DBU catalysis in micellar medium: an environmentally benign synthetic approach for triheterocyclic 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives

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Received: 30 March 2020 / Accepted: 9 June 2020 / Published online: 23 June 2020
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Abstract

An efficient, simple, practical and scalable approach for the preparation of pharmaceutically important scaffold 4*H*-pyrimido[2,1-*b*]benzothiazoles using one-flask three-component cyclo-condensation of β -ketoester, substituted aromatic aldehydes and 2-aminobenzothiazole under micellar medium as an environmentally benign protocol is reported. The reaction is catalyzed by DBU and CPB as a green, easily available, cheap and sustainable catalyst. The product formation takes shorter duration with good to excellent yield of the products. The method is also demonstrated on multi-gram level. The Atom economy, environmentally benign, easy to work-up, no use of hazardous solvents, short reaction time are the most outstanding advantages of the developed methodology.

Graphic abstract

Keywords DBU · Micellar medium · Green Synthesis · Scalable Synthesis · Atomic Economy

1 Introduction

In heterocyclic chemistry the development of novel synthetic methodologies to facilitate the preparation of biologically active molecules is an important area of research.

In this regard, efforts have been constantly made to introduce new more efficient and environment compatible methodologies. One of the most attractive approaches to address this challenge is a search for commonly employed organic solvents from various health and environmental

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issues [1]. Keeping environmental concerns in mind, water would be the most attractive solvent to carry out chemical reactions, since it is cheap, safe, non-toxic and poses no threat to the environment [2]. As far as green chemistry is concerned, water may be used to carry out an organic transformation [3]. However, most of the organic compounds are not soluble in water, which is more important factor to carry out an organic transformation, in this case surface active agent (surfactant) may be added for the improvement of the solubility via the formation of micelles [4].

One-pot multicomponent reactions have gained a considerable attention for organic chemists and medicinal chemists [5–7] since they offer significant advantages over conventional stepwise synthetic procedures for promoting new reactions and for the development of straightforward synthetic routes to bioactive heterocycles [8]. Due to the wide spread applications of fused ring compounds (Fig. 1) as fluorescent dye (a) [9], photosensitizer (b) [10, 11] and pharmaceutical (c, d, e, f) [12].

Triheterocyclic 4*H*-pyrimido [2,1-*b*]benzothiazoles are the most important class of heterocyclic molecules and their synthesis has received much attention in the field of medicinal chemistry due to their wide range of biological activities [13] such as anticonvulsant [14], antiviral [15], fungicidal [16], antiallergic [17] antimicrobial [18] anti-mycobacterial [19], anti-inflammatory [20], antiproliferative [21] antiviral [22] and antitumor [23] activities. Among the 2-aminobenzothiazole based compounds, 4*H*-pyrimido[2,1-*b*]benzothiazoles are of interest and have great potential for further synthetic transformations. In literature, various methods for the synthesis of 4*H*-pyrimido[2,1-*b*] benzothiazoles via multicomponent synthesis such as Fe₃O₄@nano-cellulose/Cu(II) [24], solvent-free [25] tetrabutylammonium hydrogen sulfate

Fig. 2 Structures of commercially available surfactant (a) and catalyst (b)

(TBAHS) [26], iron fluoride [27], 1,1,3,3-*N,N,N',N'*-tetramethylguanidinium trifluoroacetate (TMGT) [28], *N*-sulfonic acid modified poly(styrene-maleic anhydride) (SMI-SO₃H) [29], Fe₃O₄@nano-cellulose/TiCl₄ [30] anhydrous zinc chloride [31], *N,N'*-dichlorobis(2,4,6-trichlorophenyl)urea [32] and boric acid [33] have been employed for their synthesis. However, in modern era green methodologies are desirable, because many of the reported methods are unsatisfactory as they involve the use of hazardous solvents, catalyst loadings up to 30 mol %, low yields of the products, drastic reaction conditions, long reaction durations and tedious isolation procedures have been described. These drawbacks of reported procedures make further improvements for the construction of 4*H*-pyrimido[2,1-*b*] benzothiazoles essential.

