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NANO CRYSTALLINE $CUFE_2O_4$ CATALYZED DOMINO HETEROCYCLIZATION OF PYRANO- FUSED BENZOTHIAZOLOPYRIMIDINES

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ABSTRACT: An efficient and facile, one-pot domino heterocyclization of structurally diverse pyrano- fused benzothiazolopyrimidines derivatives have been achieved. The Nano sized $CuFe_2O_4$ have employed as potential catalyst for the synthesis of functionalized benzothiazolopyranopyrimidines derivatives for the one-pot three component reaction of tetrahydropyran-4-one with 2-aminobenzothiazole and aryl aldehydes in aqueous ethanol under environment benevolent condition. The combination of magnetic nano-catalyst and multicomponent reactions have ideally satisfied the development of sustainable methods in green synthetic chemistry.

KEYWORDS: Multicomponent Domino synthesis; Heterocyclization, Nanocatalysis; CuFe2O4 NPs

INTRODUCTION

Heterocyclic compounds are the core component of more than 70% of modern drugs. Among them the medicinally privileged heterosystems are always been the target for medicinal chemistry research due to their unique binding abilities with the biological substrates. Due to enhanced environmental consciousness, in recent years, the design and synthesis of small drug like fused heterocycles following green chemistry principles is on elegant target.[i]In this context, the synthetic protocols which minimizing the synthetic steps are favoured. One of the ways to fulfill these requirements is the development and use of Multicomponent Domino Reactions (MDRs).[ii] In MDRs all the reagents are added to the reaction mixture in a single operation and, isolation and purification procedure of intermediates is minimized.[iii] Therefore, the design of new selective domino protocols is a continuing challenge at the forefront of organic chemistry.

Green chemistry endeavor, '*Nanocatalysis*' is viable alternatives to the conventional catalytic materials. Among this, the Metal Oxide Nano (MON) particles have recently used as catalyst due to their large surface to volume ratio, compared to their bulk analogues.[iv] However, the isolation and recovery of these nanocatalyst from the reaction mixture is not so easy. To overcome this issue, magnetic nanoparticles have received considerable attention because of

their facile separation from the reaction mixture with an external magnet. Recently, the copper ferrite nanoparticles have been utilized as potential catalyst the multicomponent synthesis of various biologically interesting compounds viz. 1,4-disubstituted 1,2,3-triazoles[v], S-arylated thiourea[vi], 1,2,4,5-tetrasubstituted imidazolesderivatives[vii],functionalized spirooxindoles[viii], spiropyrimidinederivatives[ix], chromenopyrrol-4(1H)-one derivatives[x], 4H-chromenes and 1,2,3-triazole derivatives.[xi]

Pyrimidines compose an important class of heterocycles and their structural framework is a key constituent of numerous natural biologically active.[xii] The pyrano-fused pyrimidines, as a key pyrimidine family, showed a wide range of pharmacological[xiii] and biological activities such as anti-inflammatory, analgesic importantly, in vitro anti-aggregating, antifungal, antibacterial, antiviral and cytotoxic activity.[xiv]The 2-aminobenzothiazole core, as a privileged scaffold, represents ubiquitous structural motifs, which are frequently encountered in natural products and in the drugs for the treatment of various diseases, such as tuberculosis, viral, epilepsy, diabetes, malaria, and tumors etc.[xv]

In view of the importance of pyranopyrimidine derivatives, several methods for their synthesis were reported.[xvi] However, with a literature survey, we noticed that benzothiazole fused pyranopyrimidine has not been documented. Therefore, in continuation with our endeavours in exploring novel one-pot reactions[xvii-xxii] we hope to searching for more elegant synthetic methods for the construction of the privileged heterocyclic pharmacophore incorporating pyrano and benzothiazole fused pyrimidines in a single molecule.

Herein, an efficient and high yielding protocol for the synthesis of functionalized pyrano- fused benzothiazolopyrimidine derivatives by one-pot three-component reaction of tetrahydropyran-4-one with 2-aminobenzothiazole and aryl aldehydes using reusable magnetic $CuFe_2O_4$ nanoparticles as a novel and eco-friendly heterogeneous catalyst is reported. To the best of our knowledge, no methodology has been reported on the use of $CuFe_2O_4$ NPs for the synthesis of functionalized pyrano- fused benzothiazolopyrimidine derivatives.

