Research Article

Chemical Review and Letters
journal homepage: www.chemrevlett.com
ISSN (online): 2645-4947 (print) 2676-7279

Efficient and environmentally sustainable domino protocol for the synthesis of diversified dispiroheterocycles using 1-Butyl-3-methylimidazolium bromide [bmim]Br

Makrand V. Kulkarni[a], Chetan K. Jadhav[a], Amol S. Nipate[a], Charansingh. H. Gill [a, *], Bhausaheb K. Magar[b]

[a]*Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India*
[b]*Department of Chemistry, Shivaji Art, Commerce and Science College, Kannad, Aurangabad 431103, Maharashtra, India*
*E-mail: * chgill@gmail.com (C. H. Gill)*

ARTICLE INFO

Article history:
Received 30 March 2021
Received in revised form 5 June 2021
Accepted 14 June 2021
Available online 20 June 2021

Keywords:
Multicomponent reaction
[bmim]Br
Dispiroheterocycles
Ionic liquid

ABSTRACT

An environmentally benign, simple, and efficient procedure has been developed for the construct of some symmetrical dispiroheterocycles derivatives by the reaction of the variety of 6-amino-2-thiouracil/6-aminouracil /2-amino-1,3,4-thiadiazole, isatins and *p*-toluidine in the presence of 1-Butyl-3-methylimidazolium bromide ([bmim]Br) as a solvent as well as catalyst at room temperature. In this study, a variety of bis-spiro-indoline-chromenes, pyranopyranes, imidazo-pyridines, pyrido-pyrimidines and pyridines were obtained with excellent yields within short reaction time and without chromatographic separation. Furthermore, the green catalytic system can be recycled specific times with no decreases in yields and reaction rates.

1. Introduction

The construction of structurally diverse complex molecules in single and one-pot reaction avoiding multi-step synthesis and hazardous organic solvents in view of their concerns with the environmental sustainability and use of the newly synthesized diversity oriented drug-like complex molecules in drug discovery research.[1–3] Multicomponent reactions (MCRs) are important in the modern organic chemistry and they possess wide range of applications.[4–7] Multi-component reactions involve the formation of multiple bonds and without changing the reaction conditions in one-pot operation without isolating the intermediates.[8–10] Moreover, these reactions conserve both reagents and solvents and avoid difficult purification steps. The operational simplicity and synthetic efficiency of multicomponent reactions make them eco-friendly, time efficient and cost effective in comparison to conventional multistep synthesis.[11–13] Among the solvent, ionic liquids are the green solvent in the synthesis of organic compounds and is one of the significant examples of green solvents. These compounds could be solved inorganic and organic compounds and could be replaced with volatile organic solvents (VOCs) and have low vapor pressures.[14–18] In addition to their 'green' nature, other remarkable properties of ionic liquids are high thermal stability, recyclability and low vapor pressure are pivotal to reduce waste and its subsequent treatment, Also, ILs have been successfully used in many multicomponent reactions.[19–24] 1,3,5-triazine core show a wide range of effects on biological systems such as antiprotozoal,[25] antimicrobial,[26] antibacterial,[27] anti-HIV,[28] antifungal,[29] anticancer,[30] antitrypanosomal,[31] antimalarial,[32] anti-proliferative,[33] carbonic anhydrase IX inhibitors,[34] anti-inflammatory,[35] and diuretic activities.[36]

Pyrimido[4,5-*d*]pyrimidines are considered annulated uracils and its derivatives are an important group of heterocyclic compounds, showing valuable biological activities in the areas of agriculture and medicine.[37,38] Some of these properties are anti-HIV activity,[39] antiviral,[40] hepatoprotective,[41] anticancer activity,[42] antibacterial,[43] and antimicrobial.[44]

Dispiroheterocycles systems are of immense interest in a modern medicinal, natural product, and organic chemistry. This type of structure has been found as a core structure of several alkaloids with promising biological activity.[45] (**Figure 1**). In most of the cases as reported in the literature, the synthesis of dispiroheterocyclic scaffold's by the 1,3-dipolar cycloaddition of azomethine ylides carried out under ultrasound condition were seldom reported.[46,47] Each of these reported procedures has its own merit,

but all suffer from limitation of the synthesis to only a narrow range of dispiroheterocyclic scaffold's, a difficulty to isolate products or harsh reaction conditions and long reaction time.

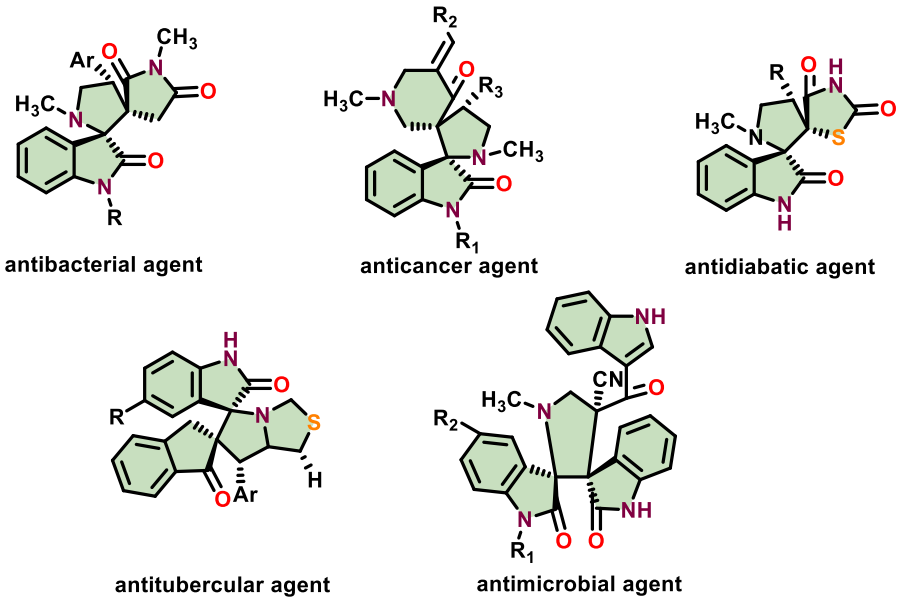
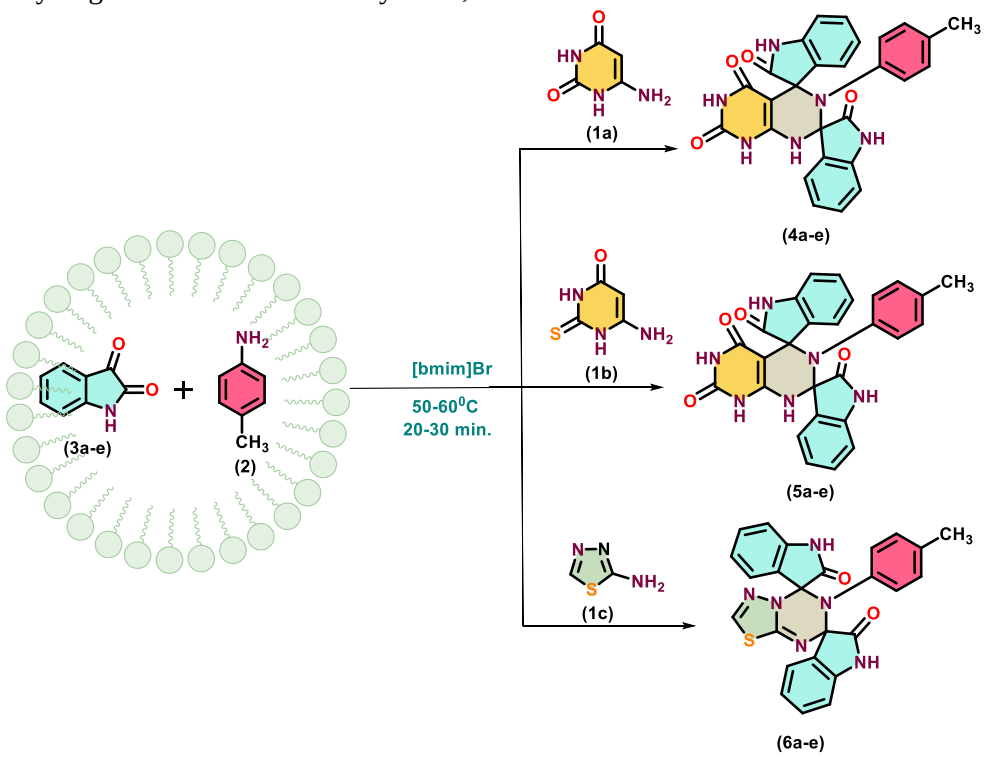


Figure 1 The chemical structures of some biologically active dispiroheterocycles.