According to literature, DBU (1,8-Diazabicyclo(5.4.0)undec-7-ene) has been found to catalyzed many organic reactions [34]. In addition to the DBU, surfactants also play an important role in catalysis chemistry [35] the structures of DBU and CPB are given in the Fig. 2.

Continuing our interest on the development of new methodologies for the synthesis of biologically active compounds [36–41] herein we wish to develop new protocol for the synthesis of biologically important triheterocyclic 4*H*-Pyrimido[2,1-*b*] benzothiazoles using DBU (1,8-Diazabicyclo(5.4.0)undec-7-ene) as an organic base catalyst in the presence of CPB (Cetylpyridinium bromide) surfactant in micellar media.

2 Experimental

2.1 General remarks

All the synthesized compounds have been identified by elemental analysis and by comparing their melting points with the authentic samples. Melting points were recorded on an electrical melting point apparatus and are reported uncorrected. The IR spectra were recorded on a Shimadzu IR spectrophotometer on KBR pellet, ¹H and ¹³C NMR

Fig. 1 Structures of some important fused heterocyclic compounds

spectra were recorded on Bruker Avance II on 400 MHz and 100 MHz in CDCl_3 solvent, mass spectra were recorded on mass spectrometer. TLC of the compounds was checked on silica gel G (E. Merck, India) plates. DBU and other reagents used in the experiments were purchased from Sigma Aldrich, Rankem and Spectrochem chemical companies.

2.2 Synthesis of triheterocyclic 4H-pyrimido [2,1-b] benzothiazole derivatives (4a-p)

A mixture of ethyl acetoacetate **1** (1.0 mmol), substituted aromatic aldehydes **2** (1.0 mmol), 2-aminobenzothiazole **3** (1.0 mmol) and DBU (60 mg, 0.4 mmol) was taken in a 2 ml homogeneous aqueous solution of CPB (3.0 mmol, 1.092 g) in a 10 ml oven dried reaction vial. Heat the content at about 60 °C for 3-4 h. The progress of the reaction was monitored by TLC in ethyl acetate-hexane (8:2 v/v). After completion of the reaction, 5 ml water was added to the content. The solid product was collected by filtration over a thin Celite pad using vacuum pump and further purified by recrystallization from hot ethanol.

2.3 Gram scaled-up synthesis of Ethyl-2-methyl-4-(phenyl)-4H-pyrimido[2,1-b] [1, 3] benzothiazole-3-carboxylate (4a)

A mixture of ethyl acetoacetate **1** (5.0 mmol), benzaldehyde **2** (5.0 mmol), 2-aminobenzothiazole **3** (5.0 mmol) and DBU (300 mg, 0.4 mmol) was taken in a 20 ml homogeneous aqueous solution of CPB (15.0 mmol, 5.46 g) in a 50 ml oven dried reaction vial. Heat the content at about 60 °C for 4 h. The progress of the reaction was monitored by TLC in ethyl acetate-hexane (8:2 v/v). After completion of the reaction, 5 ml water was added to the content. The solid product was collected by filtration over a thin Celite pad using vacuum pump and further purified by recrystallization from hot ethanol.

2.4 Characterization data of some selected synthesized compounds

2.4.1 Ethyl-2-methyl-4-(phenyl)-4H-pyrimido[2,1-b] [1, 3] benzothiazole-3-carboxylate (4a)

Pale yellow crystals, IR (λ_{max} cm^{-1}): 3041, 2965, 1672, 1583, 1468, 1241, 743; ^1H NMR (400 MHz, CDCl_3): δ 1.27 (3H, t, J = 14.21 Hz, CH_2CH_3), 2.44 (3H, s, CH_3), 4.21 (2H, m, CH_2CH_3), 6.39 (1H, s, -CH), 7.08-7.48 (9H, m, ArH); ^{13}C NMR (400 MHz, CDCl_3): 165.41, 162.61, 154.11, 141.21, 137.41, 128.22, 126.76, 122.28, 111.61, 103.53, 58.36, 56.89, 24.22, 14.84; ESI-MS: m/z Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ 350.44, found $[\text{M} + \text{H}]^+$ 351.2.

