Amino Groups Immobilized on Silica Gel: an Efficient and Reusable Heterogeneous Catalyst for the Knoevenagel Condensation

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Silica gel functionalized with amino groups is a useful insoluble catalyst for the Knoevenagel condensation: the reaction can be carried out under continuous-flow conditions and good yields are obtained when aromatic aldehydes, cyclohexanone, and acetophenone react with ethyl acetoacetate, ethyl cyanoacetate, and malononitrile. Lower yields are obtained in the case of ethyl benzoylacetate and acetylacetone; this fact and the easy dehydration of the aldol intermediate strongly suggest the participation of the residual free silanol groups of the matrix in the catalysis mechanism.

The Knoevenagel reaction involves the condensation of a carbonyl compound with compounds containing a methylene group activated by one or two electron-withdrawing substituents, such as nitrile, acyl, and nitro. According to the literature on the subject the reactive anion is generated under homogeneous conditions with a weak base, in general ammonia and ammonium salts, or primary and secondary amines and their salts.[1] Weakly and strongly basic anion-exchange resins have been shown to be effective catalysts in promoting the Knoevenagel condensation.[2]

In recent years the use of inorganic solid supports as reagents or catalysts has rapidly increased: thus adsorption on inorganic matrices with and without solvent has been reported as a useful condition for the Knoevenagel reaction using aluminium oxide,[3,4] xonotlite alone or doped with potassium t-butoxide,[5] and molecular sieves.[6]

The advantages of insoluble reagents and catalysts for organic synthesis have been reviewed in depth:[7] they mainly lie in the fact that easier work-up, milder conditions, and higher selectivity are often attained. When the reaction is fast enough, insoluble materials can be adapted to continuous column operations utilizing fixed beds. This is of particular importance for large-scale operations when insoluble catalysts can be repeatedly used.

We have previously reported that 3-aminopropyl-functionalized silica gel catalyses the Knoevenagel condensation, and allows operation under mild continuous-flow conditions.[8]

In this paper we describe a wider application of this catalyst and the data obtained with a different basic system immobilized on silica gel, together with some hypotheses on the participation of the surface of the inorganic support in the catalysis mechanism.

Table. Knoevenagel condensation with catalysts **I** and **II** [a]

	R	R'	Z	Z'	Cat.	Conv.[b] (%)	Yield[c] (%)	M.p.(°C) or B.p. (°C/Torr)	Lit. m.p. (°C) or B.p. (°C/Torr)
1	Ph	H	MeCO	CO$_2$Et	I	81	59	60	59—60[11]
2	Ph	H	MeCO	CO$_2$Et	II	75	55	60	
3	PhCH=CH	H	MeCO	CO$_2$Et	I	76	72[d]	210/17	213—214/17[12]
4	p-NO$_2$Ph	H	MeCO	CO$_2$Et	I	74	31	162	164[13]
5	p-NO$_2$Ph	H	MeCO	CO$_2$Et	II	70	29	162	
6	Ph	H	PhCO	CO$_2$Et	I	56	48	98	98—99[14]
7	Ph	H	CN	CO$_2$Et	I	100	98	53	51[15]
8	Ph	H	CN	CO$_2$Et	I	100	82[e]	53	
9	Ph	H	CN	CO$_2$Et	I	100	96[f]	53	
10	Ph	H	CN	CO$_2$Et	II	93	89	53	
11	Ph	Me	CN	CO$_2$Et	I	65	50	45	46—47[16]
12	C$_5$H$_{10}$		CN	CO$_2$Et	I	86	66	0	0[2d]
13	C$_5$H$_{10}$		CN	CO$_2$Et	I	98	83[g]		
14	Ph	H	CN	CN	I	100	91	85	83[17]
15	Ph	H	CN	CN	I	100	90[h]	85	
16	PhCH=CH	H	CN	CN	I	100	67[d]	126	128[18]
17	p-NO$_2$Ph	H	CN	CN	I	100	83	159	161[19]
18	o-MeOPh	H	CN	CN	I	100	84	83	84—85[20]
19	Ph	Me	CN	CN	I	69	58	91	92[3]
20	Ph	H	MeCO	MeCO	I	41	35	190/17	185—188/15[21]
21	Ph	H	CO$_2$Et	CO$_2$Et	I	trace			185—186/17[22]
22	Ph	H	CN	CN	SiO$_2$	0[i]			

[a] For experimental conditions, see Experimental section. [b] Referred to the consumed carbonyl compound, by ^{1}H n.m.r. and g.l.c. analyses. [c] Purified product. [d] No Michael addition product was detected. [e] Reaction carried out at 0 °C. [f] Reaction carried out with **I** (5.0 g) and reagents (0.02 mol). [g] Reaction carried out at 65 °C. [h] Referred to a catalytic bed used six times after the recovery from entry 14. [i] Reaction carried out according to Experimental section, using unfunctionalized silica gel (10.0 g).

