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Facile, catalyst-free cascade synthesis of sulfonyl guanidines *via* carbodiimide coupling with amines†

Debojit Hazarika, Arun Jyoti Borah and Prodeep Phukan *

An expeditious catalyst-free cascade coupling of *N,N*-dibromoarylsulfonamides with isonitriles and amines *via* carbodiimide intermediates has been developed. The protocol represents an elegant pathway for sulfonyl guanidines at room temperature within a short time with high yields and wide substrate scope. The carbodiimide intermediate could also be isolated in an appreciable yield.

The guanidine core is a common functionality in natural products, pharmaceuticals, agrochemicals, catalysts, superbases and superpotent sweeteners.[1] In view of their importance and usefulness, the development of an efficient pathway for the synthesis of substituted guanidines has attracted great interest from organic as well as medicinal chemists. The synthesis of acyclic guanidines has been well explored by classical methods that are based on transformation of electrophilic guanylation reagents like thioureas, isothioureas, amidine sulfonic acids, cyanamides, carbodiimides, triflyl guanidines, and carboximidamide derivatives as reagents.[2] Many of these methods usually suffer from harsh reaction conditions, multistep pathways, limited substrate scope, and/or expensive catalysts. A straightforward route for the synthesis of di-, tri-, and tetrasubstituted guanidines involves the reaction of amines with electrophilic thiourea derivatives as guanylation reagents where carbodiimides are thought to be the intermediate.[3] Catalytic direct guanylation of amines with symmetrical and unsymmetrical carbodiimides seems to be an alternative to prepare *N*-substituted guanidines.[4] Nevertheless, the preparation of carbodiimide is tedious and strict conditions are necessary along with the requirement of a transition metal catalytic system.[5] Yeung reported a method for the synthesis of guanidines *via* bromo-functionalization of olefin using NBS in the presence of a cyanamide as both a solvent and a reagent.[6] However, due to the presence of bromine at the α-position, the reaction undergoes subsequent cyclization,[7] which limits its applicability in acyclic guanidine synthesis.

Department of Chemistry, Gauhati University, Gopinath Bordoloi Nagar, Guwahati-781014, Assam, India. E-mail: pphukan@yahoo.com, pphukan@gauhati.ac.in

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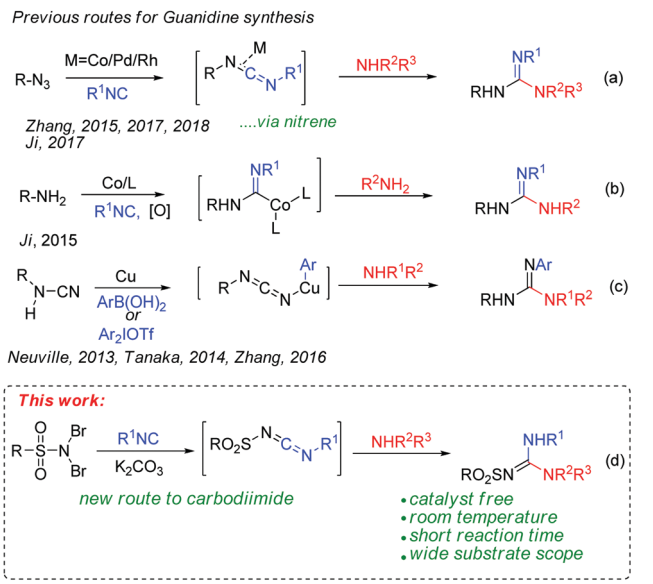
Recent methods for acyclic guanidine synthesis involve transition metal catalyzed cascade reactions of organic azides with isonitriles leading to the formation of carbodiimides followed by reaction with an amine (Scheme 1a).[8] Oxidative isocyanide insertion with amines in the presence of cobalt catalysts is an alternate pathway to generate substituted guanidines (Scheme 1b).[9] In some other approaches, cyanamide can directly provide the CN_2 core during the synthesis of trisubstituted guanidines (Scheme 1c).[10] Although these reported protocols effectively provide the synthesis of *N,N′,N″*-substituted guanidines, they require catalytic and oxidative reaction conditions.

