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EFFICIENT ONE-POT SYNTHESIS OF PYRIDO[2,3-d]PYRIMIDINES CATALYZED BY NICKEL FERRITE NANOPARTICLES IN WATER

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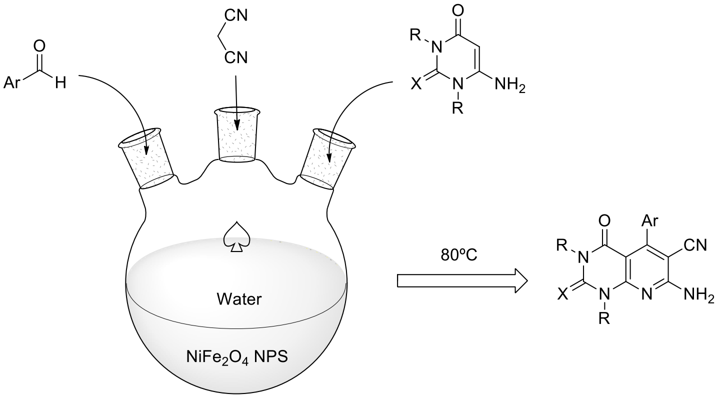
ABSTRACT:

A one pot three-component condensation of 6-aminouracil, 6-amino-2-thiouracil or 6-amino-1,3-dimethyluracil, with aryl aldehydes and malononitrile to generate a series of pyrido[2,3-d]pyrimidine derivatives has been carried using magnetically separable Nickel Ferrite nanoparticles in water as a green solvent at 80ºC. 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:
Pyrido[2,3-d]pyrimidine derivatives, One-pot synthesis, Nickel ferrite nanoparticles, Green chemistry, Multicomponent reaction

INTRODUCTION:

The need to reduce the amount of toxic waste and by-product arising from chemical processes requires increasing emphasis on the use of less toxic and environmentally compatible materials in the design of new synthetic methods. One of the most promising approaches is using water as the reaction media.[i–iv] The use of water as a solvent for organic transformations offers several "green chemistry" benefits. In many reactions, such as the Diels-Alder cycloaddition,[v] significant rate enhancements are observed in water compared to organic solvents. This acceleration has been attributed to many factors, including the hydrophobic effect,[vi–vii] enhanced hydrogen bonding in the transition state viii and the high cohesive energy density of water.[ix–x]

Uracil is one of the four nucleobases in the nucleic acid of RNA. Its chemistry and that of its derivatives e.g., 6-aminouracil, are very rich, as these molecules can act as both nucleophiles and electrophiles. Uracils are widespread in natural products and are of interest because of their biological properties.[xi] Uracil plays an important role in helping enzymes carry out different reactions to make polysaccharides. Since it helps enzymes carry out different reactions in cells, it can be of huge significance in drug development as it can help with delivering drugs throughout the body. Uracil has been found to be a common structural moiety of several bioactive compounds known for anti-inflammatory,[xii–xiii] antimicrobial,[xiv] analgesic,[xv] acaricidal,[xvi] and anticancer activities.[xvii] The diverse range of biological activities of uracil derivatives in parasitic chemotherapy has stimulated considerable interest in their synthesis.

6-Aminouracils are used as starting materials for the synthesis of heterocyclic frameworks of biological significance such as pyrido-, pyrrolo-, and pyrimido-pyrimidines.[xviii–xx] Recent literature shows resurgence of interest in the chemistry and bioactivity of 6-aminouracil derivatives, leading to improvement in procedures of several already known reactions.[xxi–xxiv]

Pyrido[2,3-d]pyrimidines are annulated uracil and have received considerable attention over the past years due to their wide range of biological and pharmacological activities such as antibacterial,[xxv–xxvii] antiallergic,[xxviii] antitumor,[xxv–xxvi] antifolate,[xxix] tyrosine kinase,[xxx] antimicrobial,[xxxi] calcium channel antagonists,[xxxii] antibacterial,[xxxiii–xxxvi] anti-inflammatory, analgesic,[xxxvii] antihypertensive,[xxxviii] antileishmanial,[xxxix] tuberculostatic,[xl] anticonvulsants,[xli] diuretic, potassium sparing,[xlii] and antiaggressive.[xliii]

