

Silica-supported heteropoly acids: Highly efficient catalysts for synthesis of α -aminonitriles, using trimethylsilyl cyanide or potassium cyanide

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Abstract

The multicomponent Strecker reaction using trimethylsilyl cyanide or potassium cyanide was performed in very short reaction times and α -aminonitriles were prepared in excellent yields in the presence of a catalytic amount of silica supported dodecatungstophosphoric acid. The simple experimental and product isolation procedure combined with easy recovery and reusability of the catalyst are expected to contribute to the development of clean and environmentally friendly strategy for the synthesis of α -aminonitriles.

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1. Introduction

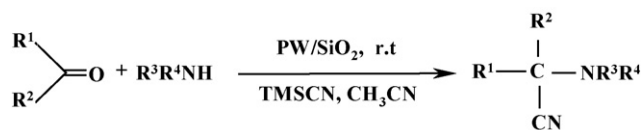
α -Aminonitriles, often synthesized by Strecker reaction [1], are highly useful synthons for the synthesis of α -amino acids [2], nitrogen-containing heterocycles such as imidazoles and thiadiazoles [3a,b] and other biologically useful molecules such as saframycin A, a natural product with anti-tumour activity or phthalascidi, a synthetic analogue, exhibits even greater potency [3c]. The classical procedure involves the treatment of an aldehyde or a ketone with alkaline cyanides and salts of amines, and was discovered a century and a half ago [1]. The efficiency of the reaction has been increased by the use of catalysts, and reactive cyanide ion sources such as hydrogen cyanide, sodium or potassium cyanide, Bu_3SnCN , bis(dialkylamino)cyanoboranes, diethylphosphorocyanidate, and trimethylsilyl cyanide (TMSCN) [4]. TMSCN is a safer, more effective, and more easily handled anion source compared to others [5]. A variety of homogeneous and heterogeneous catalysts have been used for α -aminonitrile synthesis [4–6]. Although these methods are valuable, many of

these methods involve one or more disadvantages including the tedious isolation of pure α -aminonitriles from the reaction mixtures, extended reaction times, leading to the generation of a large amount of toxic waste, use of stoichiometric or relatively expensive reagents. Furthermore, many of these protocols are limited to aldehydes only, and many of used catalysts are deactivated or sometimes decomposed by amines. In order to circumvent some of the problems associated with these procedures and in continuation of our ongoing work on solid acid catalysts for developing new synthetic methodologies [7,8], herein, we introduce supported heteropoly acids (HPAs) as catalysts for synthesis of α -aminonitriles (Scheme 1).

HPAs with Keggin structure are the most studied class within polyoxometalates, because they possess relatively high thermal stability [9] and acidity [10]. Supported HPAs are important for many applications, because bulk HPAs have low specific structure area (1–10 m²/g). It is important to increase the surface area or even better to increase the number of accessible acid sites of the HPA. This can be achieved by dispersing the HPA on solid support with high surface area [11,12]. For heterogeneous systems, it is possible to control solid strength by supporting HPAs on different carriers [12]. An immobilization of HPAs on a number of porous supports such as silica, active carbon, montmorillonite K-10, zeolite, etc. [8,13] was therefore extensively

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Scheme 1.

studied. But SiO₂, which is relatively inert towards HPAs, is the most often used [14].

2. Experimental

NMR Spectra were recorded on a Bruker Avance 200 MHz NMR instrument. All chemical reagents and solvents were analytical grade and used without further purification purchased from Fluka and Aldrich. H₃PW₁₂O₄₀ (PW), H₃PMo₁₂O₄₀ (PMo) hydrate from Aldrich, Merck and Aerosil 300 silica from Degussa were used. Silica-supported PW (PW/SiO₂) or PMo (PMo/SiO₂) catalysts were prepared and characterized by a known procedure as previously reported [8].

2.1. Typical procedure for the synthesis of α -aminonitriles

A mixture of aldehyde (1 mmol), amine (1.1 mmol), TMSCN (1.5 mmol) and PW/SiO₂ (7 mol%) in acetonitrile (3 mL) was stirred at room temperature for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC, the reaction mixture was filtered and washed with acetonitrile (2 × 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, concentrated in vacuo and purified by column chromatography on silica gel (ethyl acetate/*n*-hexane, 1:9) to afford pure α -aminonitrile. All products were identified by com-

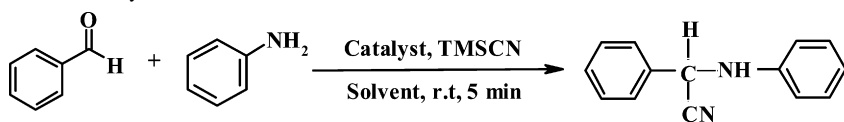
paring of their spectral data with those of the authentic samples [4a,5a,d,g].