2.4.2 Ethyl-2-methyl-4-(4-nitro phenyl)-4H-pyrimido[2,1-b] [1, 3] benzothiazole-3-carboxylate (4b)

Yellow powder, IR (λ_{max} cm^{-1}): 3351, 2942, 1621, 1517, 1271, 1118, 961-814; ^1H NMR (400 MHz, CDCl_3): δ 1.36 (3H, s, CH_2CH_3), 2.51 (3H, s, CH_3), 6.61 (1H, s, CH), 7.01-7.61 (8H, m, ArH); ^{13}C NMR (100 MHz, CDCl_3): 166.23, 161.55, 154.84, 146.91, 148.64, 138.41, 129.12, 125.87, 123.41, 123.12, 121.72, 121.45, 112.12, 103.11, 61.41, 56.12, 24.15, 13.42; ESI-MS: m/z Calcd for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_4\text{S}$ 395.46, found $[\text{M} + \text{H}]^+$ 396.4.

2.4.3 Ethyl-2-methyl-4-(3-chlorophenyl)-4H-pyrimido[2,1-b] [1, 3] benzothiazole-3-carboxylate (4d)

Pale yellow powder, IR: (λ_{max} cm^{-1}): 2923, 1669, 1563, 1612, 1221, 1312, 1167, 983, 833, 755, 694 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.32 (t, J = 7.12 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 4.14 (q, J = 7.12 Hz, 2H, OCH_2), 6.31 (s, 1H, CH), 7.12 (d, J = 8.30 Hz, 1H, Ar-H), 7.13-7.21 (m, 4H, Ar-H), 7.33-7.51 (m, 3H, Ar-H); ^{13}C NMR (100 MHz, CDCl_3): δ 15.11, 22.44, 57.21, 61.11, 102.41, 111.23, 123.11, 124.18, 124.78, 126.56, 127.17, 121.41, 124.81, 137.18, 133.14, 142.12, 153.79, 162.23, 167.1. ESI-MS: m/z 386. found $[\text{M} + \text{H}]^+$ 387.1.

2.4.4 Ethyl-2-methyl-4-(4-dimethylamino phenyl)-4H-pyrimido[2,1-b] [1, 3] benzothiazole-3-carboxylate (4e)

Pale yellow powder, IR (λ_{max} cm^{-1}): 3023, 2888, 1611, 1579, 1429, 1161, 814-751; ^1H NMR (400 MHz, CDCl_3): δ 1.32 (3H, t, J = 14.11 Hz, CH_2CH_3), 2.79 (3H, s, CH_3), 3.12 (6H, s, $\text{N}(\text{CH}_3)_2$), 4.11 (2H, m, CH_2CH_3), 6.73-7.24 (4H, m, ArH), 7.72-7.926 (4H, m, ArH); ^{13}C NMR (100 MHz, CDCl_3): 167.31, 164.23, 151.91, 151.61, 134.41, 126.65, 121.23, 123.41, 122.61, 121.55, 22.11, 13.49; ESI-MS: m/z Calcd for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_2\text{S}$ 393.54, found $[\text{M} + \text{H}]^+$ 394.2.

2.4.5 Ethyl-2-methyl-4-(4-hydroxy-3-methoxyphenyl)-4H-pyrimido[2,1-b] [1, 3] benzothiazole-3-carboxylate (4f)

Pale yellow powder, IR (λ_{max} cm^{-1}): 3023, 2945, 1712, 1567, 1511, 1244, 723; ^1H NMR (400 MHz, CDCl_3): δ 1.33 (3H, t, J = 14.13 Hz, CH_2CH_3), 2.51 (3H, s, CH_3), 3.6 (3H, s, Ar- OCH_3), 4.11-4.22 (2H, m, CH_2CH_3), 6.23 (1H, s, -CH), 6.43 (1H, d, J = 5.3 Hz, ArH), 6.56-6.79 (2H, m, ArH), 7.11-7.28 (4H, m, ArH), 9.56 (1H, s, OH); ^{13}C NMR (100 MHz, CDCl_3): 166.12, 161.32, 152.52, 146.19, 145.14, 136.16, 131.24, 121.32, 127.34, 112.13, 113.34, 111.81, 51.25, 56.54, 23.34, 14.11 ESI-MS: m/z Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ 396.49, found $[\text{M} + \text{H}]^+$ 397.2.

