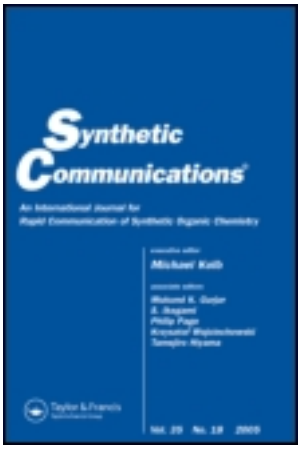

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Novel, Efficient, and Green Procedure for the Knoevenagel Condensation Catalyzed by Diammonium Hydrogen Phosphate in Water

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Novel, Efficient, and Green Procedure for the Knoevenagel Condensation Catalyzed by Diammonium Hydrogen Phosphate in Water

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Abstract: Knoevenagel condensation of various aromatic and heteroaromatic aldehydes with active methylene compounds like methyl and ethyl cyanoacetate, malononitrile, and cyanoacetamide proceeds smoothly with stirring in water in the presence of 4 mol% of diammonium hydrogen phosphate. The reactions were carried out at room temperature in short periods with very simple workup procedure and good to high yields.

Keywords: Alkene, diamamonium hydrogen phosphate, Knoevenagel condensation, water

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INTRODUCTION

The Knoevenagel condensation of aldehydes with active methylene compounds is an important and widely employed method for carbon–carbon bond formation in organic synthesis.[1] The versatile Knoevenagel reaction has numerous applications in the elegant synthesis of fine chemicals,[2] hetero Diels–Alder reaction,[3] and in synthesis of carbocyclic as well as heterocyclic compounds of biological significance.[4] The reaction is usually catalyzed by bases such as amines or their ammonium salts, ammonia, and sodium ethoxide in organic solvents.[5] Lewis acids,[6] zeolites,[7] and heterogenous catalysts[8] have also been employed to catalyze the reaction. Recently, the solvent-free Knoevenagel condensation on solid support promoted by infrared,[9] ultrasound,[10] or microwave irradiation[11] and also in support-free stoichiometric molten condition[12] has been a matter of interest. However, most of the reported procedures were carried out in organic solvents with notable amounts of waste. It should be emphasized that most of solvent-free methods still require organic solvents during workup, and this is so for the catalyst free Knoevenagel reaction in water.[13] Kaupp et al.[14] reported a green method for the Knoevenagel condensation by molten catalyst and in the absence of solvent. However, high reaction temperature (150–170°C) and long reaction time were required for a complete reaction. There are also some new catalysts such as TPP (triphenylphosphane),[15] urea,[16] ionic liquids,[17] and TBAH (tetrabutylammonium hydroxide)[18] that were used for the Knoevenagel condensation.

Today, in the development of new syntheses, ecological points of view must also be taken into account. In this process, the solvents are especially important, as they are generally used in large quantities. Many organic solvents are ecologically harmful, and their use should therefore be minimized as far as possible or even avoided altogether. One ideal alternative under investigation as solvent for organic reactions is water;[19] many biochemical processes occur in the presence of water, and the diversity of the in vivo reactions has prompted chemists to rediscover the potential of water as a solvent. Some efforts have been made to perform the Knoevenagel condensation in an aqueous medium as well as in the absence of organic solvents.[20]

RESULTS AND DISCUSSION

Because of our continued interest in Knoevenagel condensation and its applications in the synthesis of bioactive molecules,[21] we hereby report a very simple, genuine green, and highly efficient method for the condensation of various aromatic and heteroaromatic aldehydes **(1)** with several active methylene compounds **(2)** such as malononitrile, methyl- and ethyl cyanoacetate, and cyanoacetamide. The reactions were carried out in water at room temperature in the presence of 4 mol% of diammonium hydrogen

phosphate. It was exciting to observe that, except in few cases, all reactions run rapidly and were completed in just few minutes, giving excellent yields of the Knoevenagel product **3** (Scheme 1).

