Tetrahedron Letters 51 (2010) 1309–1312

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Boric acid catalyzed convenient synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines in aqueous media

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ARTICLE INFO

Article history:
Received 5 December 2009
Revised 23 December 2009
Accepted 25 December 2009
Available online 7 January 2010

Keywords:
Aldehyde
Malononitrile
Thiophenol
Boric acid
Aqueous media
Ultrasonication

ABSTRACT

A one-pot three-component condensation of an aldehyde, malononitrile, and thiophenol has been achieved by conventional and ultrasound method. The reaction has been catalyzed by boric acid in aqueous medium. This protocol afforded corresponding 2-amino-3,5-dicarbonitrile-6-thio-pyridines in shorter reaction times and high yields with the green aspects by avoiding toxic catalysts and solvents.

1. Introduction

Organic synthesis in aqueous media is rapidly gaining importance in view of the fact that the use of many toxic and volatile organic solvents contributes to pollution. Since the pioneering studies by Breslow[1] on Diels–Alder reactions, there have been profound research activities in the development of organic reactions in aqueous media offering key advantages such as rate enhancement and insolubility of the final products, which facilitates their isolation by simple filtration. Also, in the context of green chemistry, aqueous media is acting as a stepping stone in the greener synthesis of bioactive heterocyclic compounds.

For many chemical processes, a major adverse effect to the environment is the consumption of energy for heating and cooling. To overcome such problems, it is highly enviable to develop efficient methods that utilize alternative energy sources such as ultrasound and microwave irradiation to facilitate chemical reaction. Ultrasound technique has increasingly been used in organic synthesis in the recent years. Ultrasonic irradiation enhances the chemical reaction via the process of acoustic cavitation.[2] The assistance of ultrasonic irradiation efficiently shortens the reaction times. Simple experimental procedure, very high yields, increased selectivities, and clean reaction of many ultrasound-induced organic transformations offer additional convenience in the field of synthetic organic chemistry.[3] The chemical effects resulting from the irradiation of aqueous solutions with ultrasound were first time introduced by Loomis and co-workers.[4]

The pyridine ring systems represent the major class of heterocycles and their analogues exhibit diverse biological and physiological activities.[5] In particular, 2-amino-3,5-dicarbonitrile-6-thio-pyridines serves as 'privileged scaffold' due to their potential therapeutic applications.[6–13] These compounds were reported to inhibit PrP^{Sc} accumulation in scrapie-infected mouse neuroblastoma cells (ScN2a),[6a] MAPK-activated PK-2,[6b] IKK-2 for treating HBV infection,[6c] and modulate androgen receptor function.[6d] In addition, they serve as potassium channel openers for the treatment of urinary incontinence.[7] 2-Amino-3,5-dicarbonitrile-6-thio-pyridines skeleton is often used as *anti*-prion,[6a,8] *anti*-hepatitis B virus,[9] *anti*-bacterial,[10] and *anti*-cancer[11] agents. Recently, some of these compounds have been recognized as potential targets for the development of new drugs for the treatment of Parkinson's disease, hypoxia, asthma, kidney disease, epilepsy, cancer,[12] and Creutzfeldt–Jacob disease.[6a,8a,13]

A three-component condensation of aldehyde, malononitrile, and thiol is one of the most prominent existing procedure used for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines. Generally, this condensation has been carried out under basic conditions using various bases such as, Et_3N, DABCO,[8a,14a,b] piperidine, morpholine, thiomorpholine, pyrrolidine, *N,N*-DIPEA, pyridine, 2,4,6-collidine, DMAP, aniline, *N*-methylaniline, *N,N*-dimethylaniline, and *N,N*-diethylaniline.[14b] Moreover, basic ionic liquid 1-methyl-3-butylimidazolium hydroxide, that is, [bmim]OH,[14c] DBU[14d] and TBAH[14e] were also found to be an efficient basic cata-

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0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.146

lysts for the synthesis of such polysubstituted pyridines. However, most of these methods suffer by the formation of inevitable side products, which results in lower yield of desired product.

Recently, this three-component condensation has been carried out using Lewis acid catalyst ($ZnCl_2$)[15] which shows better results when compared to the base-catalyzed reactions. Inspired by this report, we focused our attention on acid catalysts for the said reaction. However, Lewis acids are moisture sensitive; they loose their catalytic activity in the presence of water.[16] Therefore, we decided to study the effect of water-soluble acid catalysts for the synthesis of polysubstituted pyridines.

