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A base-catalyzed Diels–Alder reaction of *N*-tosyl-3-hydroxy-2-pyridone

Hiroaki Okamura,* Hiroshi Nagaike, Tetsuo Iwagawa and Munehiro Nakatani

Department of Chemistry and Bioscience, Faculty of Science, Kagoshima University, 1-21-35 Korimoto, Kagoshima 890-0065, Japan

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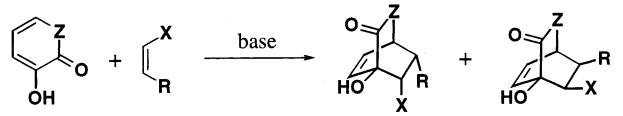
Abstract

A Diels–Alder reaction of *N*-tosyl-3-hydroxy-2-pyridone with an electron deficient dienophile was catalyzed by base. The reactivity, stereoselectivity and mechanism of this reaction are described.

Keywords: base-catalyzed Diels–Alder reaction; 2-pyridone; *endo* selective; stereospecific reaction.

The Diels–Alder (DA) reaction is one of the most useful C–C bond forming reactions.[1] To improve its reactivity and selectivities, many catalysts have been developed, and most are Lewis acids. Recently, however, we reported the base-catalyzed DA reaction of 3-hydroxy-2-pyrone (**1**), using a base-activated diene (Eq. (1)).[2] This type of DA reaction is quite rare, and its mechanism, which involves activation of the diene moiety by a base, is completely opposite the usual mechanism, activation of a dienophile by Lewis acid.



1: Z=O **3: X=EWG** **4** **5**
2: Z=N-Ts

(1)

In our continuous effort to find other base-catalyzed DA reactions, we found that the reaction of *N*-tosyl-3-hydroxy-2-pyridone (**2**) with an electron deficient dienophile (**3**) was catalyzed by a base, and afforded cycloadducts (**4** and **5**) in good yield (Eq. (1)). This paper describes the characteristic features of this reaction.

* Corresponding author. Fax: +81 99 285 8117; e-mail: okam@sci.kagoshima-u.ac.jp

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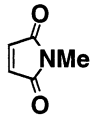
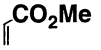
Compound **2** was easily derived from commercially available 2,3-pyridinediol by the modified Posner's method.[3,4] Table 1 summarizes the base-catalyzed cycloaddition of **2** with electron deficient dienophiles (**3a–c**). The reactivity of the diene **2** itself was very low (entries 1, 10, and 12). Even in the reaction with the most reactive *N*-methylmaleimide (**3a**), only a trace amount of adduct **4a**[5] was obtained (entry 1). However, the addition of Et_3N as a base catalyst dramatically accelerated the reaction and an almost quantitative amount of **4a** was formed within 30 min (entry 2). The yield of this reaction depended on the amount of the catalyst and the type of solvent. Decreasing the amount of base catalyst decreased the yields of the adduct (entries 2–4). When the reaction was carried out in the THF, the yield was also reduced (entry 5). Other amine bases worked as well as Et_3N and the adduct was obtained in good yields (entries 8 and 9).

Table 1
Base-catalyzed reactions of **2** with dienophiles[a]

Entry	Dienophile	Solvent	Base (eq)	Time (h)	Yield (%)[c]	**4** : **5**[d]
1		CH_2Cl_2	-[b]	48	trace	-
2		CH_2Cl_2	Et_3N (1.0)	0.5	99	**4a** only
3		CH_2Cl_2	Et_3N (0.5)	0.5	87	**4a** only
4		CH_2Cl_2	Et_3N (0.1)	0.5	54	**4a** only
5		THF	Et_3N (1.0)	0.5	81	**4a** only
6	**3a**	DMF	Et_3N (1.0)	0.5	90	**4a** only
7		MeOH	Et_3N (1.0)	0.5	95	**4a** only
8		CH_2Cl_2	*t*-$BuNH_2$ (1.0)	0.5	93	20:1
9		CH_2Cl_2	*c*-Hex_2NMe (1.0)	0.5	94	**4a** only
10		CH_2Cl_2	-[b]	48	0	-
11	**3b**	CH_2Cl_2	Et_3N (1.0)	24	66	25>:1.0
12		CH_2Cl_2	-[b]	48	0	-
13	**3c**	CH_2Cl_2	Et_3N (1.0)	24	42	1.0:1.4

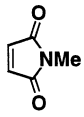
[a] All reactions were carried out at room temperature. [b] No base was added. [c] Isolated yield. [d] The ratio was determined by ^1H NMR.

