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Synthesis of Novel 2H-Pyrano[2,3-D]Thiazole-6-Carbonitrile Derivatives in Aqueous Medium

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Research Article

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ABSTRACT

A one-pot efficient, green and environmentally friendly multicomponent synthesis of novel 5-amino-7-(substituted phenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile derivative in the presence of green, low cost, mild, efficient and commercially available potassium carbonate as the catalyst with water. This method has the advantages of high yield, simple, clean reaction, short reaction time and no use of hazardous organic solvents.

INTRODUCTION

The multicomponent synthesis have emerged as an efficient, powerful tool in modern organic chemistry for generation of highly diverse, complex product, high atom economy, high purity and better product yield. They are widely used in organic synthesis and medicinal chemistry because they are one-pot processes for assembling three or more component [1,2]. The 4*H*-pyrane nucleus is biologically important molecules possessing a wide spectrum of biological and pharmacological activities, such as antibacterial [3-5], antiviral [6,7], mutagenicity [8], antiproliferative [9], sex pheromone [10], antitumor [11,12], cancer therapy [12-14] and central nervous system activity [15]. Some of these compounds could also be used as inhibitors [15,16]. Some of 4*H*-pyranes refluxing for many hours in organic solvents, complex steps, which display strong biological activity including antibacterial, anticancer, and inhibitory are shown in **Figure 1.**

The conventional synthesis in previous work several methods have been reported for the preparation of tetrahydrobenzo[b] pyrans or dihydropyrano[c]chromenes, for example the microwave [17], ultrasonic irradiation [18]. In addition, there are several modified procedures using a variety of reagents, including the use of hexadecyldimethylbenzyl ammonium bromide (HDMBAB) [19], tetrabutylammonium bromide (TBAB) [20], fluoride ion [21], ionic liquids [22-24], rare earth perfluorooctanoate [RE(PFO)$_3$] [25], Na_2SeO_4 [26], high surface area MgO [27], nanosized MgO [28], solid acid [29,30], diammonium hydrogen phosphate [31,32], silica bonded n-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride [33], DBU [34] and $ZnFe_2O_4$ [35] as catalysts in a one-pot reaction.

However aforementioned methods suffer from the drawbacks such as low yields, long reaction times, expensive, unavailability, toxicity of the reagent, toxic solvents, tedious work-up procedures, additionally the main drawback of almost existing methods is that the catalysts are decomposed under aqueous work-up conditions and their recoveries are often impossible. Therefore,

to overcome these drawbacks a great deal of efforts is directed to develop an efficient, catalytic system for synthesis of these compounds.

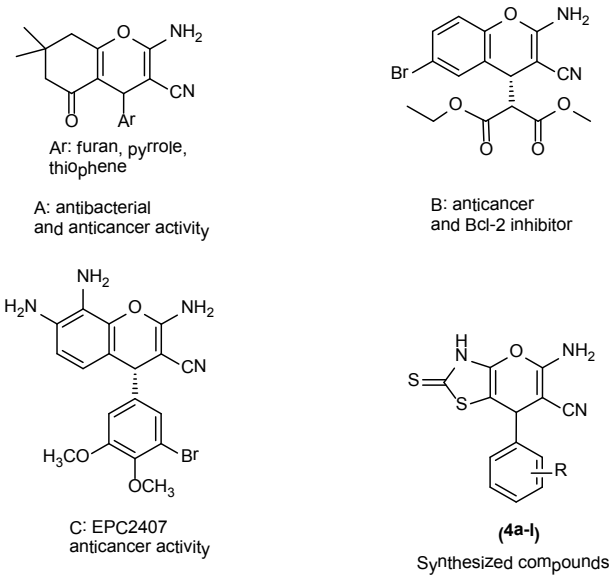


Figure 1. Previously reported biologically active agents, inhibitors and synthesized compounds.

Many of these procedures have merit, however, most require use of expensive catalysts and tedious work-up. We decided to investigate potassium carbonate for use as an organic catalyst for the synthesis of 5-amino-7-(substituted phenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile in aqueous medium.