2.4.6 Ethyl-2-methyl-4-(2-chlorophenyl)-4H-pyrimido[2,1-b][1,3] benzothiazole-3-carboxylate (**4 g**)

Pale yellow powder, IR: ($\lambda_{\max}$ cm^{-1}) 2922, 1683, 1556, 1513, 1365, 1134, 971, 826, 681; ^1H NMR (400 MHz, CDCl_3): δ 1.22 (t, $J=7.15$ Hz, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.23 (q, $J=7.32$ Hz, 2H, OCH_2), 6.71 (s, 1H, CH), 7.04–7.13 (m, 2H, Ar–H), 7.11–7.23 (m, 2H, Ar–H), 7.41 (d, $J=7.45$ Hz, 1H, Ar–H), 7.11 (d, $J=8.24$ Hz, 2H, Ar–H), 7.59 (d, $J=7.41$ Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, CDCl_3): δ 13.31, 23.32, 54.54, 59.32, 102.87, 111.44, 121.45, 123.87, 123.33, 126.76, 128.11, 129.34, 129.43, 130.34, 131.11, 138.67, 139.41, 154.21, 162.14, 163.11; ESI–MS: m/z 386 $[\text{M}+\text{H}]^+$.

2.4.7 Ethyl-2-methyl-4-(4-methoxy phenyl)-4Hpyrimido[2,1 b][1,3] benzothiazole-3-carboxylate (**4j**)

Pale yellow powder, IR ($\lambda_{\max}$ cm^{-1}): 2952, 1633, 1512, 1278, 1147, 960–816; ^1H NMR (400 MHz, CDCl_3): δ 1.24 (3H, t, $J=14.11$ Hz, CH_3CH_2), 2.44 (3H, s, CH_3), 3.69 (3H, s, Ar– OCH_3), 4.13–4.11 (2H, m, CH_3CH_2), 6.31 (1H, s, –CH), 6.67 (2H, d, $J=8.34$ Hz, ArH), 7.18–7.45 (6H, m, ArH); ^{13}C NMR (100 MHz, CDCl_3): 167.45, 161.34, 159.34, 153.54, 152.11, 138.12, 133.45, 128.43, 126.34, 121.84, 122.81, 123.11, 121.65, 116.07, 113.67, 112.56, 103.67, 61.02, 56.16, 55.15, 23.68, 14.12; ESI–MS: m/z Calcd for $\text{C}_{21}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ 380.47, found $[\text{M}+\text{H}]^+$ 381.3.

2.4.8 Ethyl-2-methyl-4-(2,6-dichlorophenyl)-4Hpyrimido[2,1-b][1,3] benzothiazole-3-carboxylate (**4 k**)

Pale yellow powder, IR (KBr) (umax , cm^{-1}): 3102, 2925, 1621, 1512, 1267, 1113, 951–814; ^1H NMR (400 MHz, CDCl_3): δ 1.02 (3H, t, $J=14.16$ Hz, CH_2CH_3), 2.42 (3H, s, CH_3), 4.14 (2H, m, CH_2CH_3), 7.12–7.53 (7H, m, Ar–H); ^{13}C NMR (100 MHz, CDCl_3): 173.84, 165.45, 162.78, 152.02, 136.34, 132.71, 131.22, 122.42, 126.01, 125.17, 124.32, 122.23, 121.33, 117.45, 116.12, 59.11, 23.54, 14.11; ESI–MS: m/z Calcd for $\text{C}_{20}\text{H}_{16}\text{N}_2\text{Cl}_2\text{O}_2\text{S}$ 419.41, found $[\text{M}+\text{H}]^+$ 419.6.

