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A novel atom-efficient, one-pot synthesis of sulfonylguanidines and sulfamoylguanidines

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ABSTRACT

An expedient one-pot procedure for the atom-efficient production of a variety of sulfonylguanidines and sulfamoylguanidines under mild conditions is described. The route constitutes an important alternative to current methods.

The guanidine moiety constitutes a key structural element in many biologically active compounds[1] and natural products.[2] Sulfonylguanidines have been applied as precursors in the synthesis of peptide 'tweezer'[3] receptors[4,5] and as chiral organocatalysts for the Michael reaction.[6] Moreover, sulfonylguanidines such as the racemic antiulcer agent osutidine,[7] and the closely related acylguanidines, exemplified by the sodium–calcium exchange blocker benzamil,[8] and the antithrombotic factor Xa inhibitor,[9] BMS-344577, are of pharmaceutical interest. The cannabinoid CB_1 antagonistic[10] pyrazoline-1-carboxamidines,[11] including the anti-obesity agent ibipinabant,[12] can be considered as sulfonylguanidine derivatives wherein one of the guanidine nitrogen atoms is part of a heterocyclic ring (Fig. 1).

Several synthetic approaches to sulfonylguanidines and acylguanidines have been described.[6,11–14] In general, an electrophilic guanylating agent is synthesized from a thiourea. In the final step of the synthetic sequence, the thiourea is coupled with a nucleophilic amine in the presence of a Hg(II) salt, EDC, the Mukaiyama reagent, 2,4-dinitrofluorobenzene or iodine.[15] The required *N*-sulfonylthioureas are either synthesized from a sulfonamide and an isothiocyanate in the presence of a base, or are obtained by the reaction of a sulfonylisothiocyanate and an amine. An alternative route[4,5] to sulfonylguanidines started from an amine which was converted with thiophosgene into the corresponding isothiocyanate, and further converted by reaction with a second amine into the corresponding thiourea. The thiourea obtained was then

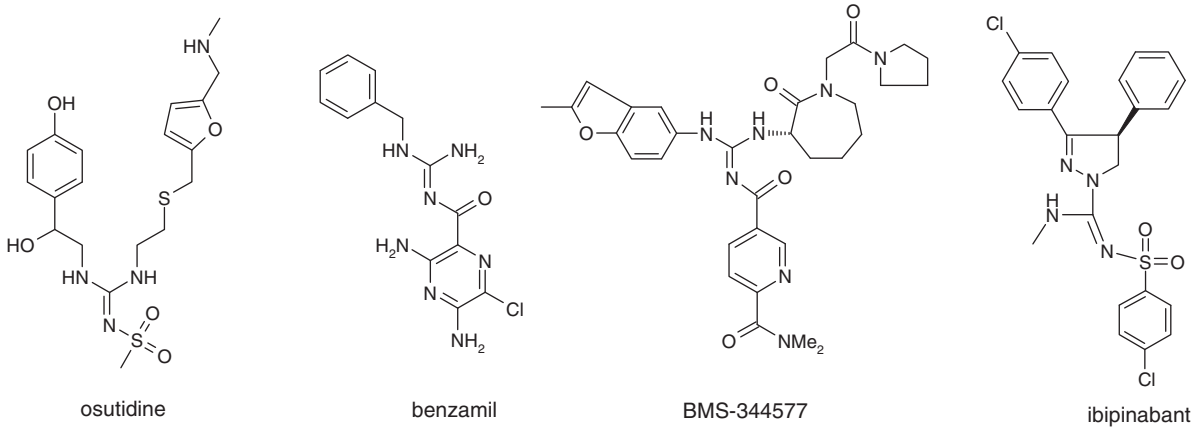

Figure 1. Examples of sulfonylguanidines and acylguanidines of pharmaceutical interest.

