

## A New Enamine Synthesis: Allylation-Enamination Reaction of Nitriles with Allylindium Reagents

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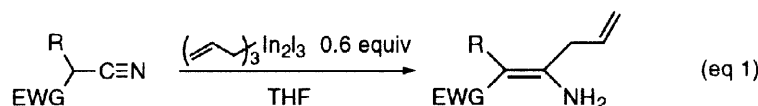
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**Abstract:** The reaction of allylindium reagents with certain nitriles **1** having another electron withdrawing group at the  $\alpha$ -position affords the corresponding allylation-enamination products **2** in high to good yields. © 1998 Published by Elsevier Science Ltd. All rights reserved.

**Keywords:** Allylation; Indium and compounds; Nitriles; Enamines

It is well known that the reaction of nitriles ( $R-C\equiv N$ ) with organometallic reagents ( $R'-ML_n$ ,  $M = Li, Mg, Zn$ , and others) including allylic compounds gives the corresponding metallated imines  $R(R')C=NM$ , which produces ketones  $R(R')C=O$  after hydrolysis.<sup>1</sup> We have found that the reaction of allylindium reagents with certain nitriles **1** takes an entirely different route to afford the corresponding allylation-enamination products **2**, **3-6** in high to good yields (eq 1). Nitriles having another electron withdrawing group at the  $\alpha$ -position can be converted to allylated enamines, providing a new procedure for the synthesis of enamines.<sup>2,3</sup>



EWG =  $CO_2R'$ , CN,  $COR'$   
R = H, Ph

**1a-d**

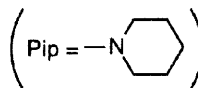
**2a-d, 3-6**

**2a:** EWG =  $CO_2Me$ , R = H

**2b:** EWG = CN, R = H

**2c:** EWG =  $CO\text{Pip}$ , R = H



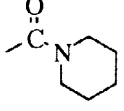


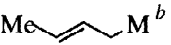
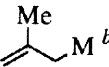
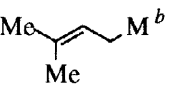

**2d:** EWG =  $CO_2Et$ , R = Ph



The results are summarized in Table 1. The reaction of methyl cyanoacetate **1a** with 0.6 equiv of allylindium,<sup>4,5</sup> generated in situ by mixing In powder (1.2 equiv) with allyl iodide (1.8equiv) in THF,<sup>6</sup> gave the allylation-enamination product **2a** regio- and (*Z*)-stereoselectively in essentially quantitative yield (entry 1). The (*Z*)-configuration was confirmed by a 400 MHz NOE experiment where signal enhancement (6.1%) of the olefinic proton next to the ester group was observed when the methylene protons of the allyl group were

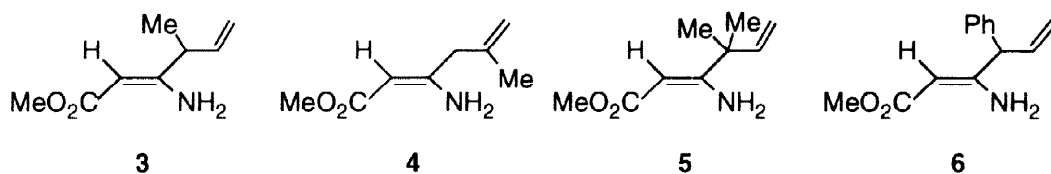
irradiated. The reactions of malononitrile **1b** and cyanoacetyl piperidine **1c** proceeded smoothly to give **2b** and **2c**, respectively, in high to good yields (entries 2 and 3). The reaction of ethyl phenylcyanoacetate **1d**, which has a bulky phenyl group at the position alpha to the cyano group, also proceeded smoothly to give the corresponding enamine product **2d** in good yield (entry 4). The reactions shown in entries 1-4 were completed within 2 h at 70 °C. The reaction of **1a** with crotylindium, prepared from In powder and crotyl bromide in THF, gave the  $\gamma$ -adduct **3** in 93% yield (entry 5); the regioisomeric  $\alpha$ -adduct was not detected. The reactions of **1a** with methallyl-, prenyl-, and cinnamylindium gave **4-6**, respectively, in high to good yields (entries 6-8). Here also, the branched  $\gamma$ -adducts **5** and **6** were obtained exclusively in the reactions of prenyl- and cinnamylindiums, respectively. The reactions shown in entries 5-8 were completed in longer reaction time depending upon the substituents in the allyl group (2-36 h).