2.4.9 Ethyl-2-methyl-4-(2-hydroxy phenyl)-4H-pyrimido[2,1-b][1,3] benzothiazole-3-carboxylate (**4 l**)

Pale yellow powder, mp 212–215 $^\circ\text{C}$.; IR ($\lambda_{\max}$ cm^{-1}): 3031, 2814, 1672, 1569, 1479, 1242, 835–745; ^1H NMR (400 MHz, CDCl_3): δ 1.34 (3H, t, $J=14.17$, CH_2CH_3), 2.41 (3H, s, CH_3), 4.13–4.24 (2H, m, CH_2CH_3), 6.31 (1H, s, –CH), 6.65–7.91 (8H, m, ArH), 8.8 (1H, s, OH); ^{13}C NMR (100 MHz, CDCl_3): 172.87, 166.91, 163.98, 156.22, 152.34, 134.71, 125.13, 127.12, 123.91, 117.12, 59.28, 55.21, 24.13, 13.12; ESI–MS: m/z Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ 366.34, found $[\text{M}+\text{H}]^+$ 367.2.

2.4.10 Ethyl-2-methyl-4-(4-hydroxy phenyl)-4H-pyrimido[2,1-b][1,3] benzothiazole-3-carboxylate (**4n**)

Pale yellow powder, IR ($\lambda_{\max}$ cm^{-1}): 3291, 3061, 2889, 1621, 1578, 1428, 1381, 814–756; ^1H NMR (400 MHz, CDCl_3): δ 1.29 (3H, t, $J=14.18$ Hz, CH_3CH_2), 2.38 (3H, s, CH_3), 2.11 (m, 2H, CH_3CH_2), 6.29 (1H, s, –CH), 6.72 (2H, d, $J=8.40$ Hz, ArH), 7.14–7.61 (5H, m, ArH), 7.62 (1H, d, $J=7.69$ Hz, ArH), 9.32 (1H, s, OH); ^{13}C NMR (100 MHz, CDCl_3): 165.57, 162.29, 157.19, 153.51, 137.62, 131.89, 128.21, 126.29, 123.61, 122.88, 122.19, 115.11, 111.78, 102.89, 59.22, 56.42, 23.11, 14.12; ESI–MS: m/z Calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ 366.34, found $[\text{M}+\text{H}]^+$ 367.2.

2.4.11 Ethyl-2-methyl-4-(2,4-dichlorophenyl)-4H-pyrimido[2,1-b][1,3] benzothiazole-3-carboxylate (**4p**)

Pale yellow powder, IR ($\lambda_{\max}$ cm^{-1}): 2942, 1685, 1586, 1511, 1391, 1242, 1196, 972, 824, 743, 661 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): δ 1.26 (t, $J=7.18$ Hz, 3H, CH_3), 2.46 (s, 3H, CH_3), 4.15 (q, $J=7.19$ Hz, 2H, OCH_2), 6.72 (s, 1H, CH), 7.13 (d, $J=7.58$ Hz, 1H, Ar–H), 7.17–7.21 (m, 1H, Ar–H), 7.26 (d, $J=7.58$ Hz, 1H, Ar–H), 7.29–7.33 (m, 1H, Ar–H), 7.36–7.41 (m, 2H, Ar–H), 7.53 (d, $J=9.08$ Hz, 1H, Ar–H); ^{13}C NMR (100 MHz, CDCl_3): δ 14.82, 24.21, 54.41, 60.51, 102.89, 111.88, 122.61, 124.59, 127.19, 128.89, 129.62, 135.23, 138.59, 138.54, 156.11, 163.71, 166.56. ESI–MS: m/z : 419 $[\text{M}+\text{H}]^+$.

