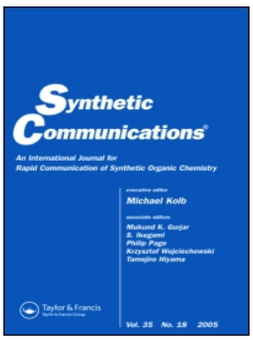

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Simple generalized reaction conditions for the conversion of primary aliphatic amines to surfactant-like guanidine salts with 1*H*-pyrazole carboxamidine hydrochloride

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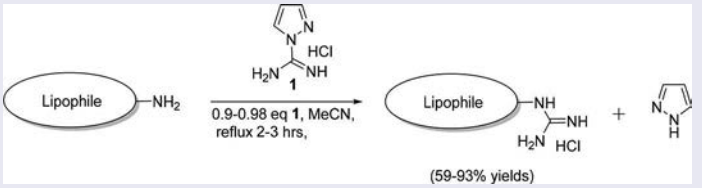
ABSTRACT

Improved reaction conditions for the electrophilic reaction between a free aliphatic amine and 1H-pyrazole carboxamidine have been discovered. The surfactant-like guanidine salts, which are often hard to work with, were obtained in decent yields with short reaction times, minimal workup, and high level of purity.

GRAPHICAL ABSTRACT



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KEYWORDS
Guanidine synthesis; 1*H*-pyrazole carboxamidine; surfactant synthesis

Introduction

1*H*-Pyrazole carboxamidine hydrochloride (**1**) is a commonly used electrophilic guanylation reagent for primary amines.[1] This guanylation agent was originally presented by Bernatowicz et al. in 1992 as a means for guanyl introduction in peptide synthesis, thus circumventing the use of the sometimes problematic protected arginines.[2] Bernatowicz reported that **1** showed better reactivity and solubility characteristics than other guanylation compounds at the time.[3–8] The reaction of **1** with a primary amine is shown in Scheme 1. A literature search shows that many have employed this method in the synthesis of a variety of compounds.[9] The most common conditions involve an amine, an organic (Hünig's base, or triethyl amine (TEA)) or inorganic base, and **1** in equimolar amounts in a solvent (most often dimethylformamide, DMF). Removal of base and solvents with high boiling points may be troublesome in the workup. Thus, many of the procedures reported employ chromatography and other techniques in the purification step. As guanidines may be troublesome to work with due to their heavily polar nature, a minimum of workup is highly preferred.

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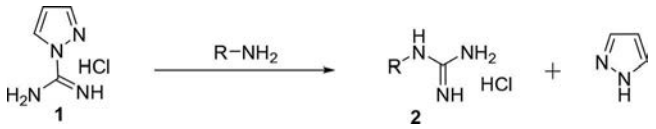
Supplemental data (experimental procedures for **2a–b** and **2d–g**, ^{1}H NMR spectra of previously synthesized compounds, and full characterization spectra (^{1}H NMR, ^{13}C NMR, and, 2D-techniques) for new compounds.) can be accessed on the publisher's website.



Scheme 1. Reaction between 1*H*-pyrazole carboxamidine (**1**) hydrochloride and a primary aliphatic amine, leading to formation of the guanylated product **2** and 1*H*-pyrazole as a by-product.

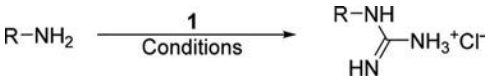
The reaction conditions presented here renders complete conversion in a matter of hours, requires minimal workup, and needs no chromatographic purification.

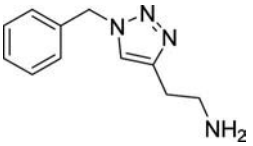
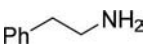
Results and discussion

In our search for simple versatile conversions of amines in order to expand a compound library of 1,2,3-triazoles for antimicrobial screening, we have found simple and efficient conditions for converting amines to guanidines utilizing the already reported reagent **1**. We have found that for many amines addition of base does not necessarily decrease reaction time nor substantially increase the yield, as can be seen from Table 1 (entry 2 and 3). In addition, by running the reactions in acetonitrile at reflux (entry 2 and 3, Table 1) we achieved rapid full conversion, compared to when using DMF (entry 1, Table 1).