In view of our constant efforts to develop greener protocol,[48–53] and in order to the overcome the above-mentioned restrictions. we have presented greener method for synthesis of dispiroheterocycles in presence of 1-Butyl-3-methylimidazolium bromide ([bmim]Br) which act as eco-friendly green medium.

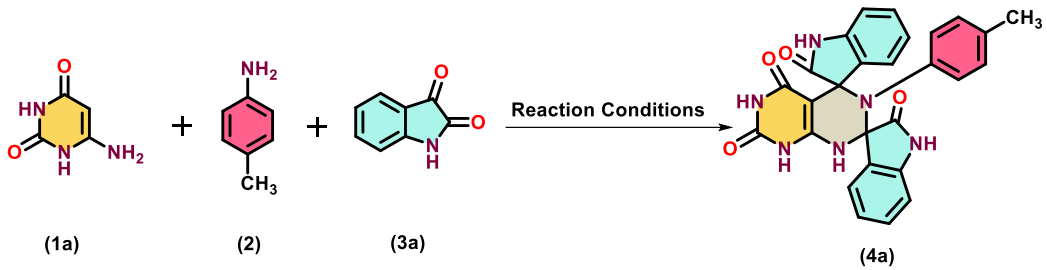
2. Results and Discussion

To avoid the drawbacks such as toxicity and volatility than many organic solvents inherently have, we employed ionic liquid into the three-component reaction as a green medium. Primarily, the three-component reaction of 6-amino-2-thiouracil/6-aminouracil/2-amino-1,3,4-thiadiazole, isatins and p-toluidine using 1-Butyl-3-methylimidazolium bromide ([bmim]Br) as catalyst at 50–60°C to afford the dispiroheterocycles spiroannulated with pyrimido[4,5-*d*]pyrimidine product (4a-e, 5a-e, 6a-e) showed in **(Scheme 1)**.



Scheme 1 General scheme for the synthesis of dispiroheterocycles spiroannulated with pyrimido[4,5-*d*]pyrimidine.

As a model reaction, synthesis of 3'-(*p*-tolyl)-1'*H*,3'*H*-dispiro[indoline-3,2'-pyrimido[4,5-*d*]pyrimidine-4',3''-indoline]-2,2'',5',7'(6'*H*,8'*H*)-tetraone (4a) was carried out by the reaction of 6-aminouracil (1a, 1 mmol), p-toluidine (2, 1 mmol) and isatin (3a, 2 mmol) as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions (**Scheme 2)**.



Scheme 2. Model reaction for one-pot three component synthesis of 3'-(*p-tolyl*)-1'*H*,3'*H*-dispiro[indoline-3,2'-pyrimido[4,5-*d*]pyrimidine-4',3''-indoline]-2,2'',5',7'(6'*H*,8'*H*)-tetraone.

Initially, the model reaction was performed in the presence of ILs were capable of catalyzing the synthesis of desired dispiroheterocycles (4a). However, the yield of the corresponding dispiroheterocycles was higher in the presence of [bmim]Br (2 ml) (Table 1, entry 10). Then, diff erent reaction conditions such as the amount of IL, temperature, and reaction time were checked (Table 1). The reaction was also tried in some traditional organic solvents, such as acetonitrile, Acetone, DMF, and Ethanol. It is observed that reaction in organic solvents takes more time and the yields are minimal compared to the solvent-free conditions (4a) (Table 1, entries 1-4). Furthermore, analogous tetrafluoroborate or hexafluorophosphate ionic liquids for this reaction (Table 1, entries 6 and 7). The yield of product (4a) was enhanced, and the reaction time was shortened as the temperature was increased from room temperature to 40 °C, with no further improvement observed at 80 °C (Table 1, entries 8-12). Therefore, the most suitable reaction temperature is 60 °C.

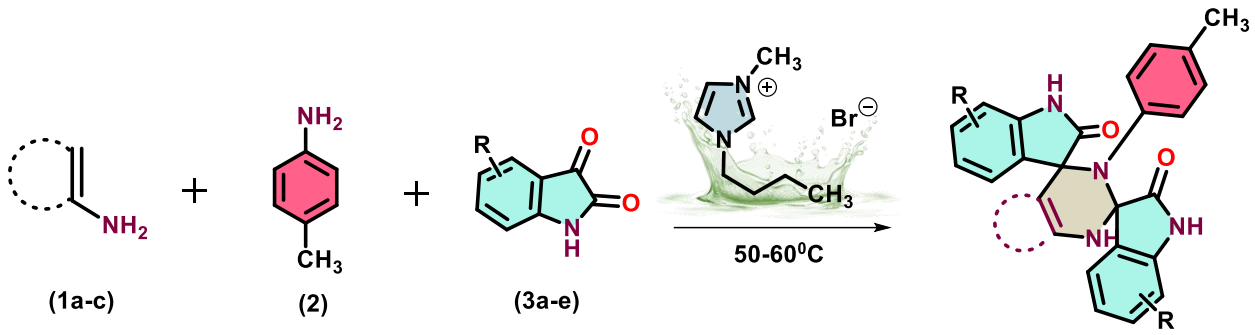
Table 1. Optimization of Reaction Conditions

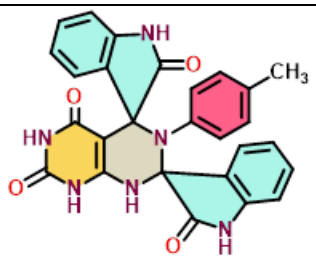
entry	solvent	*T* (°C)	time (h)	isolated yield (%)
1	acetonitrile (2 ml)	60	10 hr	32
2	Acetone (2 ml)	70	25 hr	59
3	DMF (2 ml)	80	24 hr	73
4	Ethanol (2 ml)	60	18 hr	55
5	Chloroform (2 ml)	100	8 hr	81
6	[bmim]PF_6 (2 ml)	80	4.5 hr	89
7	[bmim]BF_4 (2 ml)	80	3 hr	90
8	[bmim]Br (2 ml)	80	45 min	93
9	[bmim]Br (2 ml)	r.t.	2	53
10	[bmim]Br (2 ml)	40	1.5 hr	68
11	[bmim]Br (1 ml)	60	30 min	79
12	[bmim]Br (2 ml)	60	25 min	94

[a] reaction conditions. [b] 6-aminouracil (1a, 1 mmol), *p*-toluidine (2, 1 mmol) and isatin (3a, 2 mmol), were refluxed at 60ºC with stirring. [c] Solvents (2.0 mL), [d] Isolated yield after purification.

On the basis of the information obtained from the above-mentioned studies, the reaction was extended with 2-amino-1,3,4-thiadiazole/6-aminouracil/2-amino-1,3,4-thiadiazol/6-amino-2-thiouracil, *p*-toluidine and isatins to construct a library of dispiroheterocycles with a view to investigate the scope and feasibility of the present synthetic protocol. The synthesized spiroannulated with pyrimido[4,5-*d*]pyrimidine are presented in **Tables 2**.

