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Acid-Base Catalysts Derived from Weakly Acidic Ion Exchange Resin: Efficiency in the Knoevenagel Condensation

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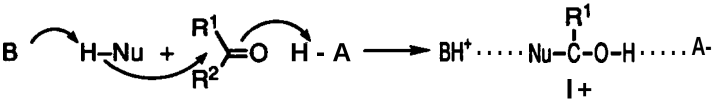
Abstract: Weakly acidic cation-exchange resins in H^+ form, partially neutralized with $H_2N(CH_2)_nN^+Me_3$ OH^- (n = 2–5), have been shown to catalyze the Knoevenagel condensation. The efficiency of catalysis depends on the aminoalkyl chain length and extent of neutralization.

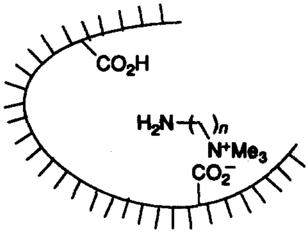
A combination of acid and base components often exhibits an efficient catalytic effect in some synthetically useful reactions. The well-known instances are successful uses of amine–carboxylic acid salts for certain condensations such as the Knoevenagel' and intramolecular aldol condensations.* In these cases, the catalysts seem to activate carbonyl substrates usually through imine or enamine formation. Meanwhile, the addition reaction of carbonyl compounds with a nucleophile containing an ionizable hydrogen can be catalyzed, in principle, by both the base and acid that function by assisting deprotonation of the nucleophile and by hydrogen bonding or protonation at the carbonyl oxygen, respectively.[3] If the two catalysts, acidic and basic, act concurrently as shown in Scheme 1, a great catalytic advantage would be expected' In practice, promising results have been obtained for systems consisting of one intermolecular general base and one intramolecular general acid catalyst.' Moreover, bifunctional tautomeric catalysis can be regarded as a special case of acid-base catalysis.[4,6]



Scheme 1

Recently, silica gel functionalixed with amino groups has been shown to be a useful catalyst for the Knoevenagel condensation and a concerted, acid-base-catalyzed mechanism has been proposed.[7] In seeking efficient acid-base catalysts for this type of condensation, we designed the catalysts (type **1**) that contain aminoalkyl groups bound (with regulating the fraction of amine) to a carboxylic acid-type cation exchange resin through ion pairs with the intramolecular ω-trimethylammonium groups. It was anticipated that a change in the amino alkyl chain length should vary the interaction between substrates and the amino anc carboxy groups in **1**, affecting catalytic nature. Here we describe the preparation of **1** and its catalytic effect on the Knoevenagel condensations of several aklehydes and ketones with active methylene compounds.

The catalysts '**la-e** were prepared as follows. A mixture of Amberlite IRC-50 in H^+ form[8] and aqueous $H_2N(CH_2)_2N^+Me_3$ OH^- (quimolar amount)[9] was allowed to stand at room temperature for 24 h. The resulting resin was filtered off, washed successively with H_2O and EtOH, and dried to give the catalyst **la** ($[N^+Me_3]/[CO_2H, CO_2^-] = 0.73$).[10] Similarly, the catalysts **lb-e** (**b**: n = 2, $[N^+Me_3]/[CO_2H, CO_2^-] = 0.30$; **c**: 3, 0.28; **d**: 4, 0.40; **e**: 5, 0.31)[10] were prepared by the use of the corresponding aqueous $H_2N(CH_2)_nN^+Me_3$ OH^- (n = 2–5)[9] (0.5 molar equiv).

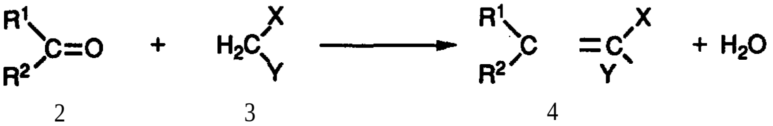


1

Amberlite IRC-50 $[H^+, H_2N(CH_2)_nN^+Me_3]$ (la-e)

Catalyst	*n*	$[N^+Me_3]/[CO_2H, CO_2^-]$
1a	2	0.73
1b	2	0.30
1c	3	0.28
1d	4	0.40
1e	5	0.31

The modified Amberlite IRC-50 resins la-e thus obtained were tested for catalytic activity in the condensation of benxaldehyde with ethyl cyanoacetate. As summarized in Table I, all **la-e manifested the catalytic activity even** at room **temperature**. The **reaction** was greatly affected by the **nature** of the resin catalyst used. The catalysts **la and lb, particularly the** former, showed notably high efficiency, whereas the catalysts holding a longer alkyl chain of amine tended to lower catalytic activity. Interestingly, replacement of the primary amino groups in **lb** by the dimethylamino **groups** resulted in considerable retention of activity. Umnodifled Amberlite IRC-50 resin showed no catalytic activity. In contrast with the **efficient** catalysis by the modified Amberlite IRC-50 resins, Amberlyst **15,**[11] a sulfonic acid-type cation exchange resin, in $[H^+, H_2N(CH_2)_3N^+Me_3]$ form exhibited no catalytic effect on the condensation at room temperature. On the other hand, a mixture of **(3-aminopropyl)trimethylammonium** hydroxide and n-caproic acid showed only a poor catalytic effect on the condensation.



