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Knoevenagel Condensation in the Heterogeneous Phase Using $AlPO_4$–Al_2O_3 as a New Catalyst

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The Knoevenagel condensation of several aldehydes and ketones was carried out at room temperature on an $AlPO_4$–Al_2O_3 catalyst and in the absence of solvent (dry reaction), using malononitrile and ethyl cyanoacetate as the acidic methylene reagents. Only the *E* isomers could be isolated.

In recent years the use of inorganic solid supports as reagents or reaction media[1] has rapidly increased, because these reactions often involve milder conditions, easier workup, and higher selectivity than similar reactions in solution. Thus, adsorptions on inorganic solids without solvents (dry reactions) have been used in the synthesis of organic compounds involving, e.g., oxidation,[2] reduction,[3] alkylation,[4] condensation,[5] and acetylation reactions,[6] although until now there have been very few reports of inorganic solids being used for C–C bond formation[5c,5d] without previous anionic activation.

We have previously described the use of the $AlPO_4$–Al_2O_3 (75:25 wt%) catalysts in several gas-phase processes, such as alcohol dehydration,[7] alkene isomerization,[7,8] esterification of carboxylic acids,[9] cyclohexanone oxime rearrangement to ϵ-caprolactam,[10] alkylation of phenol with various alcohols,[11] and in the liquid phase, retroaldolization of diacetone alcohol[12] and dehydration of cyclic alcohols.[13]

In this paper we describe the application of the $AlPO_4$–Al_2O_3 solid system as the basic catalyst for Knoevenagel condensation in the heterogeneous phase, at room temperature and in the absence of solvents. The Koevenagel condensation has been the subject of many synthetic applications since its discovery[14] and is catalyzed by very weak bases or weak base–acid mixtures, although their presence is not always indispensable.[15] When aldehydes are used the reaction is stereoselective, yielding the *E* isomer.[5c,16,17]

The activity of this catalyst is affected by two major factors: the chemical nature of the surface (number and strength of acidic and basic sites) and the textural properties of the solid.

Results and Discussion

The ability of $AlPO_4$–Al_2O_3 to serve as a basic catalyst in Knoevenagel condensations was determined by using several aldehydes and ketones, especially aromatic aldehydes, with malononitrile and ethyl cyanoacetate as the acidic, active methylene reagents.

The products obtained are summarized in Table I. All the products synthesized are known and only the *E* isomer was found.

The aromatic aldehydes readily condensed with malononitrile, although the reaction failed to proceed with the same ease with ethyl cyanoacetate. Thus, the former reaction has usually been conducted with twice the amount of catalyst (3 g) and a greater reaction time, maintaining the same reaction temperature.

Aldehydes were shown to be better than ketones in the same reaction and thus the condensation of ethyl cyanoacetate was not successful with ketones at room temperature, and practically unchanged starting materials were recovered (GLC analyses).

Greater reaction times were required for aliphatic aldehydes and ketones than for aromatic aldehydes in order to obtain moderate yields in the reaction with malono-

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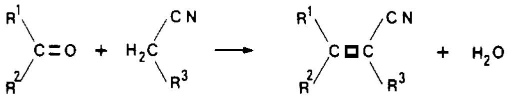
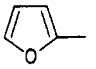
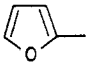
Table I. Reaction Products of Knoevenagel Condensation with $AlPO_4$–Al_2O_3 Catalyst



