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Efficient one-pot four-component synthesis of fused thiazolopyridin-2-ones in ionic liquid

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Abstract. An efficient one-pot synthesis of fused thiazolopyridinone derivatives (5-amino-6,7-diphenyl-4,7-dihydro-3H-thiazolo[4,5-b]pyridin-2-ones) by four-component reaction of aldehyde, benzylcyanide, ammonium acetate and thiazolidine-2,4-dione in ionic liquid is reported. This protocol has the advantages of environmental friendliness, higher yields, less reaction time, and convenient operation. Also, optimization of the synthesized compounds has been done using Hyperchem 8.0.

Keywords. One-pot synthesis; thiazolopyridinone derivatives; multicomponent reactions; ionic liquid.

1. Introduction

Multi-component reactions (MCRs) in which several reactions are combined into one synthetic operation has been used extensively to form carbon–carbon bonds in the synthetic chemistry. Such reactions offer a wide range of possibilities for the efficient construction of highly complex molecules in a single procedure step, thus avoiding the complicated purification operations and allowing savings of both solvents and reagents. Thus, they are perfectly amenable to automation for combinatorial synthesis. In the last few decades, there have been tremendous development in three- as well as four-component reactions and greater efforts are being continued to develop new MCRs. Thiazoles and pyrazoles are gaining importance in medicinal and organic chemistry. They have shown broad spectrum of pharmacological and biological activities, such as antibacterial, antidepressant, antihyperglycemic, antiinflammatory, and antitumour.[1–6] Many of the methods reported for the synthesis of organic compounds are associated with the use of hazardous organic solvents, long reaction time, and lack of general applicability.[7]

Room temperature ionic liquids (RTILs), have shown as an attractive substitute to conventional organic solvents, and more attention has been currently drawn on organic reactions promoted by ionic liquids. They are non-volatile, recyclable, eco-friendly, non-explosive, easily operable, and thermally robust.[8–10] We described here a simple and efficient synthesis of thiazolopyridinone derivatives (5-amino-6,7-diphenyl-4,7-dihydro-3H-thiazolo[4,5-b]pyridin-2-ones) by four-component reaction of aldehyde, benzonitrile, ammonium acetate and thiazolidine-2,4-dione in ionic liquid without any catalyst. Also, the optimization and QSAR properties of the synthesized compounds have been evaluated using Hyperchem 8.0.

2. Experimental

2.1 *General information*

Unless indicated, reagents and solvents were purchased from SRL and Merck, India Aldrich chemicals and used without purification, with the following exceptions. Methanol and dimethyl formamide were distilled from calcium hydride under nitrogen. Flash column chromatography was performed using silica gel 60 (Merck) with indicated solvents. Thin-layer chromatography (TLC) was performed using Kieselgel F_{254} plates (Merck). Infrared spectra were recorded on a Jasco FT/IR 430 spectrometer. ^{1}H- and ^{13}C-NMR

*For correspondence

spectra were recorded on Toxi-Spin 300 MHz spectrometer as solutions in deuteriochloroform ($CDCl_3$) or deuteriodimethyl sulphoxide ($(CD_3)_2SO$). Chemical shifts are expressed in parts per million (ppm, δ) downfield from an internal standard, tetramethylsilane. Optimization of the synthesized compounds has been done using Hyperchem 8.0.

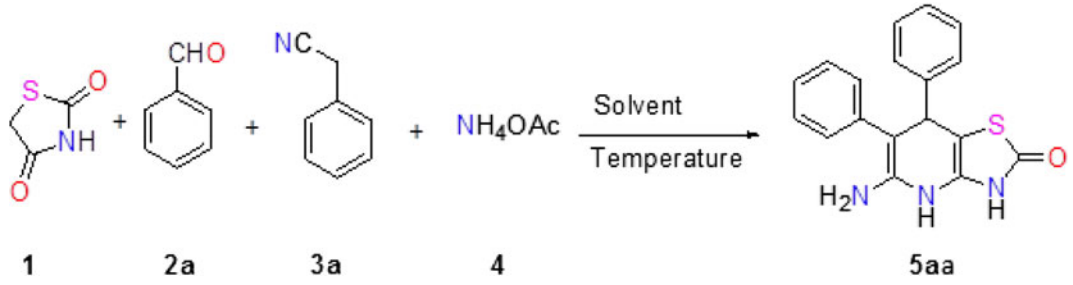
2.2 *General procedure for the synthesis of thiazolopyridinone (compound **5aa**)*

