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A simple one-pot synthesis of triflyl guanidines: access to highly substituted electron-poor guanidines

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ABSTRACT

Unsymmetrical di- and trisubstituted triflyl guanidines are accessed through a simple, one-pot protocol from the corresponding isothiocyanate and amine. Furthermore, in the presence of base, trisubstituted triflyl guanidines are alkylated to obtain tetrasubstituted triflyl guanidines in high yields and complete regioselectivity.

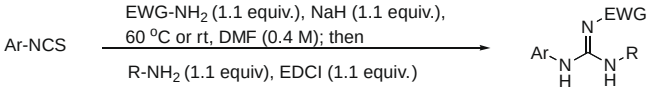
Guanidine functionalities play a key role in many biologically active natural products and pharmaceutically relevant compounds. Moreover, compounds containing a trifluoromethanesulfonyl (triflyl) guanidine moiety have been found to be useful in treating diseases prevented by or ameliorated with potassium channel openers[1] and for the treatment of chemokine mediated diseases and disorders.[2] Furthermore, Kinoshita and co-workers have reported the use of dialkylated triflyl guanidines as useful insecticides or acaricides.[3] In addition to their biological properties, Goodman and co-workers have reported the use of diacylated triflyl guanidines as a class of efficient guanylating reagents.[4]

To date, a limited number of methods to synthesize triflyl guanidines have been disclosed.[5] Among those methods, the triflyl group is introduced with triflic anhydride or in multiple steps,[6,7] some involving tedious protecting group introduction and removal.[8] We were interested in the application of electron-poor guanidines, including triflyl guanidines, as chiral catalysts. However, none of the published methods for the synthesis of triflyl guanidines could be applied to the unsymmetrical triflyl guanidines we envisioned.[9]

A one-pot method to synthesize acyl,[10] sulfamoyl, methanesulfonyl, and benzenesulfonyl guanidines[11] was developed by Shi and co-workers, following a one-pot method for the synthesis of cyanoguanidines (Scheme 1).[12] We envisioned that, with slight modifications, a similar process would allow access to unsymmetrical triflyl guanidines in a one-pot protocol. This protocol would enable the synthesis of trisubstituted triflyl guanidines without the use of protecting groups and, in addition, the substitution pattern would be dependent solely on the starting materials used.

Unfortunately, the reaction conditions were not directly applicable to the synthesis of triflyl guanidines. A thiourea side product was observed, which was typically inseparable from the desired guanidine. To circumvent the formation of the thiourea side product, the isothiocyanate needed to be completely consumed before the addition of the amine in the second step. A larger excess of trifluoromethanesulfonamide (1.5 equiv) was therefore required. In addition, the reaction was performed at elevated temperatures to ensure the complete consumption of the isothiocyanate. With the modified reaction conditions, the thiourea byproduct was not observed in the final product. Excess amine (2 equiv) was also required to cleanly furnish the guanidines in high yield, which were then precipitated out of solution through the addition of water, without the need for further purification. In the cases where the guanidine did not precipitate, the crude reaction mixture was easily purified by column chromatography.

To determine the scope and limitations of the one-pot synthesis of di- and trisubstituted triflyl guanidines, various isothiocyanates and primary and secondary amines were investigated (Table 1).



Scheme 1. Shi and co-workers' one-pot protocol for the synthesis of sulfamoyl and sulfonyl guanidines.[11] Ar = Ph, $PhCH_2CH_2$; EWG = SO_2NH_2, SO_2NMe_2, SO_2Me, SO_2Ph.

