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Electrophilic Reaction of 2,2,2-Trifluorodiazoethane with the in Situ Generated *N*-Heterocyclic Carbenes: Access to *N*-Aminoguanidines

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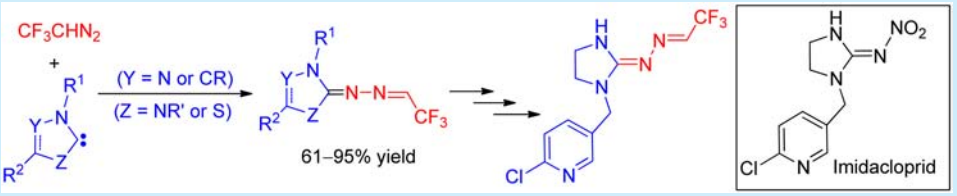
Supporting Information



ABSTRACT: A facile and efficient electrophilic reaction of 2,2,2-trifluorodiazoethane (CF_3CHN_2) with the in situ generated *N*-heterocyclic carbenes is reported. Under basic conditions, a series of trifluoromethylated *N*-aminoguanidines were obtained in good to high yields. Furthermore, this protocol was applied in the synthesis of the agrochemical Imidacloprid analogue.

The trifluoromethyl group appears in many biologically active molecules of pharmaceutical and agrochemical significance.[1] Thus, the efficient construction of CF_3-containing compounds has become the subject of intensive research in the field of synthetic chemistry.[2] In the past few years, there has been continuing interest in exploiting 2,2,2-trifluorodiazoethane (CF_3CHN_2) as a valuable trifluoromethylated building block for the development of new organic reactions, including cyclopropanation,[3] cyclopropenation,[4] cross-coupling,[5] [3 + 2] cycloaddition,[6] and *C*-nucleo- and *C*-electrophilic reactions.[7] In sharp contrast, the *N*-terminal electrophilicity of CF_3CHN_2 has been largely ignored and its utility has been rarely explored.[8] During our ongoing studies in the chemistry of 2,2,2-trifluorodiazoethane,[3,4,6] we found that an interesting electrophilic reaction of 2,2,2-trifluorodiazoethane with the in situ generated *N*-heterocyclic carbenes. The notable features of this reaction are its operational simplicity, mild reaction conditions, and easily accessible starting materials. Herein, we report our preliminary results on this subject.

Guanidine is an important structural motif found in many natural products, pharmaceuticals, agrochemicals, and bioactive compounds.[9] Among the most remarkable ones are saxitoxin (paralytic shellfish toxin), ptilomycalin A (marine alkaloid), peramine (fungal alkaloid), zanamivir (neuraminidase inhibitor), and imidacloprid (insecticide) (Figure 1, top). In addition, many guanidines have also been widely used in the field of synthetic chemistry as organosuperbases and organocatalysts, such as 1,5,7-triaza-bicyclo[4.4.0]dec-5-ene (TBD), 1,4,6-triaza-bicyclo[3.3.0]oct-4-ene (TBO), (*S*)-Ph-TBO, (*S*)-^{t}Bu-TBO, guanidine-bis(thio)urea, and bisguanidine (Figure 1, bottom).[10] Classical guanidine synthesis involves the chemical transformations of thioureas, isothioureas, cyanamides, carbodiimides, carboximidamides, and its derivatives.[11] Despite the numerous methodologies available, advances in the construction of diverse guanidines are still highly desirable. Our present transformation provides a new and efficient method, in which the C=N double bond was formed, to afford a series of *N*-aminoguanidine derivatives in good to high yields.

