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Task-specific Ionic Liquid-mediated Facile Synthesis of 1,3,5-Triaryltriazines by Cyclotrimerization of Imines and Their Biological Evaluation

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A highly efficient method for the synthesis of fluorinated 1,3,5-triaryltriazine derivatives is developed by the condensation reaction of aromatic amines and formaldehyde followed by spontaneous cyclotrimerization using task-specific 1,1,3,3-tetramethylguanidine trifluoroacetate [TMG][Tfa] ionic liquid as a environmentally benign solvent in excellent yields at room temperature. The synthesized compounds were subjected for in vitro antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain using the Löwenstein–Jensen medium.

Tuberculosis is a communicable disease which is caused by *Mycobacterium tuberculosis*. The global effect of tuberculosis is immense.[1] According to the World Health Organization, currently one-third of world's population is infected with latent tuberculosis.[2] In recent years, the 15 emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) strains have susceptible global control of TB. MDR-TB strains are defined as being resistant to the first-line antitubercular agent isoniazid which highlights the need for advance development of new antimycobacterial drugs.[3]

The increased interest in organofluorine compounds have led to the development of novel medicinal agents and new strategies in drug discovery and development. The synthesis of fluorine-containing complexes or compounds and their derivatives provide unlimited potential for creating novel pharmacologically active lead compounds for use as therapeutics.[4,5] The installation of fluorine atoms in an organic molecule changes the molecule's physicochemical properties, including its stability, bioavailability, and lipophilicity.[6,7]

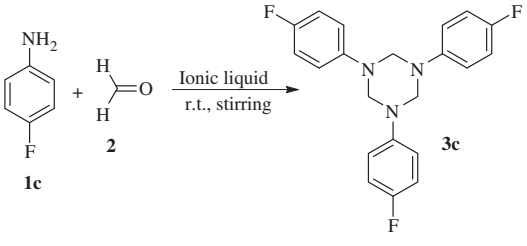
The small atomic radius, high electronegativity, and low polarizability of the carbon–fluorine bond are among the special properties that make fluorine so attractive. Thus many fluorinated compounds are stable and frequently avoid undesirable metabolic transformations.[8] In addition, the increased lipophilicity often leads to easy absorption and transportation of molecules within biological membranes, thereby improving their overall pharmacokinetic and pharmacodynamic properties.[9] However, prediction of sites in a molecule at which fluorine substitution will result in optimal desired effects is still challenging. Therefore, the synthesis of organofluorine compounds provides a diverse array of building blocks and chemical substructures for novel processes.[10,11]

1,3,5-Trisubstituted hexahydro-1,3,5-triazines have been emerged as an important target molecules for chemist due to their therapeutic and pharmacological properties such as antimicrobial,[12] anticancer,[13] antimalerial,[14] antitubercular,[15] antioxidant,[16] and anti-HIV agents.[17] They have also been used for protection of amino group as well as for the synthesis of polyamines.[18] They serve as valuable precursors for the synthesis of α- and β-amino esters, β-lactams, and natural alkaloids.[19] A number of synthetic methods to prepare these compounds have been described in the past few years.[20] All of these methods have certain limitations such as tedious procedures, long reaction time, harsh reaction conditions, low yields, high boiling solvents, or microwave activation. Therefore, further studies are still necessary for the versatile, simple, and eco-friendly process.