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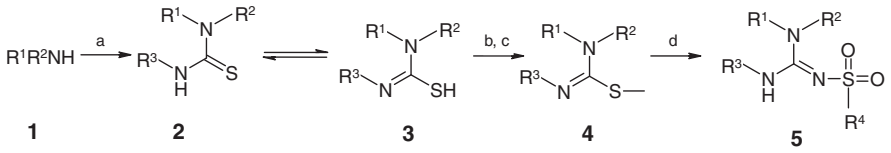


Scheme 1. Reagents and conditions: (a) $R^3N{=}C{=}S$, CH_3CN, N_2, rt, 2 h, except for **5h** (20 h); (b) CH_3I, rt, 18 h; (c) concentration in vacuo; (d) $R^4SO_2NH_2$, $KHCO_3$, MeCN, reflux, 22 h, except for **5d** and **5i** (72 h).

methylated in the presence of NH_4PF_6 and subsequently coupled with a sulfonamide in the presence of a base to produce the desired sulfonylguanidine.

Recently, we disclosed[16] an improved synthetic route to ibipinabant from inexpensive, commercially available reagents with a high degree of atom-efficiency.[17]

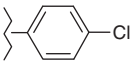
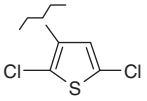
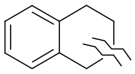
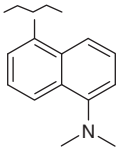
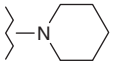
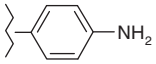
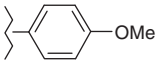
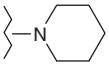
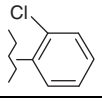
These encouraging results warranted an additional study directed at the scope of this expedient methodology as well as to further improvements of the experimental procedures involved. In particular, we attempted to develop a novel one-pot protocol[18] for the efficient production of a variety of sulfonylguanidines and sulfamoylguanidines by the consecutive reaction of a secondary amine with an isothiocyanate, methyl iodide, and a sulfonamide or sulfamide. The use of mild reaction conditions constituted the main point of attention herein since this would enable the inclusion of additional sensitive functionalities without the need for complicated protecting group strategies. A diverse set of commercially available reagents were compiled for this purpose in order to prepare a range of 16 sulfonylguanidines **5a**–**5p**. Our results are summarized in Scheme 1 and Table 1.

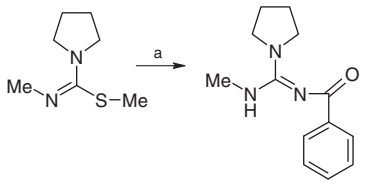
In order to gain more insight into the scope of the guanylation reaction a variety of R^1–R^4 substituents were used in different combinations. For example, the set of applied secondary amines R^1R^2NH consisted of either dialkylamines, having different degrees of steric demand, monocyclic amines with varying ring sizes and fused bicyclic tetrahydroisoquinoline, benzylic, or aromatic amines. The reagents R^3–N=C=S were selected from alkyl-, cycloalkyl-, benzyl-, and phenyl-isothiocyanates. Finally, the sulfonamides $R^4SO_2NH_2$ consisted of (substituted) aryl-, heteroaryl-, cycloalkyl-, and heterocycloalkyl-sulfonamides. In general, the observed yields of the sulfonylguanidine derivatives of general formula **5** from **1** were high. In this context it should be noted that the applied one-pot procedure encompasses three consecutive chemical conversions.

However, in some cases, the one-pot reaction was more troublesome. These specific cases are discussed in more detail below.