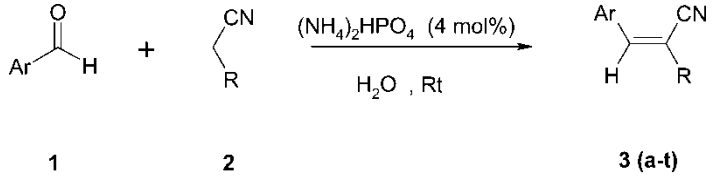
It was also shown that natural phosphate,[22] $AlPO_4$-Al_2O_3,[23] natural phosphate doped with potassium fluoride,[24] and phosphate complexes[25] are efficient catalysts for the Knoevenagel condensation, but the entire reported methods need extraction with organic solvents or advanced preparation of the catalyst. Diammonium hydrogen phosphate is a very cheap, nontoxic, and commercially available compound that can be used in practice without any special precaution. To the best of our knowledge, there is only one report on the application of diammonium hydrogen phosphate in the synthesis of some classes of heterocyclic compounds.[26]

At first, the reaction of 4-chlorobenzaldeyde with malononirlie was selected as a model to examine the effects of catalyst ranging from 0–10% at room temperature. The best yield was obtained when the reaction was carried out in the presence of 4 mol% of diammonium hydrogen phosphate in aqueous media. No other by-product was formed during the course of the reaction. Electron-deficient aldehydes gave relatively higher yields than electron-rich counterparts (Table 1).

In conclusion, we have demonstrated that the Knoevenagel condensation between aromatic and heteroaromatic aldehydes with active methylene compounds can be effectively performed at room temperature in the presence of a catalytic amount (4 mol%) of diammonium hydrogen phosphate in aqueous media, which provides a simple route to the synthesis of tri-substituted alkenes. The present method has many obvious advantages compared to those reported in literature, including simplicity of the methodology, ease of product isolation (only simple filtration), good yields, short reaction times, very cheap catalyst, and environmental friendliness.

EXPERIMENTAL

Melting points were recorded on an Electrothermal 9100 melting-point apparatus and are not corrected. IR spectra were recorded on a FT-IR Perkin-Elmer GX spectrophotometer using KBr disks. ^1H NMR spectra were recorded on Bruker DRX 500 (500 MHz) Avance spectrometer in $CDCl_3$ using TMS as the internal standard.



Scheme 1.

Table 1. Synthesis of alkenes catalyzed by diammonium hydrogen phosphate in aqueous media

Product	Ar	R	Yield[a] (%)	Mp (°C) Found	Mp (°C) Reported
3a	4-Cl-C_6H_4	CN	70	161	162[27]
3b	4-Me_2N-C_6H_4	CN	80	179	179–180[23]
3c	4-NO_2-C_6H_4	CN	85	160	160[18,27]
3d	C_6H_5	CO_2Me	90	89	89[5a,21a]
3e	4-Cl-C_6H_4	CO_2Me	75	122	
3f	2,4-Cl_2-C_6H_3	CO_2Me	90	78	79–80
3g	3-OH-C_6H_4	CO_2Me	87	145	
3h	4-Me_2N-C_6H_4	CO_2Me	92	146	146[18]
3i	3-NO_2-C_6H_4	CO_2Me	92	135	135[18]
3j	4-NO_2-C_6H_4	CO_2Me	90	178	178[18]
3k	PhCH = CH-	CO_2Me	90	144	145[21a]
3l	2-Furyl	CO_2Me	85	94	95[15,21a]
3m	2-Thienyl	CO_2Me	80	113–114	
3n	4-Cl-C_6H_4	CO_2Et	82	91–92	91[23]
3o	4-Me_2N-C_6H_4	CO_2Et	83	125	125[18]
3p	3-NO_2-C_6H_4	CO_2Et	95	139	139[18]
3q	2-Furyl	CO_2Et	90	91–93	91–93[16]
3r	2-Thienyl	CO_2Et	80	106	105–108[18]
3s	3-NO_2-C_6H_4	$CONH_2$	90	156–159	
3t	4-NO_2-C_6H_4	$CONH_2$	70	235–236	237–238[16]

[a]In all cases, the yields are related to pure isolated compounds.