A dry 100 mL flask was charged with thiazolidine-2, 4-dione **1** (5 mmol), benzaldehyde **2a** (5 mmol), benzylcyanide **3a** (5 mmol) and ammonium acetate **4** (5.2 mmol), and ionic liquid [bmim]Br (15 mL). The mixture was stirred at 90°C for appropriate time to complete the reaction and it was monitored by thin-layer chromatography. Then, 50 mL water was added. The solid was filtered off and washed with water. The crude product was purified by recrystallization from ethanol to afford the product and well characterized by FTIR, proton and carbon NMR, which confirm the sturcture of the compound.

Similarly, other derivatives are being synthesized by varying the reactants and characterized by FTIR, proton and carbon NMR techniques.

3. Result and discussion

To overcome the disadvantages such as volatility and toxicity (many organic solvents inherently have), we employed RTILs into the four-component reaction as



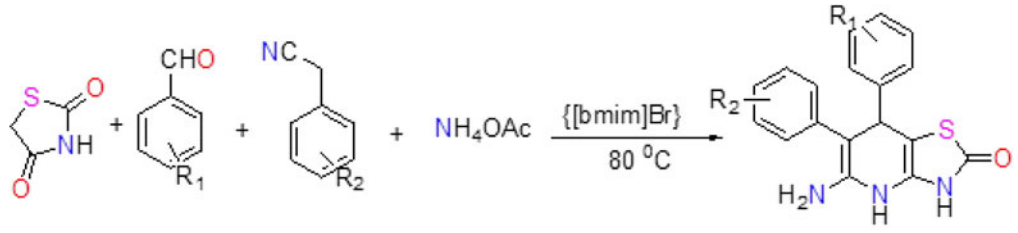
Scheme 1. One-pot synthesis of thiazolopyridin-2-ones.

Table 1. Optimization of reaction conditions (solvent, mol ratio and temperature of the reactants) for the catalyst-free multicomponent reactions.[a]

Sl. No.	Solvent	Mol ratio (1:2a:3a:4)	Time (h)	Temp (°C)	Yield (%)
1	Dioxane	1:1:1:1	8	30	65
2	Acetonitrile	1:1:1:1	10	30	64
3	DMF	1:1:1:1	12	30	65
4	Toluene	1:1:1:1	8	30	50
5	Water	1:1:1:1	60	30	No reaction
6	DMSO	1:1:1:1	12	30	55
7	THF	1:1:1:1	6	30	70
8	[Net_3][Ac]	1:1:1:1	3	30	80
9	[bmim][Cl]	1:1:1:1	3	30	78
10	[bmim][Br]	1:1:1:1	2	30	80
11	[bmim][Br]	1:1:1:1.1	2	30	82
12	[bmim][Br]	1:1:1.1:1.1	2	30	84
13	[bmim][Br]	1:1:1:1.2	2	30	79
14	[bmim][Br]	1:1:1:0.9	2	30	72
15	[bmim][Br]	1:1:1:0.8	2	30	65
16	[bmim][Br]	1:1:1.1:1.1	2	45	82
17	[bmim][Br]	1:1:1.1:1.1	2	60	90
18	[bmim][Br]	1:1:1.1:1.1	2	80	94

[a]Reactions were carried out amongst thiazolidine-2,4-dione (**1**), benzaldehyde (**2a**), benzylcyanide (**3a**) and ammonium acetate (**4**) in a solvent (15 mL)

Table 2. Catalyst-free one-pot synthesis of 9-phenyl-3,9-dihydro-chromeno [2,3-d] thiazol-2-one via MCRs in thiazolidine-2,4-dione, aromatic aldehyde and urea derivative.



