

Phosphotungstic Acid Catalyzed One-Pot Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in Aqueous Media

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Summary: In this study, we report the one-pot synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines with benzaldehyde, malononitrile, and thiophenol by using phosphotungstic acid as an efficient catalyst in aqueous media. This method has the advantages of easy separation, high storage stability, and environmental friendliness.

Keywords: Malononitrile; Thiophenol; Phosphotungstic acid.

Introduction

Pyridine derivatives have diverse biological activities [1]. Among these derivatives, 2-amino-3,5-dicyano-6-pyridine derivatives have drawn considerable attention since its special biological activity [2-5]. These compounds can inhibit the accumulation of PrP^{Sc} in the regulation of androgenic receptor [6], scrapie-infected mouse neuroblastoma cells [7], and PK-2 activated by MAPK [8]. Furthermore, these compounds act as a regulator of the identity of potassium channels in the treatment of incontinence [9]. 3,5-Dicyano-2-amino-6-thio-pyridine skeletons are available in anti-prion [8], anti-SARS-CoV [10], and anti substrates [8]. These compounds are recognized as potential targets for new drug development in the treatment of Parkinson's disease, senile dementia, neurovascular, asthma, hypoxia, epilepsy, cancer and renal disease [7, 11].

Heteropoly acid is the general term for oxygen acid composed of heteroatomic and multiatomic molecules through an oxygen atom bridging ligand [12-14]. Heteropoly acid dissolves in small molecule polar solvents such as water, ethanol, and acetone [15], and does not dissolve in macromolecular polar solvents or nonpolar solvents. Heteropoly acid has a unique acidity, and the acid can be adjusted by changing the composition of elements [13]. It has strongly acidity and redox properties and the advantages of stable structure, easy loading, high-speed regeneration, high activity, noncorrosive, low pollution, easy modification, and "pseudo-liquid phase" behavior, among others [16-19]. Hence, heteropoly acid shows high catalytic activity in numerous reactions in gas-solid and liquid-solid systems. Heteropoly acid is a type of environmentally

friendly green catalyst [20].

The most widely used and studied types of heteropoly acid are phosphotungstic acid and silicon tungstate [21]. Phosphotungstic acid has both complex and metal oxide structures [22]. Phosphotungstic has high activity because of its unique "pseudo-liquid phase" behavior, which enables reactions to be conducted both on the surface of the catalyst and inside the catalyst. Phosphotungstic acid has strong acidity and maintains a stable Keggin structure [23] in solids and in solutions. As an acid catalyst, phosphotungstic acid has high catalytic activity, good selectivity, and can be used in mild conditions [24-26]. Phosphotungstic acid has been widely used in homogeneous and non-homogeneous reactions because of its high acid strength and thermal stability.

The most important methods is the three component condensation of aldehyde, malononitrile, and mercaptan [27] in the synthesis of 3,5-2 cyano-2-amino-6-pyridine derivatives. The condensation in an alkaline environment, commonly uses alkali including Et₃N, triethylene-diamine [28], dinitrogen complex [29], tetrabutyl-ammonium hydroxide, piperidine [30], pyrrolidine, *N,N*-diisopropyl ethyl amine, pyridine, dimethyl-amino-pyridine, aniline, *N*-methyl aniline, *N,N*-dimethyl aniline, K₂CO₃ [31], zinc (II), and Cd (II) metal-organic frameworks [32]. Furthermore, basic ionic liquids such as [bmim]OH [33], [bmim]Br [34] and 2-hydroxyethylammonium acetate (2-HEAA) [35] can also be used as effective catalysts for the synthesis of multi-substituted pyridine.

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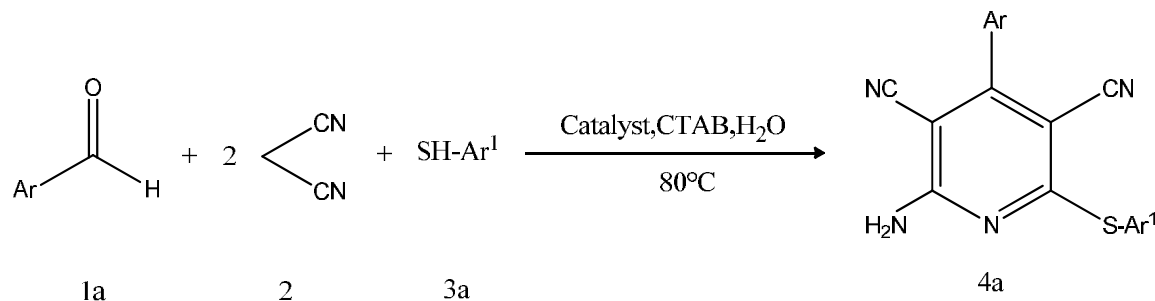
However, some synthetic methods have many shortcomings, such as by-product generation, long reaction time, low yield, and harsh reaction condition, and complex reaction process, expensive or noxious catalysts. In a recent study, the three component condensation reaction in acidic catalysts (e.g., $ZnCl_2$ [36], H_3BO_3 [37]) under catalysis, has a better catalytic effect than alkali catalysis. Given that Lewis acid is sensitive to moisture, a small amount of water will remove its catalytic activity. Thus, we try to learn the influence of hydrosoluble acid catalyst to replace pyridine synthesis.

