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A facile IL–DMSO assisted synthesis of 5-, 6-, and 7-membered benzo-annelated cyclic guanidines

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ABSTRACT

A new and facile IL–DMSO assisted method has been developed for the synthesis of biologically important cyclic guanidines like 2-aminobenzimidazole, 2-imino-4-quinazolinone, and 2-imino-5-benzotriazepinones at ambient temperatures. The desired products could be obtained by microwave irradiation[32] also, but at elevated temperatures. A plausible mechanism for catalysis has been proposed.

Cyclic guanidines are encountered frequently in biologically active natural products such as marine alkaloids.[1] Some of the polycyclic guanidine derivatives show biological activities like antitumor,[2] broncholytic,[3] antihypertensive,[4] and immunosuppressive.[5] Among the most important cyclic guanidines, compounds with 2-amino-4-quinazolinone core structure have a wide range of biological activities.[6] Interestingly, despite having an identical 2-amino-4-quinazolinone structural motif, these compounds exhibit diverse biological activities like anti-cancer,[7] anti-viral,[8] anti-microbial,[9] anti-convulsant,[10] and anti-inflammatory.[11] This diversity arises mainly due to the pharmacophoric contributions of a variety of substituents attached to the ring fused heterocyclic systems. Similarly 2-aminoimidazoles[12] and 2-aminotriazepines[13] are also of considerable importance from the medicinal chemistry point of view.

Methods are available for the synthesis of cyclic guanidines from aliphatic and aromatic diamines. Thus 2-aminobenzimidazole, 2-imino-4-quinazolinone, and 2-amino-5-benzotriazepinone can be obtained as salts by the action of cyanogen bromide on aromatic diamine,[14] amine,[15] and amide[16] derivatives, respectively. A second approach to cyclic guanidines involves the reaction of amines with 2-methylthio-1,3-diazine (available in two steps from diamines); this procedure has been used to prepare *N*-alkylguanidines of a wide variety. Two other routes for cyclic guanidine system, which have limited applicability, are hydrogenation of 2-aminopyrimidine to obtain 2-amino-3,4,5,6-tetrahydropyrimidine, and fusion of guanidine with 4,5-diamino-6-hydroxypyrimidine to afford 8-amino-6-hydroxypurine. Here, we report a comparative account of different synthetic protocols as an improvement to one of the above reported methods.

The use of room temperature ionic liquids (RTILs) as solvents or catalysts for chemical reactions offers several advantages from the environmental perspective. Therefore, RTILs[17] are attracting academic and industrial attention world wide,[18] as these can be used to replace the organic solvents in catalysis,[19] synthesis,[20,21] and separations.[22] The unique properties of RTILs enable their use as alternative solvents and may speed up the introduction of potentially 'green' solvents in the sustainable industrial processes. One of the synthetic protocols reported in this Letter involves the use of RTILs in DMSO as solvent at room temperature. The method is appealing especially for the synthesis of cyclic guanidines as it involves very mild conditions in contrast to the reported methods.

This laboratory has been actively engaged in the synthesis of 4-quinazolinones[23] from the medicinal chemistry point. It was of interest to synthesize 2-imino-4-quinazolinones **3**, the cyclic guanidine derivatives. For the preparation of the target structure **3**, substituted isatoic anhydride **1** was reacted with primary amines to afford 2-aminobenzamides **2**. It was planned to react intermediate **2** with cyanogen bromide to obtain the desired compound **3** (Scheme 1). Classical methods for the synthesis of cyclic guanidines typically require an excess of cyanogen bromide in protic polar solvent like EtOH and activated diamines at higher temperatures.[16] When the reaction of compound **2** was carried out in EtOH, it took 6–8 h for the reaction to complete, offering medium to good