1 **2a** **3a** **4** **5aa**

Equivalent 1 : 1 : 1.1 : 1.1

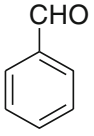
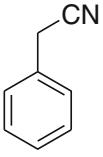
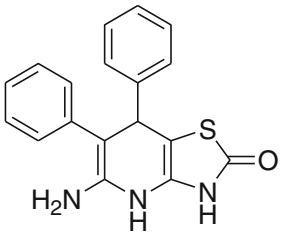
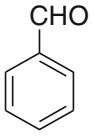
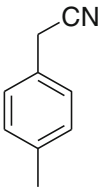
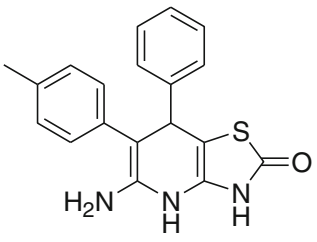
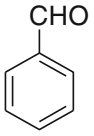
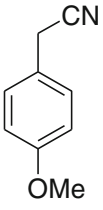
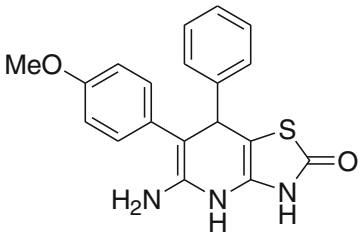
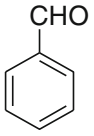
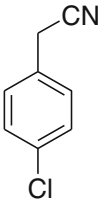
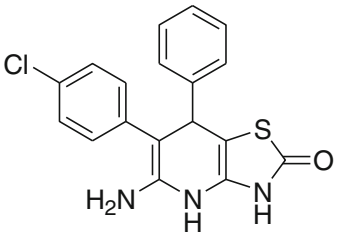
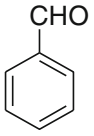
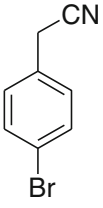
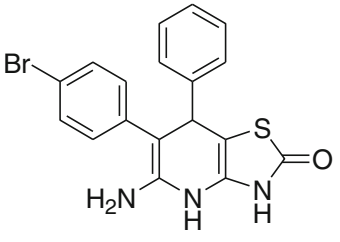
Sl. No.	Reactant[2]	Reactant[3]	Product	Compound no.	Time (h)	Yield (%)
1				**5aa**	2.5	94
2				**5ab**	2.5	88
3				**5ac**	2.5	90
4				**5ad**	2.5	95
5				**5ae**	4.0	90

Table 2. (Continued).

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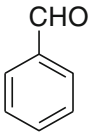
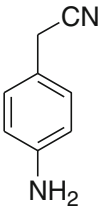
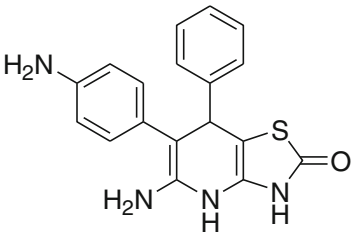
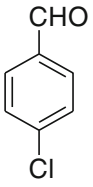
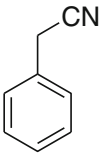
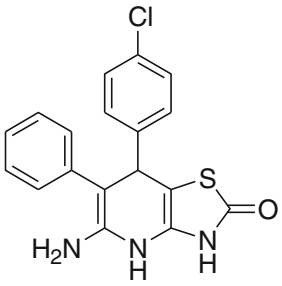
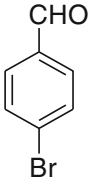
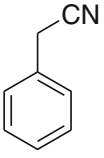
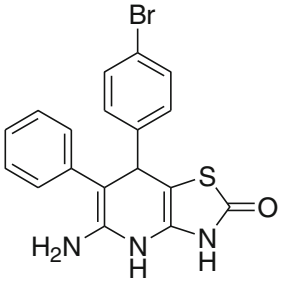
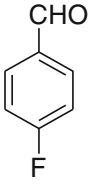
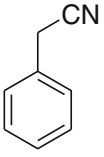
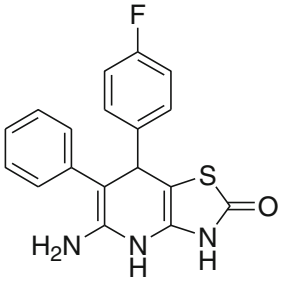
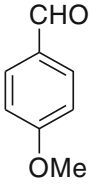
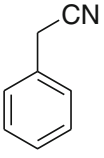
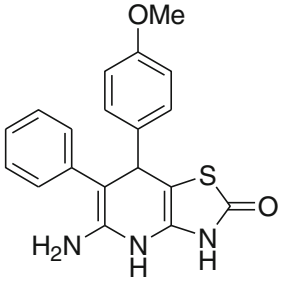
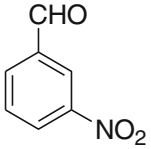
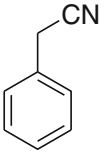
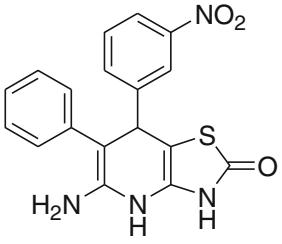
6				**5af**	5.0	98
7				**5ag**	6.0	90
8				**5ah**	7.5	85
9				**5ai**	4.0	85
10				**5aj**	9.5	84
11				**5ak**	8.5	90