EXPERIMENTAL

Material and Methods: The melting points of all the synthesized compounds were determined on the electrothermal melting point apparatus using open capillary tubes and are reported uncorrected. 2-Aminobenzothiazole were synthesized by reported method.[xvii]Tetrahydropyran-4-one and aryl aldehydes were purchased from the commercial sources and were used without purification. The purity of all the synthesized compounds was checked by thin-layer chromatography. IR spectra were recorded on a Shimadzu 8400S FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX300 Advance Spectrometer at 300.13 and 75.47 MHz, respectively. In all cases, NMR spectra were obtained in hexadeuterated dimethyl sulfoxide (DMSO-d_6) using tetramethylsilane as internal standard. The NMR signals are reported in δ ppm. Analytical and spectral data of the synthesized compounds are in agreement with their proposed structures.

General procedure:

Synthesis of Nanoparticles (NPs)

The metal oxide and mixed metal oxide at nano scale were prepared by single step chemical method. The nanostructured of α-Fe_2O_3, CaO, $CuFe_2O_4$ and Fe_3O_4 nanoparticles were designed and synthesized modifying the method.

Typical procedure for synthesis of $CuFe_2O_4$ nanoparticles

A round bottom flask was charged with 5 mmol of ferric nitrate and 2.5mmol of copper nitrate in 10 mL deionized water. The mixture was treated 7 mL of 4M NaOH in 15 min to form a reddish-black ppt. The mixture was stirred magnetically at 85 °C for 2 hours. The reaction mixture was cooled to room temperature. The particles were separated by magnet. The separated catalyst was washed with water and placed in oven overnight at 100 °C. The scanning electron microscopy (SEM) images were investigated to study the surface morphology of the prepared metal oxide nano particles (**Figure** 1).