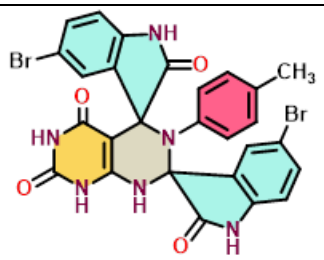
Table 2 Synthesis of dispiroheterocycles spiroannulated with pyrimido[4,5-*d*]pyrimidine





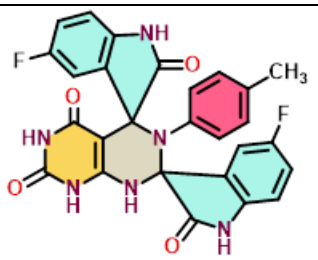
4a (25 min, 94%)

MP 298-300°C



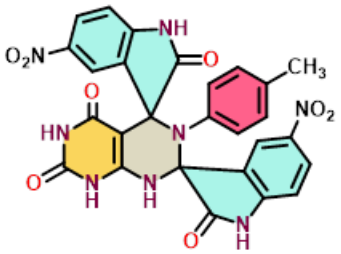
4b (30 min, 93%)

MP 300-302°C



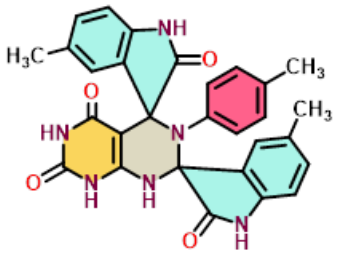
4c (25 min, 94%)

MP 295-297°C



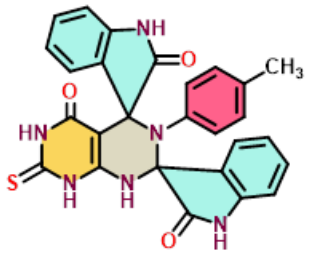
4d (30 min, 94%)

MP 296-298°C



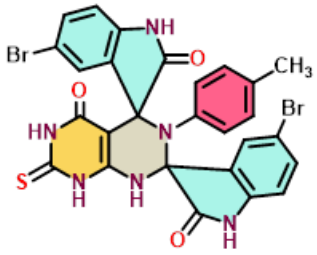
4e (25min, 93%)

MP 288-290°C



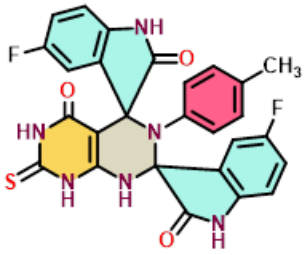
5a (30 min, 94%)

MP 300-302°C



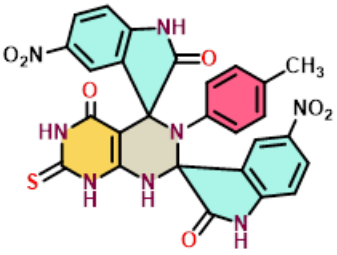
5b (30 min, 93%)

MP 297-300°C



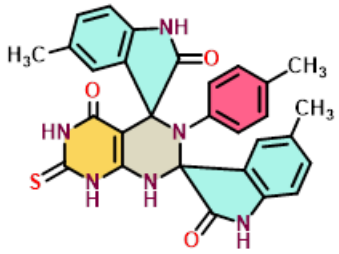
5c (25 min, 94%)

MP 292-294°C



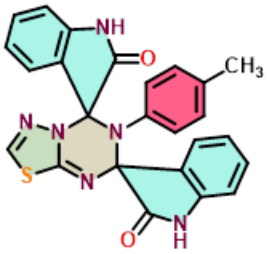
5d (30 min, 94%)

MP 294-296°C



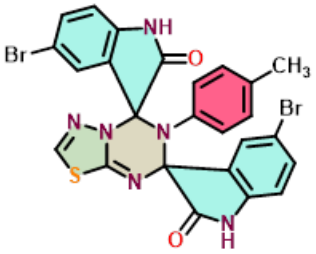
5e (30 min, 95%)

M.P. 300-302°C



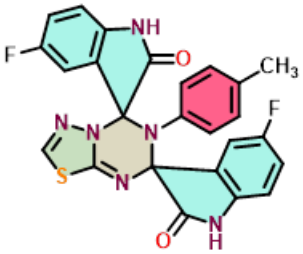
6a (25 min, 94%)

MP 209-211°C



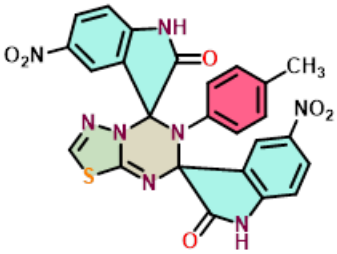
6b (30 min, 93%)

MP 225-227°C



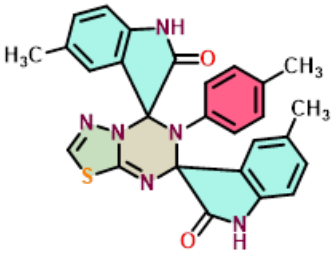
6c (30 min, 94%)

MP 256-258°C



6d (25 min, 94%)

MP 236-238°C



6e (30min, 93%)

MP 222-224°C

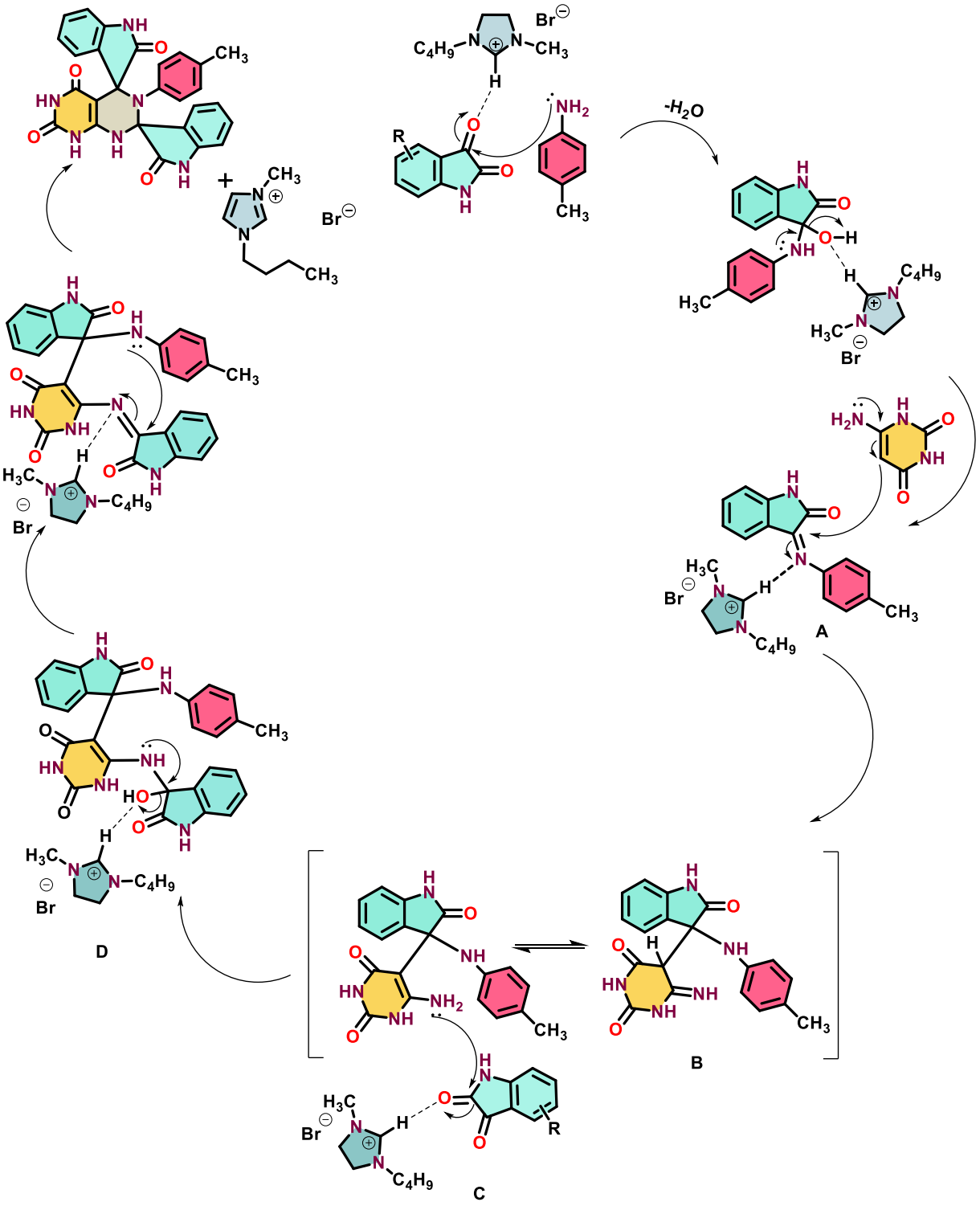
[a]Reaction conditions: 6-amino-2-thiouracil/6-aminouracil/2-amino-1,3,4-thiadiazole/2-amino- 1,3,4-thiadiazol (1.0 mmol), isatins (2.0 mmol), p-toluidine (1.0 mmol) and in 1-Butyl-3-methylimidazolium bromide ([bmim]Br) (2 ml) refluxed at 60ºC with stirring. [b]Isolated yields: Bold values are for highlighting the good result.