In continuation of our work [36-42], we have developed the new protocol for the synthesis of pyrano derivatives. The potassium carbonate has eco-friendly nature, high reactivity, easy handling and easy work-up. It is a novel organic catalyst in the one-pot synthesis of a library of heterocyclic compounds. We have reported that potassium carbonate is an efficient catalyst in the reaction of aromatic aldehydes with malononitrile and 2-thioxothiazolidin-4-one in aqueous medium at 90°C.

EXPERIMENTAL

Experimental section

All chemicals, unless otherwise specified, were purchased from commercial sources and were used without further purification. The major chemicals were purchased from Sigma Aldrich and Avra labs. The development of reactions was monitored by thin layer chromatography (TLC) analysis on Merck pre-coated silica gel 60 F254 aluminum sheets, visualized by UV light. IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. The ^{1}H NMR spectra were recorded on a 400 MHz Varian NMR spectrometer. The ^{13}C were recorded on a 100 MHz Varian NMR spectrometer. The chemical shifts are reported as NMR spectra δ_{ppm} units. The following abbreviations are used; singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer.

General procedure for the synthesis of compound (4a): In a 50 ml round bottom flask, the compounds 4-chlorobenzaldehyde **(1a)** (1 mmol), malononitrile **(2)** (1 mmol), 2-thioxothiazolidin-4-one **(3)** (1 mmol), catalyst (1 mmol) and solvent 1 mL, were added to the reaction mixture. The mixture was stirred under reflux condition for 2-15 h. The progress of the reaction was monitored by TLC (20% methanol: chloroform). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3 × 10 ml), dried, and purified by recrystallization in ethanol as solvent to give 40-98% yield.

General procedure for the synthesis of 5-amino-7-(substituted phenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4a-l): In a 50 ml round bottom flask, the compounds substituted benzaldehyde **(1a-l)** (1 mmol), malononitrile **(2)** (1 mmol), 2-thioxothiazolidin-4-one **(3)** (1 mmol), potassium carbonate (1 mmol) and water 1 mL, were added to the reaction mixture. The mixture was stirred under reflux condition for 2-4 h. The progress of the reaction was monitored by TLC (20% methanol: chloroform). After completion of the reaction, the reaction mixture was poured into the ice-cold water. The precipitate was filtered off and washed with water (3 × 10 ml), dried, and purified by recrystallization in ethanol as solvent to give 92-98% yield.

5-amino-7-(4-chlorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4a): Yellow solid, Yield: 98%, mp 230–232°C; ES-MS m/z (%): 320.85, IR vmax/cm^{-1}: 3240 (NH_2), 3213 (NH), 3020 (CH–Ar), 2250 (CN), 1603 (C=C), 1034 (C-S), 982 (C–N), 757 (C–Cl); ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.55 (s, 1H, CH), 6.40 (br, 1H, NH_2), 7.21 (d, *J*=8 Hz, 2H, Ar-H), 7.50 (d, *J*=8 Hz, 2H, Ar-H), 8.62 (br, 2H, NH), ^{13}C NMR (DMSO-*d6*): *δ*=39.5, 59.3, 71.2, 119.4, 128.4, 128.9, 130.1, 131.5, 147.6, 159.9, 188.2.

5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4b): Yellow solid, Yield: 94%, mp 195–197˚C; ES-MS m/z (%): 287.81, IR vmax/cm^{-1}: 3253 (NH_2), 3210 (NH), 3010 (CH–Ar), 2248 (CN), 1579 (C=C), 1137 (C-S), 980 (C–N). ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.25 (s, 1H, CH), 6.20 (br, 1H, NH_2), 7.20-7.30 (m, 5H, Ar-H), 8.45 (br, 2H, NH), ^{13}C NMR (DMSO-*d6*): *δ*=39.4, 59.7, 71.8, 119.3, 128.2, 128.7, 130.3, 131.2, 147.9, 159.2, 188.5.

