CHEMISTRY LETTERS, pp. 1127-1130, 1993.

Lewis Acid-Induced Hetero Diels-Alder Reaction of Conjugated Carbodiimides

Takao SAITO,* Takahiro OHKUBO, Katsuhiro MARUYAMA, Hideki KUBOKI, and Shinichi MOTOKI*
Department of Chemistry, Faculty of Science, Science University of Tokyo,
Kagurazaka, Shinjuku-ku, Tokyo 162

In the presence of a Lewis acid conjugated carbodiimides smoothly react as 2-azadienes with various dienophiles such as acetylenic compound, enamine, vinyl ether, and aldehyde under mild reaction conditions to give good yields of nitrogen heterocycles as cycloadducts.

Previously we found that conjugated carbodiimides can readily be prepared by the Wittig-type reaction of iminophosphoranes with isocyanates and be converted into nitrogen heterocycles such as tetrahydropyridines and isoquinolines via their thermal electrocyclization or Diels-Alder reaction.[1] This methodology[2] is a useful procedure for the synthesis of a variety of nitrogen heterocycles based on its simplicity and efficiency.[3-6] However, little has been explored on the Diels-Alder reaction of these conjugated carbodiimides as heterodienes. These carbodiimides show only limited reactivity in the Diels-Alder reaction. Only a strong dienophile, TCNE, could give rise to the cycloadducts.[1]

Recently, Nitta et al.[5] and Noguchi et al.[6] reported that some C=C-conjugated carbodiimides underwent the Diels-Alder reaction with highly reactive dienophiles such as dimethyl acetylenedicarboxylate and enamines under considerably high temperature conditions, resulting in fair yields of the cycloadducts. Thus, improvements in the Diels-Alder reaction with the conjugated carbodiimides are desired from the viewpoint of extension of this promising method to the synthesis of a variety of heterocycles as well as in the theoretical point of view.

Although Lewis acids are known to be often effective on Diels-Alder reactions, there is no report on the reaction using a Lewis acid. In this context we would like to demonstrate herein for the first time that proper Lewis acid could efficiently act in undergoing the Diels-Alder reaction of these conjugated carbodiimides with various dienophiles under mild reaction conditions.[7]

The carbodiimides **1**, which were prepared by the aza-Wittig reaction[3] of iminophosphoranes with isocyanates according to the previously reported procedure,[1] reacted with dimethyl acetylenedicarboxylate (DMAD) in refluxing toluene (115 °C) to afford the cycloadducts, pyridines **2**[8] in 22-28% yields (Table 1). Variation of the reaction conditions (molar ratios and temperatures)[5] did not improve the yields in the thermal reactions. Then, we utilized a Lewis acid in the reaction of **1a** as a model compound and results are shown in Table 2, entries 1-5. Use of other Lewis acids, e.g. $ZnCl_2$, $TiCl_4$, and $BF_3{\cdot}OEt_2$, at room temperature did not show satisfactory results. Finally we have found that aluminum chloride acts effectively under the conditions of entry 5 to provide the cycloadduct **2a**[8] in 77% yield. The other carbodiimides **1b,c** similarly afforded **2b,c** in satisfactory yields (entries 6 and 7).

The $AlCl_3$-promoted reaction with ethyl propiolate produced the cycloadducts **3**[8] in better yields than the thermal reaction (Table 3).

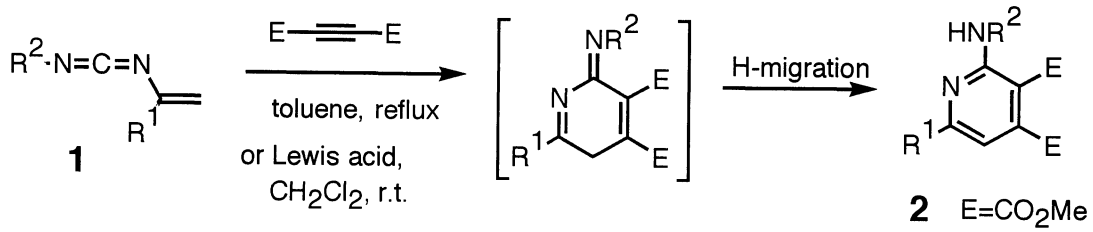


Table 1. Thermal Diels-Alder Reaction of Carbodiimides **1** with DMAD

Carbodiimide	R^1	R^2	Time / h	Product	Yield / %
1a	Ph	Ph	9	**2a**	22
1b	Ph	p-Tol	7	**2b**	22
1c	p-Tol	Ph	8	**2c**	28

Table 2. Diels-Alder Reaction of Carbodiimides **1** with DMAD in the Presence of Lewis Acid