After optimizing the reaction conditions, we subsequently extended the scope of the present method using 1-Butyl-3-methylimidazolium bromide ([bmim]Br) as a catalyst with a variety of aromatic electron rich amino heterocycles, substituted isatins and p-toluidine to prepare dispiroheterocycles. The results are given in Table 2. In all cases, electron rich amino heterocycles with substituents carrying either containing oxygen or Sulphur groups and substituted isatins carrying either electron donating or electron-withdrawing groups reacted successfully and gave the expected products in high yields and short reaction times. In addition, the reaction of electron rich amino heterocycles, substituted isatins, and some aniline other than *p*-toluidine was also investigated. No desired product was obtained under similar reaction conditions within 30 min.

A plausible mechanism of the reaction is presented in (**Scheme 3**). The rate acceleration of this one pot three component cyclocondensation leading to dispiroheterocycles is attributed to distinctive role of [bmim]Br as a medium as it has capacity to dissolve various inorganic/organic solutes readily. This might be responsible to maintain high concentrations of the reactants while commencing the reaction and even in the progression of the reaction. Hence high to saturated solutions of reactants in reaction mass would be responsible for rate acceleration of the cyclocondensation.

The [bmim]Br-IL participate in the reaction which activate the isatin carbonyl carbon followed by nucleophilic addition of *P*-toluene forming the imine intermediate [A] through addition-elimination reaction. Next, the amino rich heterocycles (6-aminouracil) enamino carbon nucleophilic attack on the carbon of C] N group to the formation of intermediate [B] then, equilibrium shifted towards more stabilized enamine adduct [C]. In next step, the nucleophilic attack of amino group of enamine adduct on carbonyl of another molecule of isatin followed by intramolecular cycloaddition of –NH group to the C] N group of the formation of adduct [D] to afford the final product. The hydrogen bonding of [bmim]Br with the reaction reactant is in fact responsible for the stabilization of transition states and lowering of energetic barriers thus. In the present reaction, the hydrogen-bonding effect may be the key factor to facilitate the reaction and unique feature of [bmim]Br-IL creating noncovalent interactions with the reagents a fundamental role in the mechanism.

Scheme 3 Proposed mechanism.



We studied the reusability of ionic liquid [bmim]Br. It was observed that the recovered IL worked with good efficiency up to the third run showed in (Figure 2), while in the third and fourth runs the product yield decreased slightly.

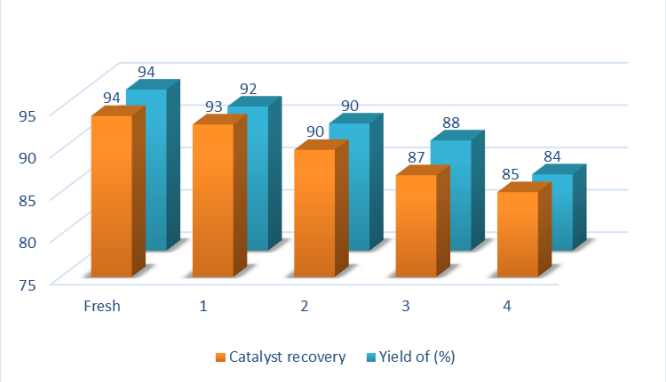


Figure 2 Recyclability of ionic liquid [bmim]Br

Conclusion

We have described an efficient one-pot three-component reaction of 6-amino-2-thiouracil/6-aminouracil/2-amino-1,3,4-thiadiazole, isatins and p-toluidine for the synthesis of dispiroheterocycles spiroannulated with pyrimido[4,5-*d*]pyrimidine derivatives in [BMIM]Br ionic liquid. This method has the advantages of milder reaction conditions, higher yields, convenient procedure, shorter reaction time, and environmental friendliness. Given the large number of commercially available building blocks, the present method should be applicable to synthesis of libraries with high diversity.

Experimental

General procedure

Chemical reagents in high purity were purchased from Merck and Aldrich and were used without further purification. Melting points were determined in open capillaries using an Electrothermal Mk3 apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DRX-400 spectrometer at 400 and 100 MHz respectively.

procedure for synthesis of [BMIM]Br Ionic liquid

6.57 g (0.03 mol) [BMIM]Br and 3.29 g (0.03 mol) $NaBF_4$ were added to the single mouth flask with a definite amount of acetone as solvent, for 10 h at 40°C under vigorous stirring. The reaction mixture was filtered, and vacuum distilled. Dichloromethane was added to the residue of [BMIM]Br and $NaBF_4$, and white solids precipitated were obtained. Then, the solid precipitate was separated by filtration. Finally, the product was vacuum dried in an oven at 80°C for 2 h to remove the traces of dichloromethane.

Typical procedure for synthesis of dispiroheterocycles

A mixture of 2-amino-1,3,4- thiadiazol/6-amino-2-thiouracil/6-aminouracil (1 mmol), isatin (2 mmol), *p*-toluidine (1 mmol) and ionic liquid [bmim]BF_4 (2 mL) were taken in round bottom flask and stirred and heated at 60°C for appropriate times (monitored by TLC). Then, water (6 mL) was added, and the product filtered off and washed with water. The aqueous layer containing the ionic liquid was extracted with diethyl ether (10 mL) for three times to remove remaining organic compound, then dried under vacuum at 90°C for about 13 h to afford ionic liquid, which was used in subsequent runs without further purification.

Spectral Data

3'-(*p*-tolyl)-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-*d*]pyrimidine-4',3''-indoline] 2,2'',5',7'(6'H,8'H)-tetraone (4a).

m.p. 298-300°C;^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.90-7.48 (m, 12H, ArH), 6.64 (s, 1H, NH), 2.35(s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.2, 168.7, 165.6, 164.8, 156.7, 150.7, 143.8, 143.2, 138.2, 133.5, 132.3, 131.4, 129.8, 129.2, 128.4, 126.4, 124.8, 123.7, 122.5, 121.2, 118.7, 98.6, 89.7, 81.5, 22.7. Anal. calcd. For $C_{27}H_{20}N_6O_4$: C 65.85, H 4.09, N 17.06%; found: C 65.22, H 3.77, N 16.98 %.

