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KSF-SUPPORTED HETEROPOLY ACIDS CATALYZED ONE-POT SYNTHESIS OF α-AMINONITRILES

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ABSTRACT. In the presence of KSF-supported heteropoly acid as a heterogeneous, reusable and inexpensive catalyst, three-component reactions between aldehydes or ketones, amines, and trimethylsilyl cyanide preceded to afford α-aminonitriles in excellent yields, very short reaction times, and low loading of catalyst. This catalyst was highly selective and other functional groups including carbon-carbon double bond, and heterocyclic moieties did not affect the reaction.

KEY WORDS: Heterogeneous catalysis, Clays, Combinatorial chemistry, α-Aminonitrile, Heteropoly acid

INTRODUCTION

Heterogeneous catalysts, in particular zeolites and clays, have reached great development in different areas of organic synthesis due to their environmental compatibility combined with the other advantages such as good yields and selectivities [1, 2].

Multicomponent reactions (MCRs) represent an especially attractive synthetic strategy for rapid and efficient library generation due to the fact that the products are formed in a single step, and the diversity can be achieved simply by varying the reacting components. The Strecker reaction, discovered in 1850 [3] for the synthesis of α-aminonitriles, has been recognized as the first MCR published ever and has a central importance to the life science [4]. α-Aminonitriles are very important intermediates, particularly in the preparation of α-amino acids, other biologically useful molecules [5], and various nitrogen containing heterocycles such as imidazoles and thiadiazoles [6]. Modified procedures, which have recently been developed for this transformation [7-24], have been used to circumvent some of the problems associated with the classical Strecker reaction. Among various cyanide ion sources [16-19], trimethylsilyl cyanide (TMSCN) is a safer and easily handled reagent compared to hydrogen cyanide, sodium or potassium cyanide. As a part of our research program concerning the use of heterogeneous catalysts in fine chemical preparation [25-27], we have investigated the synthesis of α-aminonitriles on KSF-supported heteropoly acids (HPAs).

EXPERIMENTAL

All chemical reagents and solvents were analytical grade and purchased from Fluka (Switzerland) and Aldrich (USA). $H_3PW_{12}O_{40}$ (PW), $H_3PMo_{12}O_{40}$ (PMo), and $H_3SiW_{12}O_{40}$ (SiW) from Aldrich (USA), Merck (Germany) and KSF montmorillonite from Fluka (Switzerland) were used. NMR Spectra were recorded on a Bruker Avance 200 MHz NMR instrument (Germany). FTIR spectra were performed using Bomem MB 104 spectrophotometer (Germany). Tungsten and carbon coked content in the catalyst was measured by inductively coupled plasma (ICP) atomic emission spectroscopy on a Spectro Ciros CCd spectrometer (Germany). The morphology of supported catalyst was studied by scanning electron microscopy (SEM) using XL30 Philips SEM (Germany).

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Preparation of the catalyst

For preparation of the HPA/KSF, KSF montmorillonite was dried in an oven at 120 °C for 2 h prior to its use as support. To prepare catalyst with 20, 40, and 60 wt.% of HPA to KSF, appropriate amount of HPA was dissolved in 4 mL of dry methanol. This solution was added dropwise to pre-dried KSF with constant stirring with glass rod. Initially, with addition of HPA solution, the clay was in the powdered form, but on further addition of HPA solution, the clay turned to a paste form. The paste on further stirring for 10 min resulted in a free flowing powder. After the impregnation, all catalysts were dried at room temperature for 24 h. Some uniformity in catalyst particle size was done by grinding and sieving then, calcined at 200 °C for 3 h.

Typical procedure for the synthesis of α-aminonitriles

A mixture of aldehyde (1 mmol), amine (1.1 mmol), TMSCN (1.5 mmol) and PW/KSF (0.2 g) in acetonitrile (3 mL) was stirred at room temperature for an appropriate time (Table 2). After reaction completion, as indicated by TLC, the reaction mixture was filtered and washed with acetonitrile (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on silica gel (ethyl acetate/n-hexane, 1:9) to afford pure α-aminonitrile.

