1,3-Dipolar Cycloaddition of Ethyl Diazoacetate to Alkynes in the Pores of Zeolite NaY

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Zeolite NaY promotes 1,3-dipolar cycloaddition of ethyl diazoacetate to alkynes having an electron-withdrawing group to afford the corresponding functionalized pyrazoles in high yields. The activation of the dipolarophile inside the pores of NaY is proposed based on the ^{13}C MAS NMR analysis.

Crystalline aluminosilicates, zeolites, have been utilized as catalysts mainly in the petrochemical industry for a long time. Recently, we have found that zeolites can not only preserve unstable, small organic molecules, but also activate them for the unique C–C bond formation for fine chemicals synthesis. For instance, labile formaldehyde stayed within zeolite NaY in the monomer form for at least 30 days even at ambient temperature, and the adsorbed formaldehyde reacted with olefins through the carbonyl–ene reaction to afford homoallylic alcohols.[1] Similarly, acrolein adsorbed in NaY underwent conjugate additions of electron-rich aromatics.[2]

As part of our continued interest in chemical behavior of labile molecules inside the zeolite pores, we report here the reaction of α-diazoacetate with electron-deficient alkynes to pyrazoles via 1,3-dipolar cycloaddition[3] with the aid of NaY. Actually, the reaction of diazocarbonyl compounds with alkynes is difficult to perform compared with that of electron-rich diazocompounds with alkynes, and a single success in the reaction has been made by Li and Jiang by using a Lewis acid catalyst, indium chloride in water.[4] They mentioned that the reaction hardly proceeded in normal organic solvents.[4] Our strategy is that if we take advantage of hydrophilic nature of zeolite, the pyrazole formation would be successful in the pores of NaY.

Although diazoacetate is recognized a relatively stable diazo compound, we at first checked whether or not diazoacetate could be intact upon contact with NaY because NaY has weakly acidic protons: We adsorbed vaporized ethyl diazoacetate (1.4 mmol) in NaY zeolite (1 g), and analyzed the sample by NMR.[5] In ^{13}C MAS NMR,[6] the carbon peaks of ethyl diazoacetate in NaY appeared at 15(CH_3), 48(CH), 64(CH_2), and 172(C=O) ppm, respectively (Figure 1a). As compared with the spectra in $CDCl_3$ (Figure 1b), the peak of the C=O was intensified as well as shifted to the downfield by ca. 5 ppm, indicating that the carbonyl group is more polarized in NaY owing to the strong interaction with sodium ions or the high electrostatic field effects of the aluminum-rich NaY. Interestingly, the NMR spectra of ethyl diazoacetate which had been stored in NaY for 3 months at room temperature (rt) scarcely changed, indicating that diazoacetate was stabilized in the NaY pores.

Secondly, we found that addition of ethyl diazoacetate to a suspended mixture of **1** and NaY in CH_2Cl_2, followed by stirring at rt for 12 h gave pyrazole **2** in 97% yield (Table 1, Entry 1). As for a solvent for the reaction, CH_2Cl_2 was superior to AcOEt, THF, and CH_3CN. The reaction was significantly slower with SiO_2 as well as without solid catalysts (Entries 2 and 3).[5] It is concluded that zeolite is essential for the promotion of the 1,3-dipolar cycloaddition reaction.

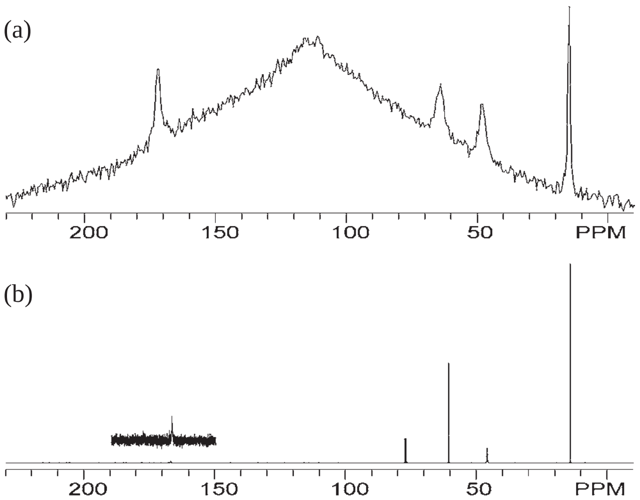
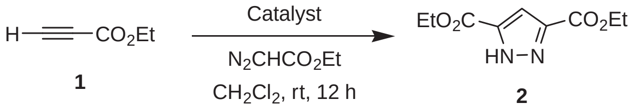