N,N-Dibromoarylsulfonamides are an important class of organic reagents in various organic transformations.[11] In continuation of our effort with such reagents,[7b,12] herein, we are reporting an expeditious method for the synthesis of *N,N′,N″*-tri-substituted acyclic guanidines utilizing *N,N*-dibromoarylsulfonamides without using any catalyst. This has been achieved through an *in situ* generated carbodiimide intermediate at room temperature (Scheme 1d).



Scheme 1 Cascade synthesis of *N,N′,N″*-substituted guanidines.

Isolable intermediates and the exclusion of metal catalysts for the synthesis of carbodiimide are the notable advantages of the present protocol.

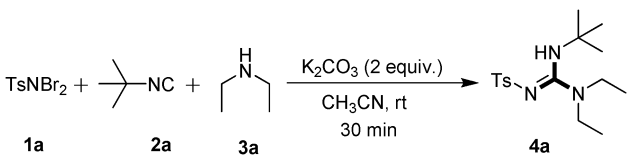
In order to evaluate the optimum conditions, an initial investigation was carried out for the reaction of $TsNBr_2$ (**1a**) and *tert*-butyl isonitrile (**2a**) with diethylamine. After a systematic study of the reaction parameters, we have found that the simple combination of $TsNBr_2$ (1 equivalent) and isonitrile (1 equivalent) with diethylamine (1 equivalent) in the presence of a weak base K_2CO_3 (2 equiv.) in MeCN at room temperature provided the desired product *N*-(*tert*-butylamino-diethylaminomethylene)-4-methylbenzenesulfonamide (**4a**) in 84% yield (Table 1, entry 1) within 30 min of reaction time. The base played a crucial role in this transformation and in its absence the product was isolated only in 21% yield (entry 2). The use of potassium fluoride was not found to be very effective in improving the reaction yield (57%, entry 5). While DCM could provide the product in an acceptable yield (entry 6, 47%), THF or 1,4-dioxane was found to have a diminishing effect on the reactivity (entries 7 and 8).

With the optimum reaction conditions in hand, we first investigated the scope of amines. The results are presented in Table 2. Secondary amines, being better nucleophiles, exhibited higher reactivity for the transformation. For example, amines such as dimethylamine, dipropylamine, dibutylamine and dioctylamine provided the desired trisubstituted guanidine product in excellent yield (82–87%, **4a–4e**, Table 2). Cyclic diamines such as pyrrolidine (**3f**), piperdines (**3g–3h**) and morpholine (**3i**) also exclusively underwent the guanylation process affording the corresponding products in 74–81% yields. Gratifyingly, secondary amines containing active functional sites like hydroxyl, alkene and alkyne could also produce the desired products in high yields (**4j–4m**, 65–72%). In particular, the tolerance of the alkene and alkyne moiety is spectacular as it is very sensitive to produce bromointermediates in the presence of $TsNBr_2$.[11b] It should be noted that compounds **4j–4l** provide a handle for further transition metal-catalyzed synthetic applications. In addition, the expected product **4n** could be isolated in 79% yield when *N*-methylbenzylamine was used.

We have also investigated the suitability of the primary aromatic amines including heterocyclic amines under the standard reaction conditions to produce the trisubstituted guanidines. It was observed that with K_2CO_3 the reactivity of aromatic amines is not impressive. However, with the use of a fluoride base, KF, we were able to isolate the desired product in moderate yield (22–57%, **4o–4v**). The fluoride ion is expected to either increase the nucleophilicity of the aromatic amine or activate the possible carbodiimide intermediate.

The scope of *N*,*N*-dibromoarylsulfonamides is wide and trisubstituted guanidines could be produced in high yields irrespective of the electronic nature and position of the substituents on the benzene ring of the dibromoarylsulfonamides (74–84%, **5a–5i**). The halo functionalities are well tolerated (F, Cl, and Br) and exhibited high reactivity highlighting the potential of this process in combination with further conventional transformations (Table 3).

