SHORT PAPER

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Urotropine: an efficient catalyst precursor for the microwave-assisted Knoevenagel reaction

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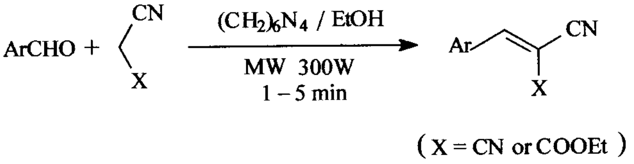
By using urotropine as a catalyst precursor, a rapid microwave-assisted Knoevenagel reaction of various active methylene compounds with aldehydes gave the corresponding olefinic products with satisfactory yields.

Keywords: urotropine, Knoevenagel condensation

The Knoevenagel condensation has been used in many synthetic applications and continues to be of importance in converting carbonyl groups into alkenes under relatively mild conditions. The catalysts for this reaction are usually gaseous ammonia, ammonium salts, amines, and their salts.[1] Recently, reports have been focused on the use of Lewis acids[2] and solid bases.[3]

The application of microwave techniques in organic synthesis has received special attention in recent years.[4] Catalysts such as piperidine,[5] LiCl,[6] silica gel,[7] P_2O_5-piperidine,[8] ammonium acetate,[9] ammonium acetate-basic alumina,[10] and NaCl or $NH_4OAc/HOAc$[11] have been employed in microwave-assisted Knoevenagel condensations.

In this work, urotropine (hexamethylene-tetraamine), a relatively inexpensive but efficient reagent, has been employed as a catalyst precursor in the Knoevenagel condensation under microwave irradiation. To our knowledge, there is no report of the use of urotropine in the Knoevenagel condensation either under conventional conditions or microwave irradiation.



Scheme 1

As a model reaction, the reaction of benzaldehyde with ethyl cyanoacetate in various solvents including methanol, ethanol, acetonitrile, and 1,4-dioxane was investigated (Table 1). Both ethanol and acetonitrile gave satisfactory results, while ethanol is obviously a better choice for safety and economy. Large amounts of a brown polymeric mass were formed in the absence of a solvent.

Table 1 Effect of solvents

Entry	Solvent	Power/W	Time/min	Yield/%
1	MeOH	300	9	86
2	EtOH	300	5	85
3	MeCN	300	6	83
4	1,4-Diox	300	15	72

By using urotropine as a catalyst and ethanol as a solvent, a systematic study was undertaken to investigate the Knoevenagel condensation reaction of various aldehydes with active methylene compounds (malononitrile and ethyl cyanoacetate) under microwave irradiation. The results are outlined in Table 2. Satisfactory yields (70–90%) were obtained after a few minutes of irradiation at ambient pressure.

In this study, urotropine was employed to promote the reaction in two ways. It served both as a catalyst precursor and as a dehydrant. The hydrolysis of urotropine released gaseous ammonia that served as a catalyst for the reaction. In the

Table 2 Urotropine catalysed Knoevenagel condensation under microwave irradiation

Entry	Aldehydes	X	Time/min	Yield (%)	M.p.s/°C	
					Obs.	Lit.
1	Benzaldehyde	CN	2	87	83	82[3a]
2	Benzaldehyde	COOEt	5	85	49	49[3a]
3	4-NO_2-C_6H_4CHO	CN	1	90	160	159[3a]
4	4-NO_2-C_6H_4CHO	COOEt	1.5	92	167	168[3a]
5	4-Cl-C_6H_4CHO	CN	2	94	164	161[3a]
6	4-Cl-C_6H_4CHO	COOEt	4	95	88	90[3a]
7	4-OH-C_6H_4CHO	CN	3	82	190	188[12]
8	4-OH-C_6H_4CHO	COOEt	5	89	173	172[9]
9	Vanillin	CN	3	83	136	134[12]
10	Vanillin	COOEt	5	87	101	100[9]
11	Cinnamaldehyde	CN	3	76	129	126[3a]
12	Cinnamaldehyde	COOEt	4	80	118	116[3a]
13	Furfural	CN	3	70	72	72[3a]
14	Furfural	COOEt	4	74	95	93[3a]

[a] All yields refer to isolated pure products characterised by comparing their melting points and IR spectra with literature values.

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meantime, it also consumed the water formed by the condensation reaction. This obviated the use of a dehydrating agent such as phosphorus pentoxide.[8] Moreover, the hydrolysis product of urotropine was gaseous, simplifying the work-up procedure.

The derivatives of benzaldehyde bearing electron-withdrawing substituents had higher reaction rates and gave higher yields when compared to those with electron-releasing groups. Malononitrile had a higher reactivity than ethyl cyanoacetate. Cinnamaldehyde (entry 13, 14) and furfural (entry 15, 16) gave relatively low yields due to the formation of tarry by-products. Thus, the use of microwave irradiation accelerated the Knoevenagel reaction in varying degrees.

In conclusion, the operational simplicity, use of inexpensive catalyst, high yields in significantly short reaction times, can make this procedure a useful and attractive alternative to the currently available methods.

Experimental

All reagents were commercially available and were used without further purification. Melting points (uncorrected) were determined on a WRS-1 capillary apparatus. IR spectra were recorded with a NICOLET NEXUS 470 FT-IR spectrophotometer. Reactions were conducted in a MW-800 II multimode cavity refluxing system made by Microwave Research Center at East China Normal University (Shanghai, China). Actual absorbed microwave energy was determined by forward / reverse power meter.

General procedure: Urotropine (0.28 g, 2 mmol) was added to the aldehydes (10 mmol), and methylene compounds (12 mmol) in ethanol (5 ml). The mixture was then subjected to microwave irradiation for a specified period of time (see Table 2). Upon completion of the reaction, the solvent was removed *in vacuo* and the resulting crude products were recrystalised from aqueous ethanol or cyclohexane / ethanol to afford pure olefinic products.

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