5,5''-dibromo-3'-(p-tolyl)-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-d]pyrimidine-4',3''-indoline]-2,2'',5',7'(6'H,8'H)-tetraone(4b).

m.p. 300-302°C; ^{1}H NMR (DMSO-d6, 400 MHz) δ (ppm): 6.93-7.51 (m, 10H, ArH) 6.66 (s, 1H, NH), 2.34(s, 3H, CH3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.3, 168.6, 166.2, 164.2, 156.8, 150.5, 143.5, 142.8, 136.3, 135.7, 133.7, 133.2, 132.5, 131.9, 131.3, 125.3, 124.6, 123.6, 121.6, 121.2, 118.5, 98.4, 89.6, 80.6, 22.7; Anal. calcd. For $C_{27}H_{18}Br_2N_6O_4$: C 49.87, H 2.79, N 12.92%; found: C 49.02, H 2.48 N 12.68 %.

5,5''-difluoro-3'-(*p*-tolyl)-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-d]pyrimidine-4',3''-indoline]-2,2'',5',7'(6'H,8'H)-tetraone (4c).

m.p. 295-297°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.88-7.70 (m, 10H, ArH), 6.62 (s, 1H, NH), 2.36 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.1, 168.7, 165.5, 164.8, 160.8, 160.3, 156.6, 150.4, 138.8, 138.3, 133.6, 132.5, 131.2, 130.6, 123.6, 119.3, 119.1, 116.8, 116.6, 113.9, 113.2, 98.4, 89.7, 81.4, 22.8; Anal. calcd. For $C_{27}H_{18}F_2N_6O_4$: C 61.36, H 3.43, N 15.90%; found: C 60.66, H 3.10, N 15.78 %.

5,5''-dinitro-3'-(*p*-tolyl)'-phenyl-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-d]pyrimidine-4',3''-indoline]-2,2'',5',7'(6'H,8'H)-tetraone (4d).

m.p. 296-298°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.92-8.40 (m, 10H, ArH), 6.68 (s, 1H, NH), 2.34(s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.3, 168.5, 165.3, 164.3, 156.9, 150.3, 148.7, 148.1, 146.7, 144.6, 133.9, 130.3, 131.7, 128.4, 127.3, 125.5, 124.4, 123.6, 118.2, 112.5, 110.0, 98.7, 80.8, 89.8, 22.8; Anal. calcd. For $C_{27}H_{18}N_8O_8$: C 55.67, H 3.11, N 19.24%; found: C 55.45, H 2.89, N 19.17 %.

5,5''-dimethyl-3'-(*p*-tolyl)-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-d]pyrimidine-4',3''-indoline]-2,2'',5',7'(6'H,8'H)-tetraone (4e).

m.p. 288-290°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.89-7.38 (m, 10H, ArH), 6.65 (s, 1H, NH), 2.33 (s, 3H, CH_3), 2.30(s, 6H, CH_3) ; ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.1, 168.8, 165.6, 164.7, 156.8, 150.8, 140.3, 139.9, 136.8, 135.6, 133.9, 133.2, 131.7, 131.1, 130.3, 129.8, 129.3, 123.7, 118.9, 116.7, 116.2, 98.5, 89.5, 81.8, 22.7,21.9; Anal. calcd. For $C_{29}H_{24}N_6O_4$: C 66.91, H 4.65, N 16.14%; found: C 66.37, H 4.35, N 16.02 %.

3'-(*p*-tolyl)-7'-thioxo-7',8'-dihydro-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-d] pyrimidine-4',3''-indoline]-2,2'',5'(6'H)-trione (5a).

m.p. 300-302°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.92(s, 1H, NH), 6.91-7.43 (m, 12H, ArH), 6.65 (s, 1H, NH), 2.32 (s, 3H, CH_3);^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.2, 168.7, 168.3, 164.8, 158.8, 150.7, 143.6, 143.1, 133.5, 138.3, 132.5, 131.9, 129.7, 129.5, 128.2, 126.6, 124.7, 123.7, 122.8, 121.5, 118.2, 95.3, 88.6, 81.2, 22.7; Anal. calcd. For $C_{27}H_{20}N_6O_3S$: C 63.77, H 3.96, N 16.53%; found: C 63.12, H 3.63, N 16.34 %.

5,5''-dibromo-3'-(*p*-tolyl)-7'-thioxo-7',8'-dihydro-1'H,3'H-dispiro[indoline-3,2'-pyrimido

[4,5-d]pyrimidine-4',3''-indoline]- 2,2'',5'(6'H)-trione (5b).

m.p. 297-300°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.75(s, 1H, NH), 6.93-7.45 (m, 10H, ArH), 6.67 (s, 1H, NH), 2.35 (s, 3H, CH_3);^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.5, 168.8, 168.5, 164.2, 158.8, 150.4, 143.7, 142.6, 136.4, 135.6, 133.5, 133.5, 132.6, 131.6, 131.2, 125.4, 124.9, 123.7, 121.6, 121.4, 118.3, 95.5, 89.6, 80.7, 22.7. Anal. calcd. For $C_{27}H_{18}Br_2N_6O_3S$: C 48.67, H 2.72, N 12.61%; found: C 48.47, H 2.45, N 12.32%.

5,5''-difluoro-3'-(*p*-tolyl)-7'-thioxo-7',8'-dihydro-1'H,3'H-dispiro[indoline-3,2'pyrimido[4,5-d]pyrimidine-4',3''-indoline]- 2,2'',5'(6'H)-trione (5c).

m.p. 292-294°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.83(s, 1H, NH), 2.36 (s, 3H, CH_3), 6.90-7.72 (m, 10H, ArH), 6.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.3, 168.5, 168.3, 164.8, 160.8, 160.1, 158.6, 138.9, 150.3, 138.2, 133.5, 132.6, 131.5, 130.5, 123.8, 119.5, 119.1, 117.9, 117.4, 113.6, 113.0, 95.4, 89.1, 81.5, 22.7. Anal. calcd. For $C_{27}H_{18}F_2N_6O_3S$: C 59.55, H 3.33, N 15.43%; found: C 59.15, H 3.02, N 15.22 %.

5,5''-dinitro-3'-(*p*-tolyl)-7'-thioxo-7',8'-dihydro-1'H,3'H-dispiro[indoline-3,2'-pyrimido[4,5-d]pyrimidine-4',3''-indoline]- 2,2'',5'(6'H)-trione (5d).

m.p. 294-296°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.89(s, 1H, NH), 6.95-8.42 (m, 10H, ArH), 6.69 (s, 1H, NH), 2.35 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.7, 168.9, 168.5, 165.1, 159.2, 150.6, 149.0, 148.4, 146.5, 144.6, 133.5, 130.6, 131.7, 127.4, 125.3, 124.6, 123.7, 118.3, 112.5, 110.5, 95.6, 89.8, 80.5, 128.7, 22.7. Anal. calcd. For $C_{27}H_{18}N_8O_7S$: C 54.18, H 3.03, N 18.72%; found: C 53.91, H 2.94, N 18.15 %.

5,5''-dimethyl-3'-(*p*-tolyl)-7'-thioxo-7',8'-dihydro-1'H,3'H-dispiro[indoline-3,2' pyrimido

[4,5-d]pyrimidine-4',3''-indoline]- 2,2'',5'(6'H)-trione (5e).

m.p. 300-302°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 9.95(s, 1H, NH), 6.88-7.41 (m, 10H, ArH), 6.64 (s, 1H, NH), 2.35 (s, 3H, CH_3), 2.32(s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.4, 168.8, 168.6, 164.5, 156.9, 150.6, 140.1, 139.8, 136.6, 135.6, 133.8, 133.5, 131.7, 131.3, 130.1, 129.9, 129.3, 123.5, 118.7, 116.9, 116.4, 95.5, 89.7, 81.6, 22.7, 21.8. Anal. calcd. For $C_{29}H_{24}N_6O_3S$: C 64.91, H 4.54, N 15.66%; found: C 64.33, H 4.20, N 15.04 %.

