactions; Hydrazines.*

Electrophilic amination to carbanion equivalents is recognized as a useful alternative to access natural/unnatural amino acids or their derivatives and there have been a number of reports on this issue.[1-6] For this purpose, azodicarboxylates,[2] trisyl azide,[3] α-chloronitroso compounds[4] or oxaziridines[5] are employed as typical electrophilic nitrogen sources. Although α-hydrazino-α,β-unsaturated compounds are regarded as potential precursors for these bioactive compounds,[7] only a few methods have been known to prepare them.[8,9] Additionally, one of the methods, consisting of two steps of reaction, uses pyridinium ylids from pyridinium salts which are not always easy to handle unless they solidify.[8] The Baylis-Hillman reaction is a powerful tool so that β-hydroxy-α-methylene compounds are prepared in one pot from α,β-unsaturated compounds and aldehydes under mild conditions.[10,11] The reaction has been extended to use imines as electrophiles that give β-amino-α-methylene compounds.[12] To the best of our knowledge, however, there have been no examples to apply the reaction to any nitrogen electrophiles. Here, we will report a facile and effective method to prepare α-(*N*,*N*'-bisalkoxycarbonyl)hydrazino-α,β-unsaturated ketones in one step from alkyl vinyl ketones and azodicarboxylates *via* Baylis-Hillman conditions.



1 **2a**; R^2 = Et **2b**; R^2 = *t*-Bu **3**

Scheme 1

The reaction procedure was quite simple: DABCO was added to a solution of alkyl vinyl ketone **1** and azodicarboxylate ester **2** in THF and the reaction mixture was allowed to stand at room temperature for several to 24 hours. Upon direct chromatographic purification, α-(*N*,*N*'-bisalkoxycarbonyl)hydrazino-α,β-unsaturated ketone **3** was obtained in good yield (Scheme 1). The results are summarized in Table 1.

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Table 1. Preparation of α-hydrazino-α,β-unsaturated ketones **3** via aza-Baylis-Hillman conditions

entry	R^1	R^2	catalyst (eq)	temp. (°C)	time (h)	**3**;	yield (%)
1	Me	Et	DABCO (1.0)	r.t.	8	**3a**;	73
2	Me	Et	DABCO (0.2)	r.t.	8	**3a**;	83
3	Me	Et	Et_3N (0.2)	r.t.	3	**3a**;	8
4	Me	Et	Bu_3P (0.2)	r.t.	120	**3a**;	0
5	Et	Et	DABCO (0.2)	r.t.	24	**3b**;	78
6	C_6H_{13}	Et	DABCO (0.2)	r.t.	24	**3c**;	79
7	C_7H_{15}	Et	DABCO (0.2)	r.t.	8	**3d**;	61
8	PhCH=CH-	Et	DABCO (0.2)	r.t.	8	**3e**;	90
9	OMe	Et	DABCO (1.0)	r.t.	120	**3f**;	0
10	Me	*t*-Bu	DABCO (1.0)	40	24	**3g**;	63
11	Et	*t*-Bu	DABCO (1.0)	40	24	**3h**;	34
12	PhCH=CH-	*t*-Bu	DABCO (1.0)	40	24	**3i**;	52

The reaction with diethyl azodicaboxylate needed catalytic amounts of DABCO to accomplish the reaction effectively (entries 1 and 2). Since other catalysts (Et_3N and Bu_3P[13]) were not useful for the reaction and small amounts or none of desired product **3** were formed, DABCO was the best of the catalyst for the reaction. Usual alkyl vinyl ketones were reactive enough for the reaction in THF, whereas methyl acrylate gave no Baylis-Hillman adduct under the conditions even after 5 days (entries 5-10). With a divinyl ketone, the reaction occurred only for the terminal vinyl site and β-substituted olefin unit remained untouched (entry 8). Di-*tert*-butyl azodicarboxylate **2b**, though a more useful nitrogen source than **2a**, showed slightly less reactivity than it; this may be due to the steric effect of the *tert*-butyl group. To enhance the reaction rate, we used an equimolar amount of DABCO at 40 °C and obtained corresponding **3g** to **3i** in moderate yields (entries 10-12). Further investigation and application of the reaction will be reported in due course.

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