Physical and spectroscopic data for products are as follows. Peak integrations in ^{1}H NMR are consistent with the pure product. The IR spectral data reported, 3305-3408 and 2214-2234 cm^{-1}, show the N-H and C≡N absorbtion of the products, respectively.

*Compound **1a***. M.p. 83–85 °C. IR (KBr): ν = 3337, 2239 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.05 (broad s, 1H), 5.30 (s, 1H), 6.71 (d, *J* = 7.9 Hz, 2H), 6.85 (t, *J* = 7.4 Hz, 1H), 7.25 (t, *J* = 7.9 Hz, 2H), 7.39 (m, 3H), 7.51 (m, 2H).

*Compound **2b***. Oil. IR (nujol): ν = 3321, 2235 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.91 (m, *J* = 13.5 Hz, 2H), 4.70 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 7.16 (t, *J* = 7.8 Hz, 1H), 7.24–7.40 (m, 6H), 7.47–7.50 (m, 2H).

*Compound **3c***. Oil. IR (nujol): ν = 3317, 2228 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.1 Hz, 3H), 1.25–1.53 (m, 4H), 2.74 (m, 2H), 4.77 (s, 1H), 7.36 (m, 3H), 7.62–7.70 (m, 2H).

*Compound **4d***. Oil. IR (nujol): ν = 3320, 2221 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 6.2 Hz, 6H), 2.07 (m, 1H), 2.51 (m, 2H), 3.20 (m, 1H), 4.72 (s, 1H), 7.34–7.53 (m, 5H).

*Compound **5e***. M.p. 61–63 °C. IR (KBr): ν = 3352, 2224 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.75 (s, 3H), 4.12 (broad d, *J* = 8.3 Hz, 1H), 5.31 (d, *J* = 8.3 Hz, 1H), 6.73 (d, *J* = 7.6 Hz, 2H), 6.82 – 6.95 (m, 2H), 7.10–7.21 (m, 4H), 7.30 (t, *J* = 7.6 Hz, 1H).

*Compound **6f***. Oil. IR (nujol): ν = 3321, 2221 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.83 (broad s, 1H), 3.76 (s, 3H), 3.95 (q, *J* = 13 Hz, 2H), 4.65 (s, 1H), 6.86 (m, 1H), 7.22 (m, 2H), 7.25–7.39 (m, 6H).

*Compound **7g***. Oil. IR (nujol): ν = 3320, 2222 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.93 (t, *J* = 7.1 Hz, 3H), 1.52 (m, 4H), 2.84 (m, 2H), 3.71 (s, 3H), 4.77 (s, 1H), 6.87 (m, 1H), 7.07–7.13 (m, 2H), 7.26 (t, *J* = 9.8 Hz, 1H).

Compound ***8h***. M.p. 110–112 °C. IR (KBr): ν = 3407, 2235 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.02 (s, 1H), 5.40 (s, 1H), 6.77 (d, J = 8.0 Hz, 2H), 6.92 (t, J = 7.9 Hz, 1H), 7.15 (t, J = 7.9 Hz, 2H), 7.37 (d, J = 7.8 Hz, 2H), 7.60 (d, J = 8.0 Hz, 2H).

Compound ***9i***. M.p. 77–78 °C. IR (KBr): ν = 3305, 2227 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 3.91 (s, 1H), 5.41 (s, 1H), 6.77 (d, J = 8.0, 2H), 6.90 (t, J = 7.8, 1H), 7.20–7.33 (m, 4H), 7.50 (d, J = 8.0, 2H), 7.52 (d, J = 8.0, 2H).

Compound ***10j***. M.p. 69–71 °C. IR (KBr): ν = 3357, 2236 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 4.06 (d, J = 8.1 Hz, 1H), 5.41 (d, J = 8.1 Hz, 1H), 6.43 (m, 1H), 6.57 (m, 1H), 6.79 (d, J = 8.0 Hz, 2H), 6.93 (t, J = 7.9 Hz, 1H), 7.27 (t, J = 7.9 Hz, 2H), 7.41 (m, 1H).

Compound ***11k***. Oil. IR (nujol): ν = 3326, 2223 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.96 (broad s, 1H), 3.93 (q, J = 12.8 Hz, 2H), 4.73 (s, 1H), 6.28 (m, 1H), 7.15–7.46 (m, 7H).

