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Tandem N-Alkylation−C-Allylation Reaction of α-Imino Esters with Organoaluminums and Allyltributyltin

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Nucleophilic addition to the nitrogen atom of simple imines is, in principle, difficult due to the electron negativity of the imino functionality. Only limited examples have been available for the nucleophilic addition to the nitrogen atom of α-imino esters.[1] We have focused on the reactivity of α-imino esters and have revealed several interesting features.[2,3] During these studies, we found that on treatment of the imino ester **1a** with diethylaluminum chloride in the presence of benzoyl peroxide (BPO), diethylation product **2a** was obtained (Scheme 1).

This result induced us to explore the intriguing reactivity of the α-imino esters, and we have now found an unprecedented reaction for the synthesis of α,α-disubstituted amino acids. This paper presents a tandem N-alkylation−C-allylation reaction of α-imino esters using organoaluminum reagents and allyltributyltin.

First, the addition of two different nucleophiles to the imine **1a** was investigated. Allyltributyltin was chosen as a second alkylating reagent due to its highly nucleophilic nature as well as to the ability to act as a radical source.[4] The results are shown in Table 1. The imino ester **1a** was prepared by condensation of ethyl benzoylformate with *p*-anisidine. In DME solution, the reaction of diethylaluminum chloride gave the allylation product **4a** in 67% yield along with the diethylation product **2a** in 8% yield (entry 1). The reaction of ethylaluminum dichloride was more selective, although the yield was moderate (entry 2). Both the yield and the selectivity were improved using a mixture of diethylaluminum chloride (1 equiv) and ethylaluminum dichloride (1 equiv) (entry 3). Regarding the solvent, propionitrile was found to be the most effective, as it afforded the allylation product **4a** in 73% yield (entries 3−8).

Using optimized conditions, we examined the reaction with several imino esters **1a**−**i**. The reaction was carried out as follows: to a solution of BPO and the imino ester in propionitrile were added Et_2AlCl, $EtAlCl_2$, and allyltributyltin successively at −20 °C. After the starting material disappeared on TLC, a usual workup followed by purification gave the N-ethylation−C-allylation products **4a**−**i**. The results are summarized in Table 2. The aliphatic as well as aromatic imino esters underwent the tandem N-ethylation−allylation to give the addition products in moderate to good yields.

To increase the utility of this tandem alkylation−allylation reaction, bis(trimethylsilyl)aluminum chloride was used as an initial N-alkylation reagent,[5,6] and the results are summarized in Table 3. As shown in entry 1, a tandem N-silylation−C-allylation reaction proceeded with bis(trimethylsilyl)aluminum chloride on heating the mixture to 50 °C to afford the homoallylamine **5a** in 93% yield. On the other hand, the allylation did not proceed in the absence of BPO (entry 2). Other α-imino esters could also be used for the present N-silylation−C-allylation reaction to give the products in good to excellent yields (entries 3−7).

To clarify the reaction mechanism, several reaction conditions were examined (Scheme 2). When the imino ester **1a** was treated with a mixture of diethylaluminum chloride and ethylaluminum dichloride, N-ethylation product **2a** was obtained in 76% yield. After the N-ethylation, BPO or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with allyltributyltin was added, which actually gave the desired allylation product **4a**. To check the possibility of the involvement of a radical mechanism, the tandem reaction was carried out in the presence of galvinoxyl or 1,4-cyclohexadiene as a radical scavenger. However, the yields did not decrease, indicating that an ionic mechanism might be involved.

Scheme 1

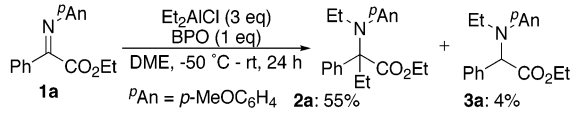
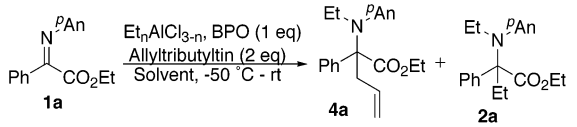


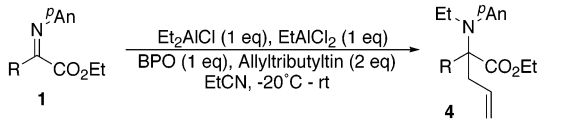
Table 1. Tandem N-Ethylation−C-Allylation Reaction under Various Conditions



entry	Et_nAlCl_{3-n}	solvent	time (h)	**4a** (%)	**2a** (%)
1	Et_2AlCl	DME	9	67	8
2	$EtAlCl_2$	DME	8	57	1
3	$Et_2AlCl + EtAlCl_2$	DME	9	73	2
4	$Et_2AlCl + EtAlCl_2$	Et_2O	9	41	6
5[a]	$Et_2AlCl + EtAlCl_2$	THF	9	65	1
6[b,c]	$Et_2AlCl + EtAlCl_2$	CH_2Cl_2	20	22	<1
7	$Et_2AlCl + EtAlCl_2$	EtCN	7	73	<1
8	$Et_2AlCl + EtAlCl_2$	MeCN	8	70	2

[a] N-Ethylation product **3a** was also obtained in 18% yield. [b] Carried out from −20 °C to room temperature. [c] N-Ethylation product **3a** was also obtained in 40% yield.