In recent years, the development of efficient and environmentally benign chemical process or methodologies for widely used recycle catalyst and eco-friendly solvent is one of the major challenges for chemists in organic synthesis. Ionic liquids (ILs) have received recognition as a new generation of solvents having unique physicochemical properties, such as nonvolatility, excellent chemical and thermal stability, nonflammability, and good solvating ability. Their dual organic and ionic nature allows them to establish ion–ion and ion–dipole as well as van der Waals interactions with reacting species, including transition states; hence they sometimes give rise to improved yields and rate enhancements. Over the past few years, a number of reactions have been successfully conducted using ionic liquids as solvents or catalysts.[21] In the search of developing simple, mild, and environmentally friendly synthetic protocols, we have recently developed highly efficient synthetic methodology for the construction of pharmaceutically important spiro heterocycles using green chemistry technique.[22]

In continuation of our ongoing program in the development of greener and sustainable process for medicinally important heterocycles[22] and our expertise in ionic liquids[23] and fluorine chemistry,[24] herein, we wish to report for the first time, a highly efficient and green protocol for the synthesis of highly substituted triazines incorporating pharmacophoric fluorine or trifluoromethyl group using task-specific [TMG][Tfa] ionic liquid as the recyclable solvent.

To approach the synthesis, we first focused our studies on the model reaction (Scheme 1), involving 4-fluoroaniline (**1c**) and formaldehyde (**2**), with the expected production of the desired triazine derivatives. In this regard, we attempted to determine the optimum conditions by examining the influence of ILs, on the progress of the trial reactions (Table 1). It can be seen



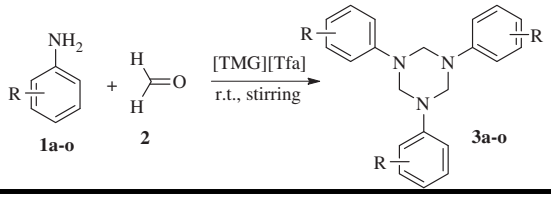
Scheme 1. Model reaction for exploring the use of room-temperature ionic liquids (RTILs) for the synthesis of 1,3,5-tris(4-fluorophenyl)-hexahydro-1,3,5-triazine (**3c**).

Table 1. Effect of ILs for the synthesis of **3c**

Entry	Solvent	Time/min	Yield[a]/%
1	[bmim]Cl	70	62
2	[bmim]BF_4	60	81
3	[bmim]PF_6	60	78
4	[TMG][Ac]	25	94
5	[TMG][Tfa]	20	97

[a]Isolated yield.

Table 2. Synthetic results of hexahydro-1,3,5-triaryltriazine derivatives **3a**–**3o**



1a-o **2** **3a-o**

Compd.	R	Time/min	Yield[a]/%	Mp/°C
3a	2-F	25	93	180–182
3b	3-F	25	93	84–86
3c	4-F	20	97	160–162
3d	2-CF_3	25	90	98–100
3e	3-CF_3	20	92	72–74
3f	4-CF_3	20	95	100–102
3g	2-Cl, 5-CF_3	25	89	72–74
3h	2-CF_3, 4-NO_2	25	91	90–92
3i	2-Br,4-F	25	92	114–116
3j	3-Cl,4-F	20	94	94–96
3k	H	25	93	142–142
3l	4-CH_3	25	95	126–128
3m	4-O CH_3	25	91	130–132
3n	4-Cl	20	96	132–134
3o	4-Br	20	93	168–170

[a]Isolated yield.

that the best results of the expected products were obtained in 1,1,3,3-tetramethylguanidine trifluoroacetate [TMG][Tfa] at room temperature in few minutes (Table 1, Entry 5).

To demonstrate the efficiency and the scope of the present method, we performed the cyclocondesation reaction using different fluorinated aniline **1**. As shown in Table 2, all aromatic amines containing different groups, gave the desired products **3** in good to excellent yields under the same reaction conditions. No obvious effects resulting from the steric nature of the aromatic ring substituent were observed.

The reusability of the ionic liquid is a significant advantage particularly for commercial applications. Thus, the recovery and reusability of [TMG][Tfa] ionic liquid was also investigated (Table 3). After the completion of the reaction, cold water was added to the reaction mixture and the products were isolated by filtration. The ionic liquid was recovered by removing the water under reduced pressure and could be reused at least five times without any appreciable decrease in yield.

