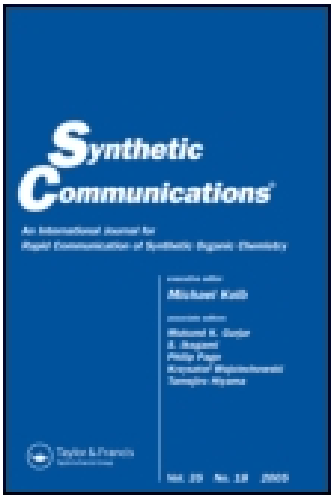

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Room-Temperature Ionic Liquid-DMSO Promoted and Improved One-Pot Synthesis of 5,6-Diaryl-1,2,4-triazines

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ROOM-TEMPERATURE IONIC LIQUID–DMSO PROMOTED AND IMPROVED ONE-POT SYNTHESIS OF 5,6-DIARYL-1,2,4-TRIAZINES

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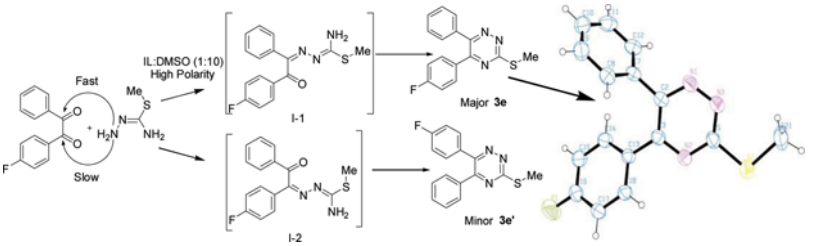
GRAPHICAL ABSTRACT



Abstract *An improved and rapid one-pot synthesis of 5,6-diarylsubstituted-1,2,4-triazines in a mixture of room-temperature ionic liquid 1,3-dibutylimidazolium bromide [Bbim]$^+$Br$^-$ and dimethylsulfoxide (DMSO) is described without the need for any added catalyst. Different polar aprotic solvents were screened along with ionic liquids and a synergistic effect with DMSO has been found. The predominance of one regioisomer over the other has also been studied with varying reaction temperatures. The one-pot methodology leading to excellent isolated yields in short span of time is achieved by simple workup procedure. The ionic liquid was efficiently recovered and reused three times without the loss of catalysis. All the compounds were characterized by infrared, NMR, mass spectrometry, and elemental analysis.*

Keywords 5,6-Diaryl-1,2,4-triazines; 1,2-diketones; DMSO; ionic liquid (IL); regioisomers

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INTRODUCTION

1,2,4-Triazine moiety has been widely studied because of its occurrence in natural antibiotics such as fervenulin, toxoflavin, and reurhycin.[1] 1,2,4-Triazines are an important class of compounds which show different physical, chemical, and biological properties.[2] Their medicinal and agricultural uses have been well documented.[3] The 1,2,4-triazine scaffold has been associated with diversified pharmacological activities such as antiplatelet,[4] antihypertensive,[5] thromboxane synthetase inhibition,[5] anti-inflammatory,[6] and antimalarial[7] activities. Because of its cytotoxic potential it has also showed anticancer activity.[8] Recently 5,6-diaryl triazine derivatives have been evaluated as potent adenosine A_{2A} antagonists in Parkinson's disease[9] and as anticytokines.[10] The neuropharmacological applications of 1,2,4-triazines attracted wide attention from scientific community because of their potent activity, particularly in neuroinflammatory diseases such as Alzheimer's disease[11] and as neuroprotective agents.[12] Tirapazamine, a benzotriazine *N*-oxide, is being used as an experimental lead for selective hypoxic cytotoxins as an anticancer drug.[13] Lamotrigine, 6-(2,3-dichlorophenyl)-1,2,4-triazine-3,5-diamine, is used as an anticonvulsant drug in the treatment of epilepsy and bipolar disorder.[14] Vardenafil, a fused imidazotriazine derivative, acts as a potent PDE_5 inhibitor (Figure 1).[15] A number of patents have been granted for the syntheses and pharmacological uses of 1,2,4-triazine derivatives, namely as topical antithrombotic agents,[16a] anti-inflammatory agents,[16b] GABA activators,[16c] and sodium channel blockers.[16d]