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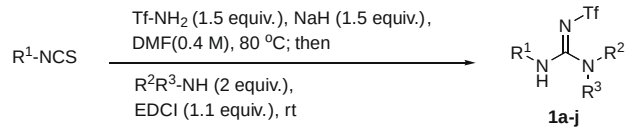
Table 1
Synthesis of triflyl guanidines



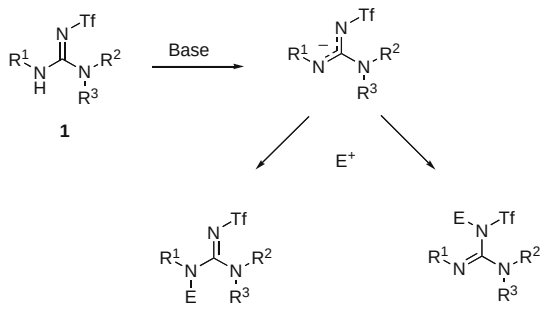
Entry	Product	R^1	R^2	R^3	Yield[a] (%)
1	**1a**	Ph	Bn	H	80
2	**1b**	Ph	Bn	Me	93
3	**1c**	Ph	Bn	Bn	99
4	**1d**	Ph	*i*Pr	*i*Pr	52
5	**1e**	Ph	*t*Bu	H	53
6	**1f**	Ph	Ph	H	66
7	**1g**	Ph	Ph	Me	53
8	**1h**	4-MeO–C_6H_4	Bn	H	90
9[b]	**1i**	3,5-$(CF_3)_2$–C_6H_3	Bn	H	75
10	**1j**	2,4,6-$(CH_3)_3$–C_6H_2	Bn	H	74

[a] Yield of isolated pure product.
[b] The first step was performed at room temperature. EDCI = *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride. Tf = CF_3SO_2.

Phenyl isothiocyanate and benzylamine furnished the desired triflyl guanidine in 80% yield (entry 1). To our delight, unhindered secondary amines afforded the desired guanidine in high yield (entries 2–3). Interestingly, even severely hindered amines such as diisopropylamine and *t*-butylamine furnished the desired guanidines **1d**–**e** in good yields. Primary and secondary aromatic amines can also be used (entries 6 and 7). The lower yield obtained for **1f** and **1g** is presumably a consequence of the steric hindrance of secondary anilines. We then examined the effect of the isothiocyanate's electronic and steric properties on the reaction outcome. Gratifyingly, both electron-deficient and electron-rich aryl isothiocyanates cleanly furnished triflyl guanidines **1h** and **1i** (entries 8 and 9). Due to the reactive nature of 3,5-bis(trifluoromethyl)phenyl isothiocyanate, heating was not required for the first step. Finally, triflyl guanidine **1j** can be synthesized from mesityl isothiocyanate in 74% yield, indicating that steric bulk in the isothiocyanate used is of no consequence to the reaction outcome (entry 10).

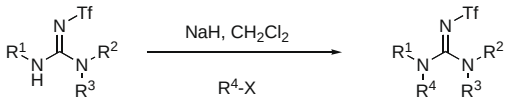
As a result of the multiple substitution patterns possible, highly substituted guanidines pose a significant challenge as synthetic targets. Although several methods have been developed for the alkylation of *symmetrical* guanidines,[5,13] alkylation of *unsymmetrical* guanidines typically suffers from poor or moderate regioselectivity (Scheme 2).[13a,c]

With the goal of synthesizing fully substituted triflyl guanidines in mind, we were delighted that trisubstituted triflyl guanidines of type **1** furnished a single regioisomer in high yield in the presence of NaH and an alkyl halide (Table 2). The alkylation occurred exclusively at the nitrogen atom bearing the R^1 group, as determined by



Scheme 2. Regioselectivity problem: alkylation of guanidines under basic conditions.

Table 2
Regioselective synthesis of tetra-substituted triflyl guanidines



Entry	Product	R^1	R^2	R^3	R^4	Yield[a] (%)
1[b]	**2g**	Ph	Ph	Me	Bn	87
2[b]	**2b**	Ph	Bn	Me	Bn	76
3[c]	**2c**	Ph	Bn	Bn	Me	100

[a] Yield of isolated pure product.
[b] Reaction was performed using 1.2 equiv of BnBr.
[c] Reaction was performed using DMF as solvent and 2.2 equiv of MeI.

