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REITERATIVE THIO-CLAISEN REARRANGEMENT USING A THIOLACTAM SUBSTRATE

Seiichi TAKANO*, Michiyasu HIRAMA, and Kunio OGASAWARA

Pharmaceutical Institute, Tohoku University, Aobayama

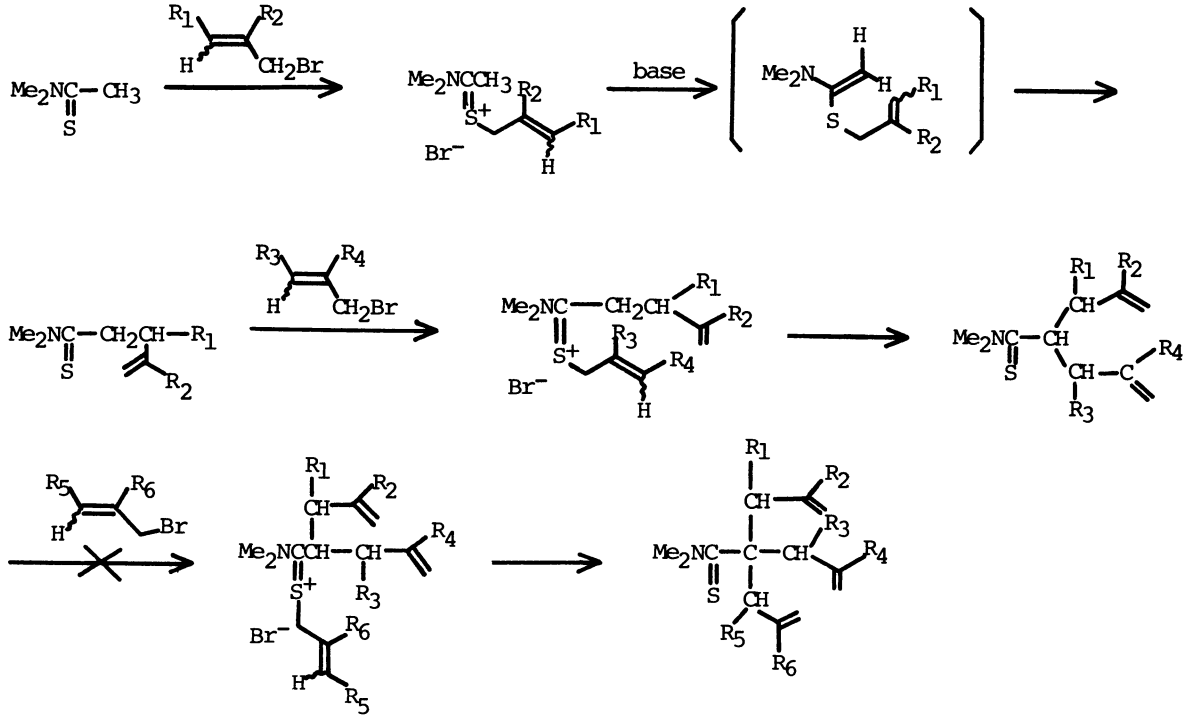
Sendai 980

A thiolactam(1) undergoes facile reiterative thio-Claisen rearrangement to give the α,α-disubstituted lactams with a variety of allyl groups.

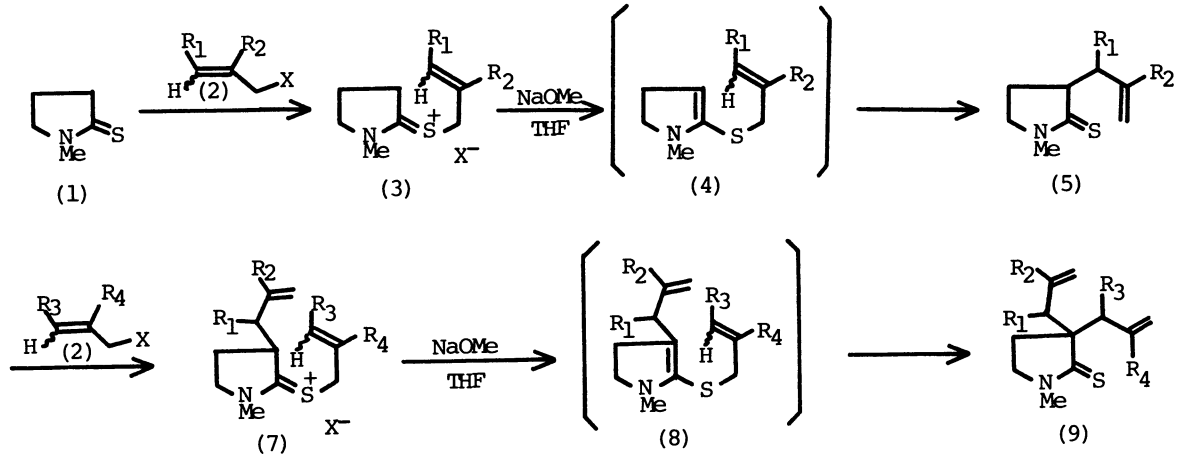
Recently we developed a reiterative thio-Claisen rearrangement reaction using acyclic tertiary thioamides as substrate[1] and exploiting the reaction we succeeded to establish a general methodology for the syntheses of the iboga[2),3)], the aspidosperma[2)], and the strychnos[4)] indole alkaloids. The reaction developed is more advantageous than both the Eschenmoser[5)] and Johnson[6)] versions of the Claisen rearrangement as it can be repeated without changing the key functional group and, in principle, it can be carried out as many times as there are α-hydrogen atoms in the thioamide substrates. In practice, however, the last rearrangement could be hardly attained to give the thioamides with quaternary α carbon owing to incapability of forming congested sulfonium intermediates[1)](Scheme 1).