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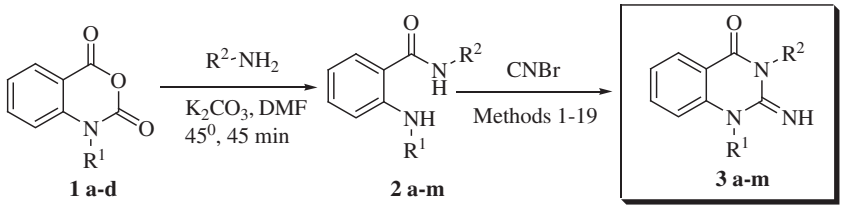
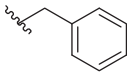
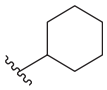
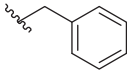
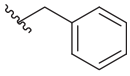
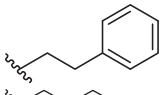
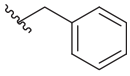
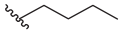
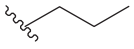
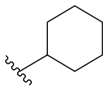
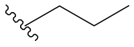
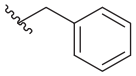
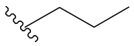
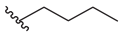
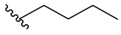
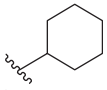
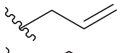
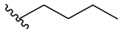
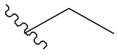
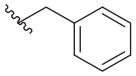
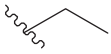
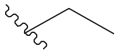
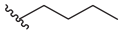


Scheme 1. Synthesis of six-membered cyclic guanidines.

Table 1
Synthesis of 1,3-disubstituted-2,3-dihydro-2-imino-4-quinazolinones[31]

Compd	Substituents		Yield (%)		
	(R^1)	(R^2)	EtOH, 70 °C, 6–8 h	EtOH M.W. 150 W 90 °C, 8–10 min	RTIL/DMSO (1:10), 90 °C, 5–8 min
3a			78	94	95
3b			80	90	92
3c			74	90	92
3d			72	89	90
3e			56	85	82
3f			85	95	94
3g			72	92	95
3h			78	89	90
3i			74	90	92
3j			73	90	94
3k			65	85	88
3l			82	90	94
3m			76	88	92

yields (Table 1). To further enhance the yield of the products (**3**), it was thought to carry out the reaction in polar aprotic solvents like DMSO or in ILs like dibutylimidazolium bromide ($[bbim]^+[Br]^-$). Surprisingly in pure DMSO or in pure IL, the desired product could not be obtained even after heating of the reaction mixture for 12 h at 90 °C. There are some reports[24–26] of catalyzing effects of IL in DMSO on some reactions. Srinivasan et al. have reported a facile esterification reaction using sodium carboxylates and alkyl halides in 1:10 ratio of RTIL and DMSO.[27,28] Thinking that this ratio might work with our reactants, the reaction was repeated using the same ratio of IL and DMSO at 90 °C. To our astonishment the ratio of 1:10 of IL and DMSO offered the desired products in high yields in a short span of time (5–8 min). Cyclization was also tried under microwave irradiation. Exposure of the reaction mixture for a brief period to microwaves offered the desired products in high yields.

Results depicted in Table 1 are quite evident to show that these protocols could be adopted for the synthesis of various aromatic motifs. In order to expand the intended diversity profile of the resulting cyclic guanidines, synthesis of 5 and 7 membered benzo-annelated systems like 2-aminoimidazole and 2-amino-5-benzo[1,2,4]triazepinone were also investigated. Further results of RTIL–DMSO protocol and microwave irradiation methods are shown in Tables 2 and 3. Synthesis of 2-aminoimidazole (**6**) was started with methyl 4-fluoro-2-nitrobenzoate and was carried out in three steps, nucleophilic substitution with suitable amines followed by reduction of nitro group and finally cyclization with