The base catalyst was effective for the reactions with the less reactive dienophiles, methyl acrylate (**3b**) and 3-buten-2-one (**3c**), and the corresponding adducts were obtained in fair yields (entries 11 and 13).

The *endo* selectivity of these reactions was very high, probably because the sterically bulky *N*-Ts group produced an unfavorable interaction with the dienophile during its *exo* approach. The bulkiness of the base catalyst also sterically influenced the approaching dienophile. Indeed, a slightly lower *endo* selectivity was observed for the reaction using the sterically less hindered *t*-$BuNH_2$ (entry 8). The reaction with 3-buten-2-one (**3c**), however, afforded a mixture of the *endo* and *exo* isomers (**4c** and **5c**, entry 13). This exceptional example could be explained by base induced epimerization via enolization of the carbonyl group. Indeed, the Et_3N treatment (rt, 24 h, in CH_2Cl_2) of pure **4c** and **5c** afforded the mixtures in 1.0:1.1 and 1.0:1.3 ratios, respectively.

Bases that contained alkali metals could also be used for the reaction with **3a** and these were more effective catalysts than the amine catalysts (Table 2). The yields of the reactions catalyzed by 0.1 equiv. Of these bases were higher than that of the reaction catalysed by Et_3N under the same conditions (entries 2–5). For the reaction with the less reactive dienophile **3b**, however, *n*-BuLi was not effective, probably due to the base instability of the dienophile (entry 6).

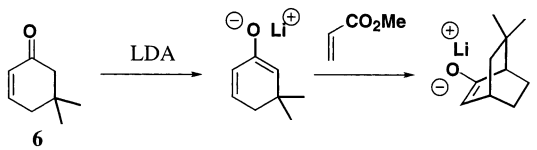
Table 2
Base-catalyzed reaction of **2** under various conditions[a]

Entry	Dienophile	Base (eq)	Yield (%)[b]	**4** : **5**[c]
1	 **3a**	n-BuLi (1.0)	88	**4a** only
2		n-BuLi (0.1)	73	**4a** only
3		MeONa (0.1)	74	**4a** only
4		*t*-BuOK (0.1)	97	**4a** only
5		Et_3N (0.1)	28	**4a** only
6	 **3b**	*n*-BuLi (0.1)	0	

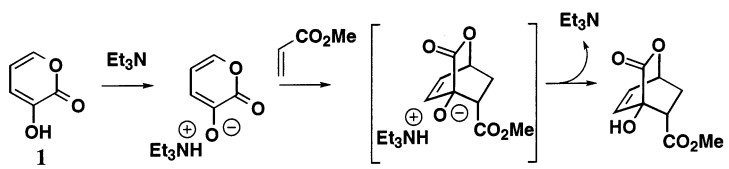
[a] All reactions were carried out at 0 C° in THF. [b] Isolated yield.

[c] The ratio was determined by ^1H NMR.

Koerner and Rickborn proposed two categories of [4+2] cycloaddition under basic conditions: *base-induced* and *base-catalyzed* cycloaddition.[7b] The former reaction gives an anionic adduct from anionic substrate,[8] and a typical example of this type is the reaction of a Michael acceptor and a dienolate anion, which is usually generated from LDA treatment of an α,β-unsaturated carbonyl compound (Eq. (2)).[8a] Most [4+2] cycloadditions using bases are classified into this category, and their reaction mechanisms generally involve a stepwise double-Michael reaction or a Michael–aldol reaction.[9] On the other hand, the *base-catalyzed* reaction gives neutral (protonated) adducts, and the *base-catalyzed* reaction of **1** is a good example.[2a] As shown in Eq. (3) initially formed anionic diene reacts with dienophile to give anionic adduct, which is immediately protonated by ammonium salt, and thus the base works as a catalyst. Reactions of this type are quite rare.[2,7,10] More interestingly, two of them are reported to be *base-catalyzed* DA reactions by both Rickborn and Koerner and by our group.[2,7] These reactions are completely opposite the ordinary acid catalyzed DA reaction, and thus they are potentially new method for catalyzed DA reaction.