Figure 1. ^{13}C NMR of ethyl diazoacetate: (a) N_2CHCO_2Et adsorbed in NaY, (b) ethyl diazoacetate in $CDCl_3$.

In order to find the optimal zeolite for the reaction, we screened different zeolites[5] using a bulkier, less reactive alkyne substrate, ethyl 2-butynoate **3** (Table 2). It is interesting to find that NaY is the best among various ion-exchanged Y-type zeolites (Entries 1–4), because sodium ions have not been made much use of in modern organic synthesis. With NaX, Na-MOR (mordenite), and Na-Beta, only a trace amount of product **4** was detected (Entries 6–9). Upon contact with proton-exchanged zeolites such as HY and H-Beta, ethyl diazoacetate decomposed with generation of nitrogen gas. Interestingly, the use of zeolite HY gave pyrazole **4** in 3% yield (Entry 5). This is because HY was prepared from NaY via partial replacement of Na^+ with H^+, and HY still contained some sodium ions in the framework.

Now we have discovered that NaY was the use of choice, we

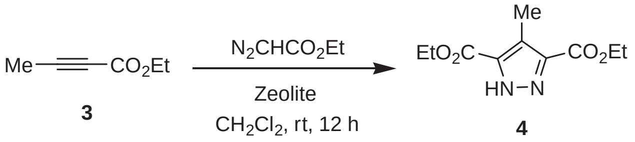
Table 1. 1,3-Dipolar cycloaddition with solid catalyst[a]



Entry	Catalyst	Yield/%
1	NaY	97
2	SiO_2	19
3	—	12

[a]Ethyl propiolate (1 mmol) was treated with ethyl diazoacetate (1.5 mmol) with or without a solid catalyst (1 g).

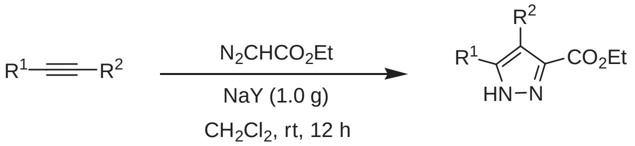
Table 2. 1,3-Dipolar cycloaddition[a] using different zeolites[b]



Entry	Zeolite	Yield/%	Entry	Zeolite	Yield/%
1	LiY	6	6	NaX	trace
2	NaY	10	7	Na-MOR	trace
3	KY	trace	8	Na-Beta	trace
4	CsY	trace	9	H-Beta	trace
5	HY	3			

[a] Ethyl diazoacetate (1.5 mmol) was treated with ethyl 2-butynoate (1 mmol) in the presence of zeolite (1 g). [b] One gram of ion-exchanged Y-type (Y), X-type (X), mordenite (MOR), and β-type (Beta) zeolites were dried at 673 K, and below 266 Pa for 4 h prior to use.

Table 3. 1,3-Dipolar cycloadditions of different alkynes with ethyl diazoacetate[a]



Entry	R^1	R^2	Yield/%
1	CO_2Et	H	97
2	CO_2Me	H	95
3	COMe	H	92
4	CHO	H	82
5	CO_2Et	Me	74[b]
6	CH_2OH	H	6[c] (73)[d]

[a] Alkynes (1 mmol) were treated with ethyl diazoacetate (1.5 mmol) in the presence of NaY (1.0 g). [b] Reflux 24 h. [c] A mixture of a major isomer ($R^1 = CH_2OH$, $R^2 = H$) and a minor one ($R^1 = H$, $R^2 = CH_2OH$) in a 13:1 ratio was obtained under CH_2Cl_2 reflux for 12 h. [d] A mixture of the above products in a 9:1 ratio was obtained under toluene reflux for 12 h.

