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CLAISEN REARRANGEMENT OF ALLYLIC α-ISOCYANOESTERS——REGIOSELECTIVE ALLYLATION OF α-ISOCYANOESTERS AT THE α-CARBON

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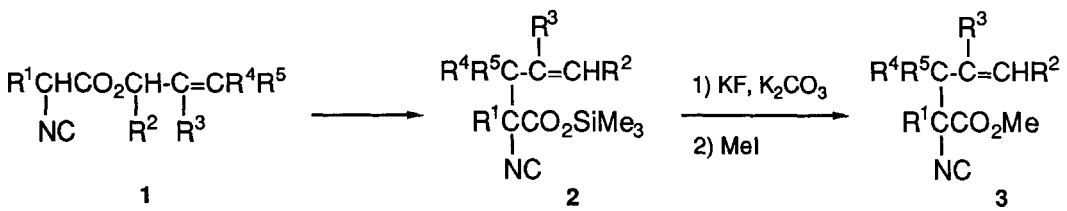
Abstract : A regioselective allylation of α-isocyanoesters at the α-carbon was achieved by the Claisen rearrangement of allylic α–isocyanoesters via the corresponding silyl ketene acetals in situ generated.

Carbon-carbon bond forming reactions at the α-carbon of α-isocyanoester provide a convenient preparative method of α-amino acid derivatives. The carbon-carbon bond formation at the α-carbon of α-isocyanoester has been conveniently achieved by carbon-electrophiles under basic conditions. Recently, we reported the palladium catalyzed allylation of α-isocyanoesters with allylic acetates, in which π-allylpalladium(II) complex intermediates are involved.[1] However, unsymmetrical π-allylpalladium(II) complexes afforded a mixture of regioisomeric allylation products. Now we wish to describe a regioselective allylation of α-isocyanoesters at the α-carbon by the Claisen rearrangement of allylic α-isocyanoesters via the corresponding silyl ketene acetals in situ generated.



1 2 3

The starting allylic α-isocyanoesters (**1**) were prepared by esterifications of patassium α-isocyanocarboxylates[2] either with 2-alkenyl bromides (Method I)[3] or with 2-alkenol by means of 2-chloropyridinium salt according to the modified Mukaiyama procedure[4] (Method II).[5] Some preparations of **1** are summarized in Table 1.

The Claisen rearrangement of **1** thus far prepared was achieved according to two procedures, [a] and [b], mentioned below.

Table 1. Synthesis of Allylic α-Isocyanoesters (**1**).

1

product	R^1	R^2	R^3	R^4	R^5	Method[a]	yield / %
1a	H	H	H	Me	H	I	85[b]
1b	Me	H	H	Me	H	II	59[c]
1i	Me	H	H	Me	$-CH_2CH_2CH=CMe_2$	II	66[d]
1j	Me	H	H	Ph	H	I	88[e]

a) Method I ; 2-alkenyl bromide, DMF, 50 ~ 60 °C. Method II ; 2-alkenol, 2-chloro-1-methylpyridinium iodide, triethylamine, THF, 40 ~ 50 °C. b) A mixture of (E)- and (Z)-2-butenyl bromide (E : Z = ~ 85:15) was used. c) (E)-2-Butenol (>95% E) was used. d) Geraniol was used. e) (E)-Cinnamyl alcohol was used.

[a] Claisen Rearrangement of Allylic α-Isocyanoesters (1) Induced by Lithium Diisopropylamide (LDA) and Chlorotrimethylsilane.

Claisen rearrangement of **1** was facilitated via the corresponding silyl ketene acetal[6] as follows. Lithium enolate (1.0 mmol) of **1** in THF (3 mL), which was in situ generated at -78 °C from **1** and lithium diisopropylamide (LDA), was treated with chlorotrimethylsilane (1.2 mmol) at -78 °C, and then stirred at 0 °C for 15 min and at room temperature for 3 h. The reaction mixture was evaporated in vacuo and subjected to esterification [KF (3.0 mmol), K_2CO_3 (2.0 mmol), DMF (3 ml), room temperature, 1 h, then MeI (2.4 mmol), room temperature, 12 h]. Results of the Claisen rearrangement of **1** were listed in Table 2.

As expected, the Claisen rearrangement of **1** permitted a regioselective carbon-carbon bond formation between the α-carbon of α-isocyanoester and 3-carbon of allylic group. Even **1e** having two substituents on 3-carbon of allylic group underwent a regioselective allylation to afford **3e** (entry 5). However, the rearrangement did not lead to stereoselective allylation, i.e., allylic α-isocyanoesters, **1a**, **1b**,[7] **1c** and **1d** were all rearranged to the corresponding α-allylation products (**2**) as diastereomeric mixtures with low stereoselectivities (1 : 1 ~ 1 : 2). No stereoselective rearrangement of **1** may be caused by concomitant generation of (E)- and (Z)-lithium enolates of **1**. Attempts to generate selectively (E)- or (Z)- lithium enolates of **1**, e.g., an investigation on effects of solvents and additives such as HMPA,[6] did not substantially improve the stereoselectivity of the Claisen rearrangement of **1**. As shown in entry 8, propargylic α-isocyanoester produced the corresponding allenic ester (**3h**, methyl 2-isocyano-2,3-dimethylpenta-3,4-dienoate) via a similar Claisen rearrangement at 50 °C.

