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Synthesis of α-Aminocarbonyl Compounds via Hetero Diels–Alder Reaction

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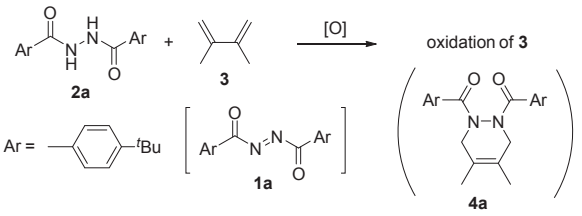
A synthetic route to α-aminoketone derivatives via a hetero Diels–Alder reaction is described. Diacylhydrazine was oxidized by *tert*-butyl hypochlorite in the presence of pyridine. After evaporation, the hetero Diels–Alder reaction with diene was carried out without isolation of the azodicarbonyl compound. Quantitative hetero Diels–Alder reaction was possible with 1 equivalent of diene when $Hf(OTf)_4$ or AgOTf was used as the catalyst. The N–N bond of the product was cleaved by SmI_2-reduction in the presence of *tert*-BuOH in THF. Further, ozonolysis of the C=C double bond afforded the α-aminoketone derivative in excellent yield.

Keywords: α-Aminocarbonyl compound | Hetero Diels–Alder reaction | Azodicarbonyl compound

α-Aminocarbonyl compounds are important synthetic intermediates, which have been used as building blocks for the synthesis of nitrogen-containing compounds.[1] While the oxidation of α-aminoalcohol derivatives has been widely used to obtain α-aminocarbonyl compounds,[1a–1k] aldol reaction using an azodicarbonyl compound as the electrophile has also attracted much attention[1l–1n] because of its potential application in asymmetric synthesis. In the latter process, however, one of the two nitrogen atoms in the electrophile is discarded. We noted that hetero Diels–Alder (HDA) reaction[2] can be used instead of the aldol reaction for the preparation of α-aminocarbonyl compounds. Thus, reduction of the N–N bond in the HDA product, followed by ozonolysis, can be a straightforward and atom-economical method for the synthesis of α-aminocarbonyl compounds from azodicarbonyls (Scheme 1), although such an approach for α-aminocarbonyl compounds has not been reported.

First, the HDA reaction of azodicarbonyl **1a** with 2,3-dimethylbutadiene **3** was investigated. Since **1a** is thermally unstable, diacylhydrazine **2a** was used as its precursor. Selective oxidation of **2a** in the presence of **3** and subsequent HDA reaction of **1a** with **3** were investigated. However, **3** was more easily oxidized than **2a** regardless of the oxidant, and no HDA product **4a** was obtained (eq 1).

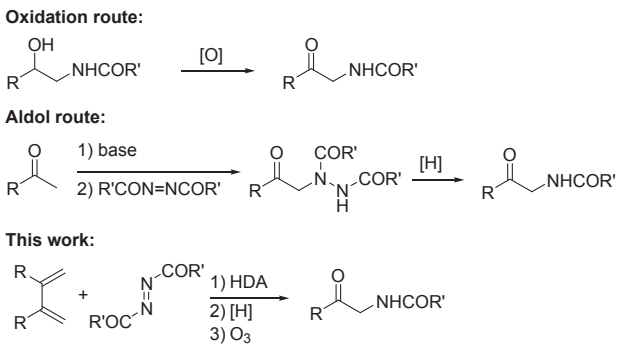


(1)

To avoid the oxidation of diene, the oxidation of **2a** was carried out before the addition of **3**. The formation of azodicarbonyl compound was easily confirmed by the change from white suspension to orange-red solution. Since **1a**, which was produced by the oxidation of **2a**, decomposed during the purification procedure, a volatile oxidant was used for the oxidation of **2a**, and **1a** was isolated simply by evaporation. As a volatile oxidant, *tert*-butyl hypochlorite was found to be the most effective.[3] For quantitative oxidation, the use of excess hypochlorite was necessary. Addition of a catalytic amount of pyridine greatly accelerated the oxidation of **2a**. Thus, **2a** was treated with 3 equiv of ^{t}BuOCl and 12 mol % of pyridine in dichloromethane at 0 °C. After evaporation of volatiles, the residue was dissolved in dichloromethane, and **3** was added to initiate the HDA reaction.