Table 1 Optimization of the reaction conditions[a]

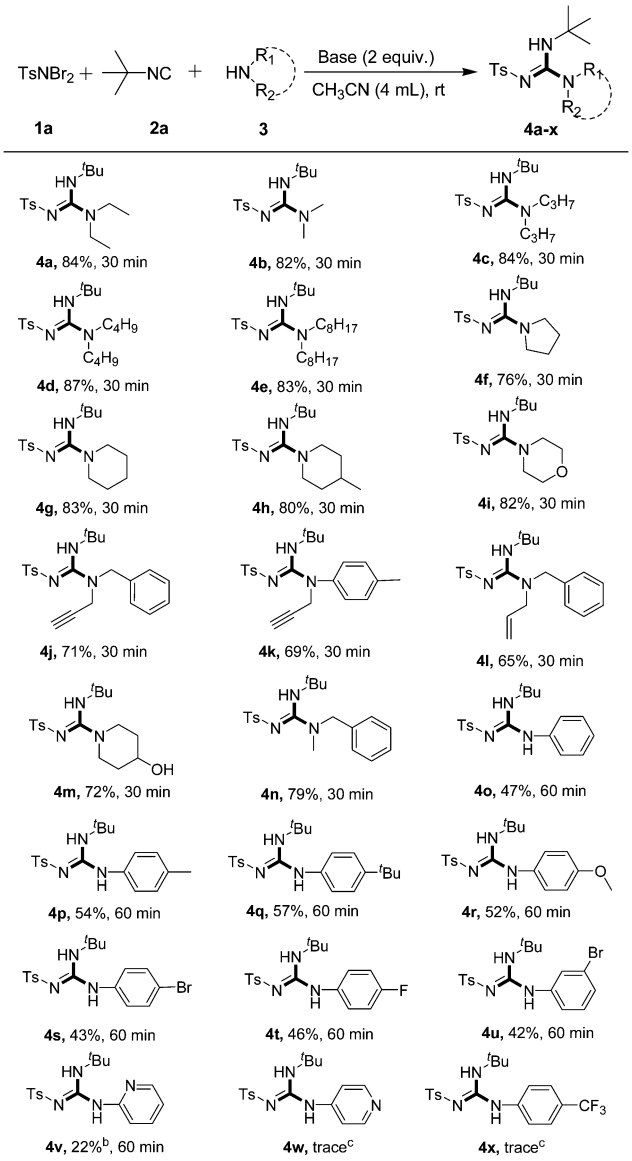


1a 2a 3a 4a

Entry	Variation from "standard conditions"	Yield[b] (%)
1	None	84
2	Without K_2CO_3	21
3	Using 1 equiv. K_2CO_3	46
4	Using 1.5 equiv. K_2CO_3	54
5	KF instead of K_2CO_3	57
6	CH_2Cl_2 instead of CH_3CN	47
7	THF instead of CH_3CN	Trace
8	1,4-Dioxane instead of CH_3CN	Trace

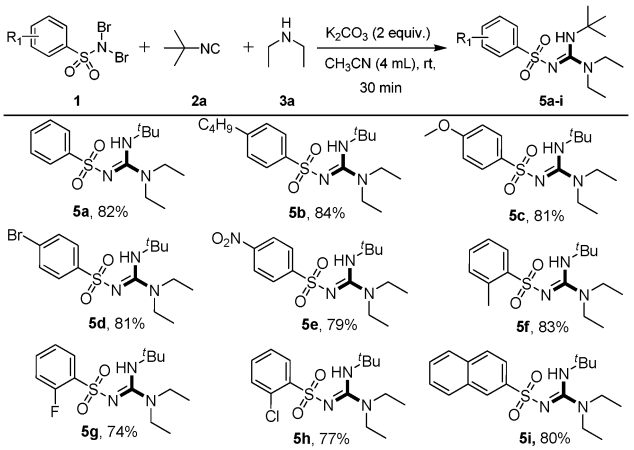
[a] Standard conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), K_2CO_3 (1 mmol) in CH_3CN (4 mL) at room temperature for 30 min. [b] Isolated yields.