a green medium. Initially, the four-component reaction of thiazolidine-2, 4-dione **1**, benzaldehyde **2a**, benzylcyanide **3a** and ammonium acetate **4** as a simple model substrate was investigated to establish the feasibility of the strategy and to optimize the reaction conditions to afford **5aa** (scheme 1).

Table 2. (Continued).

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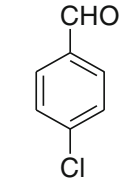
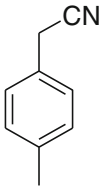
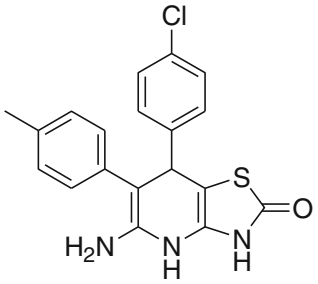
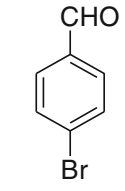
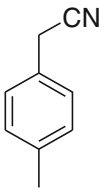
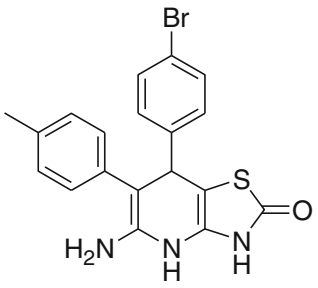
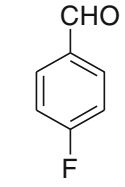
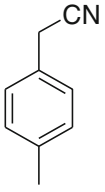
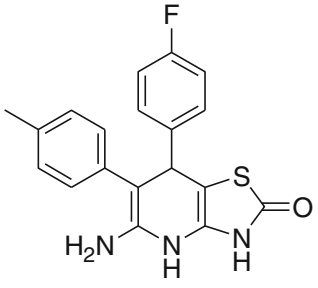
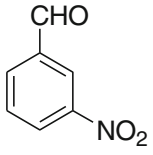
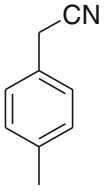