HMBC (see Supplementary Material).[14] Benzylation of **1g** selectively furnishes **2g** in 87% yield (entry 1). Simply modifying the starting materials can control the substitution pattern of tetrasubstituted triflyl guanidines. Regioisomers **2b** and **2c** can be accessed selectively in high yields by simply varying the alkylating reagent and the amine used to synthesize the trisubstituted triflyl guanidine precursor (entries 2–3). To the best of our knowledge, this method constitutes the first example of highly regioselective alkylation of unsymmetrical guanidines.

In summary, the synthesis of di- and trisubstituted guanidines can be achieved in high yield using a simple, one-pot protocol. Furthermore, tetrasubstituted triflyl guanidines can be synthesized with complete regioselectivity from the corresponding trisubstituted guanidine. This modular approach allows control over the substitution pattern, which poses a significant challenge to access highly substituted guanidines.

Experimental

General procedure for the synthesis of trisubstituted triflyl guanidines: *N*-((benzylamino)(phenylamino) methylene) trifluoromethanesulfonamide (1a)

Sodium hydride (22 mg, 0.56 mmol, 60% in mineral oil) was added to a stirring solution of trifluoromethanesulfonamide (95 mg, 0.56 mmol) in dry DMF (1.0 mL) at room temperature. After 5 min, phenyl isothiocyanate (44 μL, 0.37 mmol) was added and the reaction mixture was heated to 80 °C until the complete consumption of the isothiocyanate was observed by thin layer chromatography, then the reaction was cooled to room temperature. Benzylamine (39 μL, 0.74 mmol) was added, followed by EDCI (78 mg, 0.37 mmol), and the reaction was stirred for 20 h. The reaction was quenched with distilled water (2 mL) and stirred for 5 min at room temperature. The white precipitate formed was filtered and washed with water (3 × 10 mL) and hexanes (3 × 10 mL). White solid (105 mg, 81% yield). Mp: 119–124 °C. IR ν_{max} 3330, 1604, 1335, 1209, 1180, 1049 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 8.91 (br s, 1H), 7.48–7.45 (m, 2H), 7.41–7.38 (m, 1H), 7.36–7.28 (m, 3H), 7.23–7.20 (m, 4H), 5.34 (br s, 1H), 4.57 (d, J = 5.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0, 136.6, 133.9, 130.9, 129.2, 128.3, 127.7, 126.9, 124.2, 117.8 (q, J = 320 Hz), 45.9; HRMS (EI^+) *m/z* calcd for $C_{15}H_{14}F_3N_3O_2S$ $[M]^+$: 357.0759, found: 357.0756.

General procedure for the synthesis of tetrasubstituted triflyl guanidines: *N*-((benzyl(phenyl) amino) methyl(phenyl)-amino) methylene)trifluoromethanesulfonamide) (2g)

Sodium hydride (5 mg, 0.12 mmol, 60% in mineral oil) was added to a solution of guanidine **1g** (36 mg, 0.10 mmol) and benzyl

bromide (12 μL, 0.101) in dry CH_2Cl_2 (500 μL) at 0 °C. The reaction was warmed up to room temperature and stirred for 20 h. The reaction was quenched with distilled water (2 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic extracts were dried over Na_2SO_4, then concentrated under reduced pressure. The crude product was purified by column chromatography (4:1 hexanes/EtOAc, R_f = 0.38) to yield a white solid (39 mg, 87% yield). Mp: 62–64 °C. IR ν_{max} 1511, 1409, 1333, 1213, 1136, 693 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 7.27–7.22 (m, 5H), 7.08–7.03 (m, 6H), 6.70 (dd, J = 12.5, 7.3 Hz, 2H), 6.50 (d, J = 6.7 Hz, 2H), 4.97 (s, 2H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.6, 143.9, 142.1, 135.5, 129.5, 129.4, 128.7, 128.3, 127.2, 126.7, 126.5, 125.1, 120.0 (q, J = 319 Hz), 57.4, 43.2; HRMS (EI^+) m/z calcd for $C_{22}H_{20}F_3N_3O_2S$ $[M]^+$: 447.1228, found: 447.1233.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.040.

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