Microwave-assisted three-component cyclocondensation of 6-aminouracils, benzaldehyde, and alkyl nitriles afforded pyrido[2,3-d]pyrimidines in high yields.[xliv] Antiviral and cytotoxic activities of these derivatives were evaluated.[xlv] This reaction was also reported in the presence of other catalysts such as triethylbenzylammonium chloride (TEBAC),[xlvi] [bmim]Br,[xlvii] triethanolamine (TEOA),[xlviii] ZrO_2 & MgO nanoparticles,[xlix–li] SBA-Pr-SO_3H,[lii] or under ultrasonic irradiation using tetra-n-butyl ammonium bromide (TBAB).[liii]

Most of these reported methods require forcing conditions, high temperature, long reaction times, and complex synthetic pathways. Thus, new routes for the synthesis of these molecules have attracted considerable attention in the past. Herein, magnetic nanocrystalline $NiFe_2O_4$ has been successfully applied as a catalyst for the synthesis of pyrido[2,3-d]pyrimidine derivatives.

EXPERIMENTAL:

GENERAL:

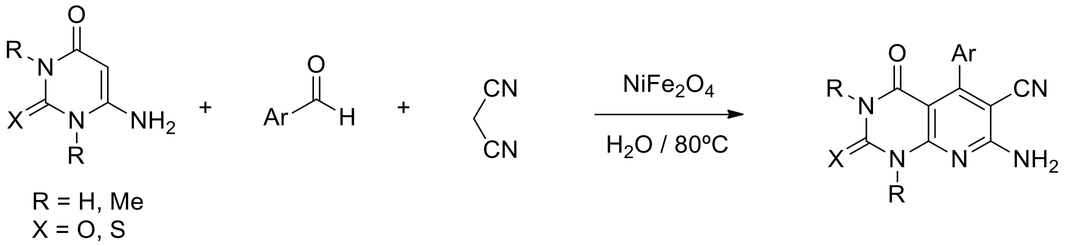
Unless and otherwise noted, all Chemicals used were of commercial grade and they were used without any further purification. All reactions were monitored by thin layer chromatography using aluminium sheets precoated with silica gel 60 F254 (Merck) using either UV light or iodine vapours as visualizing agents. The products were identified fully or by comparison of melting points and spectroscopic data with the previously reported ones.

General procedure for the synthesis of 6-aminouracil/ 6-amino-2-thiouracil/ 6-amino-1,3-dimethyluracil 1

Equimolar amounts of urea / thiourea / N,N-dimethyl urea (12.5 mmol) and cyanoacetic acid (12.5 mmol) were thoroughly mixed and then acetic anhydride (25 mmol) was added to the reaction vessel of the microwave reactor. The reaction mixture was exposed to microwave irradiation at 40% power for 10 min keeping the temperature below 60ºC. The reaction vessel was cooled to room temperature and ethanol (5 ml) was added. 5% NaOH solution (6 ml) was added with stirring whereby the product precipitated. The solid compound was collected by filtration and recrystallized from water as a white crystalline solid.

General procedure for the synthesis of pyrido[2,3-d]pyrimidines 4 a -u

A mixture of aromatic aldehyde (3 mmol), 6-aminouracil/ 6-amino-2-thiouracil / 6-amino-1,3-dimethyluracil (3mmol) and malononitrile (3 mmol) in the presence of $NiFe_2O_4$ (20 mol %) was stirred in water (10 ml) at 80ºC for the appropriate time, as shown in Table 5.3. Completion of the reaction was indicated by TLC monitoring [ethyl acetate: n-hexane (3:7)]. The catalyst was separated by using a magnet and the reaction mixture was cooled to ambient temperature. The crude solid residue was recrystallized from ethanol and water to afford pure crystals of the product.