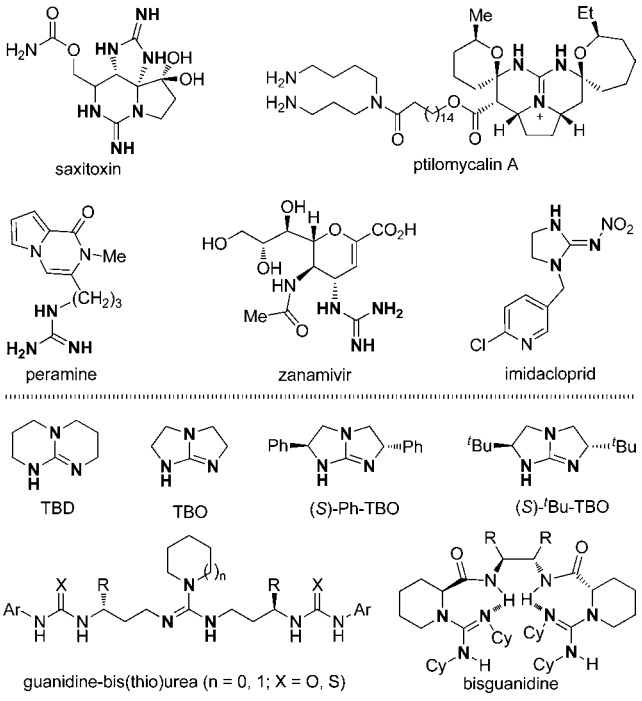


Figure 1. Guanidine-based biological and chemical compounds.

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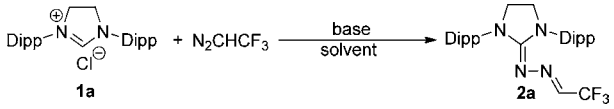
Our studies were initiated with the electrophilic reaction of dihydroimidazolium salt **1a** and CF_3CHN_2 under basic conditions. The results are listed in Table 1. By screening a

Table 1. Optimization of Conditions for the Electrophilic Reaction of CF_3CHN_2 with Dihydroimidazolium Salt 1a[a]



1a 2a

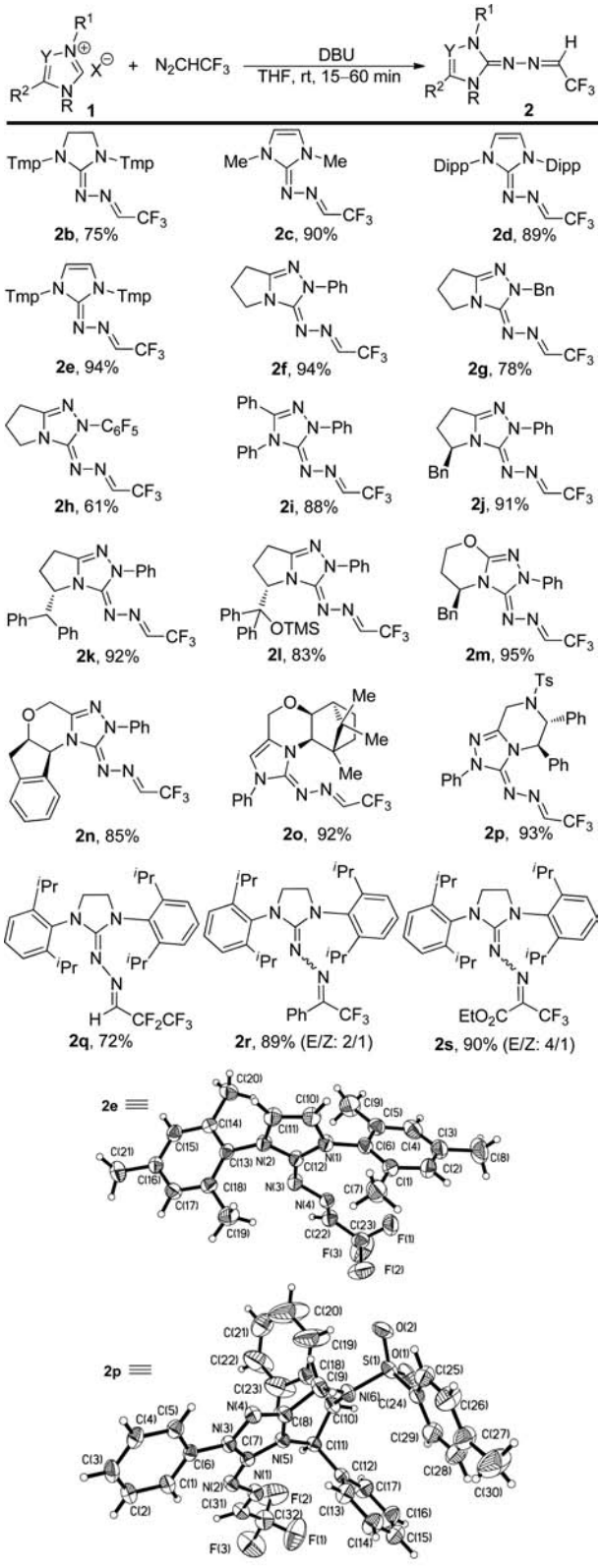
entry	base	solvent	temp (°C)	yield (%)[b]
1	Et_3N	THF	25	0
2	DMAP	THF	25	3
3	DABCO	THF	25	8
4	DBU	THF	25	95 (92)
5	Na_2CO_3	THF	25	5
6	K_2CO_3	THF	25	55
7	Cs_2CO_3	THF	25	90 (85)
8	DBU	THF	50	94 (92)
9	DBU	toluene	25	71 (65)
10	DBU	CH_3CN	25	30
11	DBU	DMF	25	20