Various methods have been reported to date for the synthesis of 1,2,4-triazines. A survey of the literature revealed several attempts involving condensation of substituted 1,2-dicarbonyl compounds with acid hydrazides in different solvents such as acetic acid,[17] *n*-butanol, ethanol, and methanol for prolonged time periods[18,7c,19] to yield trisubstituted-1,2,4-triazines. Other variations include reaction of the dicarbonyl compounds with monoarylhydrazones in alkaline ammonia under pressure;[20] refluxing with ammonium bicarbonate,[21] sodium *tert*-butoxide,[22] or with hydrazides/amidrazones;[23a,23b] microwave irradiation;[24] using metal salt catalysts such as $ZrOCl_2 \cdot 8H_2O$ at 100 °C;[25] using cuprous iodide,[26] and refluxing in the presence of NaOAc/KOAc/AgOAc.[27] Srinivasan and coworkers have reported this condensation in monobutylimidazolium ionic liquids alone.[28] Generally 3-methylthio-1,2,4-triazine synthesis has been reported with either *S*-methylthiosemicarbazide hydroiodide[29] or in two steps with thiosemicarbazide and then with alkyl halides in the presence of a base.[10–12,16]

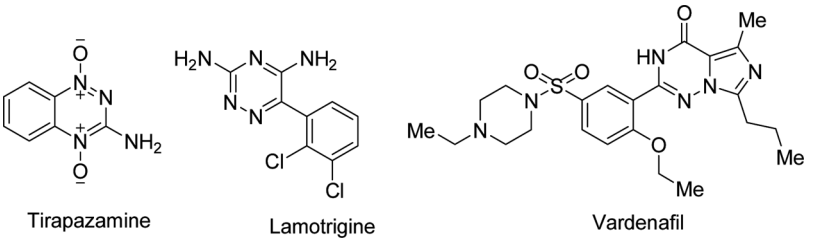


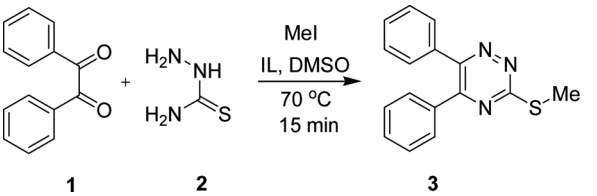
Figure 1. Some important drug molecules containing the 1,2,4-triazine scaffold.

In the past decade, significant attention has been given to synthetic protocols using room-temperature ionic liquids (RTILs). Imidazolium ILs are becoming solvents of choice because they have shown great promise as an alternative to conventional solvents, due to their low volatility and vapor pressure, larger liquidous range, and thermal stability.[30] Herein we report a rapid synthesis of 5,6-diarylsubstituted-1,2,4-triazines by one-pot condensation reaction of 1,2-diketones, thiosemicarbazide, and methyl iodide in a fixed ratio (1:10) of Brønsted acidic IL 1,3-dibutylimidazolium bromide ($[Bbim]^+Br^-$) and dimethylsulfoxide (DMSO) at ambient temperatures. The effect of temperature variations on the formation of both of the regioisomers is also discussed.

RESULTS AND DISCUSSION

Although many synthetic protocols for 1,2,4-triazines have been reported in the past, as mentioned, there still exists a need for the development of more efficient processes for the synthesis of 1,2,4-triazines. All of the mentioned procedures have one or more disadvantages, such as formation of undesired condensed jelly-like masses as side products, harsh reaction conditions, formation of more than one regioisomer, activation by toxic metals, use of inorganic supports such as silica, use of NaOAc or AgOAc, longer reaction times, use of corrosive acids, high temperature or reflux conditions, multistep procedures such as preliminary isolation of the 1,2-diketone-monoacylhydrazones followed by ring closure, and use of scarcely available substituted carbazides as starting materials. Modifications have been done by substituting solvents and acids/bases, but problems including longer reaction times, high-temperature conditions, and low to moderate reaction yields still persisted. Additionally, almost all of the known methods make use of volatile organic solvents, leading to complex isolation and recovery procedures. Therefore, we sought to develop a more efficient and convenient method that was flawless and amenable to both laboratory and industrial scales.