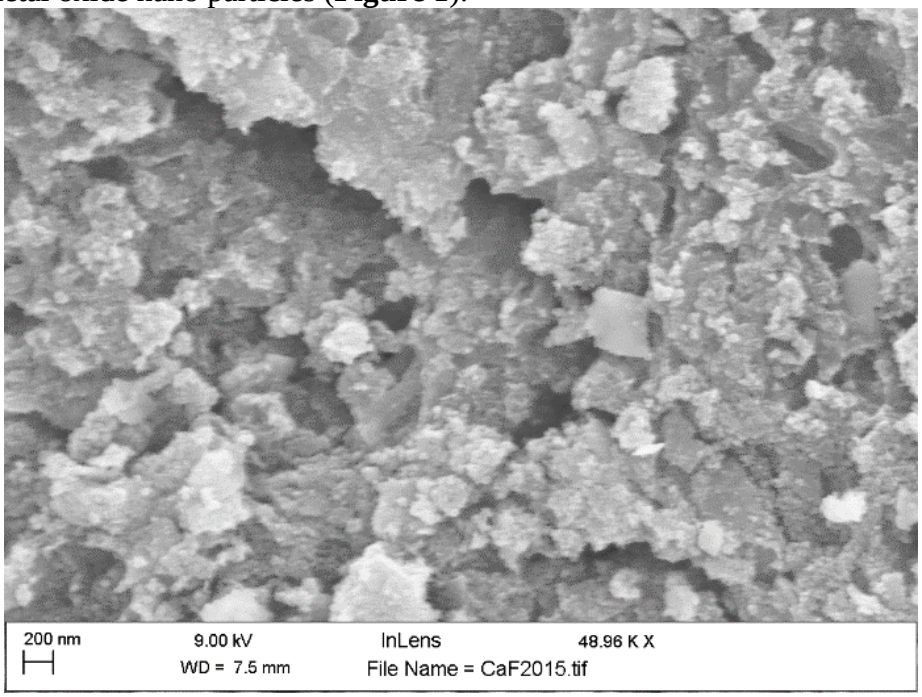


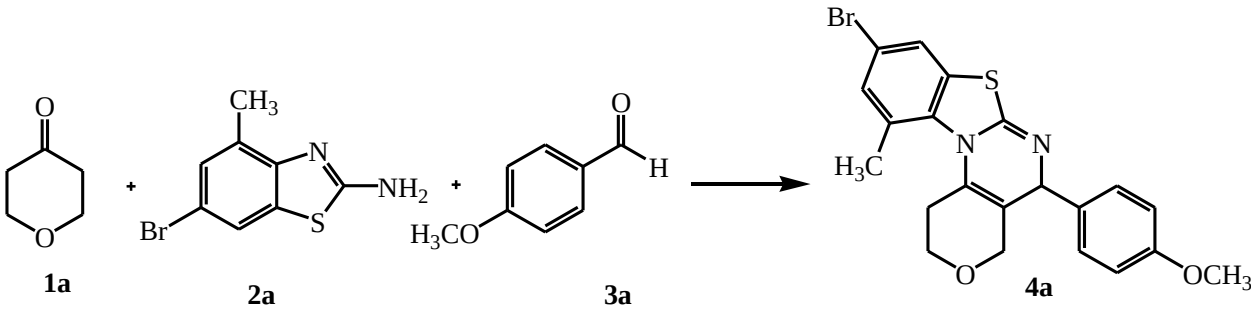
Figure. 1SEM image of $CuFe_2O_4$ NPs

Typical procedure for synthesis of benzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine derivatives

A mixture of tetrahydropyran-4-one, 2-aminobenzothiazole (2 mmol) and aryl aldehyde (2 mmol) were placed in a 25 ml round-bottomed flask in 5 mL of aqueous ethanol (ethanol: water: v: v/1:1). Sequentially Nano $CuFe_2O_4$ (10 mol %, 24 mg) was added. The reaction mixture was stirred at 80 °C for requisite time. The reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled to room temperature and added with 10 mL ethanol. The reaction mixture was stirred with 10 ml ethanol for 3 min. A few seconds after, stirring was stopped, the catalyst was easily separated by a magnet. The catalyst could be separated easily by simple magnetic separation for the reaction mixture. The crude product was recrystallized by ethanol to afford the product.

RESULTS AND DISCUSSION

At the onset of our investigation, for the synthesis of pyrano- fused benzothiazolopyrimidine, the reaction of tetrahydropyran-4-one **1** (2 mmol), 2-amino-6-bromo-4-methylbenzothiazole **2** (2 mmol) and *p*-anisaldehyde **3** (2 mmol) was selected as prototypical reaction (**Scheme 1**) to screen the experimental conditions using different catalysts and solvents as presented in Table 1.



Scheme 1: Model reaction

At first, we employed Brønsted and Lewis acid catalysts such as sulfamic acid, and*p*-toluenesulphonic acid judge their catalytic efficacy for the three-component reaction in ethanol at 80 ^{o}C. It is also noteworthy to mention that poor yield of the desired product was obtained, when three component coupling reaction was performed with Sulfamic acid and *p*-TSA (Table 1, entries 1–2).

As shown in table **1**, NPs (Fe_3O_4, Cao, α-Fe_2O_3, $CuFe_2O_4$) shown pronounced catalytic activity and results into very good to excellent yield of the desired product (Table 1, entries 3–7). However, when the reaction was performed in the presence of Copper Ferrite, $CuFe_2O_4$ nanoparticles as catalyst in ethanol and water as solvent, the yield of the desired product was 90% and 83% respectively with shorter reaction time. It was observed that best results (yield 92 % in 52 min) was obtained when the reaction was performed in ethanol: water (v:v/1:1) solvent system. The effect of catalyst loading was also examined and observed that 10 mol % of $CuFe_2O_4$ NPs is sufficient to give the maximum yield of the product in shortest time. The yield remained unaffected when the catalyst loading was increased to 15 mol%. The effect of temperature on catalytic activity of $CuFe_2O_4$ nanoparticles was also examined and 80 ^{o}C was found to be the optimum temperature for maximum catalytic efficiency of $CuFe_2O_4$ nanoparticles.

Table 1: Optimization of reaction conditions[a]

Entry	**Catalyst[b]**	**Solvent[c]**	**Time**	**Yield (%)[d]**
1	Sulfamic acid	Ethanol	10 h	40
2	*p*-TSA	Ethanol	10 h	42
3	Fe_3O_4 NPs	Ethanol	2 h	90
4	Cao NPs	Ethanol	4 h	75
5	α-Fe_2O_3 NPs	Ethanol	3 h	86
6	Fe_3O_4 NPs	Water	3 h	85
7	$CuFe_2O_4$ NPs	Ethanol	1 hr 40 min	90
8	$CuFe_2O_4$ NPs	Water	3 h	83
9	$CuFe_2O_4$ NPs	Ethanol:water (v:v/1:1)	52 min	92
10	$CuFe_2O_4$ NPs	1,4-dioxane	2 h	59
11	$CuFe_2O_4$ NPs	Dicholoroethane	3 h	55
12	$CuFe_2O_4$ NPs	DMF	2 h	50
13	$CuFe_2O_4$ NPs	Methanol	55 min	88