Boric acid is a water soluble catalyst and has been found to be effective in various organic transformations such as esterification of hydroxycarboxylic acids,[17a] aza Michael,[17b] thia Michael[17c] addition, and bromination.[17d] In our previous work, we have used it for the synthesis of 2,5-disubstituted-1*H*-triarylimidazole[18a] and 1,1-diacetate.[18b]

In continuation of our interest toward the exploitation of boric acid as a catalyst in organic synthesis[18] and development of new synthetic methodologies[18,19] herein, we wish to report a one-pot multicomponent synthesis of highly substituted pyridines. Experimental procedure is simple and has been achieved by the reaction of aryl/heteroaryl aldehydes, malononitrile, and substituted thiophenols using boric acid and cetyl trimethyl ammonium bromide (CTAB) in aqueous medium by conventional and non-conventional method (Scheme 1).

In search of the best experimental reaction conditions, the reaction of benzaldehyde **1a**, malononitrile **2,** and thiophenol **3a** in the presence of CTAB as a surfactant in aqueous medium was considered as a standard model reaction (Scheme 2).

In the absence of surfactant, the reaction takes longer time for completion and leads to a sticky product due to the insolubility of substrates in water which may cause them to react slowly. Hence we have decided to employ surfactant (CTAB); since it reduces the interfacial tension between organic and aqueous layer, and increases the concentration of substrates due to formation of micelle particles in water.[16]

When the reaction was carried out in the absence of catalyst the product formed in a very trace amount (Table 1, entry 1). In the next step, we have screened different water-soluble catalysts for the model reaction viz sulfamic acid, oxalic acid, EDTA·2Na salt, and boric acid. With the use of sulfamic acid the product was formed in poor yields, 42% (Table 1, entry 2). Whereas using oxalic acid and EDTA·2Na salt the product was obtained in moderate 53% and 61% yields, respectively (Table 1, entries 3–4). In comparison with these, boric acid proved to be most efficient catalyst which gave higher yield (78%) within 40 min (Table 1, entry 5).

Table 1
Screening of catalysts

Entry	Catalyst	Time (min)	Yield[a] (%)
1	—	120	Trace
2	Sulfamic acid	120	42
3	Oxalic acid	120	53
4	EDTA·2Na	120	61
5	Boric acid	40	78

Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol), CTAB (10 mol %), Catalyst (10 mol %) in water (5 mL) at 80 °C.
[a] Isolated yields.

Table 2
Effect of concentrations of catalyst

Entry	Boric acid (mol %)	Yield[a] (%)
1	5	67
2	10	78
3	15	90
4	20	90

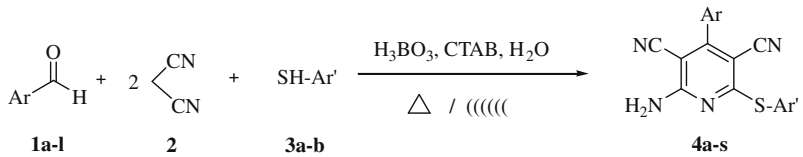
Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol), CTAB (10 mol %), in water (5 mL) at 80 °C for 40 min.
[a] Isolated yields.

Table 3
Screening of solvents

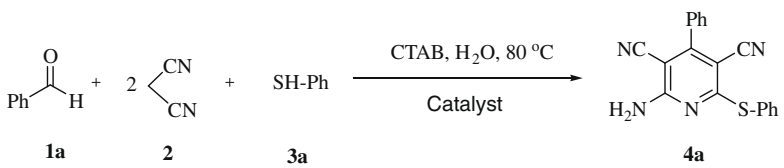
Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (%)
1	Isopropyl alcohol	80	3	—
2	PEG-400	80	3	Trace
3	Ethanol	Reflux	3	46
4	Aq ethanol (70%)	Reflux	3	58
5	Water	80	40 min	90

Reaction conditions: **1a** (1 mmol), **2** (2 mmol), **3a** (1 mmol), CTAB (10 mol %), boric acid (15 mol %) in solvent (5 mL).
[a] Isolated yields.

The reaction was proposed to proceed[14a,b] via the Knoevenagel condensation of an aldehyde and malononitrile, followed by the Michael addition of second molecule of malononitrile on Knoevenagel product. This then reacts with thiophenol, and undergoes air oxidation to afford final product. As the reaction involves two major steps, Knoevenagel condensation and Michael addition; we were keen to know the time required for completion of these individual steps. In this analysis, we have carried out the model



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



Scheme 2. Standard model reaction.