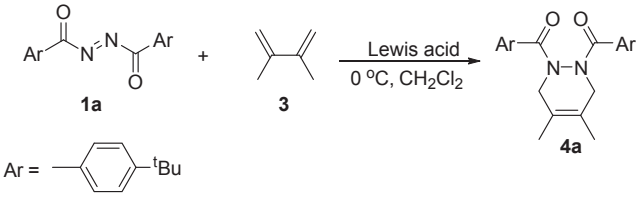
When an excess of **3** was used, the HDA product **4a** was obtained in good yield. However, from the viewpoint of atom efficiency, the HDA reaction with 1 equiv of **3** was investigated. The results are summarized in Table 1. In the absence of a catalyst, the yield was moderate even at elevated temperatures. Thus, the reaction was carried out in the presence of a Lewis acid at 0 °C. It was found that $Hf(OTf)_4$ was the most effective Lewis acid, with which **4a** was obtained quantitatively. The amount of $Hf(OTf)_4$ could be reduced to 18 mol % without loss of the yield. AgOTf was also an effective catalyst to obtain **4a** almost quantitatively. Further, the amount of ^{t}BuOCl could be reduced to 2 equiv without loss of the yield. Due to less availability of $Hf(OTf)_4$, AgOTf was used as the Lewis acid in the following experiments.

The HDA reaction was carried out using various diacylhydrazines. The results are summarized in Table 2. When a substituted benzoyl group was used as the acyl group, the yield of the HDA product strongly depended on the substituent on the benzene ring. The electron-withdrawing ester group in **2c** inhibited the oxidation with ^{t}BuOCl, and no HDA product was obtained. Halogen-substituted HDA products were obtained in



Scheme 1. Approaches to α-aminocarbonyl compounds.

Table 1. HDA reaction with a stoichiometric amount of diene in the presence of Lewis acid[a]



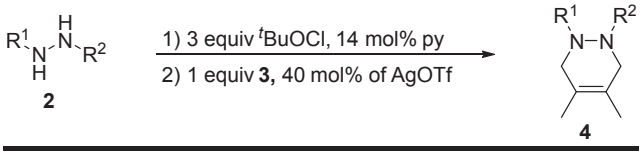
Lewis acid (mol %)	Time /h	Yield[b] /%
none	17	0
none	6	69[c]
$Ga(OTf)_3$ (41)	16	30
$In(OTf)_3$ (41)	17	29
$Sc(OTf)_3$ (40)	3	25
$Y(OTf)_3$ (40)	3	9
$La(OTf)_3$ (41)	4	17
$Yb(OTf)_3$ (40)	4	23
$Cp_2Zr(OTf)_2$ (40)	3	14
$Hf(OTf)_4$ (39)	1	100
$Hf(OTf)_4$ (18)	1	100
$NbCl_5$ (43)	2	23
AgOTf (40)	1	95
AgOTf (40)	1	97[d]
AgOTf (40)	1	79[e]

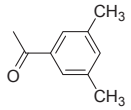
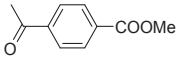
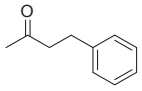
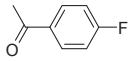
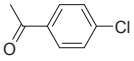
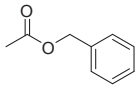
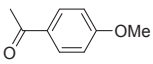
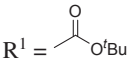
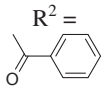
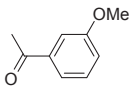
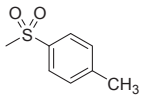
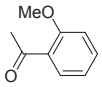
[a]After the treatment of **2a** with 3 equiv of ^{t}BuOCl and 12 mol % of pyridine at 0 °C for 1 h, the volatiles were evaporated before the addition of dichloromethane, 1.0 equiv of **3**, and Lewis acid. [b]Isolated yield. [c]In a sealed tube at 90 °C. [d]2 equiv of ^{t}BuOCl was used. [e]1 equiv of ^{t}BuOCl was used.

