$H_{14}[NaP_5W_{30}O_{110}]$ as an Efficient Catalyst for the One-Pot Synthesis of α-Amino Nitriles

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Abstract: In this study, the synthesis of some α-amino nitriles is reported. The compounds were prepared by the nucleophilic addition reaction of aldehydes and amines with TMSCN in the presence of a catalytic amount of $H_{14}[NaP_5W_{30}O_{110}]$, Preyssler's heteropoly acid, in excellent yields. The catalyst can be recovered and reused in subsequent reactions.

Key words: α-amino nitriles, heteropoly acids, TMSCN, trimethylsilyl cyanide

α-Amino nitriles are very useful and important intermediates for the synthesis of α-amino acids[1] and many nitrogen-containing heterocycles,[2] such as imidazoles and thiadiazoles.

There are many methods reported in the literature for the preparation of α-amino nitriles.[3–14] The most important route for the synthesis of α-amino nitriles is the Strecker reaction.[15] The classical Strecker reaction is generally carried out with alkaline cyanides in aqueous solution. However, most of these methods involve the use of expensive reagents, long reaction times, strongly acidic conditions and tedious work-up procedure leading to the generation of a large amount of toxic waste. Considering these facts, there is still a need to introduce new catalysts for this conversion.

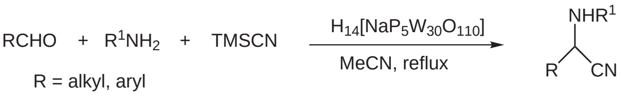
A variety of cyanating agents such as α-trimethylsiloxy nitriles and diethylphosphorocyanidate have been used for the preparation of α-amino nitriles under various conditions.[3,16] Trimethylsilyl cyanide (TMSCN) is a safe, easy-to-handle and very effective cyanide anion source for the synthesis of α-amino nitriles.[17]

Heteropoly acids (HPAs) have been extensively studied as acid and oxidation catalysts for many reactions and found industrial application in several processes. HPAs are promising solid acids to replace environmentally harmful liquid acid catalysts such as H_2SO_4.[18]

Due to their acidic and redox properties, heteropoly compounds (heteropoly acids and their salts) are useful and versatile catalysts in a number of transformations.[19]

Recently, we reported that 12-tungstophosphoric acid a type of heteropoly acid, to catalyze the Biginelli reaction for the synthesis of 3,4-dihydropyrimidiones.[20]

As part of our ongoing research in heterogeneous catalysis,[21] we present here an efficient and simple strategy to prepare differently substituted α-amino nitriles directly from aldehydes, amines and TMSCN, in a one-pot procedure catalyzed by Preyssler's heteropoly acid, $H_{14}P_5$ (Scheme 1). The use of the heteropoly acid, $H_{14}P_5$, which is nontoxic, noncorrosive, eco-friendly and easily available, is an interesting feature of the process.



Scheme 1

The reaction of benzaldehyde and aniline with TMSCN in the presence of a catalytic amount of $H_{14}P_5$ afforded the corresponding 2-(*N*-anilino)-2-phenylacetonitrile in 96% yield. Similarly, the methodology applied to a variety of aldehydes gave in all cases very good results with benzylic and aromatic amines.

We found that the best reaction conditions require the presence of a small amount of $H_{14}P_5$ (0.02 g, 0.003 mmol), aldehyde (1 mmol), amine (1 mmol) and TMSCN (1.2 mmol) in refluxing MeCN. The obtained results are summarized in Table 1.

The catalyst is very active, stable to air and moisture, nontoxic, and inexpensive. In addition, it can be quantitatively recovered by filtration, reactivated and reused. Both aromatic and aliphatic aldehydes afforded excellent yields. The results summarized in Table 1 clearly indicate the scope and generality of the reaction with respect to various aldehydes and amines.