Table 4
Synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines

Entry	Compd	Ar	Ar′	Conventional		Ultrasound		Mp[b] (°C)
				Time (min)	Yield[a] (%)	Time (min)	Yield[a] (%)	
1	**4a**	Ph	Ph	40	90	10	92	218–219
2	**4b**	4-Cl-Ph	Ph	35	86	10	91	222–223
3	**4c**	4-F-Ph	Ph	25	92	08	92	224–225
4	**4d**	4-OMe-Ph	Ph	40	85	10	90	242–243
5	**4e**	4-OH-Ph	Ph	45	82	12	86	314–316
6	**4f**	4-NO_2-Ph	Ph	35	84	10	83	290–291
7	**4g**	4-Me-Ph	Ph	40	90	12	93	208–210
8	**4h**	4-OH-3-OMe-Ph	Ph	40	91	13	92	216–218
9	**4i**	3,4-OMe-Ph	Ph	45	92	12	92	228–230
10	**4j**	Piperonyl	Ph	30	91	10	94	232–234
11	**4k**	2-Thienyl	Ph	35	79	12	86	208–210
12	**4l**	2-Furfuryl	Ph	35	82	12	85	176–178
13	**4m**	Ph	2-NH_2-Ph	40	85	11	84	224–226
14	**4n**	4-Cl-Ph	2-NH_2-Ph	30	87	10	88	234–236
15	**4o**	4-OMe-Ph	2-NH_2-Ph	40	84	12	89	230–232
16	**4p**	4-OH-Ph	2-NH_2-Ph	50	80	15	86	174–176
17	**4q**	4-NO_2-Ph	2-NH_2-Ph	40	86	11	88	206–208
18	**4r**	4-Me-Ph	2-NH_2-Ph	50	87	15	90	208–210
19	**4s**	4-OH-3-OMe-Ph	2-NH_2-Ph	40	90	13	94	234–236

[a] Isolated yields.
[b] Melting points match with literature reports.[14c,d,15]

reaction in two different steps using above-mentioned catalysts. It is worthy to point out that, the time required for Knoevenagel condensation is more in case of EDTA·2Na salt when compared to oxalic and sulfamic acid. Nevertheless it catalyzes the overall reaction fast. This is because, sulfamic and oxalic acids proceed fast to give Knoevenagel product but fail to carry out further steps efficiently. Finally, it was observed that boric acid catalyzes both steps quickly and stands out as a better catalyst.

To determine the appropriate concentration of the catalyst boric acid, we investigated the model reaction at different concentrations of boric acid such as 5, 10, 15, and 20 mol %. The product was formed in 67%, 78%, 90%, and 90% yield, respectively (Table 2). This indicates that 15 mol % of boric acid is sufficient to carry out the reaction smoothly.

In order to evaluate the effect of solvent, various solvents such as isopropyl alcohol, PEG-400, ethanol, aq ethanol (70%), and water were used for the model reaction in the presence of boric acid. Surprisingly, use of isopropyl alcohol stopped the reaction at Knoevenagel condensation step and no further reaction took place (TLC), while PEG-400 afforded insignificant yield of the desired product (Table 3, entry 2). Reaction in ethanol and aqueous ethanol resulted in moderate yields 46% and 58%, respectively. Whereas, water brought the reaction to completion efficiently to furnish the product in excellent 90% yield (Table 3, entry 5).

The model reaction was further investigated under ultrasound irradiation in the presence of boric acid with a view to explore whether, (i) the reaction could be expedited and, (ii) the product yield could be enhanced. In this case, no significant improvement in the product yield (92%) was observed, but the reaction time enormously reduced to 10 min when compared to conventional method (40 min).

In both methods, the temperature of 80 °C was chosen as optimum temperature. Any further increase in the temperature failed to enhance the reaction rate substantially, while lowering the temperature below 80 °C did slow down the reaction rate.