[a]General reaction conditions: **1a** (0.2 mmol), CF_3CHN_2 (0.4 mmol), and base (0.4 mmol) in solvent (2 mL) at the given temperature for 15 min. [b]Yields were determined by ^{19}F NMR with $C_6H_5CF_3$ as an internal standard. The values in parentheses represent the isolated yield. Dipp = 2,6-diisopropylphenyl; DMAP = 4-dimethylaminopyridine; DABCO = 1,4-diazabicyclo[2.2.2]octane.

series of organic and inorganic bases (entries 1−7), it was found that the use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and Cs_2CO_3 delivered the desired *N*-aminoguanidine **2a** in high yields, whereas all the other bases tested resulted in poor to moderate yields. The increase of the reaction temperature did not improve the yield when compared to that obtained at 25 °C (entry 8 vs 4). In addition, the solvent was found to have an important effect on the reactivity (entries 9−11). Among the solvents tested, tetrahydrofuran (THF) was found to be the solvent of choice for this electrophilic reaction. It was noteworthy that in all cases the dehydrogenation or denitrogenation cross-coupling of the in situ generated aminocarbene with 2,2,2-trifluorodiazoethane was not a detectable side reaction for these base-mediated processes.

With the optimized reaction conditions in hand, we next investigated the scope of this electrophilic reaction of CF_3CHN_2 with a series of imidazolium salts. As shown in Scheme 1, the reaction of dihydroimidazolium salt **1b** and imidazolium salts **1c−e** with CF_3CHN_2 proceeded well to afford the corressponding *N*-aminoguanidines **2b−e** in good to high yields. The in situ generated 1,2,4-triazol-5-ylidenes also delivered the desired products **2f−i** in 61−94% yields. In addition, a series of chiral azolium salts[12] were subjected to the current electrophilic reaction under the optimal conditions. We were pleased to find that the corresponding chiral *N*-amnioguanidines **2j−p** were obtained in good to excellent yields (83−95%). Furthermore, the molecular structures of **2e** and **2p** were further confirmed by means of X-ray crystallographic analysis (see the Supporting Information).[13] This protocol can also be readily extended to the use of other diazo compounds. For example, 2,2,3,3,3-pentafluorodiazopropane ($CF_3CF_2CHN_2$)[14a] reacted with the in situ generated carbene to afford the desired *N*-amnioguanidine **2q** in 72% yield. (1-

Scheme 1. Scope for This Electrophilic Reaction



Tmp = 2,4,6-trimethylphenyl; Ts = 4-toluenesulfonyl.

Diazo-2,2,2-trifluoroethyl)benzene and ethyl 2-diazo-3,3,3-trifluoropropanoate[14b] also participated in this electrophilic reaction, furnishing the corresponding products **2r** and **2s** in high yields with low *Z*/*E*-selectivity.