Recently, we reported the synthesis of five-, six-, and seven-membered cyclic guanidines by the synergy of specific ratio of IL and DMSO at ambient conditions.[31] Hence, to utilize this synergistic phenomenon of the mixture, we envisaged evaluating its effect on the formation of 5,6-diaryl-substituted 1,2,4-triazines from nonsymmetrical diketones and thiosemicarbazide. We extended the investigation of this system towards the synthesis of 1,2,4-triazines by a one-pot condensation of thiosemicarbazide, substituted diketones, and methyl iodide to afford the 5,6-diaryl substituted 3-methylthio-1,2,4-triazines in excellent yields in much shorter reaction times without any added catalyst (Scheme 1).



1 2 3

Scheme 1. One-pot synthesis of 3-methylthio-5,6-diphenyl-1,2,4-triazine.

Table 1. Screening of different molar ratios of reactants

Entry	Molar ratio[a]	Yield[b] (%)	Time (min)
1	1.0:1.0:1.0	75	17
2	1.0:1.5:1.2	27	21
3	1.0:1.0:1.2	96	15
4	1.0:1.0:0.0	85 (thiol)	25

[a]Benzil/thiosemicarbazide/methyl iodide.
[b]Isolated yields.

To determine the optimum conditions for the one-pot synthesis of alkylthiotriazines, the model reaction of benzil, thiosemicarbazide, and methyl iodide was selected. The optimum yields were found with equimolar quantities of benzil and thiosemicarbazide with 1.2 eq. of methyl iodide at 70 °C (Table 1, entry 3). When the ratio of benzil and thiosemicarbazide was changed to 1:1.5, the mixture of sticky polymeric complex was observed after workup, which showed a spot at the base (with low Rf value) in thin-layer chromatography (TLC) with trace amounts of desired cyclized product. This is probably because formation of bishydrazones or dimers which failed further cyclization (Table 1, entry 2).

For ascertaining the role of solvent for the reaction, different polar aprotic solvents with and without IL were employed to the model reaction as shown in Table 2. DMSO gave the best results and hence was used for subsequent reactions (Table 2, entry 5).

DMSO was further investigated as the most desired solvent with different ionic liquids. In each case, the ionic liquid used was in catalytic ratio of 1:10 to DMSO. Different ionic liquids (*viz.* 1-butylimidazolium tetrafluoroborate $[HbIm]^+BF_4^-$, 1,3-dibutylimidazolium tetrafluoroborate $[BbIm]^+BF_4^-$, 1-butyl-3-methylimidazolium bromide $[BmIm]^+Br^-$, and 1-butyl-2,3-dimethylimidazolium tetrafluoroborate $[BmmIm]^+BF_4^-$) were evaluated, and the results are given in Table 3. The ionic liquid $[Bbim]^+Br^-$ in DMSO gave the best results. To justify these results and to scour down the possibility of catalysis of ionic liquid or DMSO alone, the reaction was performed in pure IL without DMSO and separately in DMSO alone. Longer reaction times and moderate yields were observed in both these cases (Table 2, entries 6 and 7).

Table 2. Screening of different solvents with IL $[Bbim]^+Br^-$

Entry	Solvent	Time	Yield[b] (%)
1	DMF[a]	>2.5 h	42
2	THF[a]	>5 h	69
3	Acetone[a]	>3 h	62
4	Acetonitrile[a]	>2 h	65
5	DMSO[a]	15 min	96
6	DMSO alone	>1.5 h	65
7	$[Bbim]^+Br^-$ alone	>2.5 h	45

[a]1:10 ratio with IL.
[b]Isolated yields.

Table 3. Screening of different ILs with DMSO

Entry	IL with DMSO (1:10)	Time	Yield (%)[a]
1	$[HbIm]^+BF_4^-$	48 min	75
2	$[BbIm]^+BF_4^-$	42 min	81
3	$[Bbim]^+Br^-$	15 min	96
4	$[BmIm]^+Br^-$	45 min	75
5	$[BmmIm]^+BF_4^-$	>1 h	45

[a]Isolated yields.