3 Results and discussion

In the present work, our exposure was focused on the preparation of substituted 4H-pyrimido- [2,1-b]benzothiazoles (Scheme 1), which have been synthesized successfully by cyclo-condensation of ethylacetoacetate (**1**), aromatic aldehydes with different substituents (**2**) and 2-aminobenzothiazole (**3**) in good to excellent yields (91–96%). In the reaction, DBU was used as an organic base catalyst under micellar media which was developed by adding CPB a cationic surfactant at 60 $^\circ\text{C}$ temperature. Keeping environmental concerns in mind, water was chosen as reaction solvent instead of traditional solvents.

Initially, the product was obtained in only in 15% yield in 24 h with DBU in SDS surfactant solution at 60 $^\circ\text{C}$. After that the reactions condition of the reaction was optimized using various cationic, anionic and neutral surfactants viz. SDS, CTAC, HDBAC, TEBA, CTAB, CPB, Triton X-100 and Tween 40 (Table 1) with various organic and inorganic bases like DBU, DMAP, TEA and K_2CO_3 . After optimization of surfactants and catalyst, it was concluded that, product may be obtained in excellent yield with CPB surfactant with DBU as a base in 3–4 h only. After synthesis,

Scheme 1 Synthesis of tricyclic 4H-pyrimido[2,1-b]benzothiazoles derivatives

Table 1 Screening of surfactants

Entry	Surfactant (mmol)	Base (mol %)	Time (h)	Yields (%)
1	SDS (1)	–	12	–
2	SDS (1)	DBU (10)	12	15
3	SDS (2)	DBU (10)	12	23
4	SDS (3)	DBU (10)	12	31
5	SDS (4)	DBU (10)	12	36
6	CPB (2)	DBU (10)	12	41
7	CPB (2)	DBU (20)	12	53
8	CPB (2)	DBU (30)	6	69
9	CPB (3)	DBU (30)	4	84
10	CPB (3)	DBU (40)	3	93
11	CPB (4)	DBU (40)	3	76
12	CPB (3)	DBU (50)	3	51
13	CPB (3)	K ₂ CO ₃ (40)	6	–
14	CPB (3)	DMAP (40)	3	12
15	CPB (3)	TEA (40)	3	17
16	CTAB (3)	DBU (40)	3	54
17	HDBAC (3)	DBU (40)	3	65
18	TEBA (3)	DBU (40)	3	50
19	CTAC (3)	DBU (40)	3	47
20	Triton X-100 (60)	DBU (40)	12	–
21	Tween 40 (60)	DBU (40)	12	–

^aReaction condition: Ethyl acetoacetate (1.0 mmol), benzaldehyde (1.0 mmol), 2-aminobenzothiazole (1.0 mmol) under DBU catalysis in micellar media at 60 °C for 3–12 h

the products were recrystallized using hot ethanol and characterized by ¹H-NMR,

¹³C-NMR, IR and Mass spectral studies which were in close agreement with the product which was synthesized by a method reported in literature. After optimization of reaction conditions for the reaction, sixteen derivatives with various substitution have designed and synthesized in good to excellent yields under standard reaction conditions and concluded that, from the variations of the yields of the products (**4a–p**), the presence of an electron-donating group in the substituted aldehydes used facilitates the reaction, and lower yield of the product is obtained when electron-withdrawing group is used. Within the

perspective, the similar results were obtained when gram scale experiment was performed for the same reaction. The physico-chemical data of all the synthesized products have been illustrated in the Table 2.

In order to check the greenness of the reaction, various credentials for green chemistry of the newly developed protocol have been calculated using the well defined formulas reported in literature [42–44].

The calculated green credential indices contain atom economy (AE), atom efficiency (AEf), carbon efficiency (CE), reaction mass efficiency (RME), optimum efficiency (OE) and E-factor. Atom economy (90.68–92.07) and atom efficiency (83.40–87.98) for the method measures are obtained. The process shows a good profile of calculated carbon efficiency (100%). Reaction mass efficiency (83.47–88.37) which may be regarded as the most useful metric to determine the greenness of the developed process; calculations of RME also support excellent green credential of the present method. Similarly, the calculated E-factors (g/g) obtained in the range from 0.13–0.20, which convincingly indicate considerable green aspects of the present procedure.