Results and Discussion

The ability of insoluble systems **I** and **II** to serve as a catalyst for the Knoevenagel reaction was tested using aromatic aldehydes, cyclohexanone, and acetophenone with ethyl acetoacetate, ethyl benzoylacetate, ethyl cyanoacetate, malononitrile, acetyl-acetone, and diethyl malonate as the active methylene reagents, according to equation (1).
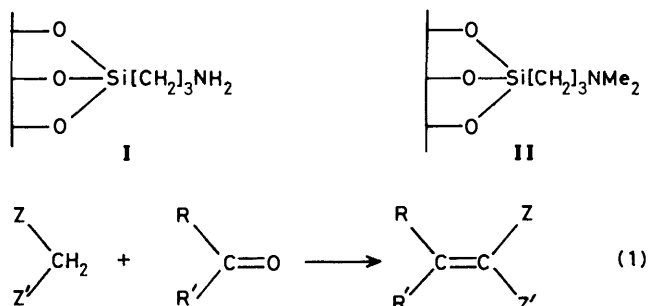
The reaction is carried out in a vertical double-jacket glass column (30 cm in length, 2 cm in diameter) thermostatted at 25 °C, containing catalyst **I** (10 g) or **II** (11.6 g) (corresponding to 7.9 mequiv. of NH_2 or of NMe_2, respectively). The reagent mixture flows through the catalytic bed, with toluene as eluant, and ca. 250 ml of solvent are used for the complete recovery of the product at the column outlet. The catalyst remains in the column and the product is obtained by simply evaporating the solvent.

The obtained results are summarized in the Table.

Aldehydes condensed with complete conversion and good yield with ethyl cyanoacetate and malononitrile, while the reactivity diminishes in the order ethyl acetoacetate > ethyl benzoylacetate > acetylacetone, being negligible with diethyl malonate.

As expected, ketones failed to react with the same ease.

In all the reactions system **I** is a more active catalyst than system **II**.

We think that the reactivity of the methylene active compounds, which do not follow the same trend as their respective pK_as (acetylacetone 9; ethyl cyanoacetate > 9; ethyl acetoacetate 10.7; malononitrile 11,2; ethyl benzoylacetate 10.3; diethyl malonate 13)[9] suggests that the surface of the matrix is not inert towards the reacting species. Indeed, the Knoevenagel condensation usually proceeds to the α,β-unsaturated com-pound; however, in many cases better yields were obtained by using a water separator to remove the water formed during the reaction; moreover, in some applications with anion-exchange resins, the reaction mixture was heated to ~ 180 °C to effect the dehydration of the intermediate aldol.[2a] The results reported in the Table show that with silica gel-immobilized amino groups the aldol intermediate is not isolable at 0 °C. This fact can be explained by the presence on the silica gel surface of residual free silanol groups that may either activate the carbonyl compound or promote the dehydration of aldol.

According to these observations we propose the mechanism reported in the Figure. In accordance with the Figure the following steps are postulated to occur: (i) the immobilized amino group extracts a proton from the active methylene compound, as in the mechanism of the Knoevenagel condensation under homogeneous conditions; (ii) the silanol group promotes the nucleophilic addition on the carbonyl compound via a hydrogen bond, and restores the free amine thus regenerating the catalyst; (iii) the aldol, protonated by the silanol hydrogen, easily dehydrates, and the water thus produced is removed from the reaction's organic milieu since it is strongly adsorbed on the hydrophilic matrix surface.
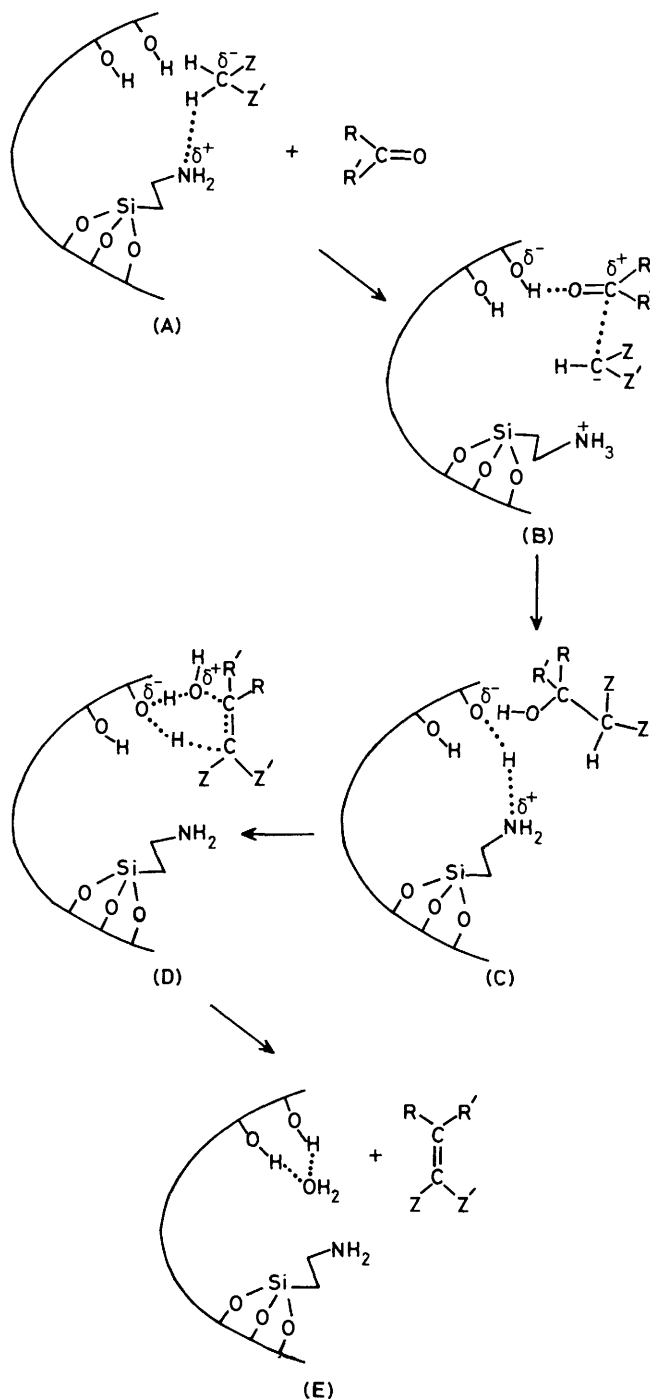