Table 2 Substrate scope of amines[a]



[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), **3a–3n** (0.5 mmol)-K_2CO_3 (1 mmol), **3o–3w** (0.5 mmol)-KF (1 mmol), CH_3CN (4 mL), rt; isolated yields. [b] 3 equiv. KF. [c] 2–4 equiv. KF.

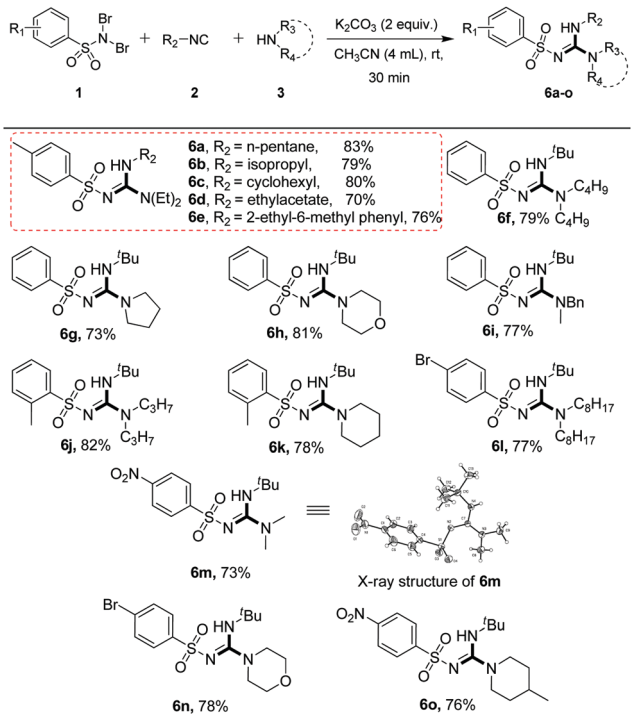
Table 3 Substrate scope of *N,N*-dibromoarylsulfonamides[a]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.5 mmol), **3a** (0.5 mmol), K_2CO_3 (1 mmol), CH_3CN (4 mL), rt, 30 min; isolated yields.

After having success in implementing our process for various amines and dibromoarylsulfonamides, we extended the reaction to check the compatibility of various sulfonamides with different isocyanides and secondary amines. These experiments generated a library of *N*-sulfonyl guanidines (Table 4). While investigating the scope of isocyanides under the optimal conditions, it was found that isocyanopentane, isocyanocylohexane, 2-isocyanopropane, ethyl isocyanoacetate and aryl isocyanide worked well to furnish the desired products **6a–e** in high yields (70–83%). The reactions of dibromoarylsulfonamides with different amines proceeded smoothly

Table 4 Scope of isonitriles and compatibility of various *N,N*-dibromoarylsulfonmaides with different secondary amines[a]



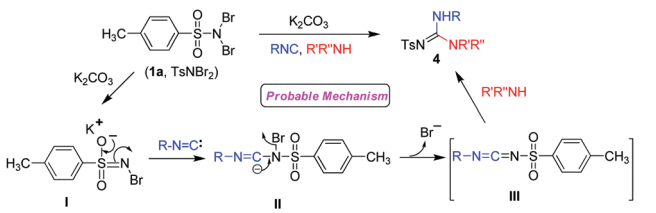
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), **3** (0.5 mmol), K_2CO_3 (1 mmol), CH_3CN (4 mL), rt, 30 min; isolated yields.

to afford the desired guanidines exclusively in high yields (**6f–6o**, 73–82%). We have also confirmed the structure of **6m** by X-ray analysis. The X-ray structural analysis reveals that the C=NNs and C–NH(^{t}Bu) bond distances are nearly the same (1.333 Å and 1.338 Å, respectively). The reactivity of the carbodiimide intermediate is very fast with the amines and in the course of the observations we did not observe formation of any byproduct *via* its degradation. An important aspect of the present protocol is its amenability to gram-scale applications (77% for **4a**, pl. see the ESI†).