The last step, reaction with dansylamide, in the synthesis of **5d** appeared to proceed more slowly than in the other cases and gave rise to the concomitant formation of some impurities. By prolonging the reaction time to 72 h and subjecting the crude **5d** obtained to flash chromatographic purification followed by recrystallization (EtOH), pure **5d** was isolated in a moderate yield of 49%. It was observed that in the first stage of the attempted synthesis of **5f** the addition of sterically demanding *N*-*tert*-butylisopropylamine to methyl isothiocyanate did not take place at ambient or elevated temperatures. This initial step also proceeded slowly in the synthesis of **5h** which could be rationalized by invoking the low nucleophilicity[19] of aromatic *N*-methyl-*p*-anisidine. However, coupling of the *p*-anisidine to methyl isothiocyanate could be achieved by increasing the reaction time from two to 20 h, thereby eventually leading to a satisfactory overall yield of pure **5h** (70%). Furthermore, it was observed that the rate of conversion from **4i** into **5i** was significantly slower than in the other studied cases, leading to a modest isolated yield of **5i**. For the small and polar compounds **5l** and **5m** modest yields (~40%) were initially obtained. It was observed that in the final washing step a significant amount of the crude product was lost in the extraction process. This could be overcome by eliminating the extraction/washing step from

Table 1
One-pot synthesis of guanidines **5a**–**5p**

Compound	R^1	R^2	R^3	R^4	Yield (%)	Compound	R^1	R^2	R^3	R^4	Yield (%)
5a	$-(CH_2)_4-$		Me	Ph	83	**5i**	$-(CH_2)_4-$		Ph	Ph	30
5b	$-(CH_2)_5-$		Bn		93	**5j**	$-(CH_2)_4-$		*t*-Bu	Ph	67
5c	$-(CH_2)_6-$		*n*-Pr		68	**5k**	$-(CH_2)_4-$		*c*-Hexyl	Ph	83
5d			Bn		49	**5l**	$-(CH_2)_4-$		Me	Me	95
5e	El	El	Me	Ph	57	**5m**	$-(CH_2)_4-$		Me		70
5f	*t*-Bu	*i*-Pr	Me	Ph	0	**5n**	$-(CH_2)_4-$		Me		76
5g	Bn	Me	Me	Ph	84	**5o**	$-(CH_2)_4-$		Me		84
5h		Me	Et		70	**5p**	$-(CH_2)_4-$		Me		97



4a **6a**

Scheme 2. (a) $C_6H_5CONHNa$, THF, reflux, 22 h (12%).

the reaction procedure in these two cases. The reaction mixtures obtained which contained crude **5l** and **5m** were diluted with a small amount of ethyl acetate and the remaining solid material (mostly $KHCO_3$ salt) was removed by filtration. Subsequently, the filtrate was concentrated and subjected to flash chromatographic purification. This specific modification led to a significant increase in chemical yield for both **5l** (95%) and **5m** (70%), respectively.

In general, the atom-efficiencies of the one-pot conversions of **1** into **5** were high. In our set of compounds, **5a–5p** the atom-efficiency ranged from 54% for the smallest molecule **5l** to 74% for the largest compound **5d**.

In addition, we attempted to prepare the acylguanidine **6a** via an analogous one-pot protocol by reaction of the in situ formed **4a** with benzamide. However, the desired product **6a** was not formed in this reaction which could be rationalized by invoking insufficient nucleophilicity of the carboxamide under the neutral reaction conditions. After a brief survey of the reaction conditions we succeeded in preparing **6a** by the addition of three molar equivalents of benzamide sodium salt (prepared from benzamide and NaH in THF) to a solution of in situ formed **4a** in anhydrous THF (Scheme 2). However, this procedure furnished **6a** in a disappointingly low 12% yield. The use of potassium hexamethyldisilazide (KHDMS) as an alternative base did not improve the yield in this particular reaction. Since the analogous reaction of **4a** with 1-carbamylpiperidine did not proceed at all, it was decided to abandon this alternative synthetic approach for the synthesis of acylguanidine derivatives.

In conclusion, an efficient one-pot procedure for the atom-efficient production of a variety of sulfonylguanidines and sulfamoylguanidines under mild reaction conditions is described. The outlined synthetic methodology has a broad applicability, but sterically demanding amines R^1R^2NH appear to limit the scope.

Acknowledgments

Willem Gorter and Hugo Morren are gratefully acknowledged for analytical support.

Supplementary data

Supplementary data (selected analytical data for compounds **5c–5e** and **5g–5p**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.04.031.