Compound ***12l***. Oil. IR (nujol): ν = 3326, 2223 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.04 (broad s, 1H), 3.96 (q, J = 13 Hz, 2H), 4.91 (s, 1H), 6.94–6.99 (m, 1H), 7.20–7.43 (m, 7H).

Compound ***13m***. M.p. 118–120 °C. IR (KBr): ν = 3351, 2231 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 3.81 (d, J = 8.1 Hz, 1H), 5.08 (m, 1H), 6.31 (m, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.91 (t, J = 7.9 Hz, 1H), 7.10 (m, 1H), 7.26–7.47 (m, 8H).

Compound ***14n***. Liquid. IR (nujol): ν = 3408, 2232 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.92 (t, J = 6.7 Hz, 3H), 1.18–1.40 (m, 12H), 1.51–1.67 (m, 2H), 1.81–1.90 (m, 2H), 3.79 (broad s, 1H), 4.04–4.12 (m, 1H), 6.62 (d, J = 8.0 Hz, 2H), 6.82 (t, J = 7.9 Hz, 1H), 7.21 (t, J = 7.9 Hz, 2H).

Compound ***15o***. M.p. 67–70 °C. IR (KBr): ν = 2225 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 2.52–2.64 (m, 4H), 4.70–4.81 (m, 5H), 7.33–7.56 (m, 5H).

Compound ***16p***. Oil. IR (nujol): ν = 3315, 2220 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.51–2.00 (m, 10H), 3.90 (s, 2H), 7.31–7.44 (m, 5H).

Compound ***17q***. Oil. IR (nujol): ν = 3313, 2217 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.95 (t, J = 7.0 Hz, 3H), 1.20–2.00 (m, 14H), 2.36 (t, J = 6.3 Hz, 1H), 2.72 (t, J = 6.6 Hz, 2H).

Compound ***18r***. Oil. IR (nujol): ν = 3316, 2221 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.96 (d, J = 6.4 Hz, 3H), 1.15–2.09 (m, 9H), 3.91 (s, 2H), 7.21–7.35 (m, 5H).

Compound ***19s***. M.p. 57–59 °C. IR (KBr): ν = 2214 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.95 (d, J = 6.1 Hz, 3H), 1.20–1.31 (m, 2H), 1.60–1.85 (m, 5H), 2.17–2.28 (m, 2H), 2.61–2.68 (m, 4H), 3.72 (t, J = 4.6 Hz, 4H).

RESULTS AND DISCUSSION

Catalysts characterization

The primary structure of PW/KSF was identified by comparing its FTIR absorbance bands to those of bulk PW. Keggin PW consisting of a PO_4 tetrahedron surrounded by four W_3O_{13} groups formed by edge-sharing octahedral. These groups are connected to each other by corner-sharing oxygens [28]. This arrangement gives rise to four types of oxygen bands at *ca.* 1080 cm^{-1} (P-O in central tetrahedral), 985 cm^{-1} (terminal W=O), 890 and 814 cm^{-1} (W-O-W) associated with the asymmetric vibrations in the Keggin polyanions. FTIR of KSF supported PW indicates that the primary Keggin structure is preserved after supporting PW on supports. Characteristic peaks of PW/KSF are observed at about 1076, 984, 904 and 804 cm^{-1} (Figure 1). It should be emphasized that some bands are overlapped with those of the supports.

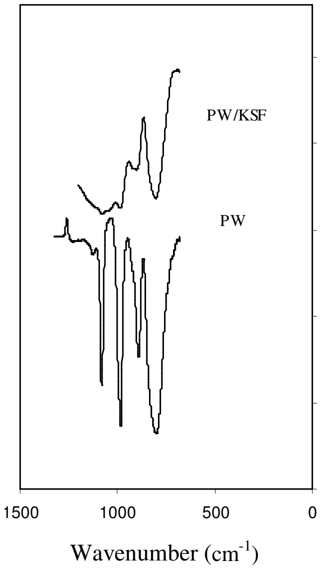
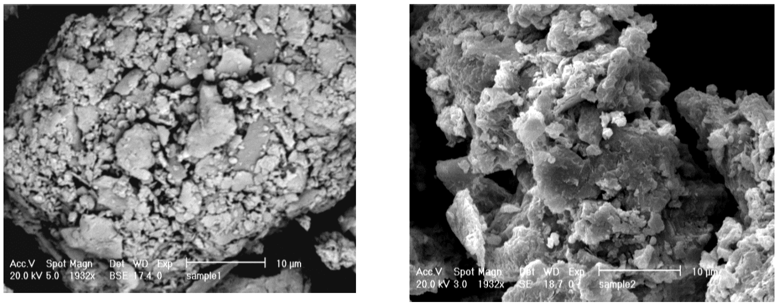


