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Original article

Propylphosphonic anhydride (T3P®) catalyzed one-pot synthesis of α-aminonitriles

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ABSTRACT

The Strecker reaction was performed *via* a one-pot three component condensation of hetero aromatic/aromatic aldehydes, secondary amines and trimetylsilyl cyanide in the presence of propylphosphonic anhydride (T3P®) to accomplish the corresponding α-aminonitriles. The main advantages of this method are very short reaction time and excellent yields.

1. Introduction

The Strecker reaction [1] provides one of the most efficient methods for the synthesis of α-aminonitriles, which are useful intermediates in the preparation of many amino acids and various nitrogen containing heterocycles such as imidazoles, thiadiazoles, *etc.* [2] and other biologically useful molecules such as saframycin-A, a natural product with antitumor activity, or phthalascidin, a synthetic analog, which exhibits even greater potency [3]. They are usually prepared by the nucleophilic addition of a cyanide anion to imine intermediates. Numerous methods have been reported describing the preparation of α-aminonitriles [4–15]. The classical Strecker reaction is generally carried out with hydrogen cyanide or alkaline cyanides in aqueous solution. To overcome these limitations, several modifications of the Strecker reaction have been reported [16]. These modifications use alternative cyanating sources, such as hydrogen cyanide (HCN) [17], potassium cyanide (KCN) [18], sodium cyanide (NaCN), trimethylsilyl cyanide (TMSCN) [19], diethylphosphorocyanidate ($(OEt)_2P(O)CN$) [20], bis(dialkyl amino cyano)borans, diethyl aluminum cyanide (Et_2AlCN) [21] and tributyltin cyanide (Bu_3SnCN), *etc.* [22] under various reaction conditions. Among these cyanide agents, trimethylsilyl cyanide, has proven to be relatively safe, easy to handle, highly soluble in organic solvents, and more effective as a cyanide anion source for the nucleophilic addition of imines under mild conditions compared to other cyanating reagents [23]. Other modifications to the Strecker reaction use catalysts, such as $InCl_3$ [24], $BiCl_3$ [25], montmorillonite KSF clay [26], silica bonded scandium (III) [27], SO_4/ZrO_2 [28], ferric perchlorate [29], $Fe(Cp)_2PF_6$ [30], InI_3 [31], I_2 [32], $K_5CoW_{12}O_{40}·3H_2O$ [33], vanadyl triflate [34], Fe_3O_4 [35], guanidine hydrochloride [36], xanthan sulfuric acid [37], $[bmim]BF_4$ [38], silica sulfuric acid [39], hydrophobic sulfonic acid based nanoreactors [40] and silica-bonded *S*-sulfonic acid [41] under various conditions. However, many of these protocols suffer from disadvantages such as strongly acidic conditions, unsatisfactory yields, and longer reaction times in addition to tedious aqueous workups leading to the generation of a large amount of toxic waste and use of stoichiometric or relatively expensive reagents. Therefore, there is motivation to explore a milder, safer, and more efficient catalyst for the synthesis of α-aminonitriles within short reaction times. T3P® is a well known green coupling reagent and a powerful water scavenger with several advantages, including low toxicity, low allergic potential, broad functional group tolerance, generation of products in excellent yield, purity, and easy workup procedures due to the formation of water soluble byproducts [42–44]. Furthermore T3P® has been investigated extensively in the preparation of various heterocyclic compounds.

Though several works focused on the synthesis of α-aminonitriles have been reported, the preparation of α-aminonitriles from

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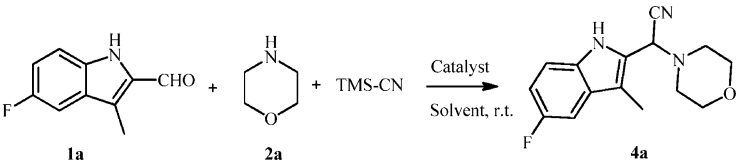
Table 1
Comparison of previously reported catalysts with our catalyst.[a]



1a **2a** **4a**

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]
1	I_2 (20)	Acetonitrile	2	70
2	L-proline (20)	Acetonitrile	4.5	79
3	Fe_3O_4 (15)	–	30 min	87
4	$InCl_3$ (30)	THF	5	80
5	$NiCl_2$ (5)	Acetonitrile	10	82
6	$BiCl_3$ (10)	Acetonitrile	7.5	80
7	Nafion® 117 (300 mg)	Acetonitrile	10	85
8	Montmorillonite KSF clay (1 g)	DCM	4	83
9	[Bmim]BF_4 (1 mL)	–	5	85
10	[Bmim]PF_6 (1 mL)	–	5	85
11	T3P (20) present work	Acetonitrile	5 min	95