1 **2** **3** **4 a-u**

Scheme 1. Synthesis of pyrido[2,3-d]pyrimidines via multicomponent reaction

SPECTRAL ANALYSIS OF SYNTHESIZED DERIVATIVES:

Melting points were measured in open capillaries and are uncorrected. IR spectra was recorded on Bruker FTIR spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker FTNMR (500MHz) spectrophotometer with DMSO-d_6 as solvent and TMS as internal standard. Solvent peaks in ^{1}H-NMR and ^{13}C-NMR spectra have been removed in tracing. The chemical shifts in parts per million (δ) are reported downfield from TMS (0 ppm). The abbreviations s, d, t, q, m and dd refer to singlet, doublet, triplet, quartet, multiplet and doublet of doublet respectively.

7-Amino -5-phenyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6- carbonitrile (4a)

Molecular Formula : $C_{14}H_9N_5O_2$.

Molecular Weight (gmol^{-1}) : 337.3

Melting Point (ºC) : > 300

IR (KBr, cm^{-1}) (Fig. 5.2a): 3404, 3328 (NH_2), 3188, 3150 (NH), 2219 (CN), 1700, 1645 (C=O).

^{1}H NMR (500 MHz, DMSO, δ ppm) (Fig. 5.2b): 7.25 (m, 2H, Ar-H), 7.42 (m, 3H, Ar-H), 7.80 (br s, 2H, NH2), 10.19 (s, 1H, NH), 10.54 (s, 1H, NH)

^{13}C NMR (500 MHz, DMSO, δ ppm) (Fig. 5.2c): 88.73, 98.31, 115.50, 127.55, 127.72, 128.36, 136.83, 150.32, 155.65, 159.09, 160.12, 160.91

7-Amino-1,3-dimethyl-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6- carbonitrile (4m)

Molecular Formula : $C_{17}H_{15}N_5O_3$.

Molecular Weight (gmol^{-1}) : 279.2

Melting Point (ºC) : > 300

IR (KBr, cm^{-1}) (Fig. 5.3a): 3403, 3331 (NH_2), 3174 (NH), 2224 (CN), 1707, 1643 (C=O).
^{1}H NMR (500 MHz, DMSO, δ ppm) (Fig. 5.3b): 3.09 (s, 3H, NCH3), 3.51 (s, 3H, NCH3), 3.82 (s, 3H, OCH3), 6.98 (dd, 2H, Ar-H), 7.17 (dd, 2H, Ar-H), 7.82 (br s, 2H, NH2)
^{13}C NMR (500 MHz, DMSO, δ ppm) (Fig. 5.3c): 27.64, 29.57, 55.03, 88.69, 98.75, 113.07, 115.54, 128.93, 129.05, 150.85, 153.63, 158.45, 159.21, 159.26, 160.22
7-Amino-5-(4-chlorophenyl)-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4p)
Molecular Formula : $C_{14}H_8ClN_5OS$
Molecular Weight ($gmol^{-1}$) : 329.7
Melting Point (ºC) : > 300
IR (KBr, cm^{-1}) (Fig. 5.4a): 3402, 3315(NH2), 3220(NH), 2214(CN), 1695, 1623 (C=O), 1585, 1546, 1192 (C=S)
^{1}H NMR (500 MHz, DMSO, δ ppm) (Fig. 5.4b): 7.27 (m, 2H, Ar-H), 7.52 (m, 3H, Ar-H), 7.80 (br s, 2H, NH2), 12.51 (s, 1H, NH), 12.19 (s, 1H, NH)
^{13}C NMR (500 MHz, DMSO, δ ppm) (Fig. 5.4c): 90.13, 100.48, 114.72, 115.27, 130.05, 132.56, 154.23, 157.31, 157.49, 157.88, 160.66, 160.71, 161.02, 175.71, 175.88

RESULTS AND DISCUSSION:

Nickel Ferrite nanoparticles is employed as a catalyst for the reaction of 6-aminouracil/ 6-amino-2-thiouracil/ 6-amino-1,3-dimethyluracil (**1**) with aryl aldehydes (**2**) and malononitrile (**3**) in water at 80ºC to provide a series of pyrido[2,3-d]pyrimidine (**4**) derivatives in high yields. The reaction of benzaldehyde (3 mmol), malononitrile (3mmol) and 6-aminouracil (3 mmol) to prepare compound **4a** was used as a model to screen optimal conditions.