entry	R_1	R_2	R_3	mass of catalyst, g	$t_{stirring}$, min	yield,[a] %	R_f	mp or bp (mmHg), °C	lit. mp or bp (mmHg), °C	ref
1	Ph	H	CN	1.5	15	80	0.664	82	83	16
2	*p*-ClPh	H	CN	1.5	15	81	0.640	161	162-3	18
3	*p*-NO_2Ph	H	CN	1.5	15	82	0.443	159	159-160	18
4	*p*-MeOPh	H	CN	1.5	15	79	0.611	113	115	19
5	*p*-MePh	H	CN	1.5	15	79	0.717	134	134	19
6	*o*-OHPh	H	CN	1.5	15	43[b]	0.220	160 dec	167 dec	19, 20
7	PhCH=CH-(*E*)	H	CN	1.5	15	63	0.595	126	128	21
8		H	CN	1.5	15	56	0.525	72	73	22
9	*i*-Pr	H	CN	1.5	30	75	0.677	20 (0.03)	20 (0.03)	5c
10	Ph	Me	CN	1.5	30	traces[c]			92	5c
11	PhCH=CH-(*E*)	Me	CN	3.0	60	56	0.673	129	130	21b, 23
12	$(CH_2)_5$		CN	1.5	30	52	0.654	147 (15)	138 (10)	24
13	Me	Me	CN	1.5	30	31	0.615	112 (25)	108 (23)	5c
14	Ph	H	COOEt	3.0	60	74	0.664	49	51	25
15	*p*-ClPh	H	COOEt	1.5	60	47	0.684	90	91	26
16	*p*-NO_2Ph	H	COOEt	1.5	60	85	0.566	168	170	16
17	*p*-MeOPh	H	COOEt	3.0	60	52	0.511	79	80–84	27
18	*p*-MePh	H	COOEt	3.0	60	62	0.675	90	92	19
19	*c*-OHPh	H	COOEt	3.0	60	58[d]	0.123	135		28
20	PhCH=CH-(*E*)	H	COOEt	3.0	60	79	0.603	116	118	29
21		H	COOEt	3.0	60	89	0.500	93	94	25
22	*i*-Pr	H	COOEt	3.0	60	traces			86–89 (47)	30
23	Ph	Me	COOEt	3.0	60	traces			46–47	31
24	PhCH=CH-(*E*)	Me	COOEt	3.0	60	*e*			86	21b, 23
25	$(CH_2)_5$		COOEt	3.0	60	traces			112–114 (1.5)	32
26	Me	Me	COOEt	3.0	60	traces			105–109 (10)	33

[a] Indicated yields correspond to purified products by recrystallization or column chromatography ($CHCl_3$). [b] The reaction product is characterized by its transformation in 2-oxo-1-2H-benzopyran-3-carbonitrile (see Experimental Section). [c] Determined with GLC (internal standard method, 4%) and GC–EM (Hewlett-Packard 5992 B) spectra. [d] The reaction product is characterized by its transformation in 2-oxo-1-2H-benzopyran-3-carboxylic acid ethyl ester (see Experimental Section). [e] The starting materials are recovered unchanged.

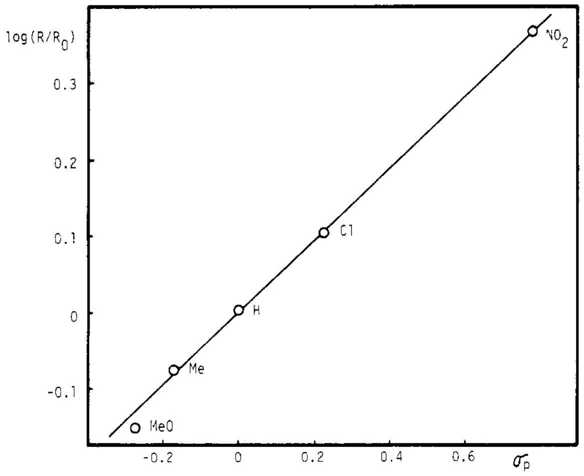


Figure 1. Hammett plot for the Knoevenagel condensation of parasubstituted benzaldehydes with ethyl cyanoacetate catalyzed by $AlPO_4$–Al_2O_3 at room temperature.

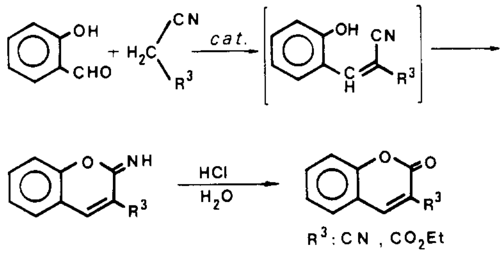
nitrile (entries 9, 12 and 13), while aromatic ketones (e.g., acetophenone, entry 10) were practically unchanged in the reaction.

In the reaction of aromatic α,β-unsaturated carbonyl compounds (entries 7 and 11) the Knoevenagel condensation product was obtained without any Michael addition product. Thus, for example, the reaction of (*E*)-4-phenyl-3-buten-2-one with malononitrile led to 1,1-dicyano-2-methyl-4-phenyl-1,3-butadiene in 56% conversion after 1 h of reaction with 3 g of catalyst (entry 11). However, an aliphatic α,β-unsaturated ketone (isophorone) was not modified after 72 h of reaction.

In the reaction of *o*-hydroxybenzaldehyde with the active methylene compounds (entries 6 and 19) the products obtained were not the simple Knoevenagel condensation products, but ones from further transformations, generated by nucleophilic attack of the anionic phenol oxygen atom on the carbon of the cyano group, which is held in a stereochemically favorable position by the olefinic bond.