It is interesting to note that when the reaction was carried out with both the reactants without methyl iodide to form triazine-3-thiol derivative, the reaction time increased in comparison to that of alkylthiotriazine (Table 1, entry 4).

It was observed that under similar conditions, a wide range of diketones containing electron-withdrawing as well as electron-donating groups such as halo, methyl, thiomethyl, and nitro easily underwent condensation with thiosemicarbazide and methyl iodide to give 5,6-diaryl substituted 1,2,4-triazines in 10–45 min with excellent isolated yields. The results are summarized in Table 4.

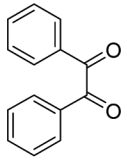
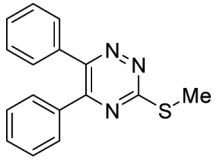
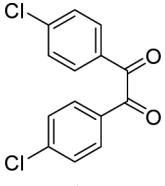
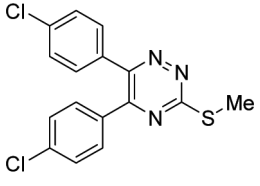
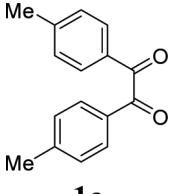
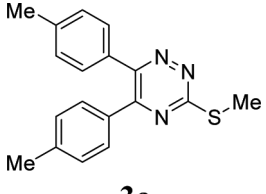
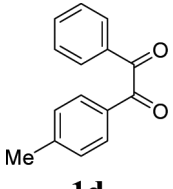
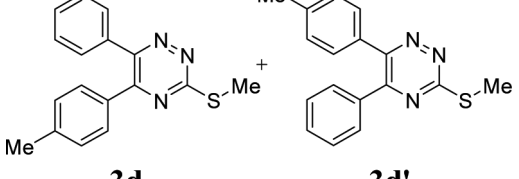
The unsymmetrical diketones were also explored for the synthesis of 1,2,4-triazines (Scheme 2). In each case a mixture of regioisomers was obtained, which was separated by flash chromatography. The predominance of one isomer over the other has been observed depending on the substituent on the aryl ring. When the reaction temperature was increased to 100 °C both isomers were observed in approximately equal proportions with trace quantities of bishydrazones. When the same reaction was performed at room temperature, only one isomer was obtained with minor quantity of the other one while at 0 °C only one isomer was exclusively obtained. This observation can be utilized to synthesize only one isomer selectively by varying the temperature of the reaction. As we intended to use both of these isomers we performed all the reactions at 70 °C. The structures of all 16 newly synthesized compounds **3d–k′** were characterized on the basis of infrared (IR), ^{1}H NMR spectral data, and elemental analyses. The known compounds **3a–c** were identified by the comparison of their ^{1}H NMR with those reported in the literature.[11,12] The structure of compound **3e** has been confirmed by its crystal structure (Figure 2). The rest of the isomers were assigned their structures accordingly.

It may be postulated that the inherent Brønsted acidity of the ionic liquid plays an important role in the formation of hydrazone and high polarity of combined solvents serves to form *S*-methyl-thiosemicarbazide in situ and facilitates the cycloaddition reaction.

In the case of unsymmetrical diketones, the relatively enhanced solvent polarity gave rise to the formation of one hydrazone exclusively by route "a" as shown in Scheme 3, which resulted in the formation of one isomer predominantly. It was reported that use of highly polar solvents and either acidic/basic conditions might give predominantly one isomer.[26,32] Because of the superior polarity of the said mixture (IL-DMSO) at ambient temperatures in combination with Brønsted acidity of IL one isomer predominantly was obtained, achieving the regioselective synthesis at 0 °C.