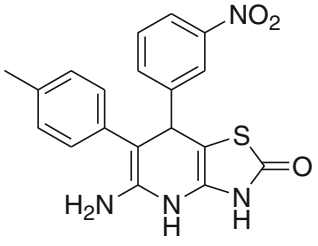
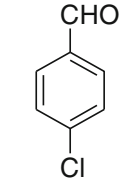
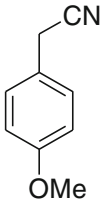
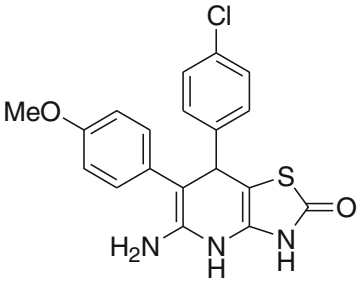
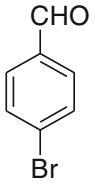
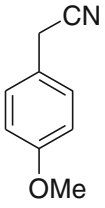
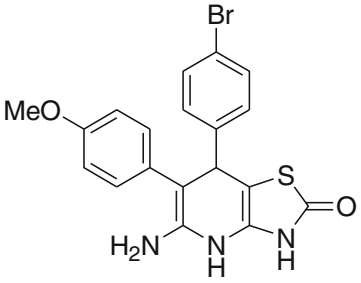
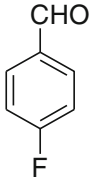
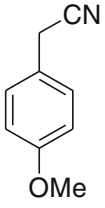
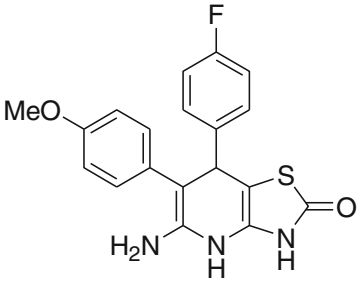
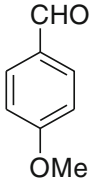
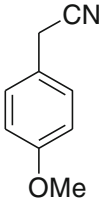
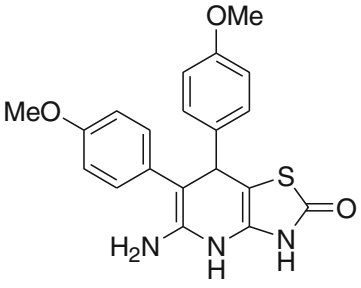
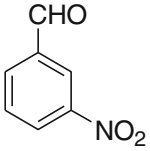
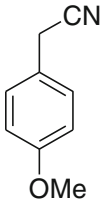
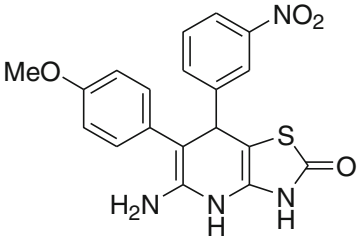
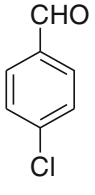
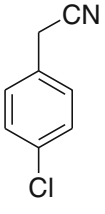
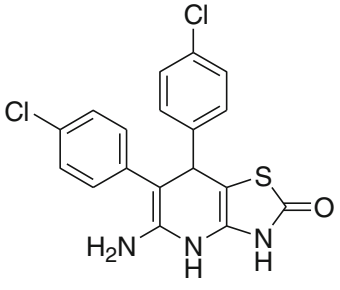
12				**5al**	8.5	92
13				**5am**	3.0	95
14				**5an**	4.0	89
15				**5ao**	7.0	90
16				**5ap**	4.5	80