3. Results and discussion

Initially, the reaction of benzaldehyde, aniline and TMSCN in the presence of PW/SiO₂ and PMo/SiO₂ as catalysts were carried out in a one-pot condensation reaction. Usually, tungsten HPAs are preferred over molybdenum ones as acid catalysts because of their stronger acidity, higher thermal stability and low reducibilities [11] (Table 1, entries 1 and 4). It is known, that HPAs strongly interact with supports at low loading levels, while the bulk properties of HPAs prevail at higher loading [11]. PW/SiO₂ with different weight percent of PW was examined as evidenced in Table 1, entries 2–4, 40 wt.% of PW/SiO₂ shows the best result. To establish the optimal conditions, a set of experiments varying solvent and the amount of the catalyst were carried out (Table 1, entries 4–9). The use of just 7 mol% of 40 wt.% PW/SiO₂ is sufficient to promote the reaction and no additives are required for this conversion. It is remarkable to note that no improvements in the reaction rates and yields were observed by increasing the amount of the catalyst from 7 to 12 mol% and lesser amount (4 mol%) also worked with longer reaction times (Table 1, entries 5 and 6). Different solvents were compared and acetonitrile was chosen. The others including benzene, chloroform, tetrahydrofuran showed lower yields (Table 1, entries 7–9). In comparison with other catalysts employed for the anilincyanation of benzaldehyde, 40 wt.% of PW/SiO₂ showed more catalytic reactivity than others in term of reaction time, and yield of the product (Table 2).

The reaction was extended to other substituted aromatic, aliphatic, and heterocyclic aldehydes under the optimum conditions (Table 3). The method was equally effective for aromatic,

Table 1
Effect of catalysts under different reaction conditions



Entry	Catalyst (mol% ^a)	Solvent	Yield (%) ^b
1	40% PMo/SiO ₂ (12 mol%)	CH ₃ CN	80
2	20% PW/SiO ₂ (12 mol%)	CH ₃ CN	75
3	60% PW/SiO ₂ (12 mol%)	CH ₃ CN	84
4	40% PW/SiO ₂ (12 mol%)	CH ₃ CN	97
5	40% PW/SiO ₂ (4 mol%)	CH ₃ CN	77 ^c
6	40% PW/SiO ₂ (7 mol%)	CH ₃ CN	98
7	40% PW/SiO ₂ (7 mol%)	THF	65
8	40% PW/SiO ₂ (7 mol%)	C ₆ H ₆	32
9	40% PW/SiO ₂ (7 mol%)	CHCl ₃	50
10	40% PW/SiO ₂ (7 mol%) ^d	CH ₃ CN	96
11	40% PW/SiO ₂ (7 mol%) ^d	CH ₃ CN	96
12	40% PW/SiO ₂ (7 mol%) ^d	CH ₃ CN	94
13	40% PW/SiO ₂ (7 mol%) ^d	CH ₃ CN	92
14	SiO ₂ (7 mol%)	CH ₃ CN	5

^a Percent of HPA to aldehyde or ketone.

^b Isolated yield.

^c 96% after 20 min.

^d Catalyst reused in five successive runs; the catalyst was filtered off, washed with acetonitrile and dried at 150 °C/0.5 Torr for 1.5 h.

Table 2
Effect of different catalysts for condensation of benzaldehyde, aniline and cyanating agents at room temperature

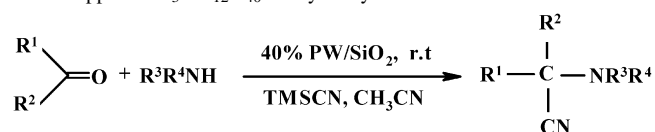
Entry	Catalyst	Cyanating agent	Time (h)	Yield (%)
1	Sc(OTf) ₃ (10 mol%) ^a	Bu ₃ SnCN	20	88 [4e]
2	RuCl ₃ (20 mol%)	TMSCN	20	74 [6a]
3	Pr(OTf) ₃ (10 mol%)	TMSCN	10	89 [6b]
4	NiCl ₂ (5 mol%)	TMSCN	12	92 [5g]
5	InCl ₃ (30 mol%)	KCN	6	75 [4a]
6	[HP(HNCH ₂ CH ₂) ₃ N]NO (20 mol%)	TMSCN	12	94 [5b]
7	I ₂ (10 mol%)	TMSCN	1	94 [4c]
8	BiCl ₃ (10 mol%)	TMSCN	10	84 [5e]
9	KSF (10 g)	TMSCN	3.5	90 [5a]
10	Yb(OTf) ₃ (5 mol%) ^a	TMSCN	20	88 [6c]
11	40% PW/SiO ₂ (7 mol%)	TMSCN	5 min	98

