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On Water: An Efficient Knoevenagel Condensation using 12-Tungstophosphoric Acid as a Reusable Green Catalyst

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Abstract: 12-Tungstphosphoric acid is found to be an efficient, environmentally attractive, and reusable catalyst for Knoevenagel condensation of malononitrile and ethylcyanoacetate with various aldehydes.

Keywords: Aqueous media, Knoevenagel condensation, rapid reactions, reusable catalysts, 12-tungstophosphoric acid

Water is a desirable solvent for chemical reactions for reasons of cost, safety, and environmental concerns, and the study of organic reactions in aqueous solvents has an intriguing history.[1]

Knovenagel condensation of carbonyl compounds on molecules containing an active methylene group is one of the most important methods for the preparation of substituted alkenes.[2] This reaction between carboxylic compounds and methylene malonic esters produces several important products that include nitriles used in anionic polymerization and α-β-unsaturated ester intermediates employed in the synthesis of several

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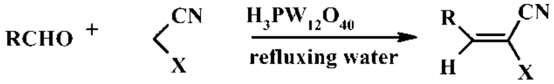
therapeutic drugs (e.g., niphedipine and nitredipine) and pharmacological products (calcium channel blockers and antihypertensives). As an important carbon–carbon forming reaction, Knoevenagel condensation has been extensively studied. Alkali metal hydroxides (e.g., NaOH and KOH), pyridine, and piperidine are the traditional catalysts used in this reaction. The reaction can be catalyzed with Lewis acids, $TiCl_4$/base,[3] $ZnCl_2$,[4] Clays,[5] and modified Mg-Al.[6] Recently Bigi and his coworkers reported Knoevenagel condensation in refluxing water in the absence of a catalyst with in 1 h.[7] However, they did not claim the reaction of ethyl acetoesters with carbonyl compounds under the same conditions. In connection with our studies on implementing organic reactions in an ecofriendly manner,[8–10] we explored the catalytic Knoevenagel condensation in water. In recent decades, an applicable industrial catalyst that is ecofriendly, green, and simply recycled in the reaction mixture has been sought. Green chemistry has been defined as a set of principles that reduces or eliminates the use or generation of hazardous substances throughout the entire life of chemical materials.[1] Using heteropolyacids (HPAs) and their salts, which are low in toxicity, highly stable in humidity, recyclable, and stable in air, have found more attention. They show very high catalytic activities for acid-catalyzed reactions. HPAs are usually insoluble in nonpolar solvents but soluble in polar solvents; the poor solubility of HPAs in reaction products improves product selectivity and also allows easy separation of the reaction and the product.[11]

We have recently started on the catalytic properties of heteropolyacids, which are cheap, reusable, and easily available catalysis.[12] In continuation of our work on the catalytic properties of heteropolyacids here in, we have developed a convenient, efficient, and ecofriendly procedure for Knoevenagel condensation using a catalytic amount of $H_3PW_{12}O_{40}$ (Scheme 1).

To start our investigation, we studied different solvent effects on the course of the reaction of benzaldehyde with malononitrile. From the results given in Table 1, it follows that the best solvent for this reaction is water. Only low yields of products were isolated after conventional heating in CH_2Cl_2 and $CHCl_3$. Yields and times were the same for the reaction in water and Dimethyl formamide (DMF), but water is an excellent solvent in terms of cost, availability, and environmental impact.

A variety of different aromatic aldehydes, containing electron-withdrawing or donating groups and heterocyclic aldehydes, were subjected to this reaction to investigate the generality of this methodology. All results are summarized in Table 2. In the presence of HPA, the reaction times for malononitrile are shorter



Scheme 1.

Table 1. Knovenagel reaction of benzaldehyde with malonitrile in different solvents under reflux

Solvent	Reaction time (h)	Yield
DMF	1	95
$CHCl_3$	8	80
CH_3CN	1.5	95
H_2O	0.25	97

(5–15 min) than those reported by Bigi and colleagues (60 min). However, the condensation with ethylcyanoacetate has been overlooked, so we studied the Knoevenagel reaction with ethylcyanoacetate in aqueous media. In the absence of HPA the reaction of 4-chlorobenzaldehyde as a model substance with ethylcyanoacetate in aqueous media completed after 135 min. When the catalyst was added, the reaction was completed after 60 min.

Our studies showed, in this reaction heteropolyacid is reusable and could be used for at least 3 runs for the condensation reaction. After removing the catalyst and washing that with diethylether, it could be reused and subjected to a second run of the same reaction. The results of the first experiment and our subsequent experiments were almost consistent in yield (96%, 94%, and 90%).

It is worthwhile mentioning that Knoevenagel condensation with ketones in this condition does not occur. We used acetophenone as an example of ketones that did not react in these conditions even after a prolonged reaction time (24 h).

Table 2. Knoevenagel condensation using a catalytic amount of $H_3PW_{12}O_{40}$ as catalyst in aqueous media

Entry	R	x	Time (min)	Yield (%)	Mp (°C) Found	Mp (°C) Lit.
1	Ph-	CN	15	91	87	84[13]
2	4-MeO Ph-	CN	5	92	114	114[13]
3	4-Me Ph-	CN	10	91	137–139	135[13]
4	4-Cl Ph-	CN	15	92	169	163[14]
5	4-OH Ph-	CN	15	91	184	Viscous liquid[15]
6	Furyl-	CN	15	92	70–72	72[13]
7	2-NO_2 Ph-	COOEt	90	85	100–102	96[16]
8	3- NO_2 Ph-	COOEt	90	87	136–137	128–132[17]
9	4-Cl Ph-	COOEt	60	89	92–93	86[17]
10	4-MeO Ph-	COOEt	120	89	88	88[17]

Our studies showed that in this reaction HPA is reusable for at least 5 runs of the condensation reaction.

In summary, we have developed a novel, ecofriendly, and efficient method for Knoevenagel condensation using HPA as an inexpensive, green, and reusable catalyst in water. The advantages of the present method are simplicity of workup, high yields, short reaction times, recyclability of the catalyst, and the most important, use of water as solvent.

EXPERIMENTAL

The reagent is commercially available. All of the products are known compounds and identified by melting-point and spectroscopic data.

General Procedure

A mixture of aldehyde (10 mmol), malononitrile or ethylcyanoacetate (10 mmol), and $H_3PW_{12}O_{40}$ (1 mol%) in water (10 mL) was refluxed. Upon completion of the reaction, as monitored by TLC, the reaction mixture was cooled to room temperature. The precipitated solid was filtered and recrystalized from absolute EtOH to obtain pure products. 12-Tungstophosphoric acid was soluble in water and was separated by filtration: by evaporation of filtrate and washing with diethyl ether, the catalyst could be recycled and reused in the same reaction.

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