In the last few years, more and more researchers have attached importance to green chemistry for organic synthesis because of environmental friendly [38, 39]. In the current study, we report the preparation of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in aqueous media through one-pot synthesis by using phosphotungstic acid as a valid catalyst. The reaction will take a long time to finish without surfactants because reactants are insoluble in water. Hence, we used cetyltrimethylammonium bromide (CTAB) as the surfactant owing to its ability to reduce the surface tension of aqueous phase and organic phase. This method will increase the relative concentration of reactants (Scheme-1).

Results and Discussion

Different Structures of Reactants

We used benzaldehyde, malononitrile, and thiophenol in the experiment under the condition of condensation reaction, to synthesize 3,5-dicyano-2-amino-6-thio-pyridine derivatives. The effect of the different structures of the reactants was studied at 80 °C by varying the substituted aromatic aldehydes with thiophenol for condensation reaction. The result is shown in Table-1



Scheme-1: Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.

Reaction Conditions

Concentration of the Catalyst

To determine the appropriate dosage of phosphotungstic acid catalyst, benzaldehyde (1mmol), malononitrile (2mmol), thiophenol (1mmol), CTAB, and different concentrations of catalysts were mixed at 80°C. The yield increased with increasing catalyst concentration. If the catalyst concentration ranges from 0.5 to 1.5 mol%, the reaction will be complete, with yields of 63%, 76% and 85%. If the concentration reaches 2 and 2.5mol%, both yields will be 89%.

Effect of Solvents

To evaluate the effects of solvents on the reaction, we used benzaldehyde (1mmol), malononitrile(2mmol), thiophenol(1mmol), CTAB, and phosphotungstic acid as reactants. The reaction was conducted under 80°C in different solvents. We used isopropanol, ethanol, water-ethanol (70%), and water for the reference reaction. We found that isopropyl alcohol makes the reaction stay at the Knoevenagel condensation level, and we obtained yields of 44% and 56% in the ethanol and water-ethanol (70%) systems. By contrast, we obtained perfect yield of 89% in aqueous media.

Amount of Solvent

To determine the effect of the amount of solvents on the yield, we conducted a reaction in different water volumes. The result is shown in Table-2. We conclude that the yield increased with the increasing amount of water. However, the yield decreased when the volume of water was more than 5mL. Hence, the best amount of water is 5mL.

Table-1: Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines.

Number	Product	Ar	Ar ¹	Traditional heating		Melting point(°C)	Melting point(°C) [ref]
				Time (min)	Yield (%)		
1	4a	Ph	Ph	35	86	204-205	215-216 [27]
2	4b	4-Cl-Ph	Ph	30	82	219-220	222-224 [33]
3	4c	4-OH-Ph	Ph	40	80	311-313	314-317 [27]
4	4d	4-NO ₂ -Ph	Ph	35	84	288-289	284-286 [27]
5	4e	4-Me-Ph	Ph	45	93	207-209	208-211 [33]
6	4f	4-OMe-Ph	Ph	45	89	253-254	250-252 [33]
7	4g	4-CHO-Ph	Ph	40	70	178-179	179-180 [27]
8	4h	4-OH-3-OMe-Ph	Ph	35	87	214-216	216-217 [33]
9	4i	Ph	4-NH ₂ -Ph	40	83	226-228	224-226 [3]
10	4j	4-Cl-Ph	4-NH ₂ -Ph	35	87	232-235	234-236 [3]
11	4k	4-CHO-Ph	4-NH ₂ -Ph	30	72	169-171	168-170 [3]
12	4l	4-NO ₂ -Ph	4-NH ₂ -Ph	40	86	206-208	203-206 [3]
13	4m	4-OH-3-OMe-Ph	4-NH ₂ -Ph	50	90	233-235	232-235 [3]
14	4n	4-Me-Ph	4-NH ₂ -Ph	35	81	230-232	233-235 [3]
15	4o	4-OMe-Ph	4-NH ₂ -Ph	45	85	206-208	205-206 [3]
16	4p	4-OH-Ph	4-NH ₂ -Ph	45	78	168-170	167-170 [3]

Reaction conditions: reactant molar ratio=1:2:1, CTAB (10 mol%), water(5ml) and phosphotungstic acid (2 mol %), the temperature was 80 °C.