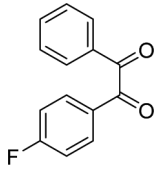
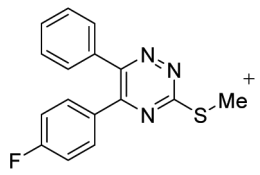
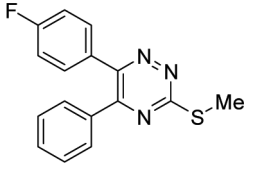
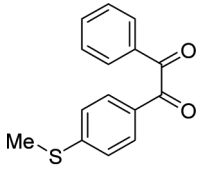
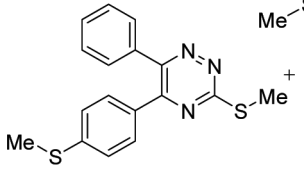
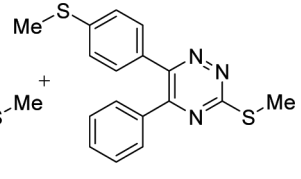
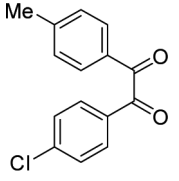
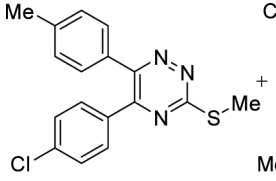
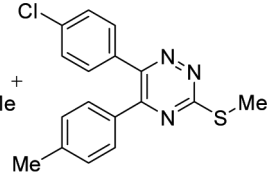
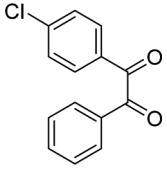
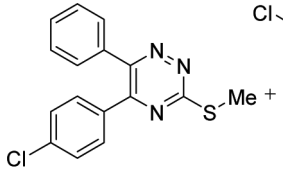
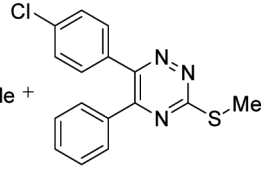
The mechanism of IL-promoted synthesis has also been postulated. The hydrogen bonding of amine with molecular solvents may hinder the reaction rate, while IL enhances the reaction rate due to lesser degree of hydrogen bonding

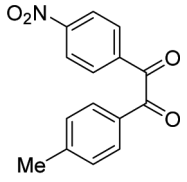
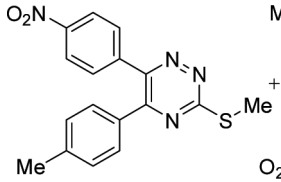
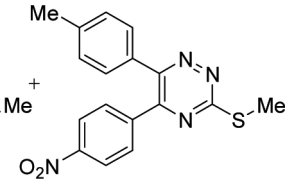
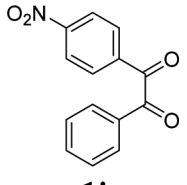
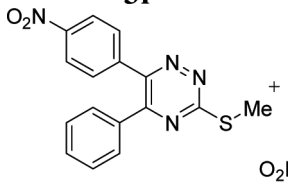
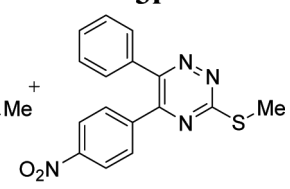
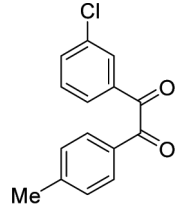
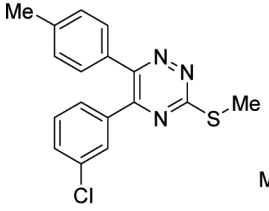
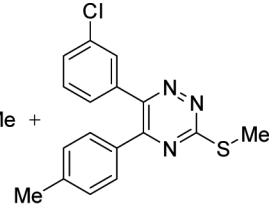
Table 4. Synthesis of 1,2,4-triazines from symmetrical and unsymmetrical 1,2-diketones at 70 °C

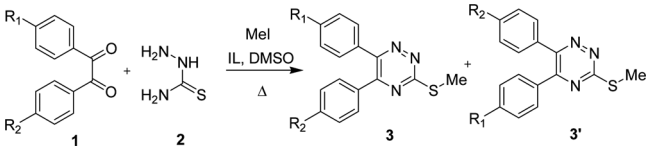
Entry	1,2-Diketone (1)	Product (3)	Time (min)	Yield[b](%)
1	 **1a**	 **3a**	15	96[12]
2	 **1b**	 **3b**	20	93[12]
3	 **1c**	 **3c**	40	73[11]
4	 **1d**	 **3d** **3d'**	45	63 (3d/3d′: 60/40)