General Procedure for the Preparation of Alkenes at Room Temperature

To a stirred solution of malononitrile (2.2 mmol, 145 mg) in water (10 ml), diammonium hydrogen phosphate (7 mg, 0.04 mmol) and benzaldehyde (212 mg, 2 mmol) were added. Progress of the reaction was monitored by TLC (eluent, petroleum ether–EtOAc, 3 : 1). After 1 min, the produced solid material was isolated by simple filtration. Further purification for some samples was made by recrystallization from EtOH.

Selected Data for Compounds 3a–t

3a: 2-(4-Chlorophenylmethylene)malononitrile: mp 161°C [lit. 162°C][27]; IR (KBr, cm^{-1}): 3038, 2227, 1583,1486; ^1H NMR (δ,$CDCl_3$) 7.56 (d, 2H, $J = 8.4$ Hz,H-Ar), 7.77 (s,1H,H-C═C), 7.89 (d, 2H, $J = 8.4$ Hz,H-Ar).

3b: 2-(4-N,N-Dimethylphenylmethylene)malononitrile: mp 179°C [lit. 179–180][18,23]; IR (KBr, cm^{-1}): 3010, 2208, 15609.

3c: 2-(4-Nitrophenylmethylene)malononitrile: mp 160°C [lit. 160][18,27]; IR (KBr, cm^{-1}): 3038, 2227, 1582, 1519; ^1H NMR (δ, $CDCl_3$) 7.88 (s,1H, H-C═C), 8.10 (d, 2H, $J = 7.20$ Hz, H-Ar), 8.39 (d, 2H, $J = 7.2$ Hz,H-Ar).

3d: Methyl-(E)-2-cyano-3-phenyl-2-propenoate: mp 89°C [lit. 89][5a,21a]; IR (KBr, cm^{-1}): 3038, 2227, 1725, 1608, 1428; ^1H NMR (δ, $CDCl_3$) 3.90 (s, 3H, OMe), 7.70–8.15 (m, 5H, Ar), 8.25 (s, 1H, H-C═C).

3e: Methyl-(E)-2-cyano-3-(4-chlorophenyl)-2-propenoate: mp 122°C; IR (KBr, cm^{-1}): 3060, 2227, 1725, 1583; ^1H NMR (δ, $CDCl_3$) 3.99 (s, 3H, OMe), 7.53 (d, 2H, $J = 8.60$ Hz, H-Ar), 7.98 (d, 2H, $J = 8.60$ Hz, H-Ar), 8.25 (s, 1H, H-C═C).

3f: Methyl-(E)-2-cyano-3-(2,4-dichlorophenyl)-2-propenoate: mp 78°C; IR (KBr, cm^{-1}): 3050, 2250, 1731, 1577; ^1H NMR (δ, $CDCl_3$) 4.00 (s, 3H, OMe), 7.45 (dd, 1H, $J = 8.50$, 1.70 Hz, H-Ar), 7.59 (d, 1H, $J = 1.70$ Hz, H-Ar) 8.25 (d, 1H, $J = 8.50$, H-Ar), 8.65 (s, 1H, H-C═C).

3g: Methyl-(E)-2-cyano-3-(3-hydroxyphenyl)-2-propenoate: mp 145°C; IR (KBr, cm^{-1}): 3412, 3032, 2227, 1725, 1596; ^1H NMR (δ, $CDCl_3$) 3.98 (s, 3H, Me), 5.90 (brs, 1H, OH), 7.12 (m, 1H, Ar), 7.41 (t, 1H, $J = 7.80$ Hz, H-Ar), 7.47 (d, 1H, $J = 7.80$ Hz, H-Ar), 8.25 (s, 1H, H-C═C).