We report here an extension of this reaction to a cyclic substrate(1), which allowed the reiterative rearrangement leading to a formation of quaternary center at the α carbon of the thiolactam group(Scheme 2).[7)] The reaction could be carried out under mild conditions using a variety of allyl halides as shown in the Table. Among the reactions carried out, when the allyl group bearing carbomethoxy group(2g), concomitant stereoselective double bond migration occurred to give the α,β-unsaturated ester(10) with E-configuration in 77.0% yield. The migration could be suppressed by using sodium hydride in place of sodium methoxide(Table: entry 7), though the former base, upon longer treatment(15h), converted the β,γ-unsaturated

ester(5e) into the α,β-unsaturated ester(10), in 71.8% yield. Treatment of (10) with allyl bromide(2a), followed by sodium methoxide gave the α,α-disubstituted thiolactam(11) in 37.5% yield(scheme 3).



Scheme 1



Scheme 2

The following experimental procedure is representative of the conversion: The thiolactam(1), 2.3g, 20mmol, in acetonitrile(30ml) was stirred with allyl bromide(2a), 4.84g, 40mmol, at room temperature under nitrogen for 2 days. The reaction mixture was concentrated in vacuo to give the crude sulfonium base(3). The crude(3) in THF(75ml) was stirred with sodium methoxide, 1.62g, 30mmol, at 0°C for 15min and the stirring was continued for 15h at room temperature. To a mixture was added aqueous NH_4Cl solution and was extracted with methylene chloride. The extract was washed with water, dried over Na_2SO_4, and was evaporated in vacuo. The crude product was purified using a column chromatography(silica gel) to give pure (5a), 2.8g, 90.3%. The second rearrangement could be carried out under the same conditions.

Table

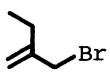
entry	lactam	allyl halide	product[8] R^1	R^2	R^3	R^4		yield (%)	bp(Torr)[c]
1	(1)	(2a)	H	H			(5a)[a]	90.3	89-91°(0.3)
2	(1)	(2b)	H	H			(5a)[a]	82.6	
3	(1)	(2c)	Me	H			(5b)[a]	91.1	178-183°(13)
4	(1)	(2d)[2]	H	Et			(5c)[a]	86.5	120-125°(0.55)
5	(1)	(2e)	H	Cl			(5d)[a]	39.8[d]	mp 69-70°
6	(1)	(2f)	H	Cl			(5d)[a]	77.8	
7	(1)	(2g)[9]	CO_2Me	H			(5e)[b]	81.2	147-150°(0.85)
8	(5a)	(2a)	H	H	H	H	(9a)[a]	70.3	123-126°(0.5)
9	(5a)	(2c)	H	H	Me	H	(9b)[a]	61.1	126-130°(0.9)
10	(5a)	(2d)	H	H	H	Et	(9c)[a]	48.6[d]	135-138°(0.4)
11	(5b)	(2a)	Me	H	H	H	(9b)[a]	77.0	
12	(5b)	(2f)	Me	H	H	Cl	(9d)[a]	31.6[d]	129-131°(0.1)
13	(5c)	(2a)	H	Et	H	H	(9c)[a]	63.7	
14	(5c)	(2d)	H	Et	H	Et	(9e)[a]	51.3	145-150°(0.45)
15	(5d)	(2c)	H	Cl	Me	H	(9d)[a]	70.5	

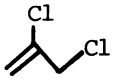
a: Sodium methoxide (1.5 equiv) was used as base.
b: Sodium hydride (2.5 equiv) was used as base.
c: Distilled using a Kugelrohl.
d: Low yield was attribtuted to incomplete quaternization of the substrate.

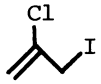
2a: 

2b: 

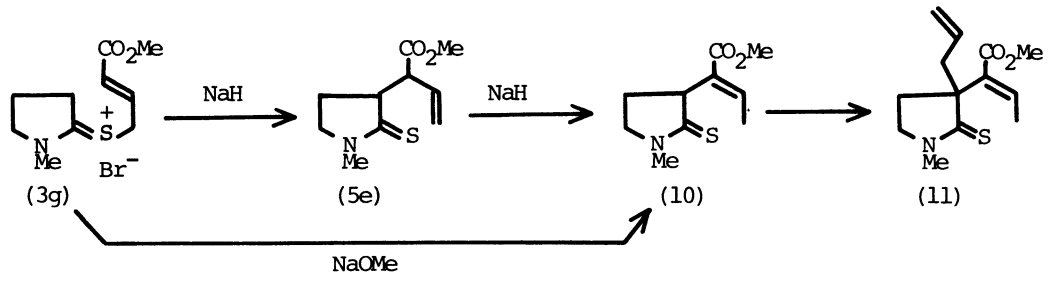
2c: 

2d: 

2e: 

2f: 

2g: 



Scheme 3

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7) We have succeeded the construction of a quaternary center at the α carbon of a certain thiolactam via the thio-Claisen rearrangement as described in reference 2, but this was the only example we have made.

8) Satisfactory spectroscopic(IR, ^{1}H-NMR, MS) and analytical data were obtained for all new compounds.

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