Figure 1. FTIR spectra of 40 wt.% PW/KSF and PW.

The SEM image of the gross morphology of the samples, KSF only and PW/KSF are displayed in Figure 2. It was observed that PW particles were randomly distributed over the support surface. It should be noted that PW layer formed in the present work was constituted by several aggregates of PW particles and not by a continuous film.



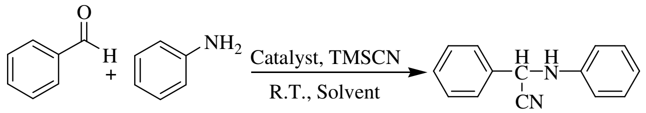
(a) (b)

Figure 2. SEM images of (a) KSF; (b) 40 wt.% PW/KSF.

Catalytic reaction

The blank experiment, in the absence of catalyst, showed that the presence of the catalyst is essential in the Strecker reaction (Table 1, entry 1). Thus, initial optimizations were carried out using different KSF supported HPA catalysts in the reaction of benzaldehyde, aniline, and TMSCN. Usually, tungsten HPAs are preferred over molybdenum ones as acid catalysts because of their stronger acidity, low reducibility, and higher thermal stability [28]. All the three supported HPAs gave excellent results in comparison with KSF only, with using lower amount of catalyst (Table 1, entries 2-5). To establish the optimal conditions, a set of experiments varying the weight percent of PW, catalyst loading, and solvent were carried out (Table 1, entries 5-12). Further studies showed that increasing the amount of PW on KSF to 60 wt.% could not improve the reaction yield significantly (entries 5-7). Inspired by the results, catalyst loading has been changed from 0.2 to 0.4 g, and 0.2 g of the catalyst was chosen as an ideal amount (entries 5, 8, 9). The reaction proceeded smoothly at room temperature in acetonitrile, dichloromethane, THF, and benzene to afford 2-anilino-2-phenylacetonitrile. Among these solvents, acetonitrile gives the best yield. Thus, 0.2 g of 40 wt. % of PW/KSF gives the best result in acetonitrile as solvent at room temperature.

Table 1. Effect of different catalysts under different reaction conditions for condensation of benzaldehyde, aniline and TMSCN.



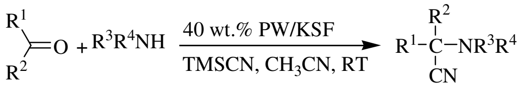
Entry	Catalyst	Solvent	Yield (%)[a]	Time (min)
1	-	CH_3CN	90	180 [16]
2	KSF (1.0 g)	CH_2Cl_2	90	210 [7]
3	40% PMo/KSF (0.2 g)	CH_3CN	94	2
4	40% SiW/KSF (0.2 g)	CH_3CN	95	2
5	40% PW/KSF (0.2 g)	CH_3CN	98	2
6	20%PW/KSF (0.2 g)	CH_3CN	96	5
7	60%PW/KSF (0.2 g)	CH_3CN	98	2
8	40% PW/KSF (0.1 g)	CH_3CN	94	5
9	40% PW/KSF (0.4 g)	CH_3CN	98	1
10	40% PW/KSF (0.2 g)	CH_2Cl_2	71	15
11	40% PW/KSF (0.2 g)	C_6H_6	33	15
12	40% PW/KSF (0.2 g)	THF	64	15

[a] Isolated yield.