6'-(*p*-tolyl)-6'H-dispiro[indoline-3,5'-[1,3,4]thiadiazolo[3,2- a][1,3,5]triazine-7',3''-indoline]-2,2''-dione (6a).

m.p. 209-211°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.96 (s, 1H, ArH), 6.90-7.50 (m, 12H, ArH), 2.34 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.5, 168.8, 156.8, 151.6, 144.6, 144.2, 142.5, 140.1, 132.6, 131.8, 131.4, 130.1, 129.5, 129.2, 128.2, 126.7, 124.6, 118.9, 118.4, 116.8, 93.7, 89.8, 22.4. Anal. calcd. For $C_{25}H_{18}N_6O_2S$: C 64.37, H 3.89, N 18.01%; found: C 63.68, H 3.52, N 17.95 %.

5,5''-dibromo-6'-(*p*-tolyl)-6'H-dispiro[indoline-3,5'-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7',3''-indoline]-2,2''-dione (6b).

m.p. 225-227°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.98 (s, 1H, ArH), 6.92-7.60 (m, 10H, ArH), 2.32 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.3, 168.7, 156.5, 151.9, 143.3, 142.8, 142.3, 137.5, 137.3, 134.6, 133.4, 132.7, 132.2, 131.8, 124.6, 124.3, 123.8, 121.9, 121.5, 116.4, 93.5, 89.9, 22.4. Anal. calcd. For $C_{25}H_{16}Br_2N_6O_2S$: C 48.10, H 2.58, N 13.46%; found: C 47.90, H 2.29, N 13.25 %.

5,5''-difluoro-6'-(*p*-tolyl)-6'H-dispiro[indoline-3,5'-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7',3''-indoline]-2,2''-dione (6c).

m.p. 256-258°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.94 (s, 1H, ArH), 6.90-7.70 (m, 10H, ArH), 2.36 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ

(ppm): 169.4, 168.8, 158.7, 158.3, 156.2, 151.4, 138.6, 138.2, 134.7, 132.4, 131.5, 130.8, 124.6, 121.2, 120.5, 117.2, 116.9, 116.4, 115.7, 115.3, 93.4, 89.6; Anal. calcd. For $C_{25}H_{16}F_2N_6O_2S$: C 59.76, H 3.21, N 16.72%; found: C 59.40, H 3.07, N 16.49%.

5,5''-dinitro-6'-(*p*-tolyl)-6'H-dispiro[indoline-3,5'-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7',3''-indoline]-2,2''-dione (6d).

m.p. 236-238°C; ^{1}H NMR(DMSO-d_6, 400 MHz) δ (ppm): 7.99 (s, 1H, ArH), 6.91-8.40 (m, 10H, ArH), 2.37 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.5, 168.8, 156.8, 151.7, 149.8, 149.3, 148.6, 148.3, 132.7, 132.2, 131.5, 130.4, 127.7, 127.3, 126.2, 125.1, 124.6, 116.3, 112.7, 112.3, 93.7, 89.6,22.4; Anal. calcd. For $C_{25}H_{16}N_8O_6S$: C 53.96, H 2.90, N 20.14%; found: C 53.12, H 2.57, N 19.95%.

5,5''-dimethyl-6'-(*p*-tolyl)-6'H-dispiro[indoline-3,5'-[1,3,4]thiadiazolo[3,2-a][1,3,5]triazine-7',3''-indoline]-2,2''-dione (6e).

m.p. 222-224°C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 7.96 (s, 1H, NH), 6.89-7.48 (m, 10H, ArH), 2.35 (s, 3H, CH_3), 2.31(s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 169.7, 168.9, 156.4, 151.6, 142.4, 141.6, 137.2, 136.8, 134.1, 133.7, 132.6, 131.5, 130.9, 130.4, 129.9, 129.3, 124.1, 118.2, 117.5, 116.6, 93.8, 89.5, 22.4, 21.8; Anal. calcd. For $C_{27}H_{22}N_6O_2S$: C 65.57, H 4.48, N 16.99%; found: C 65.17, H 4.18, N 16.57%.

ASSOCIATED CONTENT

AUTHOR INFORMATION

Corresponding Author

Charansingh. H. Gill-Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India *Tel.: +919822037127; E-mail: chgill16@gmail.com.

ORCID Charansingh. H. Gill: 0000-0002-3419-8233

Author Contributions

The manuscript was written through the contributions of all authors. All authors have approved the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The author M.V.K. and C.K.J. is grateful to the Authority of Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad-431004, India, for providing laboratory facility. We are also thankful to BITS-Pilani and, SAIF, CSIR-CDRI, Lucknow, India. For providing spectral analysis data.

SUPPORTING INFORMATION

Analytical, spectroscopic data; a copy of ^{1}H NMR, and ^{13}C NMR spectra;(4a-e, 5a-e, 6a-e), (PDF).

References

[1] K. Verma, Y.K. Tailor, S. Khandelwal, E. Rushell, M. Agarwal, M. Kumar, Efficient and environmentally sustainable domino protocol for the synthesis of diversified spiroheterocycles with privileged heterocyclic substructures using bio-organic catalyst in aqueous medium., Mol. Divers. 24 (2020) 1355–1365. https://doi.org/10.1007/s11030-019-09999-4.

[2] P. Slobbe, E. Ruijter, R.V.A. Orru, Recent applications of multicomponent reactions in medicinal chemistry, Medchemcomm. 3 (2012) 1189. https://doi.org/10.1039/c2md20089a.

[3] L. Weber, The Application of Multi-Component Reactions in Drug Discovery, Curr. Med. Chem. 9 (2002) 2085–2093. https://doi.org/10.2174/0929867023368719.

[4] C.K. Jadhav, A.S. Nipate, A. V. Chate, V.S. Dofe, J.N. Sangshetti, V.M. Khedkar, C.H. Gill, Rapid Construction of Substituted Dihydrothiophene Ureidoformamides at Room Temperature Using Diisopropyl Ethyl Ammonium Acetate: A Green Perspective, ACS Omega. 5 (2020) 29055–29067. https://doi.org/10.1021/acsomega.0c03575.

[5] C.K. Jadhav, A.S. Nipate, A. V. Chate, V.D. Songire, A.P. Patil, C.H. Gill, Efficient Rapid Access to Biginelli for the Multicomponent Synthesis of 1,2,3,4-Tetrahydropyrimidines in Room-Temperature Diisopropyl Ethyl Ammonium Acetate, ACS Omega. 4 (2019) 22313–22324. https://doi.org/10.1021/acsomega.9b02286.

[6] L.Z. Fekri, M. Nikpassand, R. Maleki, 1,4-Diazabicyclo [2.2.2] octanium diacetate: As an effective, new and reusable catalyst for the synthesis of benzo[d]imidazole, J. Mol. Liq. 222 (2016) 77–81. https://doi.org/10.1016/j.molliq.2016.07.009.

[7] M. Nikpassand, L. Fekri, S. Sahrapeima, S. Shariati, Synthesis of Bis Coumarinyl Methanes Using Fe3O4@SiO2@KIT-6 as an Efficient and Reusable Catalyst, Lett. Org. Chem. 13 (2016) 578–584. https://doi.org/10.2174/1570178613666160927111534.

[8] X.-B. Chen, S.-L. Xiong, Z.-X. Xie, Y.-C. Wang, W. Liu, Three-Component One-Pot Synthesis of Highly Functionalized Bis-Indole Derivatives, ACS Omega. 4 (2019) 11832–11837. https://doi.org/10.1021/acsomega.9b01159.

[9] Y. Hayashi, Pot economy and one-pot synthesis, Chem. Sci. 7 (2016) 866–880. https://doi.org/10.1039/C5SC02913A.