Figure. Curved lines represent the surface of silica gel containing silanol groups and immobilized amino functions, dotted lines indicate breaking and forming bonds. (A), Amino group interacts with the acidic methylene compound, affording the carbanion that reacts with the carbonyl compound activated by the silanol group via a hydrogen bond, (B). (C), The silica oxygen regenerates the amino function. (D), The aldol intermediate, protonated by the silanol group, dehydrates and transfers the leaving proton to silica oxygen. The water obtained remains adsorbed on the surface of silica gel, (E)

In conclusion the influence of the inorganic matrix might account for: (i) the easy dehydration of the aldol intermediate, which spontaneously takes place at 0 °C; (ii) the high reaction rate that allows the reaction to be conducted in continuous-flow conditions; (iii) the reduced reactivity of those methylene

compounds that can be adsorbed in enolic form on the matrix surface.[10]

Moreover the surface may exert steric hindrance to the methylene compound that interacts with the immobilized amino group in order to generate the reactive carbanion. In this connection methylene compounds with small nitrile groups will be favoured in comparison with those with bulky ethoxy carbonyl groups.

We think that the participation of the silanol groups in the catalysis mechanism might be also confirmed by the fact that by use of Dowex 3 resin the Knoevenagel reaction is promoted in the presence of acetic acid. The authors supposed that the free acid might be associated with the carbonyl group, proposing a concerted mechanism.[2d]

Experimental

Reagents were obtained commercially and were used without further purification. Silica gel was Merck art. 7734. G.l.c. analyses were performed on a Varian Vista 6000 instrument equipped with a CDS 111L integrator. The column used was a Hewlett-Packard fused silica capillary column (25 m × 0.20 mm) with crosslinked methyl silicone. [1]H N.m.r. spectra were recorded on a Hitachi–Perkin-Elmer R-24B spectrometer at 60 MHz, with tetramethylsilane as the internal standard in $CDCl_3$. I.r. spectra were obtained on a Perkin-Elmer FT-1500 spectrometer. A Neslab RTE-5B thermostat was connected to the reaction column. Light petroleum refers to the fraction boiling in the range 40—60 °C.

3-Aminopropyl-functionalized Silica Gel I.—Silica gel (100.0 g) dried in an oven at 120 °C for 6 h was suspended in anhydrous toluene (500 ml) and allowed to react with 3-aminopropyltrimethoxysilane (24.7 g, 0.14 mol) added dropwise during 15 min. The reaction mixture was stirred under reflux for 2 h; toluene containing methanol was distilled off and the reflux was continued for 1 h. After filtration, careful washing, and drying to constant weight, catalyst I (107.0 g) was obtained, corresponding to a titre of 0.79 mequiv. $-NH_2$ g^{-1} from the weight increase.

3-(N,N-Dimethylamino)propyl-functionalized Silica Gel II.— According to the procedure described for I, starting from silica gel (50 g) and 3-(*N,N*-dimethylamino)propyltrimethoxysilane (14.2 g, 0.07 mol), catalyst II (54.1 g) was obtained, corresponding to a titre of 0.68 mequiv. $-NMe_2$ g^{-1} from the weight increase.

General Procedure for Condensation.—The double-jacket glass column was charged with catalyst I (10 g) or II (11.6 g) suspended in toluene and thermostatted at 25 °C. A mixture of carbonyl compound (10 mmol) and methylene compound (10 mmol) was deposited on the column head [neat if liquid, dissolved in toluene (10 ml) if solid] and eluted with toluene. The reaction product began to be collected after *ca.* 50 ml of pure eluant had passed, and *ca.* 250 ml of solvent were used for the complete recovery. The solvent was removed under reduced pressure and the product was purified by column chromatography [light petroleum–diethyl ether (80:20) as eluant] or recrystallization (from cyclohexane).

The reaction products were identified by comparison of their physical data and [1]H n.m.r. and i.r. spectra with those described in the literature. The m.p.s are uncorrected.

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