(*Continued*)

Table 4. Continued

Entry	1,2-Diketone (1)	Product (3)	Time (min)	Yield[b](%)
5	 **1e**	 **3e** +  **3e'**	25	98 (3e/3e′: 70/30)
6	 **1f**	 **3f** +  **3f'**	20	84 (3f/3f′: 58/42)
7	 **1g**	 **3g** +  **3g'**	25	63 (3 g/3 g′: 51/49)
8	 **1h**	 **3h** +  **3h'**	25	79 (3 h/3 h′: 65/35)

9	 **1i**	 **3i** +  **3i'**		10	97 (3i/3i′: 65/35)
10	 **1j**	 **3j** +  **3j'**		25	99 (3j/3j′: 74/26)
11	 **1k**	 **3k** +  **3k'**		30	68 (3k/3k′: 68/32)



Scheme 2. One-pot synthesis of 1,2,4-triazine isomers from unsymmetrical diketones.

and stabilization of transient states. The acidic C2-H of imidazolium cation could assist carbonyl carbon to have higher electrophilicity, resulting in rapid hydrazone formation.

The methods reported so far for the synthesis of 1,2,4-triazines utilize either acidic conditions using acids such as acetic, hydrochloric, trifluoroacetic and sulfuric or solvents such as methanol and ethanol, requiring very harsh reaction conditions such as refluxing for 8–24 h. Compared to the reported methods, this method allowed safe, convenient, and easy isolation procedures under ambient conditions by simple workup of the reaction mixture in ice-cold water. The use of catalytic amounts of IL in DMSO as a cosolvent is significant as compared to the previously reported method[28] in which excess of IL was utilized as reaction medium and promoter. There were noteworthy improvements in yields observed in the current method in comparison to the previously reported method.[28] Another advantage of the method reported herein is that a pure regioisomer can be obtained when the reaction is performed at low (0 °C) temperature.

The IL could be recovered easily from the aqueous filtrate by subjecting it to evaporation on rotary evaporator and removal of DMSO in high vacuum. The recovered IL has been used for the same reaction three times and showed no loss of its catalytic activity. In conclusion, we have developed a mild, convenient, and efficient protocol for the synthesis of 1,2,4-triazines by the condensation of diketones, thiosemicarbazide, and methyl iodide using a mixture of IL and DMSO (1:10 proportions) as a solvent as well as a promoter. The process gave excellent isolated yields of 1,2,4-triazines in 10–45 min under ambient reaction conditions in shorter reaction times than hitherto reported synthetic procedures.

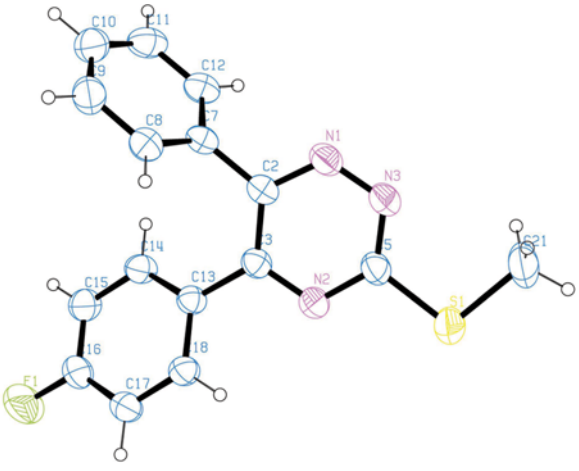
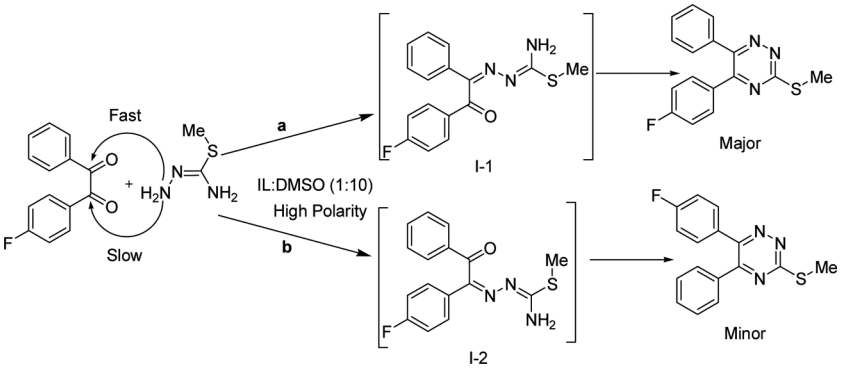


