One pot synthesis of Pyrano [2,3-d][1,3]Thiazole-6-Carbonitrile Derivatives in Aqueous Medium

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Abstract
A one pot three-component condensation of rhodanine, malanonitrle and aryl aldehydes to generate a series of 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile derivatives. Reaction has been carried using magnetically separable $CuFe_2O_4$ nanoparticles in water as a green solvent at 90ºC. This methodology offers significant advantages with regard to the yield of products, simplicity in operation, and green aspects by avoiding toxic catalysts and solvents.

Keywords: Aromatic aldehydes, Rhodanine, Malanonitrile, Catalyst.

Introduction
Multicomponent reactions (MCRs) are one of the most important processes for the preparation of highly functionalized organic compounds in modern synthetic chemistry in which three or more reactants combined in a single chemical step to produce products that incorporate substantial portion of all the reactants. In recent years MCR becomes as an important tool in synthetic chemistry because of their high atom economy, energy efficiency, lower cost and simple purification technique. These reactions are effective in building highly functionalized small organic molecule and complex heterocyclic with high selectivity.[1] Therefore nowdays, MCR process has become an integral part of pharmaceutical chemistry as well as discovery of new life saving drugs.[2] Hence the development of novel and effective MCR protocols for synthesis of heterocyclic compound has attracted significant interest from heterogeneous catalyst, pharmaceutical group and scientific community across the world.[3]

5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile derivatives are biologically important molecules possessing a wide spectrum of biological and pharmacological activities, such as antibacterial, [4-6] antiviral, [7,8] mutagenicity, [9] antiproliferative, [10] sex pheromone, [11] antitumor, [12,13] cancer therapy, [13-15] central nervous system activity. [16] and some of these compounds could also be used as inhibitors. [17]
Analogously, antipyrine derivatives reacted with these derivatives gives attraction to the several research groups due their potential activities. [18-22] In this, a broad spectrum of bioactive derivatives have been investigated and diversities of bioactivities such as analgesic, [23, 24] anti-inflammatory, [25] antimicrobial, [26-28] and anticancer activity have been reported.[29]
In view of the immense biological significance of these heterocycles, many synthetic processes have been described and reported, for example the microwave, [30] ultrasonic irradiation. [31] In addition, there are several modified procedures using a variety of reagents, including the use of hexadecyldimethylbenzyl ammonium bromide (HDMBAB), [32] tetrabutylammonium bromide (TBAB), [33] fluoride ion, [34] ionic liquids, [35-37] rare earth perfluorooctanoate [$RE(PFO)_3$], [38] Na_2SeO_4, [39] high surface area MgO, [40] nanosized MgO, [41] solid acid, [42,43] diammonium hydrogen phosphate, [44,45] silica bonded n-propyl-4-aza-1-azoniabicyclo[2.2.2]octane chloride, [46] DBU, [47] and $ZnFe_2O_4$ [48] as catalysts in a one-pot reaction. But, many of the above methods suffer from limitations such as prolonged reaction time, high temperature and tedious work-up processes, low yield, hazardous reaction conditions are environmentally unacceptable from green chemistry view point

Having the above subjects in mind, we report here copper ferrite catalyze simple and highly efficient method for the one-pot synthesis for the formation of 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile derivatives. A green point of view, this method have many advantages shortened reaction time, high selectivity, recyclability of catalyst and excellent yield in water as solvent.

Material and Methods

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. 1H NMR spectra were recorded on BRUKER 500 MHz NMR Spectrophotometer using DMSO-*d*6 as solvent and TMS as an internal standard (chemical shifts in δ ppm).

Result & Discussion

$CuFe_2O_4$ nanoparticles were synthesized by sol gel method. The structural characterization of $CuFe_2O_4$ nanoparticles were done by X-ray Diffraction using CuKα radiation (λ = 1.54059 Å) at 40 kV and 15 mA shown in Fig.1