[a] tetrahydropyran-4-one (2 mmol), 2-amino-6-bromo-4-methylbenzothiazole (2 mmol) and *p*-anisaldehyde (2 mmol) were stirred at 80 ^{o}C till completion of the reaction as indicated by TLC;

[b] 10 % mol of catalyst loaded;

[c] solvents (5.0 mL);
[d] isolated yield

In order to explore the scope of the identified optimal reaction conditions, the catalytic domino reaction protocol was extended to the variety of substrates (Table 2) for synthesis of benzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine (scheme 2)

Scheme 2 Schematic presentation of synthesis of benzothiazolo[2,3-*b*]pyranopyrano[3,4-*d*]pyrimidine derivatives

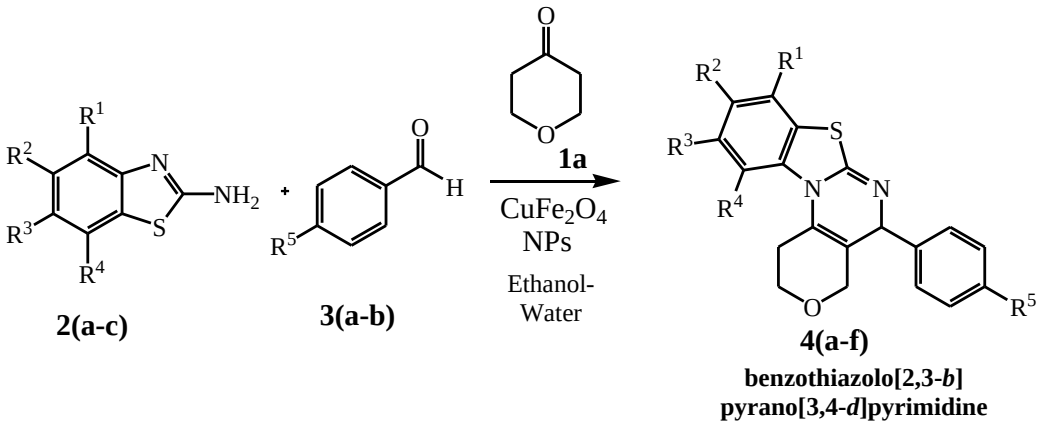


Table 2: Synthesis of benzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine derivatives

S.No.	R^1	R^2	R^3	R^4	R^5	Product	Reaction time	% yield
1.	CH_3	H	Br	H	OCH_3	4a	25 min	95
2.	H	CH_3	H	CH_3	OCH_3	4b	36 min	94
3.	H	H	CH_3	H	OCH_3	4c	30 min	94
4.	CH_3	H	Br	H	Cl	4d	34 min	91
5.	H	CH_3	H	CH_3	Cl	4e	23 min	92
6.	H	H	CH_3	H	Cl	4f	30 min	95

[a] tetrahydropyran-4-one (2 mmol), 2-aminobenzothiazole (2 mmol) and arylaldehyde (2 mmol) were stirred at 80 ^oC till completion of the reaction as indicated by TLC;
[b] 10 % mol of catalyst loaded;
[c] solvent; Ethanol:water (v:v/1:1); 5.0 mL;
[d] isolated yield

The reaction mechanism probably involves the formation of adduct by the *Knoevenagel*-type reaction of aryl aldehydes **3** and tetrahydropyran-4-one**1**, followed by 3+3 cyclization with 2-aminobenzothiazole **2** to give the desired product **4**facilitated by $CuFe_2O_4$ NPs.

Recyclability and Reusability of the Nano catalyst

The possibility of recyclability and reusability of nano- $CuFe_2O_4$ catalyst was examined on the model reaction under optimized reaction conditions. After completion of the reaction, the reaction mixture was stirred with 10 ml ethanol for 3 min. A few seconds after, stirring was stopped, the catalyst was easily separated by a magnet. The recovered catalyst was then washed successively with ethanol and distilled water and dried under vacuum. The recycled catalyst was found to be reusable for at least four cycles without any considerable loss of activity (Figure 2).