Table-2: Effect of the dosage of solvent on yield.

Number	Volume (mL)	Yield (%)
1	1	62
2	3	77
3	5	89
4	7	83
5	9	80

Reaction conditions: benzaldehyde (1mmol), malononitrile (2mmol), thiophenol (1mmol), CTAB (10 mol%) and phosphotungstic acid (2 mol %), the temperature was 80 °C.

Table-3: Reactants proportion effect on the reaction.

n(benzaldehyde):n(malononitrile):n(thiophenol)	1 2 1	1 2 2	2 2 1	2 : 2 : 2
Yield (%)	89	78	63	85

Reaction conditions: CTAB (10 mol%), water(5ml) and phosphotungstic acid (2 mol %), the temperature was 80 °C.

Ratio of the Reactants

After we choosing the appropriate catalyst and solvents, we studied the effect of the ratio of reactants on the reaction. The different reactant molar ratios were as follows: 1:2:1, 1:2:2, 2:2:1, and 2:2:2 (benzaldehyde: malononitrile: thiophenol). The result is shown in Table-3. We can obtain the highest yield when the molar ratio is 1:2:1.

Effect of Temperature

Through the experiment, we have learned that the formation of the product increased with temperature and reached the highest yield at 80°C. From a dynamic point of view, the reason why we obtain a low yield at low temperature is because the acid center cannot activate the reactants, thus leading to a low rate of positive and reverse reaction. However, a high temperature (>80 °C) is adverse to exothermic reactions.

Experiment

Chemicals and Apparatus

All reactants and solvents were

commercially available and were used as received without purification. Melting points were measured by using an XRC-1 melting point apparatus. Melting points were recorded on an electrothermal apparatus and uncorrected. A TLC thin-layer board with silica gel GF254 (Qingdao Marine Chemical Inc.) and 0.6% sodium hydroxymethyl cellulose self-control, was directly used without activation for thin-layer chromatograph and were observed under UV light.

General Procedure

The reaction was a mixture of aromatic aldehyde (1mmol), malononitrile (132mg, 2mmol), substituted thiophenol (1mmol), phosphotungstic acid (2mol %), CTAB (10 mol %) and water (5 mL) in a 50mL round bottom flask. The reaction temperature was maintained at 80°C by using an oil bath (TLC monitors, silica gel, ethyl acetate, and hexyl alcohol = 1:7 v/v). After completion of the reaction, the round bottom flask was removed and the product was cooled to room temperature. The product was then filtered by using an air pump and washed with a small amount of water to obtain the crude product. With 95% ethanol recrystallization, the products were

dried in an oven and weighed. All products were fully characterized by infrared (IR) and melting points, consistent with existing literature.

Conclusion

In conclusion, we developed a environmental, expedite, and efficient method for the synthesis of 2-amino-3,5-dicyano-6-thio pyridine derivatives by using phosphotungstic acid as a green catalyst.

The reaction can perform efficiently if we use 2mol% phosphotungstic acid as catalyst, 5mL water as solvent, CTAB as surfactant, and a 1:2:1 reactant molar ratio (aromatic aldehyde: malononitrile: substitutedthiophenol) under 80°C. We made repeated trials in optimal conditions, the reactants are benzaldehyde, malononitrile, thiophenol, yield respectively are 87%, 90%, 88%, our experiment result is 89%, it is little different between them, so the experiment has good reproducibility. We think the catalytic mechanism is the structure of phosphotungstic acid. Benzaldehyde reaction with malononitrile predominantly resulted in formation of the Knoevenagel [27], at this moment the proton provided by phosphotungstic acid can promote the reaction. PW12 is by heteroatomic P and coordination atoms W in a structure through the oxygen atoms of ligand bridging oxygen polybasic acid. It has the structure of complexes and metal oxide, also have acidity and oxidation. Compared with traditional acid catalyst, the phosphotungstic acid used as a catalyst has the advantages of high activity, high storage stability, easy separation, no emulsification, and no pollution. The process is environmental protection and economically feasible.

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