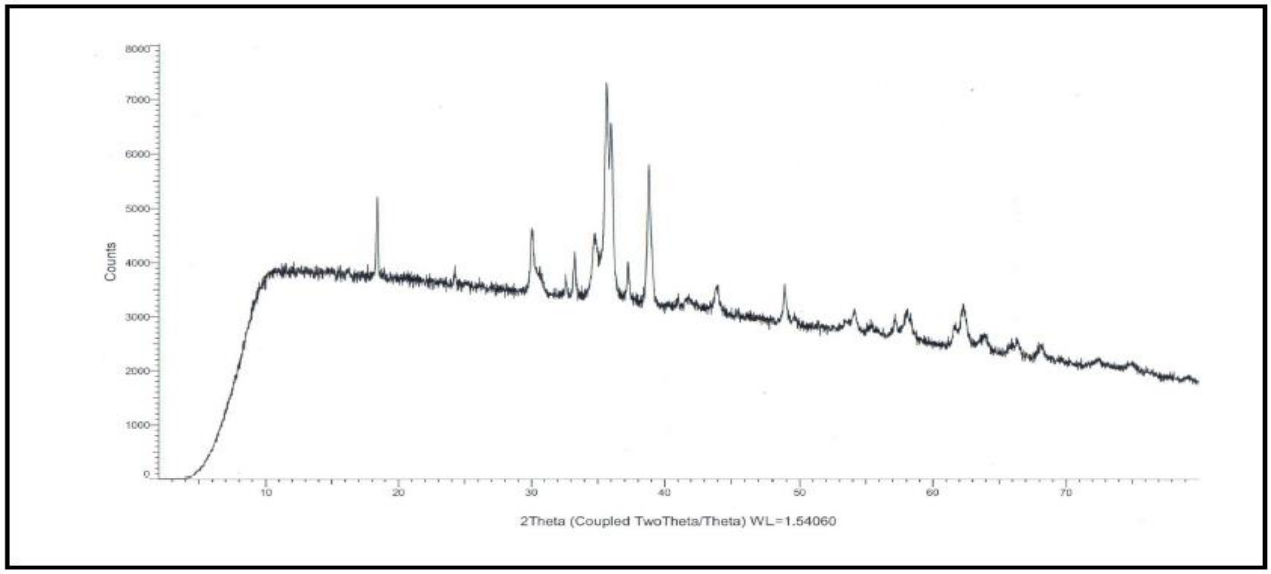


Fig 1. XRD patterns for $CuFe_2O_4$ nanoparticles sintered at 600°C.

Screening and Optimization of solvent.

(Table 1.) Synthesis of 5-amino-7-phenyl-2-thioxo-3, 7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitriles under different solvent systems at 90°C.

Entry	Solvent	Yield of product (%)	Time (min)
1	MeOH	82	120
2	EtOH	84	120
3	ETOH:Water	92	100
4	**Water**	**98**	**90**
5	DMF	85	120
6	EtOH: DMF(1:1)	86	180
7	DMSO	55	240
8	Toluene	40	300
9	Without solvent	20	360

Table 1. Reaction conditions: *Rhodanine (3mmol), malononitrile (3mmol), aryl benzaldehyde (3mmol), solvent (5ml), $CuFe_2O_4$ (0.03g), at 90°C.*

After optimizing the different solvent for the reaction, we found that water is the best solvent for the reaction. Almost, all the employed aromatic aldehydes resulted in high yield of the corresponding product.

In addition to the above, the effect of catalyst concentration was also studied shown in (Table2) Which indicated that 0.03g of the $CuFe_2O_4$ nanocatalyst was sufficient to catalyzed the reaction and increase the quantity of catalyst beyond this did not increase the yield.

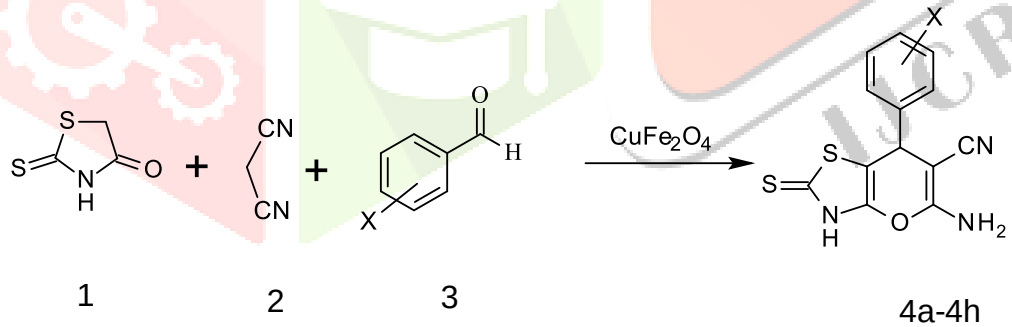
Screening and Optimization of catalyst.

Table .2. ***Effect of different quantity of catalyst on reaction*.**

Entry	Catalyst quantity (g)	Yield of product (%)
1	0.01	78
2	0.02	94
3	**0.03**	**98**
4	0.04	94
5	0.05	88

Table 2. Reaction conditions: *Rhodanine (3mmol), malononitrile (3mmol), aryl benzaldehyde (3mmol), water (5ml) for different concentration of $CuFe_2O_4$ catalyst.*

After optimizing the reaction conditions, we applied this catalyst for the synthesis of 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile derivatives using substituted aromatic aldehyde. Almost, all the employed aldehyde resulted in good to excellent yield of the corresponding product.