Finally the structure of triazine derivatives was confirmed by single-crystal X-ray diffraction and determined by full matrix least-squares calculations.[25] The compound 1,3,5-tris(4-fluoro-

Table 3. Results for the recyclability of the ionic liquid [TMG][Tfa] for the synthesis of **3c**

Cycle	Yield[a]/%	ILs recovered (W/W %)
1	97	98
2	95	96
3	94	95
4	92	93
5	92	90

[a]Isolated yield.

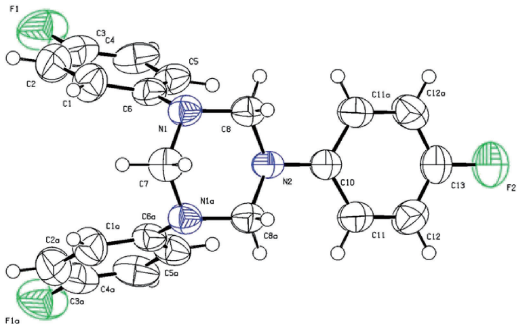


Figure 1. ORTEP diagram of compounds **3c**.

Table 4. Antimycobacterial activity of tested compounds (MIC in $\mu g\,mL^{-1}$)

Compounds	*M. tuberculosis* H37Rv
3a	100
3b	62.5
3c	25
3d	100
3e	62.5
3f	25
3g	50
3h	62.5
3i	50
3j	62.5
3k	125
3l	250
3m	250
3n	100
3o	125
Isoniazid	0.20

phenyl)-hexahydro-1,3,5-triazinane (**3c**) have diaxial–equatorial chair conformation (Figure 1). The angle between the equatorial aromatic ring and the symmetry plane of triazacyclohexane ring is 90° and there is maximum *N*-lone pair–π-orbital overlap.

The synthesized compounds were screened for their in vitro antimycobacterial activity against *Mycobacterium tuberculosis* by using isoniazid as standard antimycobacterial agent. Unfortunately no significant antimycobacterial activity was detected and results are summarized in Table 4. The compounds **3c** and **3f** having fluoro or trifluoromethyl group at *para*-position on the phenyl ring showing highest potency among all the screened compounds.

The determination of minimum inhibitory concentration (MIC) of synthesized compounds against *M. tuberculosis* H37Rv were performed by the Löwenstein–Jensen (L–J) agar (MIC) method,[26] where primary 1000, 500, and 250 $\mu g\,mL^{-1}$ and secondary 200, 100, 62.5, 50, 25, 12.5, 6.25, and 3.25 $\mu g\,mL^{-1}$ dilutions of each test compound were added liquid L–J medium, and then media were sterilized by inspissations method. A culture of *M. tuberculosis* H37Rv growing on L–J medium was harvested in 0.85% saline in bijou bottles. All test compound make first stock solution of 2000 $\mu g\,mL^{-1}$ concentration of compounds was prepared in DMSO. These tubes were then incubated at 37 °C for 24 h followed by streaking of *M. tuberculosis* H37Rv (5×10^4 bacilli per mL). These tubes were then incubated at 37 °C. Growth of bacilli was seen after 12, 22, and finally 28 days of incubation. Tubes having the compounds were compared with control tubes where medium alone was incubated with *M. tuberculosis* H37Rv. The concentration at which no development of colonies occurred or <20 colonies was taken as MIC of test compound. The standard strain *M. tuberculosis* H37Rv was tested with known drug isoniazid.

In conclusion, we have developed a highly efficient and green protocol for the synthesis of pharmaceutically important hexahydro-1,3,5-triaryltriazine derivatives in task-specific [TMG][Tfa] ionic liquid avoiding the use of hazardous solvents, additional bases as well as costly reagents, etc. The reactions were carried out at room temperature to afford the desired products in excellent yields in shorter reaction times, which is an additional greener attribute of this reaction. The synthesized compounds **3c** and **3f** showed higest potency among all the screened compounds.[27]

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