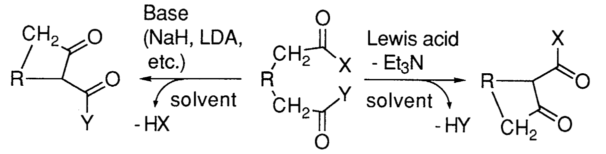
New Reaction Mode of the Dieckmann-Type Cyclization under the Lewis Acid-Et_3N Conditions

Satoshi Tamai,[#] Hideki Ushirogochi, Shigeki Sano, and Yoshimitsu Nagao*
Faculty of Pharmaceutical Sciences, The University of Tokushima, Sho-machi, Tokushima 770

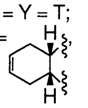
(Received January 5, 1995)

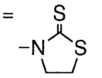
Dieckmann-type cyclization reactions of various dicarboxylic acid derivatives were readily promoted by employing Lewis acids such as $AlCl_3$, $MgBr_2$, $MgCl_2$, and $Sn(OSO_2CF_3)_2$ in the presence of Et_3N or *N*-ethylpiperidine. The cyclization reactions of half thiol diesters under the $AlCl_3$-Et_3N conditions exhibited different chemoselectivity from the cyclization under the basic conditions.

Dieckmann cyclization reactions under the basic conditions have been widely utilized as one of the efficient synthetic methods for the functionalized carbocyclic synthons toward natural product syntheses.[1,2] In the Dieckmann reactions, it is a serious problem to control regioselective cyclization of unsymmetrical diesters. Thus, the chemoselective Dieckmann-type cyclizations were developed by exploiting half thiol diesters under the basic conditions [NaH, LDA, and $LiN(SiMe_3)_2$][3,4] or methoxymethyl methyl dicarboxylates in the presence of $TiCl_2(OSO_2CF_3)_2$-tertiary amine.[5] On the basis of previous Dieckmann-type cyclization reactions[1,3-5] and various Lewis acid-promoted aldol type reactions,[6] we anticipated a possibility of the complementary reaction mode (**1** → **2**) for the known (**1** → **3**) mode as shown in Scheme 1.



3a-**l** **1a**-**l** **2a**-**l**

a R = $(CH_2)_2$, X = Y = T; **b** R = $(CH_2)_2$, X = T, Y = OEt; **c** R = $(CH_2)_2$, X = Y = OMe; **d** R = $(CH_2)_2$, X = SPh, Y = OMe; **e** R = $(CH_2)_3$, X = Y = T; **f** R = CH_2SCH_2, X = Y = T; **g** R = CH_2SCH_2, X = Y = OMe; **h** R = , X = Y = T; **i** R = $(CH_2)_2$, X = SEt, Y = OEt; **j** R = SCH_2, X = SEt, Y = OEt; **k** R = SCH_2, X = SPh, Y = OMe; **l** R = $(CH_2)_2$, X = SPh, Y = OEt

T = 

Scheme 1.

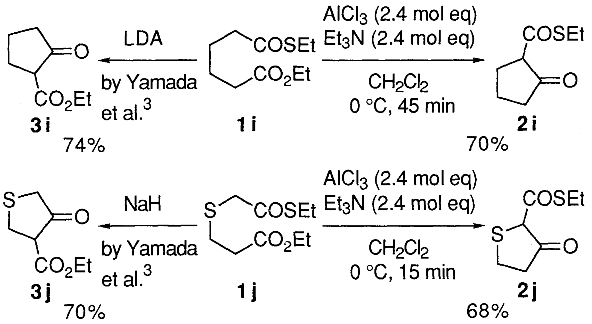
Herein we report new Lewis acid-promoted Dieckmann-type cyclization reactions. All results employing $Sn(OSO_2CF_3)_2$, $SnCl_4$, $MgCl_2$, $MgBr_2$, and $AlCl_3$ as the Lewis acids are summarized in Table 1. All reactions were carried out in a suitable solvent (CH_2Cl_2, CH_2Cl_2-MeCN, or MeCN) in the presence of 2.4 mol eq of each Lewis acid and 2.4 mol eq of Et_3N (*N*-ethylpiperidine[6b] in Entry 1 of Table 1) under the various conditions as shown in Table 1. Among several attempts (Entries 1-6) employing five kinds of Lewis acids in the cyclization reactions of **1a**, the four examples (Entries 1 and 4-6) with $AlCl_3$, $MgCl_2$, $MgBr_2$, and $Sn(OSO_2CF_3)_2$ seemed to be promising for the further study. However, in the cases of $MgCl_2$ and $MgBr_2$, both X and Y groups (X, Y = T) in the starting compounds **1** as well as reaction solvent (CH_2Cl_2-MeCN or MeCN) are essential (successful examples: Entries 4, 5, 13, 14, 16, and 17 *vs* failure and unsatisfactory examples: Entries 3, 7-10). On the other hand, $AlCl_3$ can readily promote all desired Dieckmann-type cyclization reactions, regardless of substituents X and Y (Entries 6, 11, 12, 15, and 18). Interestingly, in the cases of compounds **1b** and **1d**, chemoselective cyclization reactions were observed (Entries 11 and 12). The chemoselectivity in the case of half thiol diester with the $AlCl_3$-