3.1 Gram-Scaled up reaction

In the perspective, for checking the practicality of the reaction, a gram scaled up experiment was performed at 5.0 mmol scale (Scheme 2) under optimized reaction conditions, the results of the reaction are quite similar to the small scale reaction in 4 h.

3.2 Competitive experiment

By encouraging the results obtained, a competitive experiment was performed (Scheme 3) for investigation of the variation of the yields of the products, which alters due to starting materials.

In the experiment, ethyl acetoacetate **1** and 2-aminobenzothiazole **3** were permitted to react with an equimolar mixture of *p*-nitrobenzaldehyde and *p*-methoxybenzaldehyde **2**, products **4b** and **4h** were obtained in 18% and 67% yields respectively, which was concluded that

Table 2 Physico-chemical and green chemistry metrics data of synthesized 4*H*-pyrimido[2,1-*b*]benzothiazole derivatives^a

Compound	R	R _f values	M.P. (°C)	Mol. formula (Mol. weight)	Elemental Analysis (%) found/calculated			Yield (%)	Calculated Green Chemistry Metrics						
					C	H	N		AE ^c (%)	AE ^d (%)	CE ^e (%)	RME ^f (%)	OE ^g (%)	E-factor	
4a	-H	0.89	172–174	173–175 [28]	C ₂₀ H ₁₈ N ₃ O ₂ S (350.44)	68.51/68.55	5.09/5.18	7.92/7.99	94	90.68	85.23	100	85.34	99.79	0.17
4b	-4-NO ₂	0.56	151–153	150–152 [28]	C ₂₀ H ₁₇ N ₃ O ₄ S (395.43)	60.89/60.95	4.31/4.33	10/5010.63	91	91.65	83.40	100	84.50	92.19	0.18
4c	-3-CH ₃	0.78	148–150	147–149 [24]	C ₂₁ H ₂₀ N ₃ O ₂ S (364.46)	69.12/69.21	5.49/5.53	7.61/7.69	92	91.00	83.72	100	88.33	91.57	0.20
4d	-3-Cl	0.69	ND ^h	–	C ₂₀ H ₁₇ ClN ₃ (384.88)	62.37/62.41	4.38/4.45	7.21/7.28	95	91.44	86.87	100	86.51	94.61	0.16
4e	-4-N(CH ₃) ₂	0.71	176–178	175–178 [24]	C ₂₂ H ₂₃ N ₃ O ₂ S (393.51)	67.21/67.15	5.81/5.89	10.62/10.68	91	91.61	83.37	100	83.72	91.39	0.19
4f	-4-OH-3-OCH ₃	0.69	192–194	192–194 [24]	C ₂₁ H ₂₀ N ₃ O ₂ S (396.46)	63.58/63.62	5.12/5.08	7.12/7.07	94	91.67	86.17	100	86.05	93.87	0.16
4 g	-2-Cl	0.69	125–127	124–126 [24]	C ₂₀ H ₁₇ ClN ₃ O ₂ S (384.88)	62.44/62.41	4.48/4.45	7.21/7.28	95	91.44	86.87	100	86.51	94.61	0.15
4 h	-3-CH ₃ -4-OCH ₃	0.89	205–207	204–206 [30]	C ₂₂ H ₂₂ N ₃ O ₃ S (394.49)	66.89/66.98	5.56/5.62	7.12/7.10	92	91.65	87.97	100	84.50	92.19	0.18
4i	-3-(CH ₃) ₂	0.78	182–184	183–185 [24]	C ₂₂ H ₂₂ N ₃ O ₂ S (378.49)	69.77/69.81	5.88/5.86	7.36/7.41	92	91.31	84.01	100	83.87	91.85	0.19
4j	-4-OCH ₃	0.88	140–142	140–143 [28]	C ₂₁ H ₂₀ N ₃ O ₃ S (380.46)	66.21/66.30	5.22/5.30	7.29/7.36	94	91.35	85.88	100	85.60	93.71	0.17
4 k	-2-Cl-6-Cl	0.71	151–153	150–152 [28]	C ₂₀ H ₁₆ Cl ₂ N ₃ O ₂ S (419.32)	57.21/57.29	3.83/3.85	6.66/6.68	95	92.09	87.49	100	88.24	95.81	0.13
4l	-2-OH	0.74	213–215	212–215 [28]	C ₂₀ H ₁₈ N ₃ O ₃ S (366.49)	65.61/65.56	4.89/4.95	7.58/7.65	92	91.06	83.78	100	83.47	91.67	0.20
4 m	-3-OCH ₃	0.81	137–139	138–140 [30]	C ₂₁ H ₂₀ N ₃ O ₃ S (380.46)	66.21/66.30	5.22/5.30	7.29/7.36	94	91.35	85.88	100	85.60	93.71	0.17
4n	-4-OH	0.75	211–213	210–212 [24]	C ₂₀ H ₁₈ N ₃ O ₃ S (366.49)	65.61/65.56	4.89/4.95	7.58/7.65	92	91.06	83.76	100	83.47	91.67	0.20
4o	-3-NO ₂	0.71	223–225	222–224 [24]	C ₂₀ H ₁₇ N ₃ O ₄ S (395.43)	60.89/60.95	4.31/4.33	10/5010.63	96	91.65	87.98	100	88.37	96.42	0.13
4p	-2,4-(Cl) ₂	0.69	134–136	133–135 [24]	C ₂₀ H ₁₆ Cl ₂ N ₃ O ₂ S (419.32)	57.21/57.29	3.83/3.85	6.66/6.68	95	92.07	87.47	100	87.59	95.14	0.14