**Table 1. Allylation-Enamination Reaction of Nitriles with Allylindiums**

entry	nitriles			allyl-M	product	yield <sup>a</sup> (%)
	<b>1</b>	R	EWG			
1	<b>1a</b>	H	CO <sub>2</sub> CH <sub>3</sub>		<b>2a</b>	100
2	<b>1b</b>	H	CN		<b>2b</b>	77
3	<b>1c</b>	H			<b>2c</b>	55
4	<b>1d</b>	Ph	CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>		<b>2d</b>	65
5	<b>1a</b>	H	CO <sub>2</sub> CH <sub>3</sub>		<b>3</b>	93
6	<b>1a</b>	H	CO <sub>2</sub> CH <sub>3</sub>		<b>4</b>	90
7	<b>1a</b>	H	CO <sub>2</sub> CH <sub>3</sub>		<b>5</b>	64
8	<b>1a</b>	H	CO <sub>2</sub> CH <sub>3</sub>		<b>6</b>	75

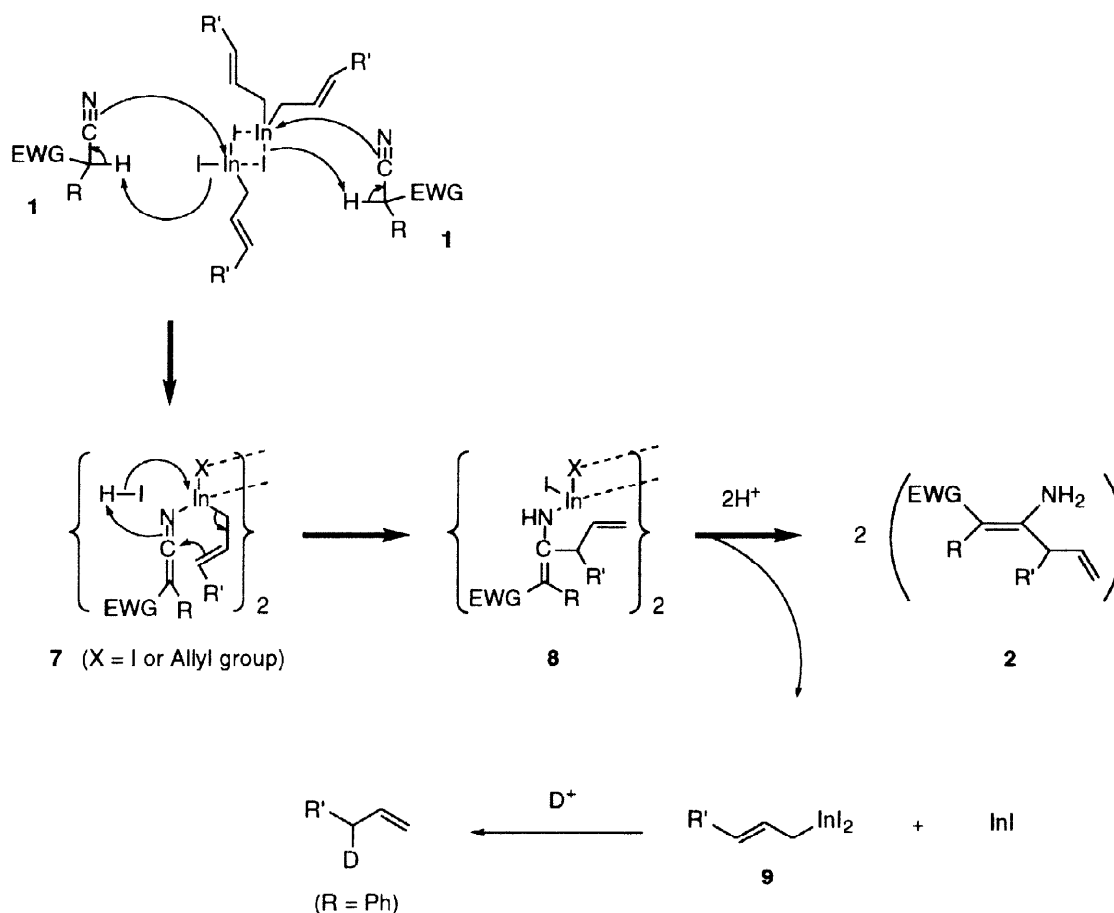
<sup>a</sup> Isolated yield.

<sup>b</sup> Bromides were used as starting materials instead of iodide.