[10] Z. El Asri, Y. Génisson, F. Guillen, O. Baslé, N. Isambert, M. del Mar Sanchez Duque, S. Ladeira, J. Rodriguez, T. Constantieux, J.-C. Plaquevent, Multicomponent reactions in ionic liquids: convenient and ecocompatible access to the 2,6-DABCO core, Green Chem. 13 (2011) 2549.

https://doi.org/10.1039/c1gc15635g.

[11] E. Rushell, Y.K. Tailor, S. Khandewal, K. Verma, M. Agarwal, M. Kumar, Deep eutectic solvent promoted synthesis of structurally diverse hybrid molecules with privileged heterocyclic substructures, New J. Chem. 43 (2019) 12462–12467. https://doi.org/10.1039/C9NJ02694K.

[12] S.K. Singh, K.N. Singh, Eco-friendly and facile one-pot multicomponent synthesis of acridinediones in water under microwave, J. Heterocycl. Chem. 48 (2011) 69–73. https://doi.org/10.1002/jhet.508.

[13] M. Nikpassand, S. Atrchian, Chemical Review and Letters DFT study of azo linkage effect on homoaromatization of some 1,4-dihydropryridines, Chem Rev Lett. 3 (2020) 53–60. https://doi.org/10.22034/crl.2020.220974.1038.

[14] L. R. Melo, W. A. Silva, Ionic Liquid in Multicomponent Reactions: A Brief Review, Curr. Green Chem. 3 (2016) 120–132. https://doi.org/10.2174/2213346103666160530143059.

[15] A.J. Greer, J. Jacquemin, C. Hardacre, Industrial Applications of Ionic Liquids, Molecules. 25 (2020) 5207. https://doi.org/10.3390/molecules25215207.

[16] I.R. Siddiqui, D. Kumar, S. Shamim, Ionic Liquid Promoted Multicomponent Reaction: A Good Strategy for the Eco-Compatible Synthesis of Functionalized Pyrroles, J. Heterocycl. Chem. 50 (2013) E111–E115. https://doi.org/10.1002/jhet.1085.

[17] A.A. Abdelhamid, H.A. Salah, A.A. Marzouk, Synthesis of imidazole derivatives: Ester and hydrazide compounds with antioxidant activity using ionic liquid as an efficient catalyst, J. Heterocycl. Chem. 57 (2020) 676–685. https://doi.org/10.1002/jhet.3808.

[18] S.S. Mansoor, K. Aswin, K. Logaiya, S.P.N. Sudhan, [Bmim]BF 4 ionic liquid: An efficient reaction medium for the one-pot multi-component synthesis of 2-amino-4,6-diphenylpyridine-3-carbonitrile derivatives, J. Saudi Chem. Soc. 20 (2016) 517–522. https://doi.org/10.1016/j.jscs.2012.07.011.

[19] B. Jiang, T. Rajale, W. Wever, S.-J. Tu, G. Li, Multicomponent Reactions for the Synthesis of Heterocycles, Chem. - An Asian J. 5 (2010) 2318–2335. https://doi.org/10.1002/asia.201000310.

[20] J.E. Biggs-Houck, A. Younai, J.T. Shaw, Recent advances in multicomponent reactions for diversity-oriented synthesis, Curr. Opin. Chem. Biol. 14 (2010) 371–382. https://doi.org/10.1016/j.cbpa.2010.03.003.

[21] A.M. Shahi, M. Nikpassand, L.Z. Fekri, Acidic Ionic Liquid-catalyzed Synthesis of Pyrano[4,3-b]pyran-5(4H)-ones using 4,4,4-trifluoro-1-phenylbutane-1,3-dione as a Building Block, Curr. Org. Synth. 17 (2020) 648–653. https://doi.org/10.2174/1570179417666200520111536.

[22] A.M. Shahi, M. Nikpassand, L.Z. Fekri, An Efficient and Green Synthesis of New Benzo[f]chromenes Using 1,4-Disulfo-1,4-diazoniabicyclo[2.2.2]octane Chloride as a Novel Medium, Org. Prep. Proced. Int. 51 (2019) 521–529. https://doi.org/10.1080/00304948.2019.1666637.

[23] H. Taherkhorsand, M. Nikpassand, One-pot Synthesis of Novel 2-pyrazolo-3-phenyl-1,3-thiazolidine-4-ones Using DSDABCOC as an Effective Media, Comb. Chem. High Throughput Screen. 21 (2018) 65–69. https://doi.org/10.2174/1386207321666180124090455.

[24] Z. Gharib, M. Nikpassand, 3,3-(Butane-1,4-diyl)bis(1,2-dimethyl-1H-imidazole-3-ium)bromide–cerium(IV) ammonium nitrate: A novel reagent for mild synthesis of 12-aryldibenzo[i,b]pyrano[4,3-b]chromenone of benzyl alcohols, Russ. J. Gen. Chem. 86 (2016) 2759–2767. https://doi.org/10.1134/S1070363216120379.

[25] C. Zhou, J. Min, Z. Liu, A. Young, H. Deshazer, T. Gao, Y.-T. Chang, N.R. Kallenbach, Synthesis and biological evaluation of novel 1,3,5-triazine derivatives as antimicrobial agents, Bioorg. Med. Chem. Lett. 18 (2008) 1308–1311. https://doi.org/10.1016/j.bmcl.2008.01.031.

[26] N.C. Desai, A.H. Makwana, K.M. Rajpara, Synthesis and study of 1,3,5-triazine based thiazole derivatives as antimicrobial agents, J. Saudi Chem. Soc. 20 (2016) S334–S341. https://doi.org/10.1016/j.jscs.2012.12.004.

[27] V. Dubey, M. Pathak, H.R. Bhat, U.P. Singh, Design, Facile Synthesis, and Antibacterial Activity of Hybrid 1,3,4-thiadiazole-1,3,5-triazine Derivatives Tethered via -S- Bridge, Chem. Biol. Drug Des. 80 (2012) 598–604. https://doi.org/10.1111/j.1747-0285.2012.01433.x.

[28] R.P. Modh, E. De Clercq, C. Pannecouque, K.H. Chikhalia, Design, synthesis, antimicrobial activity and anti-HIV activity evaluation of novel hybrid quinazoline–triazine derivatives, J. Enzyme Inhib. Med. Chem. 29 (2014) 100–108. https://doi.org/10.3109/14756366.2012.755622.

[29] K.M. Al-Zaydi, H.H. Khalil, A. El-Faham, S.N. Khattab, Synthesis, characterization and evaluation of 1,3,5-triazine aminobenzoic acid derivatives for their antimicrobial activity, Chem. Cent. J. 11 (2017) 39. https://doi.org/10.1186/s13065-017-0267-3.

[30] W. Yan, Y. Zhao, J. He, Anti- breast cancer activity of selected 1,3,5- triazines via modulation of EGFR- TK., Mol. Med. Rep. 18 (2018) 4175–4184. https://doi.org/10.3892/mmr.2018.9426.

[31] M. Venkatraj, I.G. Salado, J. Heeres, J. Joossens, P.J. Lewi, G. Caljon, L. Maes, P. Van der Veken, K. Augustyns, Novel triazine dimers with potent antitrypanosomal activity., Eur. J. Med. Chem. 143 (2018) 306–319. https://doi.org/10.1016/j.ejmech.2017.11.075.

[32] H.R. Bhat, U.P. Singh, P. Gahtori, S.K. Ghosh, K. Gogoi, A. Prakash, R.K. Singh, 4-Aminoquinoline-1,3,5-triazine: Design, synthesis, in vitro antimalarial activity and docking studies, New J. Chem. 37 (2013) 2654. https://doi.org/10.1039/c3nj00317e.

[33] H.H. Al Rasheed, A.M. Malebari, K.A. Dahlous, D. Fayne, A. El-Faham, Synthesis, Anti-proliferative Activity, and Molecular Docking Study of New Series of 1,3-5-Triazine Schiff Base Derivatives, Molecules. 25 (2020) 4065. https://doi.org/10.3390/molecules25184065.