^aReaction conditions: Ethyl acetoacetate (1.0 mmol), substituted aromatic aldehydes (1.0 mmol), 2-aminobenzothiazole (1.0 mmol) under DBU catalysis in micellar media at 60 °C for 3–4 h.^bReported in literature. ^cAE (atom economy). ^dAEf (Atom Efficiency). ^eCE (Carbon Efficiency). ^fRME (Reaction Mass Efficiency). ^gOE (Optimum Efficiency). ND = ^hNot Determined (Yellow oil)

when the substrates with electron-donating and electron-withdrawing groups were permitted to react individually, they give better yields as compared to a substrate with electron-withdrawing group. Nonetheless, in the mixture, substrate with electron-donating groups not only reacts faster, but also gives higher yields of the product as compared to substrates with electron-withdrawing group.

3.3 Mechanistic study

For the reaction, a plausible mechanistic pathway is depicted in Fig. 3 using DBU in CPB surfactants may

Scheme 2 Gram-Scaled up synthesis of tricyclic 4H-pyrimido[2,1-b]benzothiazoles

Scheme 3 Competitive experiment for tricyclic 4H-pyrimido[2,1-b]benzothiazole synthesis

Fig. 3 Mechanistic picture diagram representing the role of CPB

4 Conclusions

In conclusion, we have established a multicomponent three component and green synthesis of biologically active molecule triheterocyclic 4*H*-pyrimido [2,1-*b*]benzothiazole and its derivatives by the cyclocondensation reaction of β -ketoester, aromatic aldehydes and 2-aminobenzothiazole as reagents in aqueous micellar medium, using CPB as the surfactant and DBU as a organic base. The notable advantages of this present protocol include use of easily available cheap starting materials and eco-friendly greener catalyst, metal-free one-pot synthesis, energy-efficiency, short reaction durations, clean reaction profiles, operational simplicity, ease of product purification without column chromatography, large-scale synthetic applicability, good to excellent yields, high atom-economy and low E-factor over reported protocols which provides a useful platform to synthesize the novel biologically active scaffolds in molecular designing.

Acknowledgements Authors are thankful to Dr. K.N. Modi University, Newai, Rajasthan, India for providing seed grant No. DKNMU/R&D/2019/01.

Compliance with ethical standards

Conflict of interest Authors have no conflict of interest.

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