Scheme:

Rhodanine (3mmol), malanonitrile (3mmol), aromatic benzaldehyde (3mmol), water (5 ml) and $CuFe_2O_4$ (0.3g) nanoparticles in water at 90°C temperature.

5-amino-7-phenyl-2-thioxo-3, 7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitriles.

Preparation of library of substituted 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitriles. (Table 3)

Sr.No.	Ar	Product	Time/min	%Yield	M.P/°C Found	M.P/°C Reported
1	C6H5-	4a	90	98	194-196	195-197
2	3-NO2C6H4-	4b	90	96	186-188	186-188
3	4-NO2C6H4-	4c	85	98	181-183	182-184
4	4-ClC6H4-	4d	95	96	231-233	230-232
5	3-ClC6H4-	4e	90	95	182-184	180-182
6	4-OHC6H4-	4f	100	94	223-225	224-226
7	4-MeC6H4-	4g	100	96	162-164	160-162
8	MeOC6H4-	4h	110	96	135-136	135-137

***Reaction condition*: (Table 3.)** *rhodanine (3mmol), malanonitrile (3mmol), aromatic benzaldehyde (3mmol), water (5 ml) and $CuFe_2O_4$ (0.3g) nanoparticles in water at 90°C temperature.*

Experimental Section

General procedure for the preparation derivatives of *5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile*:

A mixture of rhodanine (3mmole), malanonitrile (3 mmol), various aromatic aldehydes (3 mmol), water (5ml) followed by $CuFe_2O_4$ NPs (0.03g) was stirred at 90°C for 90-110 min. Reaction mixture was monitored by TLC. After completion of reaction, filtered the solid which contained product and catalyst. Ethanol (10 mL) was added to the solid, warmed and filtered to separate the catalyst. Filtrate was evaporated followed by recrystallization from ethanol to afford the desired product. The separated catalyst was dried and reused for subsequent reactions.

5-amino-7-(4-nitrophenyl)-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile (4c)
IR (KBr, cm-1)

IR (KBr, cm−1): νmax 3463 (NH_2), 3134 (N-H), 2983 (C-H), 2193 (CN), 1673 (C=C), 1432 (NO_2), 1338 (C=S), 1020 (C-O), 801 (ArC-H).

^{1}H NMR (500MHz, DMSO-*d*6)

^{1}H NMR (500MHz, DMSO-*d*6) δ: 3.29 (s, 1H, CH), 6.19 (s, 2H, NH_2), 7.26 (s, 1H, NH), 7.73-8.29 (m, 4H, ArH)

^{13}C NMR (500 MHz, DMSO- *d*6, δ ppm)

^{13}C NMR (500 MHz, DMSO- *d*6, δ ppm): 8.59, 45.71, 120.82, 124.04, 130.26, 140.20, 141.83, 146.10, 182.94, 202.21

5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile (4a)
IR (KBr, cm-1)

IR (KBr, cm−1): νmax 3336 (NH_2), 3186 (N-H), 2852 (C-H), 2200 (CN), 1601 (C=C), 1194 (C=S), 763 (ArC-H).

^{1}H NMR (500MHz, DMSO-*d*6)

^{1}H NMR (500MHz, DMSO-*d*6) δ: 4.02 (s, 1H, CH), 5.28 (s, 2H, NH_2), 7.33 (s, 1H, NH), 7.53-7.66 (m, 5H, ArH)

^{13}C NMR (500 MHz, DMSO- *d*6, δ ppm)

^{13}C NMR (500 MHz, DMSO- *d*6, δ ppm): 14.06, 20.74, 59.73, 125.48, 127.89, 128.4, 128.95, 129.92, 130.44, 131.62, 132.93, 169.33, 195.66

Conclusion

1. A convenient one-pot procedure for the synthesis of 5-amino-7-phenyl-2-thioxo-3,7-dihydro-2H-pyrano[2,3-d][1,3]thiazole-6-carbonitrile derivatives by a three-component coupling reaction of rhodanine, aromatic aldehydes, and malanonitrile in the presence of a catalytic amount of magnetic $CuFe_2O_4$ as a reusable catalyst in the absence of any organic solvents or additives, has been developed.

2.Easy and clean work-up for the isolation of the products without any chromatographic purification, high atom economy, green solvent, reusability of the catalyst, short reaction time, excellent yields and environmentally benign procedures are the main advantages of this method.

Acknowledgement:

Authors are thankful to the Management of Guru Nanak College, Mumbai- 37 for constant encouragement and for providing necessary facilities.

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