5-amino-7-(2-chlorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4c): Yellow solid, Yield: 92%, mp 180–182˚C; ES-MS m/z (%): 320.85, IR vmax/cm^{-1}: 3240 (NH_2), 3214 (NH), 3011 (CH–Ar), 2242 (CN), 1553 (C=C), 1234 (C-S), 766 (C–Cl). ^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.70 (s, 1H, CH), 6.50 (br, 1H, NH_2), 7.22-7.25 (m, 3H, Ar-H), 7.60 (d, *J*=8 Hz, 1H, Ar-H), 8.60 (br, 2H, NH), ^{13}C NMR (DMSO-*d6*): *δ*=39.1, 59.2, 71.6, 119.7, 126.4, 127.4, 128.4, 128.9, 130.2, 131.5, 147.4, 159.3, 188.4.

5-amino-7-(4-methoxyphenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4d): Yellow solid, Yield: 94%, mp 135–137˚C; ES-MS m/z (%): 317.39, IR vmax/cm^{-1}: 3210 (NH_2), 3150 (NH), 3011 (CH–Ar), 2232 (CN), 1546 (C=C), 1014 (C-S), 1076 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.60 (s, 1H, CH), 3.85 (s, 3H, OH), 6.40 (br, 1H, NH_2), 6.90 (d, *J*=8 Hz, 2H, Ar-H), 7.12 (d, *J*=8 Hz, 2H, Ar-H), 8.50 (br, 2H, NH), ^{13}C NMR (DMSO-*d6*): *δ*=39.3, 55.2, 59.2, 71.3, 119.2, 126.7, 127.7, 128.5, 130.3, 131.6, 147.7, 188.4.

5-amino-7-(4-fluorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4e): Yellow solid, Yield: 92%, mp 198–200˚C; ES-MS m/z (%): 305.35, IR vmax/cm^{-1}: 3233 (NH_2), 3114 (NH), 3019 (CH–Ar), 2248 (CN), 1541 (C=C), 1017 (C-S), 1083 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.50 (s, 1H, CH), 6.30 (br, 1H, NH_2), 7.20 (d, *J*=8 Hz, 2H, Ar-H), 7.42 (d, *J*=8 Hz, 2H, Ar-H), 8.35 (br, 2H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=39.1, 59.2, 71.6, 119.7, 126.4, 127.4, 128.4, 130.2, 147.4, 159.3, 188.4.]

5-amino-7-(4-hydroxyphenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4f): Yellow solid, Yield: 92%, mp 224–226˚C; ES-MS m/z (%): 303.02, IR vmax/cm^{-1}: 3233 (NH_2), 3119 (NH), 3039 (CH–Ar), 2237 (CN), 1544 (C=C), 1018 (C-S), 1089 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.80 (s, 1H, CH), 5.40 (s, 1H, OH), 6.15 (br, 1H, NH_2), 6.90 (d, *J*=8 Hz, 2H, Ar-H), 7.02 (d, *J*=8 Hz, 2H, Ar-H), 8.45 (br, 1H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=39.1, 59.4, 71.2, 119.3, 126.1, 127.2, 128.7, 130.4, 147.7, 159.1, 187.4.

5-amino-7-(4-nitrophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4g): Yellow solid, Yield: 94%, mp 182–184˚C; ES-MS m/z (%): 332.35, IR vmax/cm^{-1}: 3238 (NH_2), 3111 (NH), 3009 (CH–Ar), 2233 (CN), 1548 (C=C), 1017 (C-S), 1083 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.95 (s, 1H, CH), 6.10 (br, 1H, NH_2), 7.30 (d, *J*=8 Hz, 2H, Ar-H), 8.12 (d, *J*=8 Hz, 2H, Ar-H), 8.62 (br, 2H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=39.1, 59.9, 71.6, 119.2, 126.4, 128.4, 130.2, 144.4, 148.3, 159.2, 188.4.

