Conjugate Addition of Electron-rich Aromatics to Acrolein in the Confined Space of Zeolite Y

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Acrolein gas was spontaneously entrapped in supercages of NaY zeolite and the sorption was confirmed by solid ^{13}C MAS NMR spectra. In the confined cavities, acrolein smoothly underwent conjugate addition with electron-rich aromatics such as indoles and anisole.

Sorption of organic molecules in zeolite has been studied in order to demonstrate their behavior in the cavities and the availability of the zeolite cavities for reaction media which induce selective organic reactions. For instance, labile, polar formaldehyde was sorbed and preserved in NaY zeolite cavities as a monomer form for a long period even at ambient temperatures, and underwent prompt carbonyl-ene reactions with various olefins.[1] Similarly, non-polar aromatics such as benzene were encapsulated in supercages of NaY.[2] We also reported that 1,3-cyclopentadiene was trapped in NaY and that the cyclopentadiene which was highly condensed in the zeolite cavities showed enhanced Diels–Alder reactivity toward typical dienophiles.[3]

Here we describe sorption of acrolein in zeolite, and the facile Friedel–Crafts-type alkylations of electron-rich aromatics with acrolein. Acrolein has a great potential as a C3 source in organic synthesis, but is often a troublesome reagent to handle owing to a tendency to prompt dimerization or polymerization.[4] The Friedel–Crafts alkylations have been widely employed in C–C bond formations.[5] If 1,4-addition of aromatics to acrolein selectively proceeds without concurrent 1,2-addtion, the Friedel–Crafts-type alkylation becomes a promising synthetic strategy to produce aromatics with a terminally-functionalized C3 side-chain.[6] Denhart and co-workers reported the Friedel–Crafts alkylation of substituted indoles with acrolein by using an iminium catalyst.[7] In their study, both a reactant, acrolein, and a product, alkylated indole, were not so stable in the presence of trifluoroacetic acid that satisfactory yields and purity were not obtained.

In the present study, as a sorbent and catalyst we used not only NaX, NaY, and HY zeolites, but also silica as a control support.[8] Acrolein vapor in an N_2 flow was passed over a well-dried support at 273 K. When 3.6 mmol of acrolein was sorbed into one gram of NaY, which was referred to as acrolein(3.6)@NaY, the sorption was saturated. On the other hand, one gram of silica only accommodated 1.6 mmol of acrolein (acrolein(1.6)@SiO_2). With evacuation treatment on acrolein(1.6)@SiO_2 under 67 Pa for 1 h, the sorbed acrolein was completely lost. In contrast, no loss of acrolein was observed with acrolein(3.6)@NaY under the same evacuation conditions, suggesting that acrolein has strong interaction with sodium ions in NaY.

In the solid ^{13}C MAS NMR[9] and liquid ^{13}C NMR spectra of acrolein(3.6)@NaY, acrolein(1.6)@SiO_2 and acrolein in $CDCl_3$, three sharp peaks were observed in the range of δ 130–210 ppm on each spectrum, respectively (Figure 1).[10] From the spectra of acrolein(3.6)@NaY and acrolein(1.6)@SiO_2, it was confirmed that the sorbed acrolein molecules were present as a monomer. The different chemical shifts of a formyl carbon at δ 202 ppm on NaY and 200 ppm on silica envisaged that the sorbed acroleins were differently activated on each porous support.

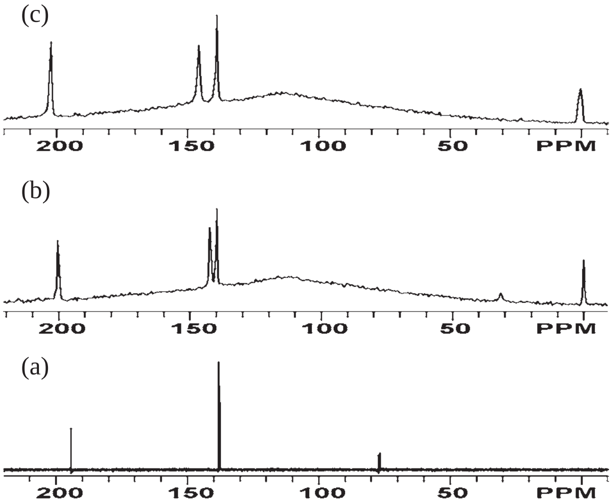


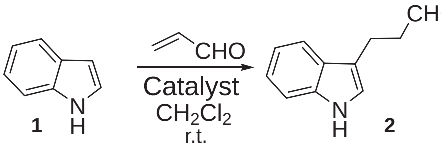
Figure 1. ^{13}C NMR spectra of sorbed acrolein. (a) acrolein in $CDCl_3$, (b) acrolein(1.6)@SiO_2, and (c) acrolein(3.6)@NaY.

The reaction of acolein(3.0)@NaY with indole proceeded in CH_2Cl_2 at room temperature to give 3-(1*H*-indol-3-yl)propanal (**2**) in 58% yield in an exclusive 1,4-fashion (Table 1, Entry 1). Interestingly, the addition of acrolein to a mixture of unsorbed NaY and indole in CH_2Cl_2 was found to produce **2** in almost the same yield (Entry 2). This is because more polar acrolein can be trapped into NaY in preference to indole in a CH_2Cl_2 solution. Thereafter, in the other experiments in Table 1, we adopted this simpler reaction procedure to omit the pre-sorption of acrolein into supports.