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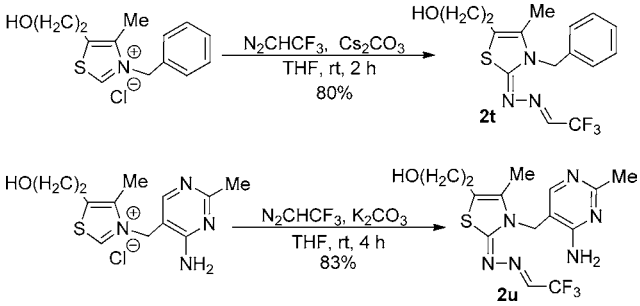
To further define the scope of our methodology, the reaction of CF_3CHN_2 with readily accessible thiazolium salts was also tested (Scheme 2). Possibly due to their intrinsic low reactivity,

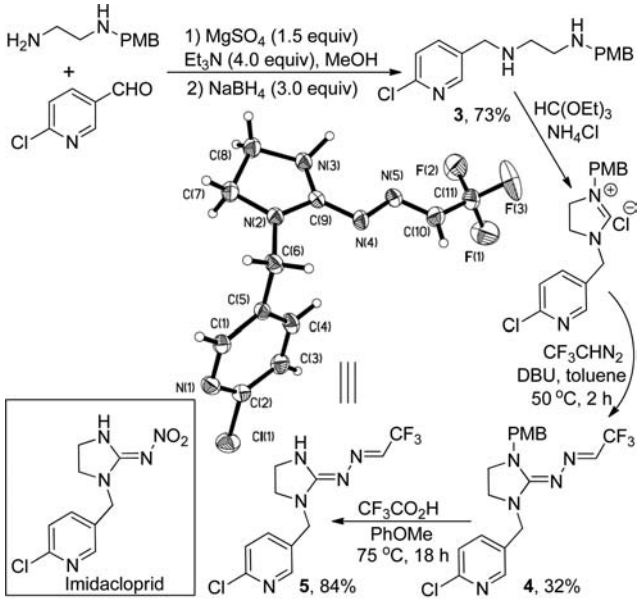
Scheme 2. Reaction of Thiazolium Salts with CF_3CHN_2



these two thiazolium salts were found to undergo the desired transformation to afford the corresponding products in low yields under current reaction conditions. Subsequently, the reaction was performed by using Cs_2CO_3 and K_2CO_3 as bases with a prolonged reaction time, and the desired products **2t** and **2u** were obtained in yields of 80% and 83%, respectively.

Finally, we turned our attention to the application of the current protocol to the synthesis of the Imidacloprid analogue.[15] As shown in Scheme 3, N^1-((6-chloropyridin-3-

Scheme 3. Synthesis of the Imidacloprid Analogue 5



yl)methyl)-N^2-(4-methoxybenzyl)-ethane-1,2-diamine **3** was synthesized in two steps in 73% yield. The cyclocondensation of diamine **3** with triethoxymethane provided the dihydroimidazolium salt, which was deprotonated and reacted with CF_3CHN_2 to give the corresponding *N*-aminoguanidine **4** in total 32% yield. Subsequent removal of the PMB group afforded the imidacloprid analogue **5** in 84% yield. The relative stereochemistry of the C=N bonds for the compound **5** was determined to be (*E*, *E*) by means of X-ray crystallographic analysis.[13]

In conclusion, we have successfully developed a facile and efficient procedure for the electrophilic reaction of CF_3CHN_2 with the in situ generated aminocarbenes. Under the basic conditions, a range of trifluoromethylated *N*-aminoguanidines can be accessed in good to high yields from inexpensive and readily available dihydroimidazolium, imidazolium, and thiazolium salts. Furthermore, this protocol was applied in the synthesis of the agrochemical Imidacloprid analogue. Further application of these *N*-aminoguanidines as ligands and catalysts in organic synthesis and investigation of the biological activity of the relative derivatives are ongoing in our laboratory, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01191.

Experimental details, NMR data of all the new compounds (PDF)
Crystallographic data for **2e** (CIF)
Crystallographic data for **2p** (CIF)
Crystallographic data for **5** (CIF)

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Notes

The authors declare no competing financial interest.

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