Table 2. Tandem N-Ethylation−C-Allylation Reaction with Various α-Imino Esters



entry	R (**1**)	time (h)	product	yield (%)[a]
1	Ph (**1a**)	7	**4a**	75
2	^{o}An (**1b**)	8	**4b**	47
3	^{p}An (**1c**)	7	**4c**	62
4	^{p}Tol (**1d**)	7	**4d**	63
5[b]	$^{p}Cl-C_6H_4$ (**1e**)	7	**4e**	76
6[c,d]	2-thienyl (**1f**)	7	**4f**	34
7[e]	cyclopropyl (**1g**)	7	**4g**	50
8	^{c}Hex (**1h**)	7	**4h**	39
9[c]	H (**1i**)	8	**4i**	18

[a] Isolated yield. [b] Et_2AlCl (1.5 equiv) and $EtAlCl_2$ (1.5 equiv) were used. [c] Carried out from −50 °C to room temperature. [d] Et_2AlCl (2 equiv) was used. [e] Carried out from −78 °C to room temperature.

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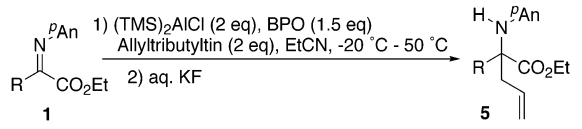
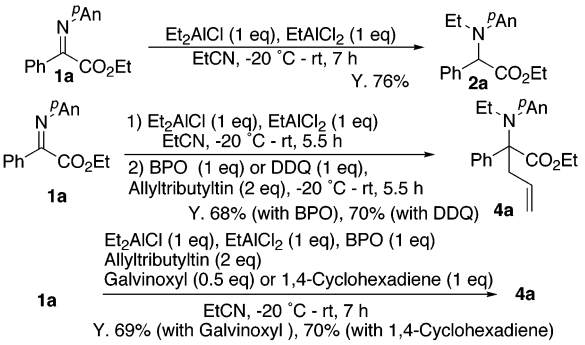
Table 3. Tandem N-Silylation−C-Allylation Reaction



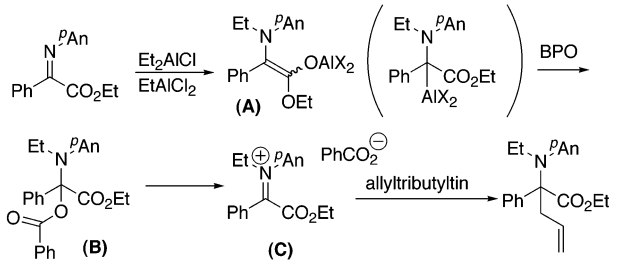
entry	R	time (h)	product	yield (%)[a]
1	Ph (**1a**)	23	**5a**	93
2[b]	Ph (**1a**)	25	**5a**	0[c]
3	*p*An (**1c**)	25	**5c**	84
4	*p*Tol (**1d**)	24	**5d**	83
5	*p*Cl−C_6H_4 (**1e**)	24	**5e**	73
6	2-thienyl (**1f**)	28	**5f**	61
7	cyclopropyl (**1g**)	23	**5g**	58

[a] Isolated yield. [b] In the absence of BPO. [c] The reduction product was obtained in 57% yield.

Scheme 2



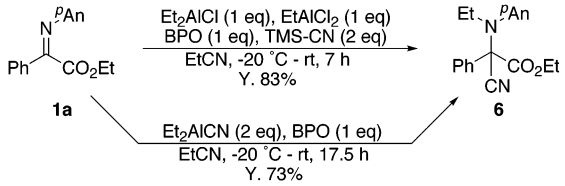
Scheme 3



On the basis of these results, a possible mechanism of the present tandem reaction is shown in Scheme 3. First, 1,4-addition of the ethyl group proceeds at the nitrogen atom of the imino ester to give an enolate species. The enolate (**A**) is subsequently oxidized with BPO (**B**) to form an iminium salt (**C**), which is attacked by allyltributyltin to afford the C-allylation product.

The tandem reaction was also carried out using trimethylsilyl cyanide instead of allyltributyltin to give the amino nitrile **6** in 83% yield (Scheme 4). It is interesting to note that in the presence of BPO, diethylaluminum cyanide acted as both ethylation and subsequent cyanation reagent to afford the amino nitrile **6** in 73% yield.[7] Although diethylaluminum cyanide has been used as the cyanide source in Strecker reaction,[8] its intriguing behavior as an ethylating reagent is unknown.

Scheme 4



In conclusion, the tandem N-alkylation−C-allylation and N-alkylation−C-cyanation reactions of several α-imino esters with organoaluminums were carried out in good to excellent yields, where two nucleophiles attacked across the C=N double bond. The tandem reaction consists of the following three sequences: nucleophilic addition to the nitrogen atom of the imino ester, oxidation of the enolate with BPO, and allylation (or cyanation) to the resulting iminium salt. The synergetic effect of Et_2AlCl and $EtAlCl_2$ is of interest, and we are currently investigating it in more detail.

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Supporting Information Available: Experimental procedures and product characterization for new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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