Similarly, a variety of aldehydes were coupled with a range of amines and TMSCN to produce corresponding α-aminonitriles in 92-98% yields. Both aromatic and aliphatic aldehydes afforded excellent yields with PW/KSF. In the presence of PW/KSF ketones are readily coupled to give corresponding α-aminonitriles in excellent yields (Table 2, entries 16-19), whereas ketones did not give any satisfactory results in the presence of KSF as catalyst [7]. Aliphatic and cyclic secondary amines as well as aromatic amines underwent the reaction to give corresponding products in short reaction times and excellent yields. Notably, reaction conditions are mild, that cinnamaldehyde provided corresponding α-aminonitrile in 97% yield (Table 2, entry 13) with no formation of α-cyanoenamine, which would be derived via double bond migration. Also, furfuraldehyde and thiophene-2-carboxaldehyde worked well without any decomposition or polymerization (Table 2, entries 10-12). The results in Table 2 illustrated the scope and generality of this method with respect to various substrates.

After reaction completion, PW/KSF was recovered by filtration, washed with acetonitrile and reused in subsequent reactions. Only a slight decrease in the yield of the 2-anilino-2-phenylacetonitrile from 98% to 90% was observed after the fourth time, which is due to coke deposition during the reaction (6 wt.% of carbon) (Figure 3). FTIR of the supported PW was checked after catalyst preparation and catalytic reaction. The Keggin structure of PW/KSF remains unchanged in this mild reaction conditions which is proved by FTIR of the catalyst.

Table 2. KSF-supported $H_3PW_{12}O_{40}$ catalyzed synthesis of α-aminonitriles.



$$R^1R^2C{=}O + R^3R^4NH \xrightarrow[\text{TMSCN, CH}_3\text{CN, RT}]{\text{40 wt.\% PW/KSF}} R^1\text{-}C(R^2)(CN)\text{-}NR^3R^4$$

Entry	Aldehyde/ketone	Amine	Product	Time (min)	Yield (%)[a]
1	Benzaldehyde	Aniline	**1a**	2	98
2	Benzaldehyde	Benzylamine	**2b**	5	98
3	Benzaldehyde	Butylamine	**3c**	35	83
4	Benzaldehyde	Isobutylamine	**4d**	150	98
5	3-Methoxybenzaldehyde	Aniline	**5e**	2	98
6	3-Methoxybenzaldehyde	Benzylamine	**6f**	15	98
7	3-Methoxybenzaldehyde	Butylamine	**7g**	10	98
8	4-Chlorobenzaldehyde	Aniline	**8h**	2	92
9	4-Methylbenzaldehyde	Aniline	**9i**	3	94
10	Furfural	Aniline	**10j**	4	94
11	Furfural	Benzylamine	**11k**	1	98
12	Thiophene-2-carboxaldehyde	Benzylamine	**12l**	15	98
13	Cinamaldehyde	Aniline	**13m**	15	98
14	Decanal	Aniline	**14n**	15	98
15	Benzaldehyde	Morpholine	**15o**	40	97
16	Cyclohexanone	Benzylamine	**16p**	30	90
17	Cyclohexanone	Butylamine	**17q**	90	95
18	3-Methyl cyclohexanone	Benzylamine	**18r**	30	98
19	3-Methyl cyclohexanone	Morpholine	**19s**	30	95

[a] Isolated yield.

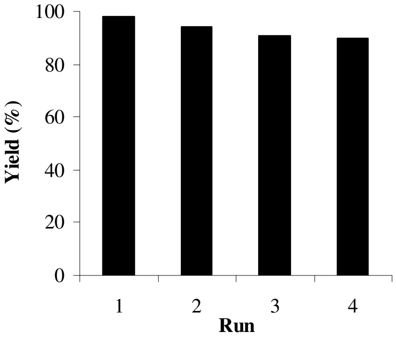


Figure 3. Reusability of 40 wt.% PW/KSF.

The catalytic efficiency of montmorillonite KSF clay was substantially enhanced in one-pot synthesis of α-aminonitriles, reducing the reaction time as well as increasing the yield of the products. Thus, the present method serves as an improvement over certain protocols in terms of the ambient quality, eco-friendly nature and catalyst economy. Excellent yields, simple work-up, mild reaction conditions, very short reaction times, survival of different functional groups, and the ability to tolerate a variety of aldehydes, ketones, and amines are some features of this new procedure. Also, supported PW is non-toxic, stable, inexpensive, and reusable catalyst.

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