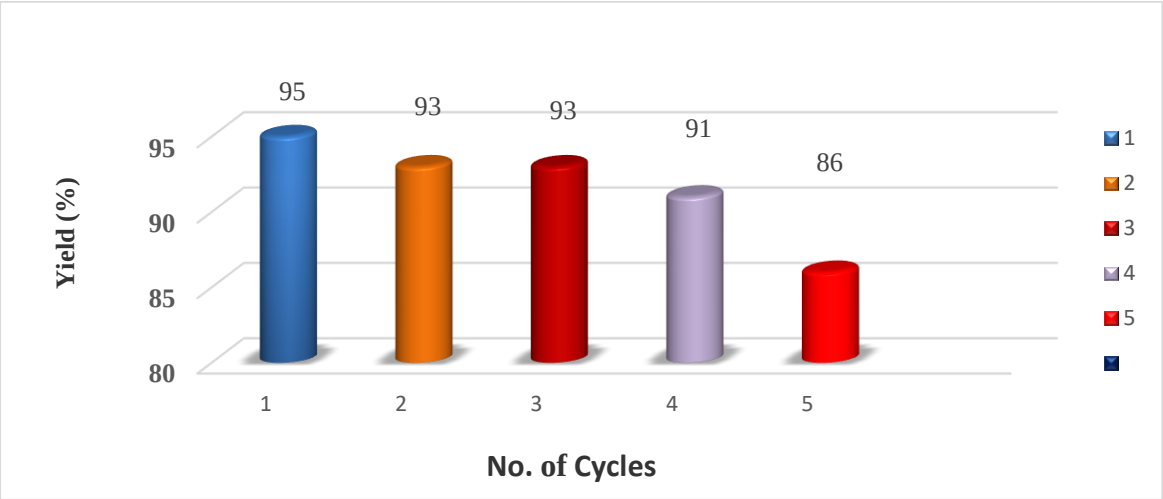


Figure 2. Recyclability of $CuFe_2O_4$ on the synthesis of benzothiazolopyranopyrimidine

9-Bromo-7-methyl-2-(4-methoxyphenyl)-3H-5,6-dihydrobenzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine**4a**

M.p. 238-241°C IR (KBr) cm^{-1}: 1188, 1133, 1061, 832, 592. ^{1}H NMR (DMSO-d_6) δ, (ppm): 2.30 (3H, s, Me), 3.48 (3H, s, MeO), 3.26-3.31 (1H, m, CH_2), 3.88 –3.92 (1H, m, CH_2), 4.76–4.96 (2H, m, CH_2), 5.69 (1H, s), 6.68-7.47 (6H, m, H-Ar). ^{13}C NMR (DMSO-d_6) δ, (ppm): 33.3, 53.4, 56.0, 66.1, 67.8, 106.8, 113.3, 113.7, 114.0, 114.1, 121.2, 126.6, 129.8, 130.0, 130.1, 130.2, 138.9, 147.1, 159.0, 163.0, 167. Anal. calc. for $C_{21}H_{19}BrN_2O_2S$: C 56.89; H 4.32; N 6.32, found: C 56.89, H 4.36, N 6.33.

8,10-dimethyl-2-(4-methoxyphenyl)-3H-5,6-dihydrobenzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine**4b**

M.p. 236-239 °C IR (KBr) cm^{-1}: 1170, 1113, 1078, 592. ^{1}H NMR (DMSO-d_6) δ, (ppm): 2.37 (3H, s, Me), 2.42 (3H, s, Me), 3.56 (3H, s, MeO), 3.47–3.53 (1H, m, CH_2), 3.94–3.99 (1H, m, CH_2), 4.36–4.47 (2H, m, CH_2), 5.85 (1H, s), 6.98-7.32 (6H, m, H-Ar). ^{13}C NMR (DMSO-d_6) δ, (ppm): 27.6, 30.2, 33.1, 53.4, 56.3, 66.1, 67.3, 106.8, 113.1, 114.0, 114.7, 116.8, 120.2, 129.3, 130.1, 130.6, 131.2, 137.5, 139.1, 147.2, 163.0, 170. Anal. calc. for $C_{22}H_{22}N_2O_2S$: C 69.81; H 5.86; N 7.40, found: C 69.84, H 5.77, N 7.41.