next applied different types of alkynes for the reaction with ethyl diazoacetate to learn the scope and the limitation of this reaction with NaY (Table 3): The terminal alkynes having an electron-withdrawing group such as alkoxycarbonyl, acetyl, and formyl functionality yielded the corresponding products in excellent yields under mild conditions (Entries 1–4). Especially, it should be noted that the reaction with propynal yielded the desired product in a high yield (Entry 4), because propynal is known very labile and polymerizable even at −20 °C. We guess that such an unstable dipolarophile could be stabilized and survive inside the zeolite pore until the reaction takes place. A moderate yield was obtained with the reaction of a bulkier, inner alkyne, ethyl 2-butynoate under reflux in CH_2Cl_2 for a longer reaction period of 24 h (Entry 5). 2-Propynyl alcohol having an electron-donating group did not show a good reactivity to diazoacetate and a mixture of isomeric products in this case. At the elevated temperature under toluene reflux, a moderate yield was obtained with a somewhat lower isomeric ratio (Entry 6).

Given the above reactivity trend, we take it for granted that an electron-deficient alkyne is activated inside the pore of NaY through the strong interaction with sodium ions or under circumstances of the strong electrostatic fields which derive from the aluminum-rich silicate framework of NaY.[7] This activation results in lowering the energy level of LUMO of the alkyne to accelerate the cycloaddition to diazoacetate.

A typical procedure is described for the reaction of ethyl diazoacetate and ethyl propiolate: Ethyl diazoacetate (1.5 mmol) was added to a mixture of ethyl propiolate (1 mmol) and NaY zeolite (1.0 g), which had been dried at 673 K and below 266 Pa for 4 h prior to use, in CH_2Cl_2 (10 mL) at rt under a N_2 atmosphere. The resulting mixture was stirred at rt for 12 h. As work-up, methanol (5 mL) was added and NaY was filtered. The NaY was washed with 20 mL of methanol. The combined filtrate was evaporated, and the resulting mixture was purified by silica gel column chromatography to afford **2** in 97% yield.

NaY is a stable aluminosilicate and can be readily removed from the reaction mixture. For these reasons, the zeolite-induced method has an advantage over the precedent using metal salt-catalyzed synthesis of pyrazoles for pharmaceutical use where impurities like metal ions included in the compounds often become a serious problem.

We dedicate this article to Professor Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

1 T. Okachi, M. Onaka, *J. Am. Chem. Soc.* **2004**, *126*, 2306.
2 S. Imachi, M. Onaka, *Chem. Lett.* **2005**, *34*, 708.
3 T. Ye, M. A. McKervey, *Chem. Rev.* **1994**, *94*, 1091.
4 N. Jiang, C.-J. Li, *Chem. Commun.* **2004**, 394.
5 NaY (HSZ-320NAA, Si/2Al = 5.5, TOSOH Co.); SiO_2 (CARiACT Q-3, Fuji Silysia Chemical Ltd.); NaX (Si/2Al = 2.5, UNION SHOWA K. K.); Na-Mordenite (JRC-Z-M15(1), Si/2Al = 15), Na-Beta (JRC-Z-B25(1), Si/2Al = 25), H-Beta (JRC-Z-HB25(1), Si/2Al = 25), and HY (JRC-Z-HY5.5, Si/2Al = 5.5) were obtained from the Catalysis Society of Japan. LiY, KY, and CsY were prepared from NaY by cation exchange using the corresponding nitrate salts.
6 ^{13}C MAS NMR measurements were performed with a CMX-300 spectrometer (300 MHz, Chemagnetics) using the single-pulse excitation with the proton decoupling (90° pulse = 5 µs, pulse delay = 5 s, 1000 scans) at rt. TMS was used as an internal standard, and the spinning rate was usually 3 kHz. A broad signal centered at around 120 ppm arose from carbonaceous materials around the sample probe in the NMR instrument.
7 In ^{13}C MAS NMR of ethyl propiolate adsorbed in NaY, the peak of the carbonyl carbon was shifted to the downfield by ca. 5 ppm compared with that in $CDCl_3$.

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