^a Result for benzylamine.

benzylic, and both primary and secondary amines to produce corresponding α -aminonitriles in high to excellent yields. It is noteworthy that, only a few reports of Strecker reaction with ketones reported in the literature [4a–d], but ketones were coupled with different amines and TMSCN in a one-pot operation in the presence of PW/SiO₂ at room temperature (Table 3, entries 17–20). Moreover the reaction conditions are mild enough to perform the reactions in the presence of acid sensitive substrates, such as furfuraldehyde and cinnamaldehyde without any decomposition or polymerization (Table 3, entries 11–14). Enolizable aldehyde such as decanal afforded the corresponding α -aminonitriles with excellent yield in very short reaction time

(Table 3, entry 15). In general, the reactions are very fast and no undesired side product was isolated. Finally reactivity of the catalyst was checked with potassium cyanide as a cyanating agent in the same reaction conditions. In all cases the reaction afforded the corresponding α -aminonitriles in high to excellent yields with longer reaction times, but the reaction times were still better than those from other methods. The results shown in Table 2 clearly indicate the scope and generality of the reaction with respect to various aldehydes, amines and cyanating agents. In addition, PW/SiO₂ was found to be reusable several times without loss of activity. Simply the catalyst should be filtered, washed with acetone, dried and reused. After reusing the cat-

Table 3
Silica-supported H₃PW₁₂O₄₀ catalysed synthesis of α -aminonitriles^a



Entry	Aldehyde/ketone	Amine	Yield (%) ^a /time (min)		Reference ^b
			KCN	TMSCN	
1	Benzaldehyde	Aniline	95/30	98/5	[5g]
2	Benzaldehyde	Benzylamine	98/10	96/1	[5d]
3	Benzaldehyde	Butylamine	98/10	80/1	[5g]
4	Benzaldehyde	Isobutylamine	64/10	92/120	[4a]
5	<i>m</i> -Methoxybenzaldehyde	Aniline	95/40	98/5	[4a]
6	<i>m</i> -Methoxybenzaldehyde	Benzylamine	91/30	98/15	[4a]
7	<i>m</i> -Methoxybenzaldehyde	Butylamine	96/10	93/8	[4a]
8	<i>p</i> -Chlorobenzaldehyde	Aniline	85/5	96/1	[5g]
9	<i>p</i> -Nitrobenzaldehyde	Aniline	90/40	91/20	[5d]
10	<i>p</i> -Methylbenzaldehyde	Aniline	83/2	97/1	[5g]
11	Furfural	Aniline	85/10	97/1	[5a]
12	Furfural	Benzylamine	87/10	93/1	[5g]
13	Cinamaldehyde	Aniline	92/12	98/2	[5g]
14	Thiophene-2-carboxaldehyde	Benzylamine	84/10	92/90	[5d]
15	Decanal	Aniline	98/15	98/3	[5d]
16	Benzaldehyde	Morpholine	90/30	90/10	[4a]
17	Cyclohexanone	Benzylamine	46/60	94/32	[4a]
18	Cyclohexanone	Butylamine	60/30	50/30	[4a]
19	<i>m</i> -Methyl cyclohexanone	Benzylamine	95/50	98/10	[4a]
20	<i>m</i> -Methyl cyclohexanone	Morpholine	95/50	98/10	[4a]

^a Isolated yield.

^b Products were characterized by comparison of their spectroscopic data with those reported in the literature.

alyst for five times, the yield of α -aminonitrile produced from the reaction of benzaldehyde and aniline with TMSCN was 92% (Table 1, entries 10–13).

4. Conclusion

The present procedure represents a clean, environmentally friendly, practical, and simple method with easy work-up. It is applicable to a wide scope of structural types, even for ketones, and produced corresponding α -aminonitriles in excellent yields in very short reaction times using low mole percent of the catalyst. Also supported $H_3PW_{12}O_{40}$ is non-toxic, inexpensive, and reusable catalyst.

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