For assessing the generality of optimized reaction condition, a wide range of substituted aldehydes were allowed to undergo this three-component condensation. Aromatic aldehydes with several functionalities such as Cl, F, OH, Me, OMe, and NO_2 were found to be compatible under the optimized reaction condition. Heteroaromatic aldehydes such as thiophene-2-carbaldehyde and furan-2-carbaldehyde were equally amenable to these conditions (Table 4, entries 11–12). Ultrasound irradiation technique was also established to be compatible with all these substrates (Table 4). Representative results[20] are summarized in Table 4. Formation of the product was confirmed with the help of IR, ^{1}H NMR, and mass spectroscopic data.[21]

In conclusion, we have developed an expedient and clean protocol for the synthesis of 2-amino-3,5-dicarbonitrile-6-thio-pyridines. The use of ultrasound irradiations has decreased the reaction time. This method has the advantages of a wide scope of substrates, operational simplicity, easy work-up procedure, shorter reaction times, and high yields.

2. Experimental

Melting points were determined on a Veego apparatus and are uncorrected. Infrared spectra were recorded on a Bruker spectrophotometer in a KBr disc, and the absorption bands are expressed in cm^{-1}. ^{1}H NMR spectra were recorded on a Varian AS 400 MHz spectrometer in DMSO-d_6, chemical shifts (δ) are in (parts per million) ppm relative to TMS. Mass spectra were taken on a macro mass spectrometer (waters) by electro-spray (ES) method . Bandelin Sonorex (with a frequency of 35 KHz and a nominal power 200 W) ultrasonic bath was used for ultrasonic irradiation with Built-in heating, 30–80 °C thermostatically adjustable. The reaction vessel was placed inside the ultrasonic bath containing water.

Acknowledgment

The authors are thankful to The Head, Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad, for providing the laboratory facility.

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20. *Typical experimental procedure*:
Conventional method: A mixture of benzaldehyde **1a** (106 mg, 1 mmol), malononitrile **2** (132 mg, 2 mmol), thiophenol **3a** (110 mg, 1 mmol) and boric acid (15 mol %) in water (5 mL) was stirred at 80 °C in the presence of CTAB (10 mol %) for 40 min. Reaction progress was monitored by TLC (ethyl acetate/*n*-hexane, 1:7). After completion of reaction, the solid product was collected by simple filtration and washed with water. The crude product (**4a**) was recrystallized from ethanol to obtain pure product.
Ultrasound method: A mixture of benzaldehyde **1a** (106 mg, 1 mmol), malononitrile **2** (132 mg, 2 mmol), thiophenol **3a** (110 mg, 1 mmol) and boric acid (15 mol %) in water (5 mL) was subjected to ultrasound irradiation at 80 °C in the presence of CTAB (10 mol %) for 10 min After completion of reaction, as monitored by TLC (ethyl acetate/*n*-hexane, 1:7) the solid product was collected by simple filtration and washed with water. The crude product (**4a**) was purified by recrystallization from ethanol.
21. *Spectroscopic data*:
Compound (**4a**): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.29–7.37 (m, 6H), 7.64–7.71 (m, 4H), 8.13 (br s, 2H); IR (KBr, cm^{-1}): ν 3367, 3244, 3061, 2219, 1630, 1548, 1251, 1032, 747; ES-MS: 329.09 (M+1).
Compound (**4j**): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.12 (s, 2H), 7.00–7.13 (m, 3H), 7.46–7.57 (m, 5H), 7.72 (br s, 2H); IR (KBr, cm^{-1}): ν 3458, 3338, 3229, 2907, 2217, 1636, 1558, 1492, 1251, 1037, 825; ES-MS: 373.14 (M+1).
Compound (**4k**): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 7.26 (t, 1H), 7.46–7.58 (m, 6H), 7.79 (br s, 2H), 7.92 (d, 1H); IR (KBr, cm^{-1}): ν 3438, 3360, 3210, 2984, 2210, 1617, 1512, 1257, 1064, 722; ES-MS: 335.07 (M+1).
Compound (**4l**): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.68 (t, 1H), 7.24 (d, 1H), 7.32–7.42 (m, 5H), 7.60 (br s, 2H), 7.94 (d, 1H); IR (KBr, cm^{-1}): ν 3380, 3328, 3210, 2992, 2215, 1650, 1518, 1264, 1029, 766; ES-MS: 319.12 (M+1).
Compound (**4s**): ^{1}H NMR (DMSO-d_6, 400 MHz): δ 3.79 (s, 3H), 5.37 (br s, 2H), 5.42–7.24 (m, 7H), 7.56 (br s, 2H), 9.65 (br s, 1H); IR (KBr, cm^{-1}): ν 3473, 3348, 3290, 2958, 2212, 1625, 1533, 1281, 1020, 756; ES-MS: 390.04 (M+1).