5-amino-7-(2,4-dichlorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4h): Yellow solid, Yield: 92%, mp 245–247˚C; ES-MS m/z (%): 356.25, IR vmax/cm^{-1}: 3253 (NH_2), 3112 (NH), 3026 (CH–Ar), 2238 (CN), 1544 (C=C), 1012 (C-S), 1063 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.96 (s, 1H, CH), 6.13 (br, 1H, NH_2), 7.11 (d, *J*=8 Hz, 1H, Ar-H), 7.25 (d, *J*=8 Hz, 1H, Ar-H), 7.56 (s, 1H, Ar-H), 8.60 (br, 1H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=34.**1**, 59.2, 71.6, 119.7, 126.4, 130.4, 131.2, 132.2, 135.4, 141.4, 147.2, 159.3, 188.4.

5-amino-7-(3-fluorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4i): Yellow solid, Yield: 96%, mp 251–253˚C; ES-MS m/z (%): 305.35, IR vmax/cm^{-1}: 3201 (NH_2), 3125 (NH), 3028 (CH–Ar), 2242 (CN), 1548 (C=C), 1019 (C-S), 1063 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.80 (s, 1H, CH), 6.12 (br, 1H, NH_2), 6.22 (s, 1H, Ar-H), 7.10-7.15 (t, 3H, Ar-H), 8.51 (br, 2H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=34.1, 59.2, 71.6, 119.7, 122.4, 132.4, 134.2, 132.8, 135.1, 141.2, 148.2, 158.3, 187.4.

5-amino-7-(2,4-dimethoxyphenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4j): Yellow solid, Yield: 94%, mp 171–172˚C; ES-MS m/z (%): 347.41, IR vmax/cm^{-1}: 3231 (NH_2), 3117 (NH), 3015 (CH–Ar), 2244 (CN), 1545 (C=C), 1016 (C-S), 1053 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 2.99 (s, 1H, CH), 3.06 (br, 1H, NH_2), 3.85 (s, 6H, OCH_3), 6.10 (s, 1H, Ar-H), 6.43 (d, *J*=8 Hz, 1H, Ar-H), 7.02 (d, *J*=8 Hz, 1H, Ar-H), 8.58(br, 2H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=33.1, 55.3, 56.4, 59.2, 71.8, 100.2, 106.2, 119.7, 126.4, 127.4, 128.2, 130.8, 147.4, 159.1, 188.2.

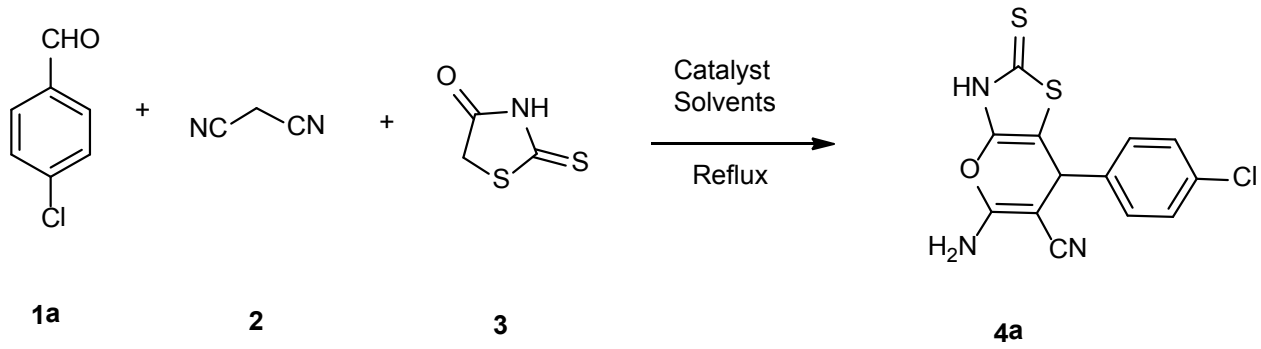
5-amino-7-(2-fluorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4k): Yellow solid, Yield: 96%, mp 175–177˚C; ES-MS m/z (%): 305.35, IR vmax/cm^{-1}: 3203 (NH_2), 3117 (NH), 3013 (CH–Ar), 2241 (CN), 1531 (C=C), 1117 (C-S), 1063 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*) δ: 3.92 (s, 1H, CH), 6.14 (br, 1H, NH_2), 7.10-7.22 (m, 4H, Ar-H), 8.55 (br, 2H, NH_2); ^{13}C NMR (DMSO-*d6*): *δ*=39.2, 59.5, 72.6, 115.5, 119.1, 124.4, 127.4, 128.2, 130.6, 147.2, 158.3, 161.2, 188.2.