excellent yields even if an electronegative fluorine atom was introduced. The effect of the electron-donating methoxy group was complicated. When a MeO group was introduced at the *p*-position, quantitative oxidation of **2f** occurred, although no HDA product was obtained, probably because the *p*-MeO group increased the electron density of **1f** to suppress the HDA reaction. *m*-MeO derivative **2g** gave the HDA product **4g** in good yield. When *o*-MeO derivative **2h** was oxidized, the product **1h** was fairly unstable, and decomposed immediately with releasing N_2, and no HDA product was obtained. When **2** had aliphatic acyl groups (**2i** and **2j**), the oxidized product **1** was extremely unstable and decomposed immediately. Thus, oxidation of **2i** was carried out for 5 min before the addition of **3** to furnish HDA product **4i** in 51% yield. When **2** had urethane-type acyl groups (**2k**, **2l**, and **2m**), the HDA product was obtained almost quantitatively. Under the same reaction conditions, sulfonyl hydrazine **2n** was not oxidized by ^{t}BuOCl.

Reductive cleavage of the N–N bond of **4** was selectively carried out using 3 equiv of SmI_2 in the presence of 1.5 equiv of ^{t}BuOH.[4] The results are shown in Table 3. Diamide **5** was obtained almost quantitatively from benzoyl-type HDA products, except for **4g**, in which the electron-donating methoxy group hindered the reduction of the N–N bond by SmI_2. Because of the high electron density of the urethane group, the reduction of **4k** and **4l** did not occur under the standard reaction conditions. When hexamethylphosphoric triamide (HMPA) was added to the system, **5k** and **5l** were obtained, although the yields were low.

Table 2. HDA reaction with **3** using various diacylhydazines[a]

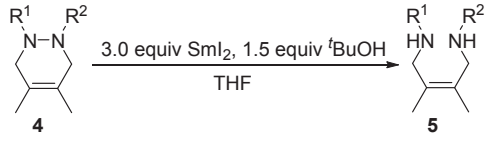


2	R^1, R^2	Yield /%	2	R^1, R^2	Yield /%
b	$R^1 = R^2 =$ 	95	**i**	$R^1 = R^2 =$ 	3 (51)[b]
c	$R^1 = R^2 =$ 	0	**j**	$R^1 = R^2 =$ 	0
d	$R^1 = R^2 =$ 	86	**k**	$R^1 = R^2 =$ 	98
e	$R^1 = R^2 =$ 	88	**l**	$R^1 = R^2 =$ 	94
f	$R^1 = R^2 =$ 	0	**m**	$R^1 =$  $R^2 =$ 	96[c]
g	$R^1 = R^2 =$ 	97	**n**	$R^1 = R^2 =$ 	0
h	$R^1 = R^2 =$ 	0			

[a]After the treatment of **2** with 3 equiv of ^{t}BuOCl and 12 mol % of pyridine at 0 °C for 1 h, the volatiles were evaporated before the addition of dichloromethane, 1.0 equiv of **3**, and 40 mol % of AgOTf. [b]Oxidation was carried out for 5 min before HDA reaction. [c]Without pyridine.

Ozonolysis of the C=C double bond was then examined. α-Aminocarbonyl compound **6** was obtained in excellent yield when ozonolysis was carried out at −98 °C, although a by-product with an undefined structure was observed when the reaction was carried out at −80 °C. The results are summarized in Table 4. When **6m** was subjected to the ozonolysis, two α-aminocarbonyl compounds were simultaneously obtained in excellent yields.

Table 3. Cleavage of N–N bond of HDA product with SmI_2[a]