Table 2
Synthesis of 1-substituted-2-aminoimidazoles

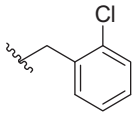
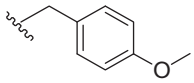
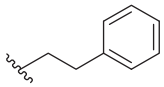
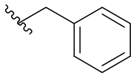
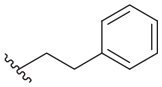
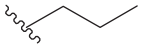
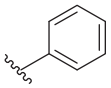
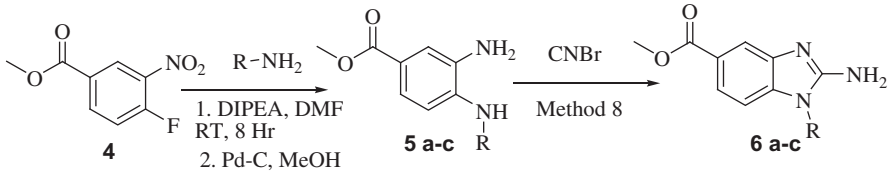
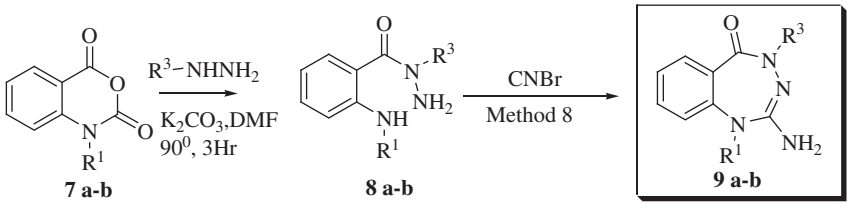
Compd	Substituent (R)	Yield (%)		
		EtOH, 70 °C, 6–8 h	EtOH, M.W. 150 W, 90 °C, 8–10 min	RTIL/DMSO (1:10), 90 °C, 5–8 min
6a		70	92	94
6b		84	94	95
6c		72	88	89

Table 3
Synthesis of 1,4-disubstituted-1,2,3,4-tetrahydro-2-amino-5-benzo[1,2,4]triazepinone

Compd	Substituents		Yield (%)		
	(R^1)	(R^3)	EtOH, 70 °C, 6–8 h	EtOH M.W. 150 W 90 °C, 8–10 min	RTIL/DMSO (1:10) 90 °C, 5–8 min
9a			68	90	90
9b			54	82	90



Scheme 2. Synthesis of five-membered cyclic guanidines.



Scheme 3. Synthesis of seven-membered cyclic guanidines.

CNBr in RTIL and separately by microwave irradiation, offering **6** in excellent yields (Scheme 2). Consequently, the synthesis of 2-amino-5-triazepinone was also achieved, starting with N-substituted isatoic anhydride and using the same protocol as described above (Scheme 3).

After improving the yields of the desired benzo-annelated cyclic guanidines it was thought of reducing the reaction temperature so that the developed experimental protocol could be applied to temperature-sensitive starting materials. Replacing EtOH with easily available MeOH proved to be disastrous as the reaction mixture did not proceed even after refluxing the reaction mixture for 18 h. Here also the IL/DMSO mixture in 1:10 ratio provided another pleasant surprise when the reaction got completed in just 25 min at room temperature to afford a high quality product (**3a**) in high yields (Table 4). The quality of the product was so good that simple dilution of the reaction mixture with ice-water, filtration and water washing of the precipitate yielded the analytical grade sample. Thinking that a simple mixture of both these solvents would yield same results, different ratios of IL–DMSO were used as solvents. Different concentrations of IL like 5%, 10%, 20%, 30%, and 50% in DMSO were used to observe the results. Among all these ratios an optimum 10–20% IL in DMSO gave the best results

Table 4
Formation of compound **3a,** using different synthetic methods

Method	Solvent/reaction cond.	Temp (°C)	Compd (**3a**)	
			Time	Yield (%)
1	EtOH	Reflux	8 h	70
2	EtOH	rt	18 h	60
3	MeOH	rt/Reflux	18 h	No rean.
4	Toluene	Reflux	12 h	No rean.
5	DMSO	rt/Reflux	28 h	58
6	IL	rt/90	18 h	52
7	IL/DMSO::1:10	rt	25 min	94
8	IL/DMSO::1:10	90	8 min	88
9	IL/DMSO:: 1:1	rt	5 h	85
10	KBr + DMSO	rt	45 min	86
11	CsBr + DMSO	rt	4 h	82
12	NaBr + DMSO	rt	6 h	84
13	LiBr + DMSO	rt	12 h	82
14	KCl + DMSO	rt	1 h	88
15	KI + DMSO	rt	16 h	62
16	Cs_2CO_3 + DMSO	rt	18 h	No rean.
17	Cu_2I_2 + DMSO	rt	18 h	No rean.
18	KBr + IL	rt	18 h	53
19	EtOH + M.W.	Reflux	5 min	92

and the reaction was completed in 25–30 min at room temperature. Bydecreasing or increasing the ratio of IL in DMSO took more time (2–8 h) to complete the reaction. Use of 10% IL in DMSO at room temperature condition was of special interest to us as this protocol could be adopted for temperature sensitive compounds with low concentrations of costly ILs.