Figure 2. ORTEP diagram of crystal structure of **3e** (with 50% probability).



Scheme 3. Plausible mechanism of regioselective synthesis of 1,2,4-triazines in IL/DMSO (1:10).

EXPERIMENTAL

Melting points were determined in capillaries using Veego programmable melting-point apparatus and are uncorrected. IR (in cm^{-1}) spectra in KBr pellets on a Bruker ALPHA-T instrument and ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance II spectrometer (400 MHz), using Tetramethylsilane (TMS) as an internal standard. Chemical shift data are reported in parts per million (δ in ppm). Elemental analyses were recorded on a Thermoscientific Flash-2000 CHN analyzer. Mass spectra were recorded on Thermoscientific DSQ-II mass spectrometer equipped with an electron-impact ionization (EI) interface. Flash column chromatography was carried out Combiflash R_F 200 (Teledyne Esco) using flash-grade silica gel (230–400 mesh). The IL $[Bbim]^+Br^-$ was synthesized as per the earlier reported procedure.[33] The diketones **1a–k** were obtained by our previous protocol.[34]

General Procedure for Synthesis of 3-Methylthio-1,2,4-triazines in IL + DMSO (1:10) (3e and 3e′ as Examples)

A mixture of diketone **1e** (2.0 mmol), thiosemicarbazide **2** (2.0 mmol), and methyl iodide (2.4 mmol) in DMSO and $[Bbim]^+Br^-$ in 10:1 (5 g : 0.5 g) proportions was stirred at 70 °C for 20 min. The progress of the reaction was monitored by TLC with an eluent mixture of *n*-hexane and ethyl acetate (4.5:0.5). After completion, the reaction mixture was added to ice-cold water. The precipitated product was filtered, washed with water, and dried. This regioisomeric mixture was subjected to flash chromatographic purification using 5% ethyl acetate in *n*. hexane as eluent, to obtain first fraction as **3e** and second fraction as **3e′**.

3-Methylthio-5-(4-fluorophenyl)-6-phenyl-1,2,4-triazine (3e)

Mp 104–106 °C; IR (KBr, cm^{-1}) 3116, 3061, 1599, 698; *m/z* 296.96 (M^+); ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.77 (s, 3H, SCH_3); 7.05–7.56 (m, 9H, Ar-*H*). Anal. calcd. for $C_{16}H_{12}FN_3S$: C, 64.63; H, 4.07; N, 14.13. Found: C, 64.71; H, 4.06; N, 14.07.

Crystal Data

$C_{16}H_{12}S_1N_3F_1$, CCDC 969264, $Mr = 297.36$, $T = 293(2)$ K, space group = $P21/c$, $a = 6.1928(2)$Å, $b = 10.6279(3)$Å, $c = 22.6088(8)$Å, $V = 1474.14(8)$Å^3, $Z = 4$, $R1 = 0.0768$, $wR2 = 0.2794$ [$I > 2\sigma(I)$].

3-Methylthio-5-phenyl-6-(4-fluorophenyl)-1,2,4-triazine (3e′)

Mp 95–97 °C; IR (KBr, cm^{-1}) 3116, 3061, 1599, 698; m/z 296.96 (M^+). ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.79 (s, 3H, SC*H*$_3$); 7.02–7.61 (m, 9H, Ar-*H*). Anal. calcd. for $C_{16}H_{12}FN_3S$: C, 64.63; H, 4.07; N, 14.13. Found: C, 64.74; H, 4.02; N, 14.09.

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SUPPORTING INFORMATION

Supplemental data for this article can be accessed on the publisher's website.

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