5-amino-2-thioxo-7-(p-tolyl)-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4l): Yellow solid, Yield: 96%, mp 160–162˚C; ES-MS m/z (%): 301.39, IR vmax/cm^{-1}: 3223 (NH_2), 3115 (NH), 3016 (CH–Ar), 2249 (CN), 1521 (C=C), 1011 (C-S), 1081 (C–N).^{1}H NMR (400 MHz, DMSO-*d6*), δ: 3.35 (s, 3H, CH_3), 6.12 (br, 1H, NH_2), 4.35 (s, 1H, CH), 7.11 (d, *J*=8 Hz, 2H, Ar-H), 7.15 (d, *J*=8 Hz, 2H, Ar-H), 8.45 (br, 2H, NH); ^{13}C NMR (DMSO-*d6*): *δ*=21.2, 39.3, 59.1, 71.6, 118.7, 126.4, 127.4, 128.3, 130.2, 147.4, 159.3, 188.2.

RESULTS AND DISCUSSION

In our initial study, the evaluation of a series of 2*H*-pyrano derivatives **(4a-l)** was carried out from aromatic aldehydes with

malononitrile and 2-thioxothiazolidin-4-one in various solvents and catalyst **(Scheme 1).** The condensation reaction conducted in various solvents such as N,N-dimethylformamide (DMF), ethanol, toluene, acetic acid, methanol, water and catalyst such as potassium carbonate, ammonium acetate and piperidine gave the corresponding product in the range of 40-98% after 2-15 h **(Table 1).** The best result obtained using potassium carbonate with water to give a yield of 98% **(Table 1).**



1a **2** **3** **4a**

Reaction condition: 4-chlorobenzaldehyde (1a) (1 mmol), malononitrile (2) (1 mmol), 2-thioxothiazolidin-4-one (3) (1 mmol), catalyst (1 mmol), solvent 1 mL, reflux 2-15 h.

Scheme 1. Screening of model reaction of compound **(4a)**.

Table 1. Screening of catalyst, solvents, reaction time, and yield for the synthesis (4a)[a].

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)
1	Potassium carbonate	DMF	5	60
2	Potassium carbonate	Ethanol	4	64
3	Potassium carbonate	Toluene	5	75
4	Potassium carbonate	Acetic acid	4	70
5	Potassium carbonate	Methanol	4	65
6	Potassium carbonate	Water	2	98
7	Ammonium acetate	DMF	10	48
8	Ammonium acetate	Ethanol	13	40
9	Ammonium acetate	Toluene	14	40
10	Ammonium acetate	Acetic acid	12	40
11	Ammonium acetate	Methanol	13	45
12	Ammonium acetate	Water	10	60
13	Piperidine	DMF	15	42
14	Piperidine	Ethanol	14	47
15	Piperidine	Toluene	12	48
16	Piperidine	Acetic acid	10	48
17	Piperidine	Methanol	11	44
18	Piperidine	Water	10	62

[a]Reaction condition (4a): All the reaction was carried out in equimolar amounts of each compound in 1 mL of solvent.