Solvent Study

To explore the scope and versatility of this method, various solvents were investigated. (**Table 1**). The best result was achieved using water as solvent. (Table 1, Entry 1)

Entry	Solvent (10ml)	Time (min)	Yield of product (%)
1	**H_2O**	**15**	**94**
2	EtOH	30	88
3	MeOH	30	84
4	EtOH : H_2O (1:1)	20	89
5	MeOH : H_2O (1:1)	25	85
6	Acetic Acid	40	82
7	DMF	30	80
8	DMSO	40	60
9	Toluene	60	28
10	DCM	50	35

Table 1 Optimization of reaction conditions for the synthesis of compound 4a.

Catalyst Quantity

The efficiency of reaction is affected mainly by the amount of nanoparticulate $NiFe_2O_4$ catalyst (**Table 2**). In absence of catalyst no product was obtained indicating that catalyst is necessary for the reaction. The best yield was obtained using 20 mol % of the catalyst (Table 5.2, Entry 6). Further addition of catalyst caused no significant change in the yield of the product.

Entry	**Catalyst quantity (mol %)**	**Condition**	**Time (min)**	**Yield of product (%)**
1	Without catalyst	RT	60	No reaction
2	Without catalyst	80ºC	60	No reaction
3	5	80ºC	15	76
4	10	80ºC	15	80
5	15	80ºC	15	83
6	**20**	80ºC	**15**	**94**
7	25	80ºC	60	93
8	30	80ºC	60	94

Table 2 Optimization of catalyst quantity for synthesis of pyrido[2,3-d]pyrimidines

Reusability of the catalyst

The catalyst was reused after washing it with ethanol and acetone. It did not show any loss of activity even after 4 successive runs. (**Fig. 1**).