Table 1. Dieckmann-Type Cyclization Reaction of **1a**-**h** under the Lewis Acid-Et_3N Conditions[a]

Entry	Compd.	LA[b]	Solv	Temp / °C	Time / h	Yield of **2** / %	Recovery of **1** / %
1[c]	**1a**	A	CH_2Cl_2	-40	0.33	60	0
2	**1a**	B	CH_2Cl_2	0	0.75	27	12
3	**1a**	C	CH_2Cl_2	rt[d]	1.5[d]	0	>90
4	**1a**	C	CH_2Cl_2-MeCN (1 : 1)	rt[d]	1.5[d]	77	0
5	**1a**	D	CH_2Cl_2-MeCN (1 : 1)	0	0.5	68	0
6	**1a**	E	CH_2Cl_2	0	1.5	75	0
7	**1b**	C	MeCN	rt[d]	18[d]	0	90
8	**1c**	C	MeCN	rt[d]	18[d]	0	98
9	**1b**	D	CH_2Cl_2-MeCN (1 : 1)	rt[d]	18[d]	13	22
10	**1c**	D	CH_2Cl_2-MeCN (1 : 1)	rt[d]	18[d]	0	82
11	**1b**	E	CH_2Cl_2	rt[d]	1[d]	52	0
12	**1d**	E	CH_2Cl_2	0	1	74	0
13	**1e**	C	MeCN	rt[d]	0.33[d]	79	0
14	**1f**	C	MeCN	rt[d]	1[d]	68	0
15	**1g**	E	CH_2Cl_2	rt[d]	3.5[d]	75	0
16	**1h**	C	MeCN	rt[d]	5[d]	60	8
17	**1h**	D	CH_2Cl_2-MeCN (1 : 1)	rt[d]	2.5[d]	79	0
18	**1h**	E	CH_2Cl_2	rt[d]	12[d]	47	2

[a] Unless otherwise indicated, all reactions were carried out in the presence of 2.4 mol eq of Et_3N. [b] Lewis acid (LA): A = $Sn(OSO_2CF_3)_2$, B = $SnCl_4$, C = $MgCl_2$, D = $MgBr_2$, E = $AlCl_3$. [c] Instead of Et_3N, *N*-ethylpiperidine (2.4 mol eq) was employed. [d] After treating at 0 °C for 1 h, the mixture was submitted to these conditions.

Et_3N system seems to be opposite to that in the previous cases under the basic conditions[3,4] employing NaH or LDA as we expected in Scheme 1. Thus, in order to compare with the basic conditions by Yamada et al.,[3] the same compounds **1i** and **1j** were submitted to the $AlCl_3$-Et_3N conditions to give the corresponding cyclic β-keto thioesters **2i** and **2j** in a good yield, respectively (Scheme 2).

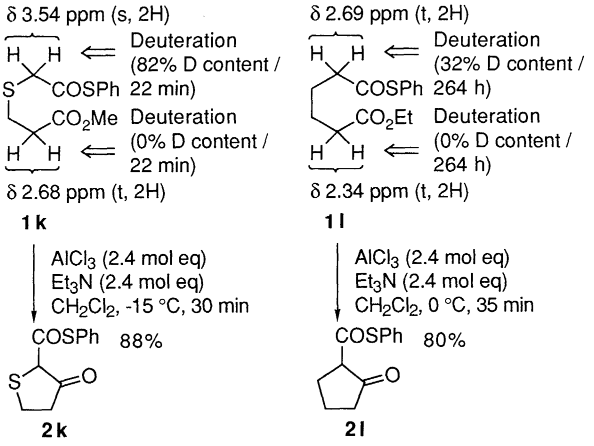


Scheme 2.

In order to get insight on the reaction pathway under the $AlCl_3$-Et_3N conditions, two kinds of half thiol diesters **1k** and **1l** were exposed to a solution of Et_3N (1.0 mol eq) in $CDCl_3$-CD_3OD (9 : 1) at room temperature. Predominant deuteration in the both compounds was observed at the active methylene position α to thioester as shown in Scheme 3. Their cyclization reactions utilizing the $AlCl_3$-Et_3N system proceeded chemoselectively to afford the corresponding cyclic β-keto thioesters **2k** and **2l** (Scheme 3).

Thus, the chemoselectivity of present reaction is understood by the preferential enolization (*e.g.*, $-CH_2COSR \gg -CH_2CO_2R$) depending upon the acidity of active methylene protons of the $-CH_2COX$ and $-CH_2COY$ moieties in Scheme 1.

This work was partially supported by Grant-in-Aid for Scientific Research on Priority Areas (No. 06225225) from the Ministry of Education, Science and Culture, Japan.



Scheme 3.

References and Notes

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