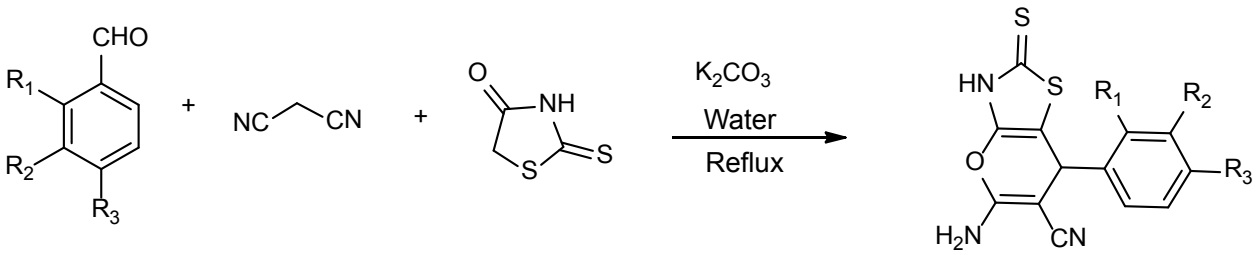
[b]Isolated yield.

Additionally, this condensation conducted in the presence of other solvents and catalyst gave corresponding product with slightly longer reaction time and lower yields **(Table 1).** The reaction with catalyst such as potassium carbonate gave good yield with all used solvents in the range of 60-98% **(Table 1).** The use of other catalyst such as ammonium acetate the result obtained with various solvents to give a yield of in the range of 40-60% after 10-14 h **(Table 1).** In this condensation conducted in the presence of solvents gave corresponding product with longer reaction time and lower yields **(Table 1).** The reaction with ammonium acetate and water as a solvent gave good yield of 60% after 10 h **(Table 1).** The used of other catalyst such as piperidine the result obtained with various solvents to give a yield of in the range of 42-62% after 10-15 h **(Table 1).** In this condensation conducted in the presence of used solvents gave corresponding product with longer reaction time and good yields **(Table 1).**

The reaction with piperidine and water as a solvent gave good yield of 60% after 10 h **(Table 1).** After preliminary experiments, it was found that a mixture of 2-thioxothiazolidin-4-one, 4-chlorobenzaldehyde and in malononitrile at reflux temperature in the presence of potassium carbonate with water afforded 5-amino-7-(4-chlorophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile **(Table 1)** in excellent yield 98% after 2 h.

All the reactions were carried out in equimolar amounts of each compound in 1 mL of solvent. Among these reactions same amounts of the solvent, namely 1 mL of water turned out to be the best choice with yields of 98%, 60% and 62% **(Table 1).** We would like to mention here that water as a solvent with potassium carbonate as catalyst was the best choice with a yield of 98% and less time required for the completion of the reaction **(Table 1).** Thus we decided to carry out the reactions in water with potassium carbonate.

We synthesized the novel series of 5-amino-7-(substituted phenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile **4a-l (Scheme 2; Table 2).** However, this reaction provided cleaner reaction, short reaction time, and the products were only required to be washed with ice-cold water. The yields were good to excellent.



1a-l **2** **3** **4a-l**

	R_1	R_2	R_3		R_1	R_2	R_3
1a, 4a =	H	H	Cl	**1g, 4g =**	H	H	NO_2
1b, 4b =	H	H	H	**1h, 4h =**	Cl	H	Cl
1c, 4c =	Cl	H	H	**1i, 4i =**	H	F	H
1d, 4d =	H	H	OCH_3	**1j, 4j =**	OCH_3	H	OCH_3
1e, 4e =	H	H	F	**1k, 4k =**	F	H	H
1f, 4f =	H	H	OH	**1l, 4l =**	H	H	CH_3

Reaction condition: Substituted aldehydes (1a-l) (1 mmol), malononitrile (2) (1 mmol), 2-thioxothiazolidin-4-one (3) (1 mmol), K_2CO_3 (1 mmol), water 1 mL, reflux 2-4 h.

Scheme 2. Synthesis of 5-amino-7-(substituted phenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile.

Table 2. Synthesis of 5-amino-7-(substituted phenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile (4a-l)[a].