3h: Methyl-(E)-2-cyano-3-(4-N,N-dimethylphenyl)-2-propenoate: mp 146°C [lit. 146][18]; IR: (KBr): [cm^{-1}] 2907, 2215, 1715, 1610, 1575; ^1H NMR: (δ, $CDCl_3$) 3.10 (s, 6H, -NMe), 3.90 (s, 3H, OMe), 6.70 (d, 2H, $J = 9$ Hz, H-Ar), 7.90 (d, 2H, $J = 9$ Hz, H-Ar), 8.20 (s, 1H, ═CH).

3i: Methyl-(E)-2-cyano-3-(3-nitrophenyl)-2-propenoate: mp 135°C [lit. 135°C][18]; IR (KBr, cm^{-1}) 3080, 2226, 1720, 1609, 1536, 1359.

3j: Methyl-(E)-2-cyano-3-(4-nitrophenyl)-2-propenoate: 178°C [lit. 178°C][18]; IR (KBr, cm^{-1}) 3119, 2847, 2225, 1731, 1613; ^1H NMR (δ, $CDCl_3$) 4.0 (s, 3H,OMe), 8.15 (d, 2H, $J = 9$ Hz, Ar), 8.34 (s, 1H, H-C═C), 8.38 (d, 2H, $J = 9$ Hz,Ar).

3k: Methyl-(E)-2-cyano-5-phenyl-2,4-pentadieneoate: 145°C [lit. 145°C][21a]; IR (KBr, cm^{-1}) 3031, 2220, 1611, 1583; ^1H NMR (δ, $CDCl_3$) 3.94 (s, 3H, OMe), 7.33 (m, 2H, HC═C), 7.42–7.48 (m, 3H, H-Ar), 7.63 (m, 2H, H-Ar), 8.06 (dd, 1H, $J = 11$, 2.9 Hz, HC═C).

3l: Methyl-(E)-2-cyano-3-(furyl)-2-propenoate: 94°C [lit. 95°C][15,21a]; IR (KBr, cm^{-1}) 3135, 2961, 2221, 1725, 1538; ^1H NMR (δ, $CDCl_3$) 3.95 (s, 3H, OMe), 6.70; (dd, 1H, $J = 4.0$, 1.9 Hz, H-Furyl), 7.45 (d, 1H, $J = 4.0$ Hz, H-Furyl), 7.78 (d, 1H, $J = 1.9$ Hz, H-Furyl), 8.05 (s, 1H, H-C═C).

3m: Methyl-(E)-2-cyano-3-(thienyl)-2-propenoate: 113°C IR (KBr, cm^{-1}) 3090, 2961, 2220, 1719, 1596; ^1H NMR (δ, $CDCl_3$) 3.96 (s, 3H, OMe),

7.27 (d, 1H, $J = 4.50$ Hz, H-thienyl), 7.83 (d, 1H, $J = 4.50$ Hz, H-thienyl), 7.89 (d, 1H, $J = 3.50$ Hz, H-thienyl), 8.39 (s,1H, H-C═C).

3n: Ethyl-(E)-2-cyano-3-(4-chlorophenyl)-2-propenoate: 91–92°C [lit. 91°C][23]; IR (KBr, cm^{-1}) 3050, 2950, 2220, 1725, 1608; ^{1}H NMR (δ, $CDCl_3$) 1.45 (t, 3H, $J = 7.12$ Hz), 4.43 (q, 2H, $J = 7.12$ Hz, OCH_2), 7.52 (d, 2H, $J = 8.56$ Hz, H-Ar), 7.97 (d, 2H, $J = 8.56$ Hz, H-Ar), 8.23 (s, 1H, H-C═C).