The iminolactone thus obtained led us to conclude that the initial products possessed adjacent hydroxyl and cyano groups (*E* configuration, for the condensation with ethyl cyanoacetate).

These iminolactones were hydrolyzed in cold dilute hydrochloric acid to 2-oxo-2*H*-1-benzopyran-3-carbonitrile and ethyl 2-oxo-2*H*-1-benzopyran-3-carboxylate.



Rate studies carried out with the parasubstituted benzaldehydes suggest that the reaction operates by the stablished mechanism for Knoevenagel reactions. Thus, the application of the Hammett equation $\log (R/R_0) = \rho\sigma$ with σ_p[34] values leads to a straight line with both active methylene compounds having the value for reaction with malononitrile ($\rho = 0$) lower than the value for the reaction with ethyl cyanoacetate ($\rho = 0.48$, Figure 1).

Higher reaction times and amounts of catalyst or higher reaction temperatures are necessary for the reaction with ketones. However, in all cases, workup is simple and nonaqueous. These results extend the scope of application of the $AlPO_4$–Al_2O_3 catalysts in organic syntheses. Moreover, studies are in progress on $AlPO_4$ and $AlPO_4$–Al_2O_3 as supports for several reagents in the synthesis of organic compounds.

Experimental Section

Melting points were determined on an oil bath apparatus and are uncorrected. Elemental analyses were performed by the Organic Chemistry Institute (C.S.I.C.) Laboratories, Madrid, Spain. Infrared spectra were obtained on a Perkin-Elmer 599 A spectrophotometer and ^1H NMR spectra were recorded on a Varian Associates EM-390 (90 MHz) instrument with Me_4Si as the internal standard.

GLC analyses were performed on a Hewlett-Packard Model 5711 apparatus (flame ionization) with a recorder integrator (Model 3380 A), using a column (3 m, diameter 3.2 mm) packed with 5% Carbowax 20 M on Chromosorb GAW-DMCS 80/100 (oven temperature 185 °C, N_2 flow rate 20 mL/min). TLC was carried out on aluminum plates coated with silica gel (Merck, Kieselgel 60 PF_{254}) using $CHCl_3$.

Unless otherwise mentioned, reagents were obtained commercially (Merck) and were freshly distilled or recrystallized before the runs.

Preparation of the $AlPO_4$–Al_2O_3 (75:25 wt %) Catalyst. This catalyst was obtained by adding aluminum hydroxide (from ammonia and aluminum nitrate aqueous solutions) in a reaction medium where the precipitation of $AlPO_4$, from $AlCl_3 \cdot 6H_2O$ and H_3PO_4 (85 wt %) aqueous solutions, was initiated by addition of propylene oxide. The total precipitation of $AlPO_4$ was then carried out by the addition of ammonium hydroxide solution. The pH value at the precipitation "endpoint" was 6.1. The sample was dried at 120 °C for 24 h and then calcined at 650 °C for 3 h in a muffle furnace. The precipitation and physicochemical characteristics of the $AlPO_4$–Al_2O_3 catalyst have been described elsewhere (surface area 237 $m^2\ g^{-1}$).[7,8] The solid (200–250 mesh size) was stored in a desiccator until required.

General Procedure for Condensations. To a mixture of carbonyl (10 mmol) and active methylene compound (10 mmol) mechanically stirred without solvent and at room temperature, the $AlPO_4$–Al_2O_3 catalyst was added. When the mixture of carbonyl and methylene compound was not liquid at room temperature, we carefully melted it. The solid system thus obtained was stirred for 15 min or 1 h depending on the active methylene compound being used.

The product was extracted with dichloromethane and then the solvent was removed in vacuo and purified by recrystallization or column chromatography ($CHCl_3$ as eluant). The reaction products were identified by a comparison of their physical data (melting point, boiling point, and elemental analyses) and IR spectra with those described in the literature.

Condensation of *o*-Hydroxybenzaldehyde. The reaction with the active methylene compound was carried out in the normal way, although the isolated products were the iminolactones (entries 6 and 19) obtained from attack of the phenolic oxygen on the cyano group. The product of the condensation reaction was hydrolyzed with dilute hydrochloric acid at 60 °C, and the resultant product was the 3-substituted 2-oxo-2*H*-1-benzopyran.