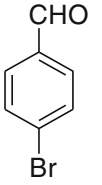
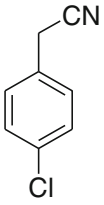
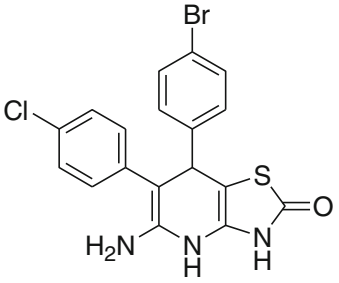
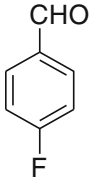
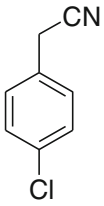
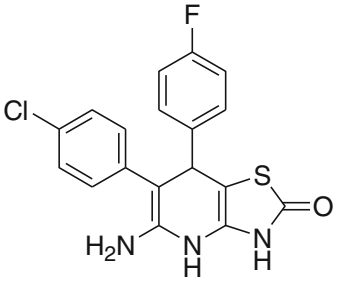
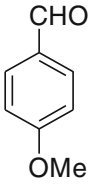
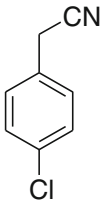
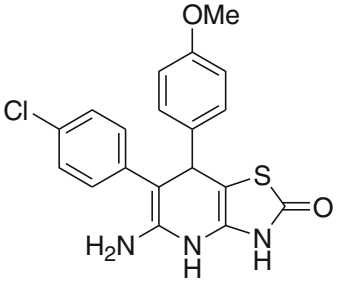
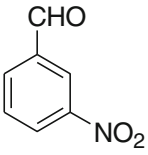
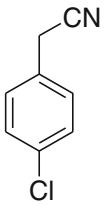
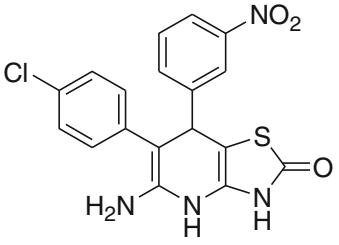
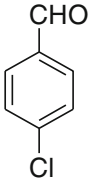
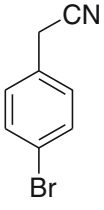
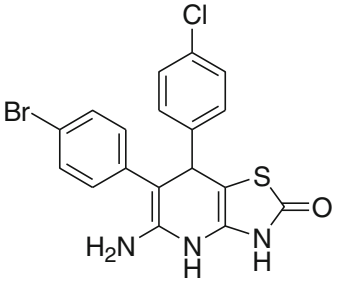
Screening of the reaction conditions was established by using suitable solvents, the mol ratio of reactants as well as temperature for the desired MCRs (table 1). It was exciting that the chosen solvents such as dioxane, N,N–dimethylformamide (DMF), acetonitrile (CH_3CN), dimethylsulphoxide (DMSO), toluene,

Table 2. (Continued).

Sl. No.	Reactant[2]	Reactant[3]	Product	Compound no.	Time (h)	Yield (%)
17				**5aq**	6.5	86
18				**5ar**	2.5	87
19				**5as**	3.5	87
20				**5at**	5.5	90
21				**5au**	6.5	94

etc. were suitable for the MCRs (table 1, entries 1–10). Ionic liquid ([bmim]Br) proved to be the best among them (table 1, entry 10). While under water, no product has been formed even after 60 h (table 1, entry 5). To modulate the ratio of reactants and improve the yield, we examined various ratios of thiazolidine-2, 4-dione

Table 2. (Continued).

Sl. No.	Reactant[2]	Reactant[3]	Product	Compound no.	Time (h)	Yield (%)
22				**5av**	8.0	80
23				**5aw**	9.0	82
24				**5ax**	2.0	87
25				**5ay**	2.5	89
26				**5ap**	3.0	92

1, benzaldehyde **2a**, benzylcyanide **3a** and ammonium acetate **4** by using acetonitrile as a solvent (table 1, entries 11–15). The best result obtained when the ratio of thiazolidine-2, 4-dione **1**, benzaldehyde **2a**, benzylcyanide **3a** and ammonium acetate **4** is 1:1:1.1:1.1 to afford the product **4a** i.e., entry 12. Further, optimization of temperature was done (table 1, entries 16–18) and we found the best yield at 90°C (entry 17). With the optimized conditions in hand, we examined the scope of the multicomponent reaction (table 2, entries 1–30). We found that the reaction proceeded smoothly, and the desired products in excellent yields. The ionic liquid used for the transformation was recovered and used for further reaction and to obtain good yields (table 3).

Hyperchem 8.0 is a powerful computational software developed by Hypercube Inc, Gainsville USA for molecular and quantum mechanics calculations. To understand the properties of a designated molecule, we need to generate a well-defined structure that represents a minimum on a potential energy surface. Hyperchem provides parameters to enable geometry optimization so as to deduce a structure with minimum energy. The QSAR approach has proved extremely useful to identify and quantify the physico-chemical properties of an organic molecule. The geometry of thiazolidine-2, 4-dione and its derivatives has been optimized based on semi-empirical calculations, using the molecular modelling program Hyperchem 8.0. Various parameters

Table 2. (Continued).