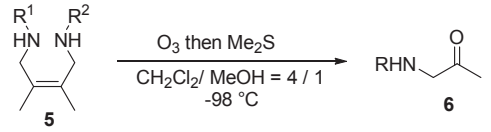


4 5

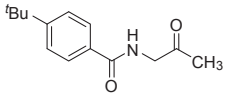
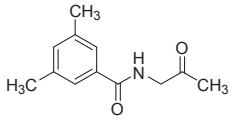
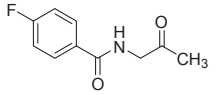
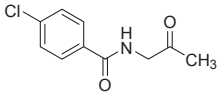
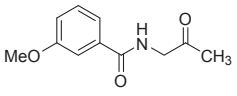
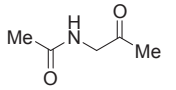
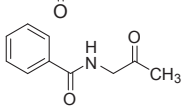
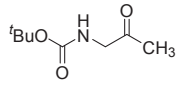
4	Temperature/°C	Time/h	Yield/%
a	r.t.	3	95
b	50	3	92
d	r.t.	2	90
e	r.t.	2	90
g	r.t.	2	52
i	50	1	47
k	reflux	15	8[b]
l	reflux	18	15[b]
m	r.t.	2	76

[a]Reactions were carried out in THF with 3.0 equiv of SmI_2 and 1.5 equiv of ^{t}BuOH. [b]In the presence of 10 equiv of HMPA.

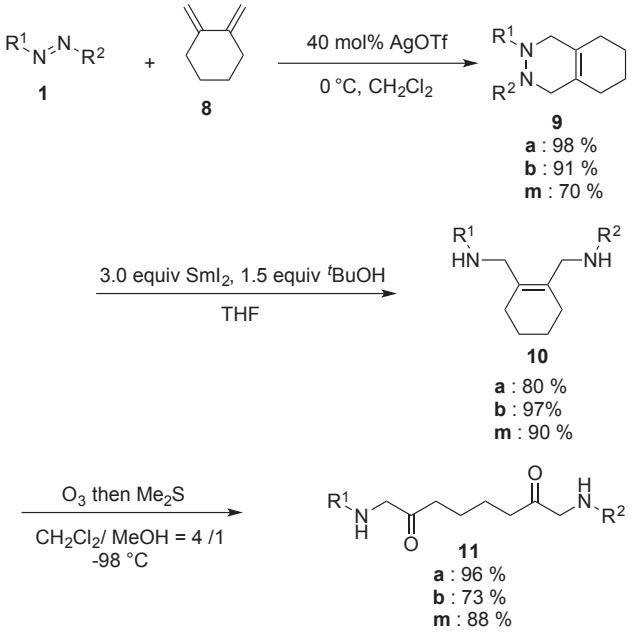
Table 4. Ozonolysis of C=C bond[a]



5 6

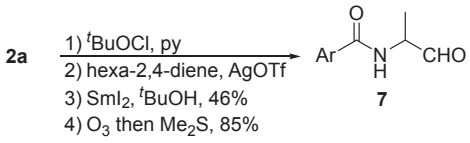
5	O_3/equiv	Product	Yield/%
a	14.6		80
b	6.4		80
d	8.8		96
e	8.2		90
g	8.2		90
i	40		62
m	8.2		99
			91

[a]After the treatment of **5** with ozone in CH_2Cl_2–MeOH (4/1, v/v) at −98 °C, dimethyl sulfide was added.



Scheme 2. Synthesis of bis(α-aminocarbonyl) compounds.

When hexa-2,4-diene was used as the diene, alanine derivative **7** was obtained from **2a** using the standard procedure (eq 2). Since hexa-2,4-diene is less reactive than **3**, the yield of HDA product was 50% when 1 equiv of diene was used. The yield of HDA product increased to 83% when 3 equiv of diene was used at 60 °C in 1,2-dichloroethane.



(2)

When exo-olefinic diene **8** was used for the HDA reaction, bifunctional α-aminoketone **11** was obtained easily (Scheme 2). When **1m** was used as the azodicarbonyl compound, an asymmetrically protected 1,8-diamino-2,6-diketone, which is difficult to prepare quantitatively by other methods, was obtained in good yield.

In summary, we have demonstrated a novel atom-economical approach for the synthesis of α-aminocarbonyl compounds using diacylhydrazine as the nitrogen source. Since the hetero Diels–Alder reaction of the azodicarbonyl compound proceeds quantitatively with 1 equiv of diene in the presence of an appropriate Lewis acid, this system is also expected to be extended to Diels–Alder polymerization.

Supporting Information is available on http://dx.doi.org/10.1246/cl.170970.

References and Notes

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