2-Imino-2*H*-1-benzopyran-3-carbonitrile had mp 160 °C dec (lit.[19,20] mp 167 °C dec) after washing with cold ethyl alcohol, since it could not be recrystallized unchanged: IR (KBr) 3340 (NH), 2230 (CN), 1645 (C=N) cm^{-1}.

2-Oxo-2*H*-1-benzopyran-3-carbonitrile had mp 182–184 °C before and after crystallization from ethanol (lit.[20,35] mp 184–185 °C): IR (KBr) 2235 (CN), 1730 (C=O), 1600 (C=C) cm^{-1}.

2-Imino-2*H*-1-benzopyran-3-carboxylic acid ethyl ester had mp 135 °C before and after crystallization from ethanol: IR (KBr) 3320 (NH), 1675 (C=N) cm^{-1}.

2-Oxo-2*H*-1-benzopyran-3-carboxylic acid ethyl ester had mp 91–92 °C before and after crystallization from ethanol (lit.[36] mp 92–94 °C): IR (KBr) 1765 (C=O), 1610 (C=C) cm^{-1}.

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Registry No. *p*-ClC_6H_4CHO, 104-88-1; (*E*)-$PhCH{=}CHCHO$, 14371-10-9; (*E*)-$PhCH{=}CHCOCH_3$, 1896-62-4; $PhCH{=}C(CN)_2$, 2700-22-3; *p*-$ClC_6H_4CH{=}C(CN)_2$, 1867-38-5; *p*-$O_2NC_6H_4CH{=}C(CN)_2$, 2700-23-4; *p*-$CH_3OC_6H_4CH{=}C(CN)_2$, 2826-26-8; *p*-$CH_3C_6H_4CH{=}C(CN)_2$, 2826-25-7; (*E*)-$PhCH{=}CHCH{=}C(CN)_2$, 41109-96-0; $(CH_3)_2CHCH{=}C(CN)_2$, 13134-03-7; $PhC(CH_3){=}C(CN)_2$, 5447-87-0; (*E*)-$PhCH{=}CHC(CH_3){=}C(CN)_2$, 66684-80-8; $(CH_3)_2C{=}C(CN)_2$, 13166-10-4; (*E*)-$PhCH{=}C(CN)COOEt$, 2169-69-9; (*E*)-*p*-$ClC_6H_4CH{=}C(CN)COOEt$, 2169-68-8; (*E*)-*p*-$O_2NC_6H_4CH{=}C(CN)COOEt$, 2017-89-2; (*E*)-*p*-$CH_3OC_6H_4CH{=}C(CN)COOEt$, 2017-87-0; (*E*)-*p*-$CH_3C_6H_4CH{=}C(CN)COOEt$, 2017-88-1; (*E,E*)-$PhCH{=}CHCH{=}C(CN)COOEt$, 41109-95-9; (*E*)-$(CH_3)_2CHCH{=}C(CN)COOEt$, 93222-76-5; (*E*)-$PhC(CH_3){=}C(CN)COOEt$, 14533-92-7; (*E,E*)-$PhCH{=}CHC(CH_3){=}C(CN)COOEt$, 66748-87-6; $(CH_3)_2C{=}C(CN)COOEt$, 759-58-0; *p*-$O_2NC_6H_4CHO$, 555-16-8; *p*-$CH_3OC_6H_4CHO$, 123-11-5; *p*-$CH_3C_6H_4CHO$, 104-87-0; $(CH_3)_2CHCHO$, 78-84-2; $PhCOCH_3$, 98-86-2; CH_3COCH_3, 67-64-1; *o*-HOC_6H_4CHO, 90-02-8; furfurylidenemalonitrile, 3237-22-7; cyclohexylidenemalonitrile, 4354-73-8; ethyl 3-furfurylidene-2-cyanopropenoate, 67449-75-6; ethyl 2-(cyclohexylidene)-2-cyanoacetate, 6802-76-2; 2-imino-2*H*-1-benzopyran-3-carbonitrile, 36937-71-0; 2-oxo-2*H*-1-benzopyran-3-carbonitrile, 15119-34-3; ethyl 2-imino-2*H*-1-benzopyran-3-carboxylate, 72799-05-4; ethyl 2-oxo-2*H*-1-benzopyran-3-carboxylate, 1846-76-0; malonitrile, 109-77-3; ethyl cyanoacetate, 105-56-6; benzaldehyde, 100-52-7; furfuraldehyde, 98-01-1; cyclohexanone, 108-94-1.

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