In conclusion, the present procedure describes the useful one-pot synthesis of α-amino nitriles catalyzed by heteropoly acid. It introduced $H_{14}P_5$ as a new catalyst, which is as efficient as the other catalysts. Excellent yields, recyclability of the catalyst with no loss in its activity, simple experimental procedure and product isolation, use of nontoxic, noncorrosive and inexpensive catalyst are important features of this new protocol to prepare α-aminonitriles. We believe that it is a useful addition to the existing methods.

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Table 1 Heteropoly Acid Catalyzed Synthesis of α-Amino Nitriles with TMSCN

Entry	Aldehyde	Amine	Time (h)	Yield (%)	Mp (°C)	
					Found	Reported
1	Benzaldehyde	Aniline	3	97	72–73	73–74[8]
2	4-Chlorobenzaldehyde	Aniline	5.5	94	108–112	109–112[8]
3	3-Methoxybenzaldehyde	Benzylamine	5	96	Yellow oil	–
4	4-Methylbenzaldehyde	Aniline	4.5	95	75–77	76–78[8]
5	4-Methoxybenzaldehyde	Aniline	5	96	93–95	94–95[8]
6	Benzaldehyde	Benzylamine	4.5	95	Oil	Oil[12]
7	Cynamaldehyde	Aniline	5	93	116–118	117–119[8]
8	Isobutyraldehyde	Benzylamine	5.15	91	Yellow oil	–
9	Isobutyraldehyde	Aniline	4.5	92	125–127	–
10	4-Chlorobenzaldehyde	Benzylamine	4.5	94	Oil	Oil[22]
11	4-Methylbenzaldehyde	Benzylamine	5	95	Oil	Oil[22]

The major advantage of this method is that it is truly a one-pot procedure that does not require a separate step to prepare an imine for subsequent use.

All products were identified by comparison of their physical and spectroscopic data with those of authentic samples.[7,8,10–12]

Synthesis of α-Amino Nitriles – General Procedure

A mixture of an aldehyde (1 mmol), amine (1 mmol), TMSCN (1.2 mmol) and catalyst $H_{14}P_5$ (0.02 g, 0.003 mmol) in MeCN (5 mL) was refluxed for the indicated time (Table 1) under vigorous stirring. The progress of the reaction was monitored by TLC. After filtration and washing of the catalyst with MeCN, the solvent was removed under reduced pressure and the crude product was purified by column chromatography over silica gel (hexane–Et_2O) or recrystallized from absolute EtOH to obtain the pure product (Scheme 1).

Spectral and Physical Data for Selected Compounds

2-(*N*-Benzylamino)-2-(3-methoxyphenylacetonitrile (Entry 3)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 (br s, 1 H), 3.76 (s, 3 H), 3.95 (AB, q, *J* = 13.0 Hz, 2 H), 4.65 (s, 1 H), 6.85 (dd, *J* = 2.4, 9 Hz, 1 H), 7.14–7.36 (m, 2 H), 7.28–7.43 (m, 6 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.6, 53.9, 55.7, 113.4, 114.8, 119.2, 119.8, 128.5, 129.7, 128.8, 130.4, 136.7, 138.6, 160.4. MS (EI): *m/z* = 252 [M$^+$], 122, 91, 77.

2-(*N*-Benzylamino)-2-isopropylacetonitrile (Entry 8)

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08 (d, *J* = 6.5 Hz, 3 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.56 (br s, 1 H), 1.97–2.02 (m, 1 H), 3.24 (d, *J* = 6.0 Hz, 1 H), 3.80 (d, *J* = 13.0 Hz, 1 H), 4.07 (d, *J* = 13.0 Hz, 1 H), 7.24–7.43 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.2, 19.3, 31.3, 51.8, 56.3, 119.3, 127.5, 128.4,128.7, 138.4. MS (EI): *m/z* = 188 [M$^+$].

2-(*N*-Anilino)-2-isopropylacetonitrile (Entry 9)

IR (KBr): 3346, 2234 cm^{-1}.

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