[a] Reaction conditions: **1a** (1 mmol), morpholine (1.1 mmol) and trimethylsilyl cyanide (1.2 mmol) in acetonitrile (7 mL).
[b] Isolated yield after column purification.

the reaction of heterocyclic aldehydes has not been extensively explored. Owing to their synthetic and biological value, there is a need to find new, accessible, cheaper, and more efficient approaches to the synthesis of α-aminonitriles. Heterocyclic skeletons serve as ideal scaffolds on which pharmacophores can be appended to yield potent and selective drugs. In view of this research and our desire to develop α-aminonitrile structures, we have designed and synthesized a series of α-aminonitriles with different heterocyclic and aromatic aldehydes. Herein, we report for the first time the finding of our investigations for the synthesis of α-aminonitriles (**4a**–**t**) by one-pot three-component coupling of various heterocyclic aldehydes/aromatic aldehydes, secondary amines, and trimethylsilyl cyanide catalyzed by commercially available, inexpensive propylphosphonic anhydride (T3P®).

2. Experimental

All reactions were performed under nitrogen conditions in anhydrous solvents such as acetonitrile, dichloromethane, and tetrahydrofuran. All reactions were monitored by TLC analysis using Merck silica gel 60 F_{254} plates with fluorescent indicator (254 nm) and visualized with a UV lamp. All commercially available reagents such as 5-fluoro-3-methyl-1*H*-indole-2-carbaldehyde, 4-(4-morpholinyl) benzaldehyde, 6-bromopicolinaldehyde, thiophene-2-carbaldehyde, 5-bromo thiophene-2-carbaldehyde, and propylphosphonic anhydride (≥50 wt% in ethyl acetate) were procured from Aldrich, Across Organics, and Apollo Scientific companies and used as received without further purification.

Melting points were recorded on Mel-Temp apparatus and are uncorrected. All the infrared spectra of the title compounds were recorded on a Bruker Alpha-Eco ATR-FTIR (Attenuated total reflection-Fourier transform infrared) interferometer with a single reflection sampling module equipped with ZnSe crystal. ^{1}H NMR and ^{13}C NMR were recorded on Bruker DRX 400 and 500 MHz spectrometers using TMS as internal standard. Chemical shifts (δ) are reported in ppm. Coupling constants are reported in Hz. Mass spectra were recorded on a Finnigan MAT 1020 mass spectrometer operating at 70 eV.

2.1. General procedure

To a stirred solution of 5-fluoro-3-methyl-1*H*-indole-2-carbaldehyde (177 mg, 1 mmol) and morpholine (96 mg, 1.1 mmol) in acetonitrile (7 mL) was added trimethylsilyl cyanide (119 mg, 1.2 mmol) followed by T3P (63 mg, 20 mol%) at ambient temperature. The reaction mixture was stirred for an approximate time and monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (3× 15 mL). The organic layers were combined, washed with brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting residue was purified by using 100–200 mesh silica and eluting with 13%–15% ethyl acetate in *n*-hexane to afford pure 2-(5-fluoro-3-methyl-1*H*-indol-2-yl)-2-morpholinoacetonitrile as a solid (**4a**) in 95% (263 mg) yield. This procedure is applied to the other reactions (**4b**–**t**).

3. Results and discussion

To find the best reaction conditions, we first examined the effect of the catalyst for the Strecker three component reaction of 5-fluoro-3-methyl-1*H*-indole-2-carbaldehyde (**1a**), morpholine (**2a**) and trimethylsilyl cyanide in presence of T3P® (20 mol%) at an ambient temperature as a model reaction, and the corresponding 2-(5-fluoro-3-methyl-1*H*-indol-2-yl)-2-morpholinoacetonitrile (**4a**) was obtained in 95% yield (Table 1). This is because of rapid formation and activation of imine intermediate with T3P® and formation of water soluble by-products. A set of experiments were

Table 2
Effect of the catalyst and solvent on the synthesis of α-aminonitriles.[a]

Entry	T3P (mol%)	Solvent	Time (h)	Yield (%)[b]
1	No catalyst	Acetonitrile	12	0
2	5	Acetonitrile	2	60
3	10	Acetonitrile	1	67
4	15	Acetonitrile	20 min	80
5	20	Acetonitrile	5 min	95
6	25	Acetonitrile	5 min	95
7	20	$CHCl_3$	30 min	78
8	20	DCM	30 min	78
9	20	THF	1	60
10	20	DMSO	1.5	45
11	20	H_2O	10	NR
12	20	–	10	NR
13	20	Toluene	40 min	69

[a] Reaction of **1a** (1 mmol), morpholine (1.1 mmol) and trimethylsilyl cyanide (1.2 mmol) in acetonitrile (7 mL).
[b] Isolated yield after column purification.
NR: no reaction.