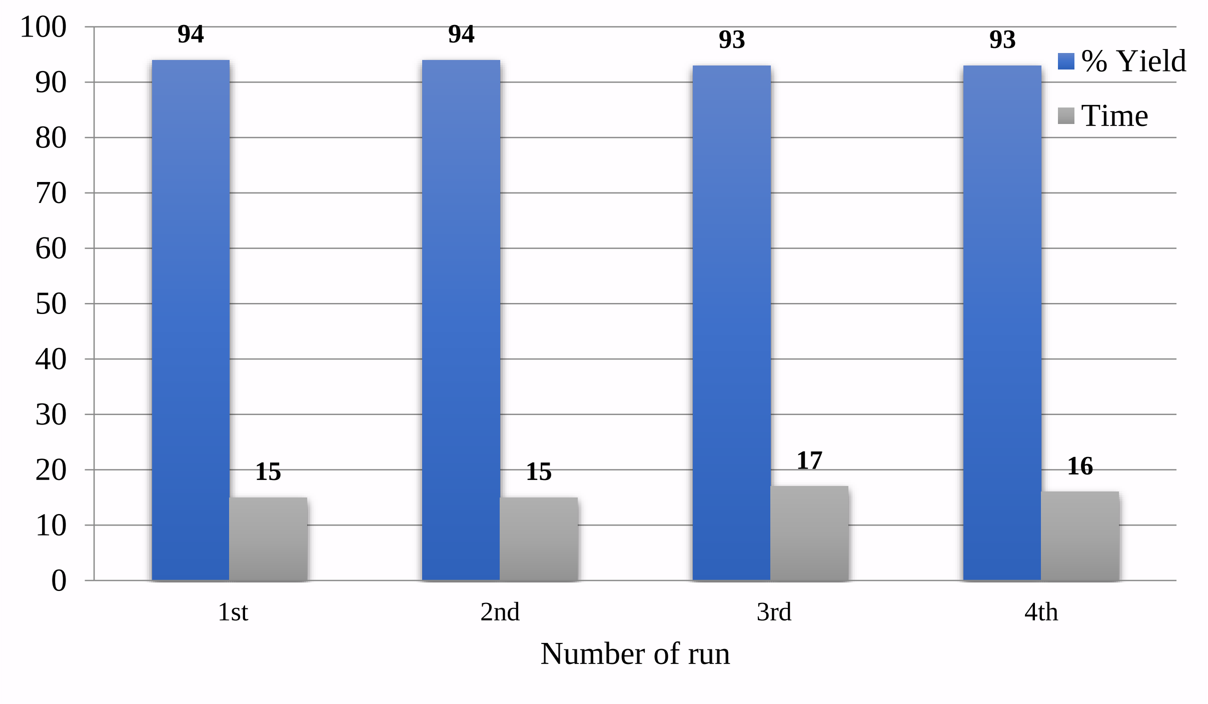


Fig. 1. Reusability of $NiFe_2O_4$ catalyst in model reaction

Preparation of pyrido[2,3-d]pyrimidine derivatives

In order to study the scope of this procedure, a series of pyrido[2,3-d]pyrimidines were synthesized with above optimized conditions as listed in **Table 3.**

Sr. No.	**Ar**	**X**	**R**	**Product**	**Time (min)**	**Yield (%)**
1	C_6H_5-	O	H	**4a**	15	94

2	4-ClC_6H_4-	O	H	**4b**	10	96
3	2,4-$Cl_2C_6H_3$-	O	H	**4c**	10	92
4	3-$NO_2C_6H_4$-	O	H	**4d**	15	90
5	4-$NO_2C_6H_4$-	O	H	**4e**	20	95
6	4-$MeOC_6H_4$-	O	H	**4f**	30	89
7	4-MeC_6H_4-	O	H	**4g**	35	84
8	C_6H_5-	O	Me	**4h**	20	92
9	4-ClC_6H_4-	O	Me	**4i**	15	95
10	2,4-$Cl_2C_6H_3$-	O	Me	**4j**	15	90
11	3-$NO_2C_6H_4$-	O	Me	**4k**	25	88
12	4-$NO_2C_6H_4$-	O	Me	**4l**	30	89
13	4-$MeOC_6H_4$-	O	Me	**4m**	35	91
14	4-MeC_6H_4-	O	Me	**4n**	40	80
15	C_6H_5-	S	H	**4o**	25	86
16	4-ClC_6H_4-	S	H	**4p**	20	91
17	2,4-$Cl_2C_6H_3$-	S	H	**4q**	25	86
18	3-$NO_2C_6H_4$-	S	H	**4r**	30	89
19	4-$NO_2C_6H_4$-	S	H	**4s**	30	86
20	4-$MeOC_6H_4$-	S	H	**4t**	35	83
21	4-MeC_6H_4-	S	H	**4u**	40	78

***Reaction condition**:* 6-aminouracil/ 6-amino-2-thiouracil/ 6-amino-1,3-dimethyluracil*(3 mmol), aryl aldehyde (3 mmol), malononitrile (3 mmol) and* $NiFe_2O_4$ *NP (20 mol%) as a catalyst in 10 ml water.* (Melting points of all the synthesised compounds were >300 ºC)

Table 3 Synthesis of pyrido[2,3-d]pyrimidine derivatives

CONCLUSIONS:

1. We have developed a simple, clean, efficient and one-pot procedure for the synthesis of pyrido[2,3-d]pyrimidines by the three-component condensation of aromatic aldehyde, 6-aminouracil/ 6-amino-2-thiouracil/ 6-amino-1,3-dimethyluracil and malononitrile using magnetic $NiFe_2O_4$ at 80ºC in water as a green solvent.
2. Operational simplicity, simple purification procedure, high yields are are some advantages of using this method.
3. Nanocrystalline $NiFe_2O_4$ is recyclable and could be reused without significant loss of activity.

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