3o: Ethyl-(E)-2-cyano-3-(4-N,N-dimethylphenyl)-2-propenoate: 125°C [lit. 125°C][18]; IR (KBr, cm^{-1}) 2944, 2212, 1713, 1611, 1575; ^{1}H NMR (δ, $CDCl_3$) 1.40 (t, 3H, $J = 8$ Hz, CH_3), 3.10 (s, 6H, 2NMe), 4.30 (q, 2H, $J = 8$ Hz, OCH_2), 6.70 (d, 2H, $J = 9$ Hz, H-Ar), 7.90 (d, 2H, $J = 9$ Hz, H-Ar), 8.10 (s, 1H, HC═C).

3p: Ethyl-(E)-2-cyano-3-(3-nitrophenyl)-2-propenoate: 139°C [lit. 139°C][18]; IR (KBr, cm^{-1}) 3036, 2226, 1727, 1609, 1537; ^{1}H NMR (δ, $CDCl_3$) $\delta = 1.50$ (t, 3H, $J = 7.2$ Hz, CH_3), 4.40 (q, 2H, $J = 7.2$ Hz, OCH_2), 7.6–8.80 (m, 4H, Ar), 8.32 (s, 1H, ═CH).

3q: Ethyl-(E)-2-cyano-3-(furyl)-2-propenoate: 91–93°C [lit. 91–93°C][16]; IR (KBr, cm^{-1}) 3130, 3040, 2223, 1716, 1621; ^{1}H NMR (δ, $CDCl_3$) 1.42 (t, 3H, $J = 7.2$ Hz, Me), 4.40 (q, 2H, $J = 7.2$ Hz, OCH_2), 6.69 (dd, 1H, $J = 3.6$, 1.5 Hz, H-Furyl), 7.44 (d, 1H, $J = 3.6$ Hz, H-Furyl), 7.75 (d, 1H, $J = 1.5$ Hz, H-Furyl), 8.05 (s, 1H, H-C═C).

3r: Ethyl-(E)-2-cyano-3-(thienyl)-2-propenoate: 106°C [lit. 105–108°C][15,18]; IR (KBr, cm^{-1}) 3086, 2219, 1717, 1599; ^{1}H NMR: (δ, $CDCl_3$) 1.39 (t, 3H, $J = 7.1$ Hz, CH_3), 4.36 (q, 2H, $J = 7.1$ Hz, CH_2), 7.26 (t, $J = 4.79$ Hz, 1H, H-Thienyl), 7.81 (d, $J = 4.90$ Hz, 1H, H-Thienyl), 7.88 (d, $J = 3.70$ Hz, 1H, H-Thienyl), 8.37 (s, 1H, H-C═C).

3s: 2-Cyano-3-(3-nitrophenyl)-2-propenamide: 156–159°C; IR (KBr, cm^{-1}) 3418, 3129, 2227, 1706, 1608; ^{1}H NMR (δ, $CDCl_3$) 5.80 (brs, 1H, NH), 6.30 (brs, 1H, NH), 7.77 (t, 1H, $J = 8$ Hz, H-Ar), 8.32 (d, 1H, $J = 7.7$ Hz, H-Ar), 8.43 (d, 1H, $J = 7.7$ Hz, H-Ar), 8.45 (s, 1H,H-C═C), 8.77 (d, 1H, $J = 1.67$ Hz, H-Ar).

3t: 2-Cyano-3-(4-nitrophenyl)-2-propenamide: 235–238°C [lit. 237–238°C][16]; IR (KBr, cm^{-1}) 3438, 3347, 2227, 1688, 1596; ^{1}H NMR (δ, $CDCl_3$) 7.35 (brs, 1H, NH), 7.45 (brs, 1H, NH), 8.12 (d, 2H, $J = 8.7$ Hz, H-Ar), 8.39 (d, 2H, $J = 8.7$ Hz, H-Ar), 8.44 (s, 1H, H-C═C).

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