NaY zeolite-catalyzed addition gave the best result among the catalysts, though silica showed moderate catalysis. In the presence of strong acid catalysts such as HY and $BF_3 \cdot OEt_2$, indole rapidly disappeared, but **2** was not detected due to instability of **1** and **2** in such acidic circumstances. When the addition was carried out using NaX which has the same porous framework but a different Si/Al ratio from that of NaY, the reaction gave poor results with only 20% yield.

Substituted indoles also yielded the corresponding adducts in moderate to good yields depending on substituents (Table 2). 5-Chloroindole with an electron-withdrawing chlorine atom

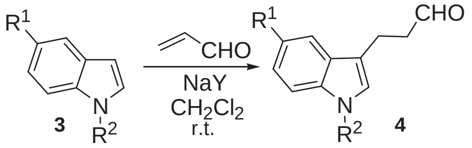
Table 1. Friedel–Crafts alkylations to acrolein using solid and liquid catalysts[a]



Entry	Catalyst	Time	Yield/%
1	acrolein(3.0)@NaY	18 h	58
2	NaY	18 h	56
3	HY	5 min	0
4	NaX	18 h	20
5	SiO_2	18 h	37
6[b]	$BF_3 \cdot OEt_2$	5 min	0

[a] Acrolein (3.0 mmol) was reacted with indole (1.0 mmol). Solid catalysts (1.0 g) were dried at 67 Pa and 673 K for 4 h and used. [b] $BF_3 \cdot OEt_2$ (1.0 mmol).

Table 2. Friedel–Crafts alkylations of indoles with acrolein[a]



Entry	R^1	R^2	Time/h	Yield/%
1	H	H	18	56
2	H	Me	18	45
3	Me	H	12	56
4	OMe	H	24	42
5	Cl	H	3	72

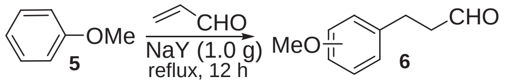
[a] Indoles (1.0 mmol) were reacted with acrolein (3.0 mmol) in the presence of NaY (1.0 g).

showed better reactivity than 5-methoxyindole with an electron-donating group (Entries 4 and 5).

The alkylation of anisole with acrolein was also successful in the presence of NaY under reflux at 154 °C to afford the conjugated adduct **6** in 29% yield after 6 h, and 66% yield after 12 h, respectively (Table 3, Entry 1). Acrolein molecules encapsulated in the confined nanospace of NaY could survive for a long reaction period at such high temperatures. By contrast, SiO_2 only gave a poor yield of 5% after 12 h (Entry 2). To our knowledge, there have been no reports on direct alkylation of benzene derivatives using acrolein as an electrophile.

A typical procedure is described for the reaction of indole with acrolein: to a mixture of indole (1.0 mmol) and NaY zeolite (1.0 g) in CH_2Cl_2 (10 mL) at room temperature (r.t.) was added acrolein (3.0 mmol) in N_2 atmosphere. The resulting suspension was stirred for 18 h at r.t. Then, acetonitrile (10 mL) was added in order to extract products sorbed in NaY zeolite, and the mixture was filtrated and the solvent was removed. The crude product was purified by preparative TLC to afford **2** in 56% yield.[11]

Table 3. Friedel–Crafts alkylations of anisole with acrolein[a]



Entry	Catalyst	Yield/%	*ortho*:*para*[b]
1	NaY	66 (29)[c]	16:84 (16:84)[c]
2	SiO_2	5	18:82

[a] Anisole (10 mL) was reacted with arolein (1.0 mmol) in the presence of catalysts (1.0 g) for 12 h. [b] Determined by ^{1}H NMR. [c] Reaction time was 6 h.

The addition of aromatics to acrolein is a 100% atom economy-type reaction without any formation of wastes or branched alkyl isomers which are often encountered in the Lewis acid-catalyzed Friedel–Crafts alkylation of aromatics with alkyl halides. In addition, a formyl group on the side-chain can react with various nucleophiles or be transformed into other functional groups. Application of the zeolite-catalyzed addition of acrolein to chemical syntheses is underway.

References and Notes

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8 NaX (Molecular sieves 13X powder, Si/Al = 1.4, SA = 820 m^2/g, Aldrich Chemical); NaY (HSZ-320NAA, Si/Al = 2.7, SA = 800 m^2/g, Tosoh Corp); HY (JRC-Z-HY-5.5, Si/Al = 2.8, SA = 570 m^2/g, provided by the Catalyst Society of Japan); silica (Silicagel 60, SA = 500 m^2/g, MERCK).
9 Solid NMR measurements were carried out by means of single pulse direct excitation with proton decoupling (90° pulse = 5 µs, 5-s pulse delay, 1000 scans) and the probe temperature was maintained at 273 K. Chemical shifts were referenced to TMS as an internal standard, and sample spinning rates were adjusted to ca. 3 kHz.
10 A broad signal near 110 ppm was inevitably derived from the carbonaceous components around the sample probe in the NMR instrument (Chemagnetics CMX-300).
11 IR (CCl_4, cm^{-1}): 3061, 2920, 2854, 2816, 2715, 1730; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.79 (t, $J = 1.6$ Hz, 1H), 8.03 (br, 1H), 7.57 (d, $J = 7.8$ Hz, 1H), 7.30 (dd, $J = 8.2$, 0.9 Hz, 1H), 7.18 (t, $J = 7.1$ Hz, 1H), 7.12 (t, $J = 7.1$ Hz, 1H), 6.90 (t, $J = 0.9$ Hz, 1H), 3.08 (t, $J = 7.3$ Hz, 2H), 2.81 (td, $J = 7.3$, 1.6 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.5, 43.8, 112.2, 114.3, 118.0, 122.4, 123.0, 125.0, 128.0, 134.6, 202.4.