Scheme 2

Table L Condensation of **Benzaldehyde** with Ethyl Cyanoacetate Using la-e and Related Catalysts

Catalyst	Reaction conditions[a]		4 (R^1 = Ph; R^2 = H; X = CN; Y = CO_2Et)
	Temp.	lime (h)	Yield[b] (%)
1a	room temp.	5	**87**
1b	room temp.	5	**77**
1b	reflux	100 min	**97**
1c	room temp.	**6**	58
1d	room temp.	**12**	**25**
1e	room temp.	7	**27**
Amberlite IRC-50 $[H^+, Me_2N(CH_2)_2N^+Me_3]$	room temp.	**5**	46
Amberlite IRC-50 (H^+)[c]	reflux	**4**	0
Amberlyst 15[d]	room temp.	**24**	**0**
$[H_2N(CH_2)_3N^+Me_3]$ $OH^-/Me(CH_2)_4CO_2H$[e]	room temp.	5	**15**

[a] Mixture containing 0.01 mol of each reactant and 0.10 g of catalyst in 3 ml of benzene, unless otherwise stated. [b] Purified product, mp 49–50°C (lit.[12] mp 49.5°C). [c] Reaction carried out with 0.60 g of catalyst. [d] In $[H^+, H_2N(CH_2)_3N^+Me_3]$ farm ($[N^+Me_3]/[SO_3H, SO_3^-] = 1$). [e] Mixture of 0.24 mmol of the hydroxide and 0.53 mmol of the acid.

Table II. Knoevenagel Condensation of2 with **3** Using the Catalyst **1a**

Entry	2		3		Reaction conditions[a]		Product 4		
	R^1	R^2	X	Y	Temp.	Time (h)	Yield (%)[b]	M.p. (°C)	Ref.
1	Ph	H	CN	CN	room temp.	5	92	82.5-83.5	12.13
2	p-$NO_2C_6H_4$	H	CN	CN	mom temp.	5	92	160.5–162	12
3	p-$MeOC_6H_4$	H	CN	CN	room temp.	5	90	113-114	12.13
4	(*E*)-PhCH=CH	H	CN	CN	room temp.	5	65	126128	14
5	–C_5H_{10}–		CN	CN	room temp.	5 min	86		15, 16
6[c]	Ph	Me	CN	CN	reflux	3	47	92.e93.5	17
7	Ph	H	CN	CO_2Et	mom temp.	5	87	49-50	12, 18
8	–C_5H_{10}–		CN	CO_2Et	room temp.	5	36	oil	15, 16, 19
9	–C_5H_{10}–		CN	CO_2Et	reflux	6	81	oil	15, 16. 19
10[d]	Ph	Me	CN	CO_2Et	reflux	47	1[e]	oil	15.19-21
11[f]	Ph	Ph	CN	CO_2Et	reflux	22	0	—	
12	Ph	H	CO_2Et	CO_2Et	reflux	6	47	oil	12.22
13	Ph	H	COMe	CO_2Et	room temp.	6	22[g]	oil	23.24

[a] Mixture containing 2.0 mmol of carbonyl compound, 2.0-2.1 mmol of active methylene compound, and 0.020 g of catalyst in 0.6-1.5 ml of benzene, unless otherwise stated. [b] Indicated yields correspond to those of products purified by recrystallization or flash chromatography. [c] Reaction carried out with 0.10 g of catalyst. [d] Reaction carried out with 5 mmol of each reactant and 0.10 g of catalyst in 1.5 ml of benzene. [e] Mixture of two isomers (*E*/*Z* = 2/1). [f] Reaction carried out with 10 mmol of each reactant and 0.10 g of catalyst in 3 ml of benzene. [g] Mixture of two isomers (*E*/*Z* = 1/3).

The successful demonstration of catalysis by the modified Amberlite IRC-50 resins la-e, particularly by **1a**, in the above condensation of benzaldehyde with ethyl cyanoacetate prompted us to examine the efficiency of the catalyst **1a** in the Knoevenagel condensations of several other aldehydes or ketones with active methylene compounds. The results am summarized in Table IL The aromatic aldehydes. when reacted with malononitrile at room temperature, were all converted to the corresponding olefins in good yields (entries l-3). Benxaldehyde was also found to condense with diethyl malonate and with ethyl acetoacetate, but in lower yields (entries 12 and 13). In the reaction of clnnamaldehyde with malononitrile, the Knoevenagel condensation product was obtained without the Michael addition product (entry 4). The condensation of cyclohexanone with malononitrile occurred very readily (entry 5). The same ketone also reacted with ethyl cyanoacetate rather slowly at room temperature (entry 8), but smoothly at the boiling point of benzene (entry 9). The reactions were much more difficult to accomplish with the aromatic ketones than cyclohexanone (entries 6, 10, and 11).

To our knowledge, this is the first example of the use of a weakly acidic resin as a catalyst in the Knoevenagel condensation.” It is uncertain as to whether or not the mechanism of the Knoevenagel condensation mediated by 1 involves a concerted acid-base catalysis. However, the efficiency of Amberlite IRC-50 $[H^+, Me_2N(CH_2)_2N^+Me_3]$ observed in the Knoevenagel condensation of benzaldehyde with ethyl cyanoacetate seems to eliminate the possibility of the imine intermediate for the reaction. Further studies are in progress in this laboratory to delineate the scope and limitations of the modified Amberlite IRC-50 catalysis.

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8. Amberlite IRC-50 (from Grgano, Japan) is a macroreticular carboxylic acid resin with a capacity of 10.0 **mequiv/dry** g.
9. The ammonium hydroxides **were prepared** from the corresponding quaternary bromide salts, which were synthesized **according** to the literanne **procedure (Dahlberg,** D. B.; Kuxemko, M. A.; Chiang. Y.; Kresge, A. J.; Powell, M. F. *J.* **Am. *Chem. Soc.* 1983,105, 5387–5390.), by** using the anion exchange resin Amberlite IRA402 in **OH^- form.**
10. The ammonium content of each modified resin was calculated by dividing the amount of the ammonium component **incorporated** into the **resin** by the amount of resin.
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