The above described observations needed a plausible explanation. During the course of reactions using various solvents under different temperature conditions, it was observed that the reaction proceeds in two steps (Scheme 4) as inferred from the TLC analysis of the reaction mixtures, when analyzed at different time intervals. It became evident that step 1 is a slower one than step 2. That means IL–DMSO mixture (1:10) might be catalyzing both the steps but definitely does catalyze step 1. Step 1 can be considered to be a nucleophilic substitution reaction while step 2 is essentially an addition step. Transition state of step 1 is expected to be much more highly polarized than the starting reactants. Factors leading to stabilization of the transition would enhance the rate of reaction in Step 1.

A high level of stabilization of the transition state can be explained by a mixture of DMSO and IL as shown in Figure 1. IL and DMSO make two pseudo ring structures with both of the reacting species thereby stabilizing the partial charges on the atoms as shown in Figure 1.

Formation of ring A increases the nucleophilicity of amino nitrogen by increasing the partial negative charge through hydrogen bonding with oxygen of DMSO and stabilizing the developing negative charge on nitrogen of cyano group through the electrostatic interaction with sulfur of DMSO. Formation of ring B is much more important as it would stabilize the developing negative charge on bromine and nitrogen atoms through hydrogen bonding with the two planar hydrogens of $[bbim]^+$.[29,30] As carbon and nitrogen atoms of cyanogen bromide would be in a state similar to sp^2 hybridization state, formation of a planar pseudo seven-membered

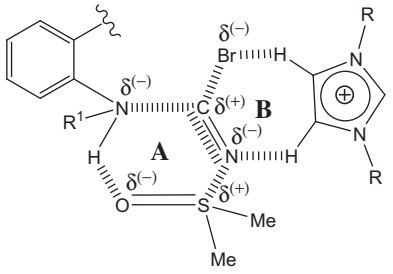


Figure 1. Formation of 6- and 7-membered pseudo-ring structures during the stabilization of transition state in Step 1.

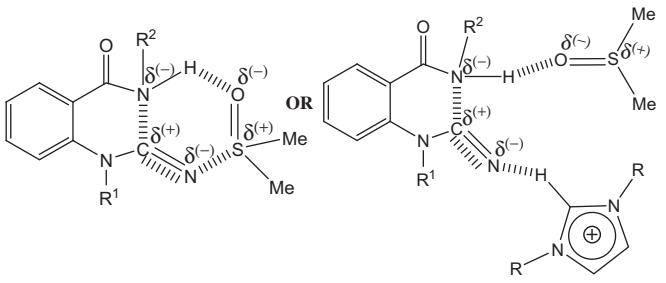
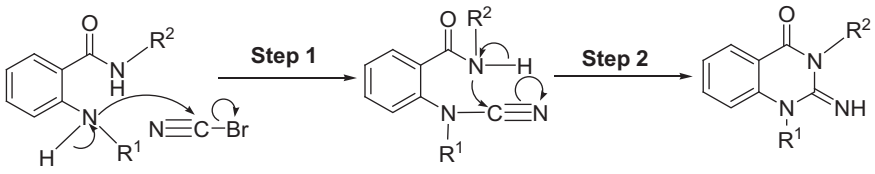


Figure 2. Formation of 6-membered pseudo-ring system with DMSO or by H-bond formation with DMSO and $[bbim]^+$ in the stabilization of the transition state in Step 2.