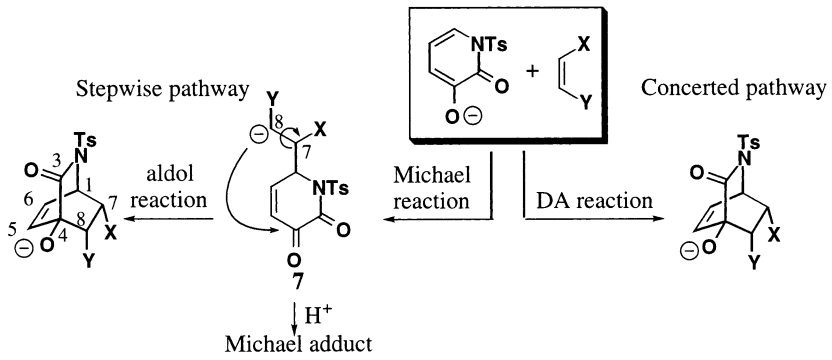


(2)

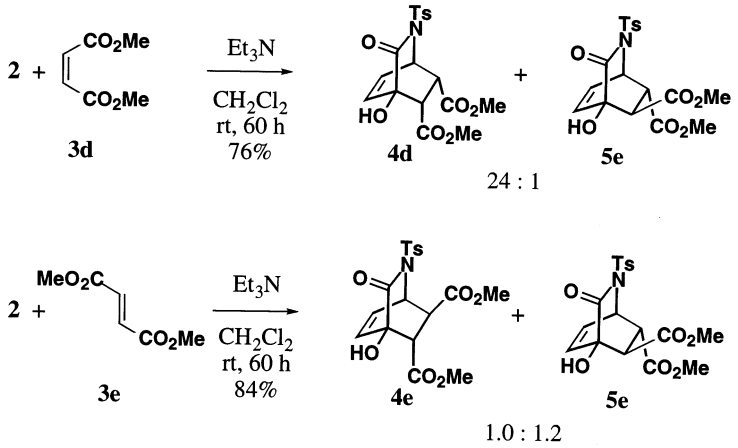


(3)

According to the above definition, the reaction of **2** with dienophile is classified as a *base-catalyzed* reaction. Determining whether its reaction mechanism is a concerted DA mechanism or a stepwise Michael–aldol mechanism was difficult, but the formation of the Michael adduct and the stereospecificity of this reaction were appropriate criteria to estimate the mechanism. If the reaction proceeds via the stepwise pathway, the Michael adduct could be formed, and the stereospecificity can be lost because of free rotation of the C–C bond corresponding to the C-7–C-8 position in intermediate **7**. However, in all the cases we examined, no Michael adduct was observed, and the stereospecificity of this reaction was also confirmed from the reactions of dimethyl maleate (**3d**) and dimethyl fumalate (**3e**), which, respectively, gave the *syn* (**4d**) and *anti* products (**4e** and **5e**) in almost complete selectivity (Schemes 1 and 2). Although a small amount of the *anti* isomer **5e** was formed from the reaction with **3d**, this was supposedly due to the base induced epimerization, as well as the epimerization between **4c** and **5c**. Indeed, Et_3N treatment of a 24:1 mixture of **4d** and **5e** decreased the ratio to 12:1 after 48 h. These observations are not direct evidence to determine the reaction mechanism, but they strongly suggest that this reaction proceeded via the concerted DA reaction mechanism.



Scheme 1. Two plausible reaction mechanisms



Scheme 2. Stereospecific base-catalyzed DA reaction

In conclusion, we found a new base-catalyzed DA reaction system using **2** as a diene. Since the resulting cycloadducts have various functional groups, including nitrogen, and the rigid

bicyclic structure, these compounds are attractive building blocks for the synthesis of biologically active compounds such as aminosugars and alkaloids. Further investigation to determine the detailed features of this reaction and application for syntheses are now in progress.

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5. ^{1}H NMR of **4a** (400 MHz, $CDCl_3$): δ 2.44 (s, 3H), 2.94 (s, 3H), 3.00 (d, 1H, $J=8.1$ Hz), 3.59 (dd, 1H, $J=8.1$, 4.0 Hz), 3.99 (s, 1H), 5.74 (ddd, 1H, $J=5.9$, 4.0, 1.8 Hz), 6.25 (d, 1H, $J=7.7$ Hz), 6.23 (dd, 1H, $J=7.7$, 5.9 Hz), 7.34 (brd, 2H, $J=8.3$ Hz), 7.87 (brd, 2H, $J=8.3$ Hz). Other adducts also showed satisfactory ^{1}H NMR data. The stereochemistry of the adducts (**4** and **5**) was assigned from the coupling constant between H-1, H-7 and H-8 based on the precedent data.[6]
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