

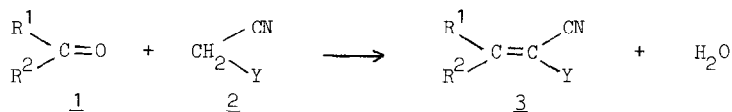
KNOEVENAGEL CONDENSATION CATALYSED BY ALUMINIUM OXIDE

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Summary - The Knoevenagel condensation of carbonyl compounds with active methylene compounds was readily carried out with aluminium oxide as catalyst.

The Knoevenagel condensation is a typically base-catalysed reaction. The catalysts are ammonia and ammonium salts, primary and secondary amines and their salts¹. In condensations involving aldehydes and cyanoacetic esters, the commonest catalyst is the piperidine in alcoholic solution^{1,2}. The Cope modification is also available³. Weakly basic ion exchange resins¹, potassium fluoride and cesium fluoride^{4,5} or $TiCl_4$ and base⁶ has also been used as catalysts⁷⁻¹². Aluminium oxide is known to effect many organic reactions under mild conditions. Having acidic and basic sites, they could promote the Knoevenagel reaction. We found that commercial alumina easily performed the condensation of aldehydes with active methylene compounds 2 malonitrile, cyanoacetic esters, cyanoacetamide and cyanophosphonates. The mixture of active methylene compound and aldehyde, without solvent, was simply adsorbed on alumina. If the mixture of aldehyde and 2 was not liquid at room temperature, we have melted it. The reaction was generally very fast (3-5 min) at room temperature or at 50-100°C, the isolation of product of good purity was very easy, the yields were high, only (E) isomer was formed.





The reaction was more difficult to accomplish with ketones than with aldehydes. Condensation of malonitrile was still possible at room temperature with dialkylketones and with acetophenone. Condensation of methyl cyanoacetate was not successful with aromatic ketones, but was performed at 100°C with acetone. When the reagents are used in solution (CH_2Cl_2 or C_6H_6), the rate of the reaction was diminished.

A general procedure is as follows. To a stirred solution of 0.01 mol of aldehyde in 0.01 mol of methylcyanoacetate was added 3 g of alumina Merck 90. The reaction was exothermic. After 3 min, the product was extracted with dichloromethane (2 x 20 ml). The solvent, removed in vacuo, gave a product of a good purity, generally, the purification was not necessary (table). An excess of alumina gave side reactions in the case of the condensation of acetaldehyde with malonitrile.

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Table

R ¹	R ²	Y	Mass of alumina ^a (g)	Reaction time	Yield ^b of <u>3</u> (%)	mp(°C) or bp/Torr
Ph	H	CN	3 (A) or (B)	3 min.	96	81-82
Ph	H	CO ₂ Me	3 (A)	3 min	100	89-90
Ph	H	CONH ₂	3 (B)	10 min ^c	85	123
Ph-CH=CH-	H	CO ₂ Me	3 (B)	3 min	100	146
Ph	Me	CN	5 (A)	3 h.	94	92
	H	CO ₂ Me	3 (B)	3 min	98	95
	H	CN	3 (A) or (B)	3 min	98-91	96
Me	H	CN	3 (B) or (C)	2 min	75	20°/0.03
Me	H	CO ₂ Me	3 (A)	10 min	54	
i Pr	H	CN	3 (B)	3 min	88	20°/0.03
Me	Me	CN	2 (B)	3 min	98	108°/23
Et	Et	CN	3 (A)	30 min	81	30°/0.03
Me	Me	CO ₂ Me	3 (A)	77 h ^d	53	97°/3
Ph	H	PO(OEt) ₂	5 (A)	48 h ^d	70	150°/0.03

a - mass of alumina for 10 mmol of 2 (A) Aluminium oxide Merck 60, catalog n° 1103. (B) Aluminium oxide Merck 90, Activity II-III, catalog n° 1097. (C) Aluminium oxide Merck 90, Activity I, catalog n° 1076.

b - Indicated yields correspond to crude product unless stated otherwise, having correct mp, IR, ¹H NMR spectra and analytical data

c - Temperature 50°C d - Temperature 100°C

References and Notes

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