Entry	Carbo-diimide	R^1	R^2	DMAD / Equiv.	Lewis acid / Equiv.	Time / h	Product	Yield / %
1	**1a**	Ph	Ph	1.1	$EtAlCl_2$ / 1.1	3	**2a**	14
2	**1a**	Ph	Ph	2.0	$EtAlCl_2$ / 2.0	2.5	**2a**	38
3	**1a**	Ph	Ph	1.1	$AlCl_3$ / 1.1	2	**2a**	26
4	**1a**	Ph	Ph	2.0	$AlCl_3$ / 1.5	2	**2a**	41
5	**1a**	Ph	Ph	2.0	$AlCl_3$ / 2.0	1	**2a**	77
6	**1b**	Ph	p-Tol	2.0	$AlCl_3$ / 2.0	0.5	**2b**	72
7	**1c**	p-Tol	Ph	2.0	$AlCl_3$ / 2.0	1	**2c**	70

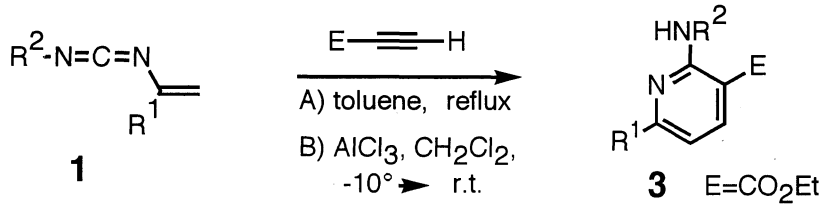


Table 3. Diels-Alder Reaction of Carbodiimides **1** with Ethyl Propiolate in the Presence of $AlCl_3$[a]

Carbodiimide	R^1	R^2	Method	Time / h	Product	Yield / %
1a	Ph	Ph	A[b]	17	**3a**	9
1a	Ph	Ph	B	1	**3a**	47
1b	Ph	p-Tol	B	1	**3b**	43
1c	p-Tol	Ph	B	1	**3c**	46

a) Molar ratios of **1**: Dienophile : $AlCl_3$ = 1.0 : 2.0 : 2.0. b) Incomplete.

In the inverse electron demand Diels-Alder reactions of *in situ* formed **5** with enamine and vinyl ether, the Lewis acid was found to be effective as well (Table 4). The reactions indeed proceeded at room

temperature to give morpholine-eliminated and dehydrogenated compounds of the cycloadducts, **6**[8] and **7**[8], in 60 and 51% yields, respectively, by one-pot procedure from the iminophosphoranes.

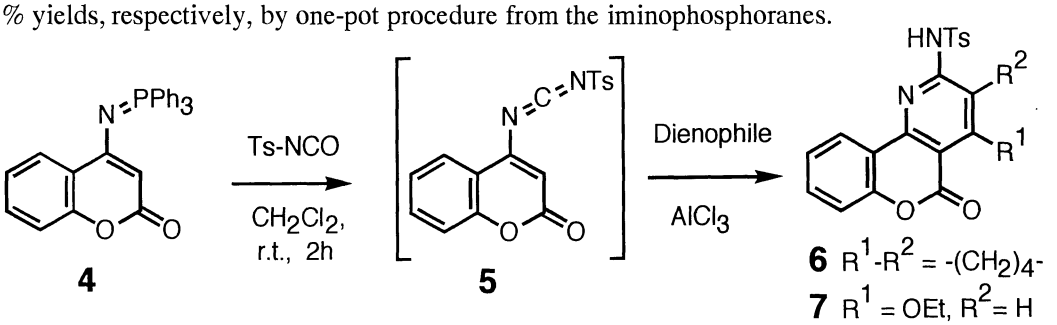
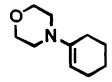


Table 4. Aza-Wittig Reaction of **4** and Lewis Acid-Induced Inverse Diels-Alder Reaction of Carbodiimide **5** with Enamine and Vinyl Ether

Entry	Dienophile	Time	Product	Yield / %
1		3 h	**6**	60
2		2 d	**7**	51

The thermal reaction of **1** with benzaldehyde did not produce the cycloadducts **8** even under heating at 115 °C in toluene for 18 h. Among the Lewis acids employed in the reactions, aluminum chloride (3.0 Equiv.) induced the Diels-Alder reaction under mild conditions, giving the best yields of **8**[8] (Table 5, entries 2, 4 and 11). Other aldehydes reacted similarly with **1a** in the presence of the Lewis acid to afford the cycloadducts **9** (Table 6).