A plausible mechanism of this allylation-enamination reaction is shown in Scheme 1. At first, allylindium would interact with the nitriles **1** to liberate hydrogen iodide and to form the ketene imine indium salt intermediate **7**.<sup>7</sup> When 2,4-hexadiene (5eq) was added at the beginning of the reaction in order to detect hydrogen iodide, 2-iodo-3-hexene was obtained, strongly supporting the formation of **7**. The allyl group on

allylindium would migrate to the carbon of the cyano group, and the ketene imine salt **7** would trap hydrogen iodide to form the imine indium salt **8**. Protonation of **8** would produce the allylation-enamination product **2**.<sup>8</sup> The third allyl group must remain in the resulting monoalkylindium diiodide **9**. Actually, when the allylation-enamination reaction using cinnamylindium was quenched with DCI/D<sub>2</sub>O, allylbenzene-*d* (Ph—CHD—CH=CH<sub>2</sub>, 96% *d*-content) was obtained, strongly suggesting the formation of **9**.



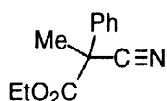
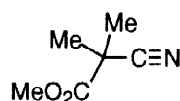
**Scheme 1.** Plausible mechanism for allylation-enamination reaction of nitriles with allylindium reagents

The reaction of 1.2 equiv of allylmagnesium chloride with **1a** resulted in recovery of **1a** and the allylation-enamination product was not obtained,<sup>9</sup> showing that the present allylation-enamination reaction takes place only with less basic allylindium reagents and failure of the Grignard reagent to react with **1a** is presumably due to deprotonation from the activated methylene position.<sup>9</sup> Enamines are important synthetic intermediates in organic synthesis since the discovery of Stork reaction.<sup>10</sup> Nevertheless, fewer reactions are available for their preparation.<sup>2</sup> The present procedure may be useful for the synthesis of certain functionalized enamines since such enamines are not easily available via conventional methods.<sup>11,12</sup>

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4. Two allyl groups among  $(\text{allyl})_3\text{In}_2\text{I}_3$  are used for the allylation reaction, and the third allyl group acts as a ligand of the In complex. Accordingly, 0.6 equiv of allylindium corresponds to 1.2 equiv of allylating agent in ordinary sense; S. Araki, H. Ito, Y. Butsugan, *J. Org. Chem.* **1988**, *53*, 1831-1833.
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6. Araki and his co-workers reported that allylindiums are inert to nitriles in DMF.<sup>4</sup>
7. We appreciate the following comments of one referee. The nitrile may coordinate to the indium before deprotonation, perhaps with displacement of iodide, and the protons next to the coordinated nitrile would become more acidic and the formation of **7** would look more reasonable.
8. The protonation would take place at the work-up stage: normally acidic silica gel column was used.<sup>11</sup> On the other hand, when the reaction was quenched with diluted HCl, the desired allylation-enamination product was not obtained.
9. Only abstraction of activated methylene hydrogen due to the basicity of allylmagnesium chloride was observed in this case. (pKa of the methylene hydrogen of **1a**  $\approx$  9; see R. G. Peason, R. L. Dillon, *J. Am. Chem. Soc.* **1953**, *75*, 2439-2443)
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11. Preparation of **2a** from **1a** is representative. Allylindium was prepared by mixing In powder (69 mg, 0.60 mmol) with allyl iodide (82  $\mu\text{L}$ , 0.90 mmol) in THF (1.0 mL) at room temperature for 1 h. To a THF solution of allylindium was added methyl cyanoacetate **1a** (44  $\mu\text{L}$ , 0.50 mmol) at room temperature. The reaction mixture was heated to 70  $^\circ\text{C}$ , stirred for 2 h, and then cooled to room temperature. THF was removed under vacuo, and the reaction product was separated with column chromatography on silica-gel (hexane/ethyl acetate = 8/1), giving **2a** (71 mg) in 100% yield.
12. The reactions of **10** and **11** with allylindium and allylmagnesium reagents were carried out. However, both substrates were recovered after a prolonged reaction time, irrespective of the reagent type. No reactions with allylindium are reasonable since there is no activated methyne proton in both substrates. No reactions with allylmagnesium chloride are presumably due to the steric bulkiness at the  $\alpha$ -position of nitriles **10** and **11**; it seems that even  $(\text{Me})_2\text{C}(\text{CO}_2\text{Me})$  of **11** is sterically demanding.

**10****11**