ring (B) would be stable in the transition state. Once the cyanamide intermediate is formed, step 2 is expected to be quite fast as an intra-molecular addition reaction takes place. There could be some degree of stabilization of the transition state by DMSO in step 2 also, as seen in Figure 2. This stabilization could be facilitated by DMSO either all alone or in conjugation with IL. Either of the acidic protons[29,30] of C-2, C-4, or C-5 can participate in the stabilization of this transition state. But the overriding factor seems to be the internal attack of the nucleophile in step 2. As the reaction rate is slower in other proportions of IL and DMSO than 10–20%, it is hypothesized that higher or lower concentrations of IL in DMSO disrupts the matrix as shown in Figure 1 in the transition state of step 1 rather than affecting the transition state of step 2.

Since the developing negative charges on bromide and nitrogen atoms in the transition stage (Step 2) could be stabilized by a cation through electrostatic interaction, it was considered worthwhile to perform the reaction in the presence of salts with varying sizes of cations in the reaction medium having DMSO as the solvent. As solvation factor of the cation and/or the anion could be an important criterion in catalytic reactions, anions of varying sizes were employed in the salts. To compare and establish the facts, a representative derivative of six-membered cyclic guanidine compound **3a** was synthesized using different salts maintaining the reaction conditions as mentioned above. The results are summarized in Table 4. These results show that the use of potassium bromide in DMSO afforded the product fastest while iodide was the least effective among the potassium salts of halides. Being a much bigger



Scheme 4. Mechanism for the formation of 1,3-disubstituted-2,3-dihydro-2-imino-4-quinazolinones.

cation cesium bromide was expected to give the product fastest but it catalyzed the reaction slower than the potassium ions. Among the halides of potassium salts, iodide was even poorer than chloride. This might be due to a lesser degree of solvation of iodide than chloride or bromide, leading to the existence of higher concentrations of potassium iodide as a tighter ion pair than that of chloride or bromide ion pairs with potassium ions. Potassium bromide in pure IL was not very effective in catalyzing the reaction, as was expected.

The cyclization reaction rate was enhanced in ethanol also by microwave irradiation. In microwave reaction conditions, stabilization of the transition state in step 1 is not that very important factor because requisite energy could efficiently be delivered to the reacting species to cross the energy barrier in the transition state.

A mild, convenient, and efficient protocol for the synthesis of benzo-annelated cyclic guanidines as 2-aminobenzimidazole, 2-imino-4-quinazolinone, and 2-amino-5-benzotriazepinone has been reported by using diamine, amine, and amide derivatives, respectively, and cyanogen bromide in a mixture of IL in DMSO (1:10 ratio). The process offered excellent yields of high quality cyclic guanidines in short reaction times (5–45 min.). A plausible explanation has been put forward for this IL–DMSO catalyzed reaction.

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Supplementary data

Supplementary data (experimental procedures and characterization data of all the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.060.

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31. *General procedure for the synthesis of 1,3-disubstituted-2,3-dihydro-2-iminoquinazolin-4(1H)-ones*: In a 50 ml round-bottom flask, substituted isatoic anhydride (**1a–d**) (1 mmol), amine (1 mmol) and K_2CO_3 (1.5 mmol) were stirred in DMF (2 ml) at 45 °C for 45 min. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool at room temperature and diluted with small amount of water. The solid (**2a–m**) that separated out, was filtered, washed with water, dried and used for next step without purification. A mixture of **2a–m** (1 mmol), in 10% mixture (2 ml) of IL in DMSO and CNBr (2.5 mmol) was stirred at 90 °C for about 8–10 min and the reaction was monitored by TLC. After completion of reaction, the reaction mixture was diluted with ice cold water (10 ml). The solid quinazolinone products (**3a–m**), which separated out, were filtered, washed with water and dried. The crude products, thus isolated, were pure enough (single spot on TLC) and obtained in excellent yields of 90–95%, and were fully characterized.
32. *Microwave method*: Microwave reactions were carried out using CEM-Discover Mono-mode Micro-reactor. Reaction mixtures were irradiated at 90 °C with 150 W micropower for 5 min. The progress of the reactions was monitored by TLC.