Subjecting the primary amines in Table 2 to the optimal conditions yielded the pure guanidine salts **2a–g** (**2e–g** >98% in high-performance liquid chromatography, HPLC), with minimal workup as depicted in the experimental section. The conditions yielding optimal results are amine and **1** in a 1:0.9–1:0.99 ratio in acetonitrile (3 mL/100 mg amine) followed by 1–3 h of reflux, leading to complete conversion of **1**. These reaction conditions were easily scalable to a preparative level (>10 g), which in turn was performed to make 13 g of guanidine **2c** (93% yield). There have been reported a couple of similar standalone reactions performed without base in acetonitrile either at room temperature or reflux.[10–12] However, these examples required a reaction time above 16 h. Also, there have been reported some reactions with short reaction times (0.5 h) in a volatile solvent (EtOH), but this was performed under microwave conditions with a base additive.[13]

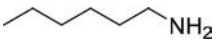
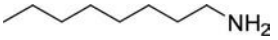
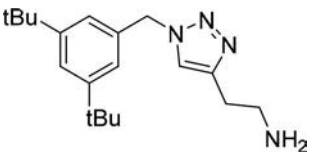
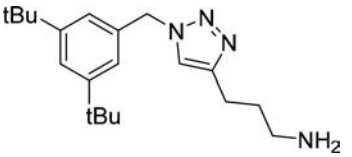
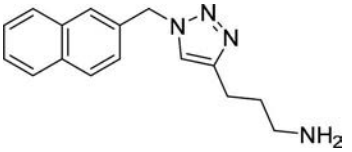
Table 1. Simplifying the conditions needed for guanylation of lipophilic amines.



Entry		Conditions	1 (eq)	Time (hrs)	Yield (%)
1		DIPEA (1 eq), DMF, rt	1.0	18	-[a]
2		DIPEA (1 eq), MeCN, reflux	0.9	3	90[b]
3		MeCN, reflux	0.9	3	84

[a]Crude 2:1 SM: product, no final product obtained due to crystallization issues.
[b]Impure with DIPEA and unindentified byproduct, additional work-up needed.

Table 2. Results of exposing amines containing lipophilic groups to the improved reaction condition in order to synthesize surfactant-like guanidine salts.

R–NH_2 → (1, MeCN, reflux)	2	1 (eq)	Reflux (hrs)	Yield (%)
	2a	0.9	3	74
	2b	0.9	3	59
	2c	0.9	3	93[a]
	2d	0.9	3	70
	2e	0.9	1.5	63
	2f	0.9	3	70
	2g	0.98	12	76

[a]Experiment performed in multi-gram scale.

It should also be noted that we have used a slight excess of amine in order to ensure complete conversion of **1**, as there sometimes were some uncertainty regarding the purity of amines synthesized through several previous steps.

The three bottom products given in Table 2 showed a level of purity acceptable for biological testing, thus making these reaction conditions favorable for compounds intended for pharmacological testing.

Summary

A simplified protocol for guanylation of primary amines is hereby reported. Seven guanidines (**2a**–**g**) were prepared, where the synthesis of **2c** also was performed on a >10-g scale. Three of these compounds (**2e**–**g**) were subjected to HPLC analysis, giving sufficiently pure compounds (>95%) for biological testing.

Experimental

General procedure for guanylation of primary aliphatic amines

Amine and **1** (0.9–0.99 eq) was added to MeCN (3 mL/100 mg amine) on a 50- to 100-mg scale and refluxed for 2–3 h. After complete disappearance of **1** (by TLC w/ 70:30:3 $CHCl_3$/

MeOH/NH_4OH) the reaction mixture was cooled down to room temperature. Furthermore, depending on whether the product precipitated out or not, the following was done:

A) If the product was precipitated by cooling the reaction mixture to room temperature, the supernatant was removed and the precipitate was washed with MeCN and dried under reduced pressure.
B) If the product was not precipitated by cooling the reaction mixture to room temperature, Et_2O was added to induce precipitation. The precipitate was then washed with Et_2O and dried under reduced pressure.

Synthesis of 2c

1. General procedure B leads to **2c** as a light yellow sticky wax (137 mg, 0.69 mmol, 84% yield).
2. General procedure B(a) leads to **2c** as an off-white solid (13 g, 65 mmol, 93% yield).

^{1}H NMR (400 MHz, *d4*-MeOH): δ = 7.36–7.22 (m, 5H, **Ph**-), 3.46 (t, 2H, J = 7.1 Hz, -NH-**CH_2**-), 2.88 (t, 2H, J = 7.1 Hz, Ph-**CH_2**-) ppm. ^{13}C NMR (100 MHz, *d4*-MeOH): 157.1 (NH-**C**=NH), 137.9 (CH-**C**-CH), 128.4 (2x**CH**), 128.3 (2x**CH**), 126.4 (**CH**), 42.3 (-**CH_2**-NH-), 34.5 (C-**CH_2**-) ppm. Spectra is highly similar to spectra of the sulfate salt in D_2O reported in a patent by the University of Strathclyde.[14]

Procedure B(a): Preparative scale workup

The reaction mixture was partially evaporated and added to Et_2O (200 mL). The ether phase was decanted and the residual oil was washed with Et_2O (3 × 200 mL), before it was added one last portion of Et_2O (200 mL) and left for 48 h. The hard crystalline precipitate was then crushed and stirred with Et_2O (3 × 100 mL) for 10 min each time. Decanting and drying afforded **2c** as an off-white solid.

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