9-methyl-2-(4-methoxyphenyl)-3H-5,6-dihydrobenzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine**4c**

M.p. 231—235 °C IR (KBr) cm^{-1}: 1153, 1110, 1063, 612. ^{1}H NMR (DMSO-d_6) δ, (ppm): 2.28 (3H, s, Me), 3.42 (3H, s, MeO), 3.31–3.38 (1H, m, CH_2), 4.02–4.10 (1H, m, CH_2), 4.41–4.49 (2H, m, CH_2), 5.67 (1H, s), 6.65-7.58 (7H, m, H-Ar). ^{13}C NMR (DMSO-d_6) δ, (ppm): 27.5, 33.1, 53.4, 56.1, 66.6, 67.7, 106,8, 114.0, 114.1, 115.3, 119.0, 126.8, 128.0, 129.3, 130.0, 130.5, 130.9, 137.5, 144.4, 159.0, 160. Anal. calc. for $C_{21}H_{20}N_2O_2S$: C 69.20; H 5.53; N 7.69, found: C 69.24, H 5.54, N 7.65.

9-Bromo-7-methyl-2-(4-chlorophenyl)-3H-5,6-dihydrobenzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine**4d**

M.p. 240-243 °C IR (KBr) cm^{-1}: 1170, 1112, 1083, 745, 694. ^{1}H NMR (DMSO-d_6) δ, (ppm): 2.36 (3H, s, Me), 3.31 (1H, s, CH_2), 3.72 –3.81 (1H, m, CH_2), 4.72-4.80 (2H, m, CH_2), 5.92 (1H, s), 6.97-7.81 (6H, m, H-Ar). ^{13}C NMR (DMSO-d_6) δ, (ppm): 28.1, 34.5, 53.4, 66.0, 67.7, 106.1, 113.3, 114.5, 121.2, 126.8, 128.3, 128.9, 129.9, 130.0, 130.7, 135.8, 137.5, 147.1, 142.3, 153.8. Anal. calc. for $C_{20}H_{16}BrClN_2OS$: C 53.65; H 3.60; N, 6.26, found: C 53.69, H 3.56, N 6.28.

8,10-dimethyl-2-(4-chlorophenyl)-3H-5,6-dihydrobenzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine**4e**

M.p. 239-242 °C IR (KBr) cm^{-1}: 1191, 1095, 1053, 675, 649. ^{1}H NMR (DMSO-d_6) δ, (ppm): 2.21 (3H, s, Me), 2.38 (3H, s, Me), 3.83–3.91 (1H, m, CH_2), 4.15-4.21 (1H, m, CH_2), 4.26–4.31 (2H, m, CH_2), 5.63 (1H, s), 6.16-7.57 (6H, m, H-Ar). ^{13}C NMR (DMSO-d_6) δ, (ppm): 26.6, 30.6, 35.1, 53.4, 66.8, 67.6, 106.8, 113.1, 114.3, 116.8, 120.2, 128.8, 128.9, 129.8, 130.1, 130.7, 135.2, 137.5, 139.1, 147.2, 163. Anal. calc. for $C_{21}H_{19}ClN_2OS$: C 65.87; H 5.00; N 7.32, found: C 65.84, H 5.01, N 7.36.

9-methyl-2-(4-chlorophenyl)-3H-5,6-dihydrobenzothiazolo[2,3-*b*]pyrano[3,4-*d*]pyrimidine**4f**

M.p. 241—244 °C IR (KBr) cm^{-1}: 1170, 1158, 1044, 890, 635. ^{1}H NMR (DMSO-d_6) δ, (ppm): 2.21 (3H, s, Me), 3.31–3.36 (1H, m, CH_2), 3.65–3.69 (1H, m, CH_2), 4.46 (2H, s, CH_2), 5.88 (1H, s), 6.71-8.18 (7H, m, H-Ar). ^{13}C NMR (DMSO-d_6) δ, (ppm): 25.5, 33.6, 53.4, 66.8, 67.9, 106.1, 115.3, 119.0, 126.8, 128.0, 128.7, 128.8, 129.6, 130.0, 130.7, 130.8, 135.8, 137.5, 144.4, 163.0. Anal. calc. for $C_{20}H_{17}ClN_2OS$: C 65.12; H 4.65; N 7.59, found: C 65.14, H 4.61, N 7.55.

CONCLUSION

In conclusion, we have developed the nano copper ferrite catalyzed highly efficient and facile one-pot domino synthesis of functionalized benzothiazolopranopyrimidine derivatives by three-component reaction of tetrahydropyran-4-one with 2-aminobenzothiazole and aryl aldehydes in ethanol-water system. The magnetic separability and reusability (up to 5 subsequent cycles) and low loading of catalyst (10% mol) in aqueous ethanol makes the protocol attractive, sustainable, and economical.

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