Entry	Substituted aldehydes	Product	Time	Yield[b] (%)	M.P. (°C)
1	4-Chlorobenzaldehyde	4a	2	98	230-232
2	Benzaldehyde	4b	3	94	195-197
3	2-Chlorobenzaldehyde	4c	2	92	180-182
4	4-Methoxybenzaldehyde	4d	4	94	135-137
5	4-Fluorobenzaldehyde	4e	4	92	198-200
6	4-Hydroxybenzaldehyde	4f	3	92	224-226
7	4-Nitrobenzaldehyde	4g	2	94	182-184
8	2,4-Dichlorobenzaldehyde	4h	2	92	245-247
9	3-Fluorobenzaldehyde	4i	4	96	251-253
10	2,4-Dimethoxybenzaldehyde	4j	4	94	171-173
11	2-Fluorobenzaldehyde	4k	2	96	175-177
12	4-Methylbenzaldehyde	4l	3	96	160-162

[a]Reaction condition (4a-l): Potassium carbonate, Water, reflux 2-4 h.
[b]Isolated yields.

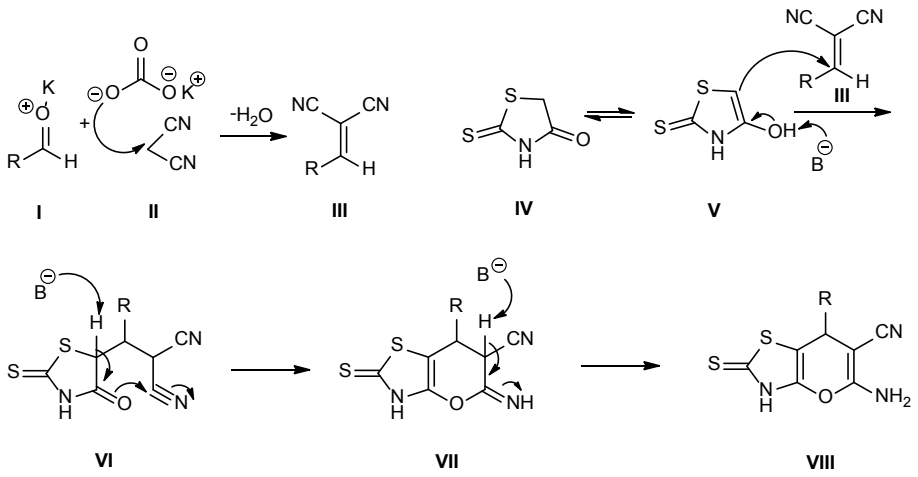
As shown in **Table 2**, this method worked a wide variety of substrates. A series of substituted aldehydes possessing either electron–withdrawing group or donating group reacted with malononitrile and 2-thioxothiazolidin-4-one under the optimized conditions to give the corresponding products in higher yields 92-98% after 2-4 h **(Table 2).**

A plausible mechanism for the reaction of 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile derivative is shown in **Scheme 3.** According to the mechanism compound I and compound **II** react to each other and formation of the compound **III** that is Knoevenagel product. The higher reactivity of the iminium ion compared to the carbonyl species facilitates Knoevenagel reaction between aryl aldehyde and malononitrile. In the presence of potassium carbonate the compound **III** react with the compound **IV** which was the enol form of the compound V, then formation of the cyclic product of **VI** and **VII** and finally got the target compound **VIII.**

CONCLUSION

We have developed a simple, highly efficient one pot three-component method for the synthesis of various 3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile derivatives by reaction of aromatic aldehydes, malononitrile and 2-thioxothiazolidin-4-

one with water in the presence of potassium carbonate. This procedure has many attractive features, such as simple method, high product yield, easy work-up and purification. Furthermore potassium carbonate and water are inexpensive and non-volatile making the method environmentally friendly and economically acceptable.



Scheme 3. A plausible mechanism for the formation of 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d]thiazole-6-carbonitrile derivative.

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