Table 2. Claisen Rearrangement of **1** Induced by LDA and $ClSiMe_3$.

entry	1	R^1	R^2	R^3	R^4	R^5	3	yield / %
1	**1a**	H	H	H	Me	H	**3a**	68
2	**1b**	Me	H	H	Me	H	**3b**	74
3	**1c**	Et	H	H	Me	H	**3c**	80
4	**1d**	*i*-Pr	H	H	Me	H	**3d**	87
5	**1e**	Me	H	H	Me	Me	**3e**	82
6	**1f**	Me	H	Me	H	H	**3f**	65
7	**1g**	Me	Me	H	H	H	**3g**	84[a]
8	**1h**	Me		$-CH_2C{\equiv}CMe$[b]			**3h**	50

a) Only (E)-**3g** was formed. b) 2-butynyl.

[b] Claisen Rearrangement of Allylic α-Isocyanoesters (1) Induced by N,O-Bis(trimethylsilyl)acetamide (BSA).

The Claisen rearrangement of **1** was also accomplished by use of N,O-bis(trimethylsilyl)-acetamide (BSA) and a catalytic amount of copper(I) triflate[8] (Table 3). In the absence of copper(I) triflate, the rearrangement of **1** was sluggish; for instance, **1d** produced only a trace amount of **3d** on treatment with BSA in THF at 50 °C for 5 h (entry 5). Of interest is that a catalytic amount of copper(I) triflate remarkably accelerated the Claisen rearrangement of **1**. The Claisen rearrangement of **1** proceeded well at 50 °C in the presence of BSA (1.5 equiv) and a catalytic amount of copper(I) triflate (~ 3 mol%) to give the rearranged products (**2**),

Table 3. Claisen Rearrangement of **1** Induced by BSA.

entry	1	R^1	R^2	R^3	R^4	R^5	catalyst	3	yield / %[a]
1	**1b**	Me	H	H	Me	H	—	—	0[b]
2	**1b**	Me	H	H	Me	H	CuOTf	**3b**	80[b]
3	**1b**	Me	H	H	Me	H	CuOTf	**3b**	91
4	**1c**	Et	H	H	Me	H	CuOTf	**3c**	87
5	**1d**	*i*-Pr	H	H	Me	H	—	**3d**	trace
6	**1d**	*i*-Pr	H	H	Me	H	CuOTf	**3d**	75
7	**1e**	Me	H	H	Me	Me	CuOTf	**3e**	74
8	**1i**	Me	H	H	Me	$-CH_2CH_2CH{=}CMe_2$	CuOTf	**3i**	66
9	**1j**	Me	H	H	Ph	H	CuOTf	**3j**	71

a) The reaction was conducted in THF at 50 °C for 3 ~ 10 h, unless otherwise noted.
b) The reaction was conducted at room temperature for 10 h.

which were esterified by a similar procedure used in [a]. Since coordination of the isocyano carbon of **1** to cationic copper(I) enhances acidity of the α-hydrogen, **1** would be more susceptible to silylation with BSA and more readily rearranged than in the absence of copper(I) triflate (entries 1 and 2, 5 and 6). The regioselective allylation was also achieved in case of geranyl α-isocyanopropionate (entry 8). Further, cinnamyl α-isocyanopropionate, whose rearrangement was unsuccessful by the procedure [a], afforded **3j** in a good yield by the reaction with BSA (entry 9).

References and Notes.

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2) D Hoppe and U. Schöllkopf, Chem. Ber., 109, 482 (1971).
3) M. Suzuki, K. Nunami, K. Matsumoto, N. Yoneda, O. Kasuga, H. Yoshida, and T. Yamaguchi, Chem. Pharm. Bull., 28, 2374 (1980).
4) K. Saigo, M. Usui, K. Kikuchi, E. Shimada, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 50, 1863 (1977).
5) Representative procedure is as follows: To the mixture of potassium α-isocyanopropionate (4.0 mmol) and 2-chloro-1-methylpyridinium iodide (4.8 mmol) in THF (12 ml) were added 2-butenol (6.2 mmol) and triethylamine (20 mmol) at room temperature. After stirring at 45 °C for 2 h, insoluble materials were filtered off and column chromatography (silica gel) of the filtrate gave **1b** (59 %).
6) R. E. Ireland, R. H. Mueller, and A. K. Willard, J. Am. Chem. Soc., 98. 2868 (1976).
7) α-Isocyanoesters (**1b**) of different E : Z ratios were prepared by Method I using 2-butenyl bromide (E : Z = ~ 85:15) and by Method II using (E)-2-butenol (>95% E). Both **1b** gave **3b** of almost 1 : 1 diastereomers ratio.
8) The isolated copper(I) triflate benzene complex was used; R. G. Salomon and J. K. Kochi, J. Am. Chem. Soc., 95, 1889 (1973).

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