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18. Yields refer to isolated pure products unless otherwise noted and were not optimized. Selected data for compounds **5a, 5b,** and **6a**. *Synthesis of compound* **5a**: The one-pot experiment was carried out in oven-dried glassware under a nitrogen atmosphere. A solution of pyrrolidine (0.36 g, 5.00 mmol) in CH_3CN (3 ml) was added dropwise to a stirred solution of methyl isothiocyanate (0.47 ml, 5.50 mmol) in CH_3CN (10 ml, anhydrous puresolve™) under cooling in an ice-bath to keep the reaction temperature below 10 °C. The ice-bath was removed and stirring was continued at room temperature for 2 h to furnish a yellow-colored solution of the intermediate **2a**. The nitrogen flow was stopped (to prevent evaporation of volatile CH_3I in the subsequent reaction), a $CaCl_2$ tube was fitted for protection against moisture and CH_3I (0.62 ml, 10.0 mmol) was added in one portion. Stirring was continued at room temperature for 18 h after which TLC analysis [eluent: EtOAc/hexanes 1:1 (v/v)] showed full conversion of **2a** into **3a**. The solvent and excess CH_3I were removed in vacuo and CH_3CN (10 ml) was added in order to dissolve the resulting dark-yellow solid. $KHCO_3$ (0.70 g, 7.00 mmol) and benzenesulfonamide (0.83 g, 5.25 mmol) were added successively and the resulting mixture was stirred at reflux temperature for 22 h. After cooling to room temperature, 2 N NaOH was added and the mixture was extracted with EtOAc (3 × 20 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4), and evaporated in vacuo to give a pale brown oil. The crude **5a** was purified by flash chromatography (gradient elution: EtOAc/hexanes 1:1, EtOAc/hexanes 3:1, EtOAc) to furnish *N*-(benzenesulfonyl)-*N′*-methylpyrrolidine-1-carboximidamide (**5a**) as a white solid (1.09 g, 83% yield). Melting point: 95–97 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82–1.92 (m, 4H), 2.85 (d, J = 5.3 Hz, 3H), 3.43–3.50 (m, 4H), 6.77 (br s, 1H), 7.40–7.50 (m, 3H), 7.90 (dd, J = 8 and 2 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.32, 31.58, 49.20, 125.86, 128.52, 131.10, 144.67, 158.34. HR-MS (ES+): calcd for $C_{12}H_{18}N_3O_2S$ $(M+H)^+$ 268.1120; found: 268.1105. *N′*-Benzyl-*N*-[(4-chlorobenzene)sulfonyl] piperidine-1-carboximidamide (**5b**). Melting point: 136–138 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53–1.67 (m, 6H), 3.30–3.37 (m, 4H), 4.26 (d, J = 6 Hz, 2H), 7.01 (br t, J = 6 Hz, 1H), 7.15–7.21 (m, 2H), 7.30–7.38 (m, 5H), 7.65 (br d, J = 8.6 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.19, 25.57, 48.93, 48.93, 49.99, 127.40, 127.59, 128.11, 128.80, 128.98, 136.91, 137.49, 142.39, 160.05. HR-MS (ES+): calcd for $C_{19}H_{23}N_3O_2S^{35}Cl$ $(M+H)^+$ 392.1200; found: 392.1200. *N*-[(Methylimino)(pyrrolidin-1-yl)methyl]benzamide (**6a**). Melting point: 199–202 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–1.99 (m, 4H), 2.97 (d, J = 4.8 Hz, 3H), 3.52–3.59 (m, 4H), 7.10–7.33 (m, 1H), 7.34–7.44 (m, 3H), 8.17 (br d, J = 8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.39, 30.34, 48.10, 127.68, 128.87, 130.34, 138.82, 162.31. HR-MS (ES+): calcd for $C_{13}H_{18}N_3O$ $(M+H)^+$ 232.1450; found: 232.1463.
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