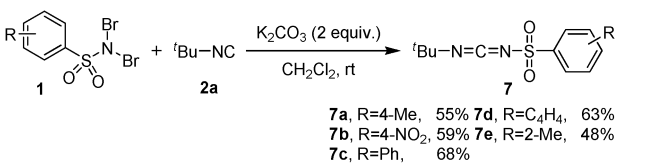
A possible mechanistic pathway for the generation of guanidine is illustrated in Scheme 2. The reaction is believed to proceed *via* the formation a carbodiimide intermediate (III). The initial step of the reaction is the abstraction of Br^+ ions from $TsNBr_2$ by the base resulting in the formation of intermediate I,[12a] which subsequently reacts with isonitrile to form carbodiimide intermediate III. To confirm the formation of carbodiimide, we have carried out a reaction between *N,N*-dibromoarylsulfonamides (**1**) and isonitrile (**2a**). Gratifyingly, we could isolate carbodiimide **7** in a moderate to high yield. A simple mixing of the sulfonamide with isonitrile in dichloromethane, at room temperature furnished the corresponding carbodiimide. To validate the method, we have synthesized a few more carbodiimides and the results are presented in Scheme 3 (entries **7a–e**). The structure of carbodiimides **7** was confirmed by analysing the NMR and HRMS data.

After isolating carbodiimide successfully, we intended to testify our proposed mechanism by reacting an isolated carbodiimide with an amine. When carbodiimide **7a** (intermediate III) was treated with diethyl amine in the presence of two equivalents of potassium carbonate in acetonitrile or CH_2Cl_2 at room temperature, the corresponding guanidine **4a** was produced in 63–90% yield (Scheme 4).

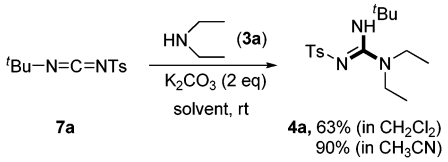
Having established a convenient procedure for acyclic guanidine derivatives, we further focused on utilizing it for the synthesis of molecules with biological importance. When propargylguanidine **4j** was subjected to an Ag-catalyzed hydroamination process in the presence of acetic acid in DCM, the reaction generated an imidazolidinone derivative (**8**, Scheme 5), which is a common



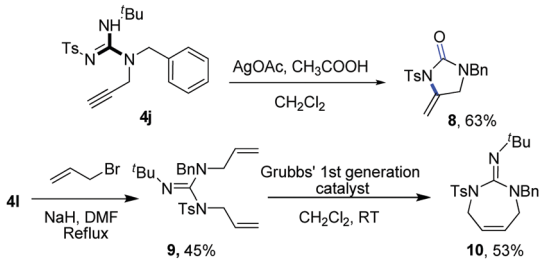
Scheme 2 Proposed mechanism for the synthesis of sulfonyl guanidines.



Scheme 3 Synthesis of carbodiimide from *N,N*-dibromoarylsulfonamides. Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol), K_2CO_3 (1 mmol), CH_2Cl_2 (4 mL), rt, 30 min; isolated yields.



Scheme 4 Synthesis of **4a** from the isolated carbodiimide.



Scheme 5 Synthetic utility of acyclic guanidine.

structural motif in both synthetic and natural bioactive compounds of medicinal relevance.[13] We have also synthesized a seven-membered cyclic guanidine (**10**, Scheme 5) through a diallylation and ring metathesis sequence from **4l** to generate a 1,3-diazepine derivative. The structure of **10** was further confirmed by hydrolyzing it to a known compound (pl. see ESI†).[14]

In summary, we have developed a catalyst-free protocol for the synthesis of sulfonyl guanidines by treating *N*,*N*-dibromoarylsulfonamides with isonitrile and amine in the presence of a base. The reaction works very fast at room temperature to produce the corresponding guanidine within a short time. Chemoselectivity of the procedure has been demonstrated by using substrates having functionalities like hydroxyl, alkene and alkyne to afford the desired sulfonyl guanidines. The synthesis and isolation of the carbodiimide intermediate under mild and catalyst-free conditions are remarkable achievements of the present method. Guanidine products were successfully transformed to core structures of biologically active molecules.

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Conflicts of interest

There are no conflicts to declare.

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