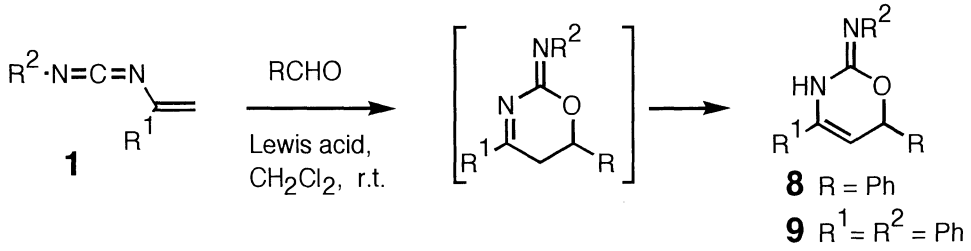


Table 5. Diels-Alder Reaction of Carbodiimides **1** with Benzaldehyde[a]

Entry	Carbodiimide	R^1	R^2	Lewis acid / Equiv.	Time / h	Product	Yield / %
1	**1a**	Ph	Ph	$AlCl_3$ / 1.5	24	**8a**	**44**
2	**1a**	Ph	Ph	$AlCl_3$ / 3.0	24	**8a**	**50**
3	**1a**	Ph	Ph	$AlCl_3$ / 4.0[b]	24	**8a**	**19**
4	**1b**	Ph	p-Tol	$AlCl_3$ / 3.0	24	**8b**	**55**
5	**1c**	p-Tol	Ph	toluene, reflux	18	**8c**	**0**
6	**1c**	p-Tol	Ph	BF_3· OEt_2 / 1.5	2	**8c**	**22**
7	**1c**	p-Tol	Ph	$TiCl_4$ / 1.5	5	**8c**	**11**
8	**1c**	p-Tol	Ph	$ZnCl_2$ / 1.5	50	**8c**	**trace**
9	**1c**	p-Tol	Ph	Me_2AlCl / 1.5	17	**8c**	**19**
10	**1c**	p-Tol	Ph	$EtAlCl_2$ / 1.5	24	**8c**	**38**
11	**1c**	p-Tol	Ph	$AlCl_3$ / 3.0	24	**8c**	**56**

a) The reaction was carried out in the molar ratios of **1**: PhCHO : L.A. = 1.0 : 3.0 (4.0)[b] : 0-4.0.

Table 6. Diels-Alder Reaction of Carbodiimide **1a** with Aldehydes

9	R	Yield / %
a	Ph	50
b	p-Tol	56
c	p-$MeOC_6H_4$	45
d	p-ClC_6H_4	44

In conclusion we have shown for the first time that Lewis acid is significantly effective on the Diels-Alder reactions of conjugated carbodiimides with a variety of dienophiles, especially with aldehydes. The fact that the reaction has been accomplished under mild reaction conditions with Lewis acid, will provide promising, fruitful entry of this method to synthesis of complex heterocycles with a thermally labile functionality and with necessity of high level of peri-, regio- and stereo-control.

References

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5) M. Nitta, H. Soeda, S. Koyama, and Y. Iino, Bull. Chem. Soc. Jpn., **64**, 1325 (1991).

6) M. Noguchi, K. Onimura, Y. Isomura, and S. Kajigaeshi, J. Heterocyclic Chem., **28**, 885 (1991).

7) We have found that Lewis acids are also effective on intramolecular version of the Diels-Alder reaction. The results will be published elesewhere.

8) Selected data for **2a**: yellow needles; mp 109-110 °C; IR 3284, 1744 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.89, 3.93 (s, OMe), 7.08-8.03 (10H, m, ArH), 7.21 (1H, s, 5-H), 9.89 (s, NH); ^{13}C NMR δ 52.60, 52.76, 102.61, 108.70, 120.99-159.80, 167.06, 168.71; m/z 362 (M^+, 100%); Found: C, 69.82; H, 4.80; N, 7.53. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.01; N, 7.73%. **3a**: yellow crystals; mp 95-96 °C; IR 3272, 1686 cm^{-1}; δ_H 1.41, 4.37, 7.05, 7.18, 7.37, 7.42-7.50, 7.84, 8.06, 8.28, 10.32; δ_C 14.29, 61.11, 105.64-160.00, 167.51; m/z 318 (M^+, 100%). **6**: colorless needles; mp 240-241 °C; δ_H 1.7-1.9 (4H), 2.40 (Me), 2.60 (CH_2), 3.20-3.35 (CH_2), 7.20-8.0 (6H), 8.26 (2H), 13.38 (NH); m/z 420 (M^+, 100%). **7:** colorless needles; mp 170.5-171.5 °C; IR 3264, 1732 cm-1; δ_H 1.41 (Me), 2.44 (Me), 4.49 (CH_2), 6.66, 7.33, 7.41, 7.42, 7.63, 7.78, 7.86, 10.49; δ_C 14.02, 21.62, 67.15, 94.25, 101.40-161.56. **8a**: colorless crystals; mp 204.5-205 °C; IR 3216, 1662 cm^{-1}; δ_H 5.32 (5-H), 5.40 (6-H), 7.06 (NH), 7.11-7.52 (15H); δ_C 64.96, 99.50, 125.16-153.38; m/z 326 (M^+, 100%); HRMS M^+, 326.1415. Calcd for $C_{22}H_{18}N_2O$: M, 326.1420.

(Received April 1, 1993)