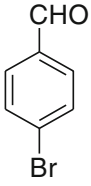
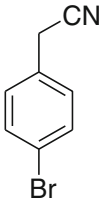
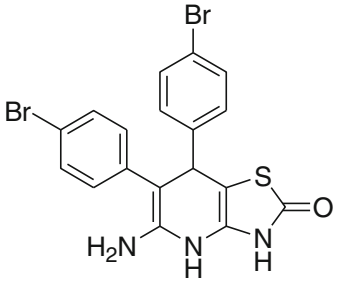
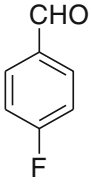
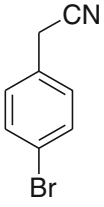
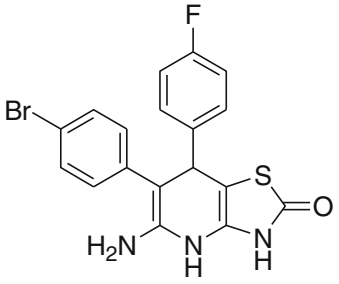
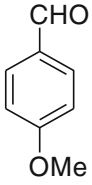
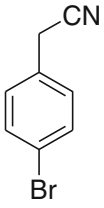
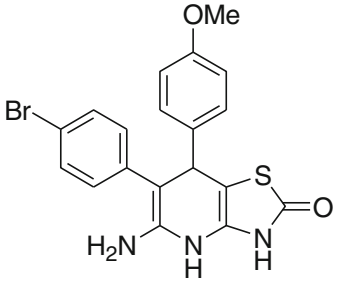
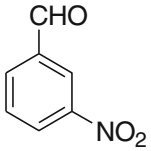
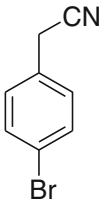
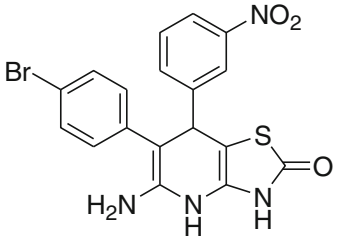
Sl. No.	Reactant[2]	Reactant[3]	Product	Compound no.	Time (h)	Yield (%)
27				**5ba**	3.0	90
28				**5bb**	2.5	86
29				**5bc**	5.5	86
30				**5bd**	6.5	85

Table 3. Optimization of the activity of ionic liquid after reuse.

Sl. No.	No. of cycle	Yield (%)
1	I	94
3	II	94
3	III	92
4	IV	92
5	V	90

were applied to calculate molecular properties of synthesized compounds like surface area, volume, refractivity, polarizability, hydrophobicity (Log P), and hydration energy. The structure of thiazolidine-2,4-dione was taken from invoke database using single point calculation parameter, the molecular energy and gradient for a given fixed geometry was set. Further geometry optimization calculations were employed for energy minimization algorithms to find the most stable conformation. Geometry optimization was taken as criteria to determine the most stable conformer for compounds as in table S1. Hydrophobicities of compounds can be readily determined by measuring partition coefficients designated as P. Partition coefficients dealing with neutral species. By convention, P is defined as the ratio of concentration of the drugs in octanol to its concentration in water. More the value of log P, more will be the hydrophobicity. The values for log P and other parameters for the following pairs {(**5aa** and **5ab**), (**5ap**, **5aq** and **5as**), (**5au** and **5av**) and (**5aw** and **5ax**)} are of same values for the compounds as in table S1. Log P value for the synthesized compounds varies from -0.58 to -2.36 which indicates that lesser the value of log P, more will be hydrophilic. Therefore, compound **5ar** is the most hydrophilic in nature.

4. Conclusion

We have described an efficient one-pot, four-component reaction of thiazolidine-2, 4-dione, benzaldehyde, benzonitrile and ammonium acetate, for the synthesis of 5-amino-6,7-diphenyl-4,7-dihydro-3H-thiazolo[4,5-b]pyridin-2-one derivatives in ionic liquid {[bmim]Br}. This method has the advantages of high yields, mild reaction conditions, short reaction time, convenient procedure, 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.

Supplementary information

Table S1 and analytical data can be seen in www.ias.ac.in/chemsci website.

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