[34] N. Lolak, S. Akocak, S. Bua, C.T. Supuran, Design, synthesis and biological evaluation of novel ureido benzenesulfonamides incorporating 1,3,5-triazine moieties as potent carbonic anhydrase IX inhibitors, Bioorg. Chem. 82 (2019) 117–122. https://doi.org/10.1016/j.bioorg.2018.10.005.

[35] G.B. Bennett, R.B. Mason, L.J. Alden, J.B. Roach, Synthesis and antiinflammatory activity of trisubstituted pyrimidines and triazines, J. Med. Chem. 21 (1978) 623–628. https://doi.org/10.1021/jm00205a006.

[36] E. Havránková, J. Csöllei, P. Pazdera, New Approach for the One-Pot Synthesis of 1,3,5-Triazine Derivatives: Application of Cu(I) Supported on a Weakly Acidic Cation-Exchanger Resin in a Comparative Study, Molecules. 24 (2019) 3586. https://doi.org/10.3390/molecules24193586.

[37] R. Santosh, P. Paul, M.K. Selvam, C. Raril, P.M. Krishna, J.G. Manjunatha, G.K. Nagaraja, One-Pot Synthesis of Pyrimido[4,5-d]pyrimidine Derivatives and Investigation of Their Antibacterial, Antioxidant, DNA-Binding and Voltammetric Characteristics, ChemistrySelect. 4 (2019) 990–996. https://doi.org/10.1002/slct.201803416.

[38] Y. Diao, X. Fang, P. Song, M. Lai, L. Tong, Y. Hao, D. Dou, Y. Liu, J. Ding, Z. Zhao, H. Xie, H. Li, Discovery and Biological evaluation of pyrimido[4,5-d]pyrimidine-2,4(1H,3H)-dione derivatives as potent Bruton's tyrosine kinase inhibitors, Bioorg. Med. Chem. 27 (2019) 3390–3395. https://doi.org/10.1016/j.bmc.2019.06.023.

[39] T. Venkatesh, Y.D. Bodke, A.R.S. J, Facile CAN catalyzed one pot synthesis of novel indol-5,8-pyrimido[4,5-d]pyrimidine derivatives and their pharmacological study, Chem. Data Collect. 25 (2020) 100335. https://doi.org/10.1016/j.cdc.2019.100335.

[40] P. Sharma, N. Rane, V.. Gurram, Synthesis and QSAR studies of pyrimido[4,5-d]pyrimidine-2,5-dione derivatives as potential antimicrobial agents, Bioorg. Med. Chem. Lett. 14 (2004) 4185–4190. https://doi.org/10.1016/j.bmcl.2004.06.014.

[41] V.J. Ram, A. Goel, S. Sarkhel, P.R. Maulik, A Convenient Synthesis and Hepatoprotective Activity of Imidazo[1,2- c]pyrimido[5,4- e]pyrimidine, Tetraazaacenaphthene and Tetraazaphenalene from Cyclic Ketene Aminals Through Tandem Addition-Cyclization Reactions ‡ ‡CDRI communication number 5986., Bioorg. Med. Chem. 10 (2002) 1275–1280. https://doi.org/10.1016/S0968-0896(01)00423-0.

[42] P. Perlíková, M. Hocek, Pyrrolo[2,3- d]pyrimidine (7-deazapurine) as a privileged scaffold in design of antitumor and antiviral nucleosides, Med. Res. Rev. 37 (2017) 1429–1460. https://doi.org/10.1002/med.21465.

[43] L. Suresh, P. Sagar Vijay Kumar, Y. Poornachandra, C. Ganesh Kumar, G.V.P. Chandramouli, Design, synthesis and evaluation of novel pyrazolo-pyrimido[4,5- d]pyrimidine derivatives as potent antibacterial and biofilm inhibitors, Bioorg. Med. Chem. Lett. 27 (2017) 1451–1457. https://doi.org/10.1016/j.bmcl.2017.01.087.

[44] A.Y. Aksinenko, T. V. Goreva, T.A. Epishina, S. V. Trepalin, V.B. Sokolov, Synthesis of bis(trifluoromethyl)pyrimido[4,5-d]pyrimidine-2,4-diones and evaluation of their antibacterial and antifungal activities, J. Fluor. Chem. 188 (2016) 191–195. https://doi.org/10.1016/j.jfluchem.2016.06.019.

[45] A.R. Suresh Babu, D. Gavaskar, R. Raghunathan, A facile synthesis of novel ferrocene grafted spiro-indenoquinoxaline pyrrolizidines via one-pot multicomponent [3+2] cycloaddition of azomethine ylides, Tetrahedron Lett. 53 (2012) 6676–6681. https://doi.org/10.1016/j.tetlet.2012.09.104.

[46] M. Zhang, W. Yang, K. Li, K. Sun, J. Ding, L. Yang, C. Zhu, Facile Synthesis of Dispiroheterocycles through One-Pot [3+2] Cycloaddition, and Their Antiviral Activity, Synthesis (Stuttg). 51 (2019) 3847–3858. https://doi.org/10.1055/s-0037-1611900.

[47] K. Martina, S. Tagliapietra, V. V. Veselov, G. Cravotto, Green Protocols in Heterocycle Syntheses via 1,3-Dipolar Cycloadditions, Front. Chem. 7 (2019) 1–21. https://doi.org/10.3389/fchem.2019.00095.

[48] A. V. Chate, S.P. Kamdi, A.N. Bhagat, C.K. Jadhav, A. Nipte, A.P. Sarkate, S. V. Tiwari, C.H. Gill, Design, Synthesis and SAR Study of Novel Spiro [Pyrimido[5,4-b]Quinoline-10,5′-Pyrrolo[2,3-d]Pyrimidine] Derivatives as Promising Anticancer Agents, J. Heterocycl. Chem. 55 (2018) 2297–2302. https://doi.org/10.1002/jhet.3286.

[49] V.S. Dofe, A.P. Sarkate, Z.M. Shaikh, C.K. Jadhav, A.S. Nipte, C.H. Gill, Ultrasound-assisted Synthesis of Novel Pyrazole and Pyrimidine Derivatives as Antimicrobial Agents, J. Heterocycl. Chem. 55 (2018) 756–762. https://doi.org/10.1002/jhet.3105.

[50] A.S. Nipate, C.K. Jadhav, A. V. Chate, K.S. Taur, C.H. Gill, β- Cyclodextrin catalyzed access to fused 1,8- dihydroimidazo[2,3- b]indoles via one- pot multicomponent cascade in aqueous ethanol: Supramolecular approach toward sustainability, J. Heterocycl. Chem. 57 (2020) 820–829. https://doi.org/10.1002/jhet.3828.

[51] A. V. Chate, A.S. Kulkarni, C.K. Jadhav, A.S. Nipte, G.M. Bondle, Multicomponent reactions and supramolecular catalyst: A perfect synergy for eco- compatible synthesis of pyrido[2,3- d]pyrimidines in water, J. Heterocycl. Chem. 57 (2020) 2184–2193. https://doi.org/10.1002/jhet.3938.

[52] C.K. Jadhav, A.S. Nipate, A. V. Chate, A.P. Patil, C.H. Gill, Ionic liquid catalyzed one- pot multi- component synthesis of fused <scp>pyridine derivatives</scp> : <scp>A strategy</scp> for green and sustainable chemistry, J. Heterocycl. Chem. 57 (2020) 4291–4303. https://doi.org/10.1002/jhet.4135.

[53] C.K. Jadhav, A.S. Nipate, A. V. Chate, P.M. Kamble, G.A. Kadam, V.S. Dofe, V.M. Khedkar, C.H. Gill, Room temperature ionic liquid promoted improved and rapid synthesis of highly functionalized imidazole and evaluation of their inhibitory activity against human cancer cells, J. Chinese Chem. Soc. (2021) jccs.202000468. https://doi.org/10.1002/jccs.202000468.