



Microwave-assisted synthesis of highly functionalized guanidines on soluble polymer support

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ABSTRACT

An efficient method for the *N,N*-di(Boc)-protected guanidines containing piperazine and homopiperazine scaffolds has been developed under multi-step microwave irradiation. Followed by alkylation of carbamate-protected guanidines with various alkyl halides is also explored. This protocol proceeds via deprotonation of the acidic *N*-carbamate hydrogen of the guanidine by sodium hydride on soluble polymer support. In this manner, highly functionalized guanidines were obtained after cleavage from the support. The reaction is tolerant of a wide range of functional groups on both the alkyl halide and guanidine components. In addition, the reaction is sufficiently simple workup by precipitation in each step to yield the substituted guanidines in high purity. In conjunction with microwave irradiation and soluble polymer support, this method provides an efficient route to access highly functionalized guanidines.

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Introduction

Guanidines are one of the most privileged structural motifs frequently occurring in natural products,¹ and have been widely recognized as useful building blocks for the synthesis of various biologically active compounds.² The compelling biological activities of guanidine derivatives have been ascribed to their ability to recognize receptors by a variety of non-covalent interactions, including hydrogen-bonding, electrostatic, and π -stacking associations.³ As important variants, heterocycles substituted guanidines exhibit a broad range of intriguing biological activities such as cytotoxic,⁴ antifungal,⁵ antiviral,⁶ antimicrobial,⁷ anticancer,⁸ and antimalarial^{4,5} activities. Saxitoxin (STX, Fig. 1), the causative agents of paralytic shellfish poisoning (PSP), is potent neurotoxins produced by dinoflagellates.⁹ Dragmacidin E was isolated from *Spongosortes* sp. and exhibited potent serine-threonine protein phosphatase inhibitory activity.¹⁰ Ptilomycalin A displays promising anticancer and antiviral activities.¹¹ Zanamivir was synthetically derived influenza inhibitor.¹² The tremendous therapeutic potential of this class of compounds has sparked our interest in the synthesis of guanidine with piperazine scaffold and their analog to further explore their biological application.¹³ Compared to other heterocycles syntheses,¹⁴ the synthetic approach to incorporate guanidine moiety is limited.¹⁵ Therefore, the development of a mild and efficient synthesis for the rapid construction of highly substituted guanidines is important. Methods wherein guanidines could be further functionalized with a variety of electrophiles to

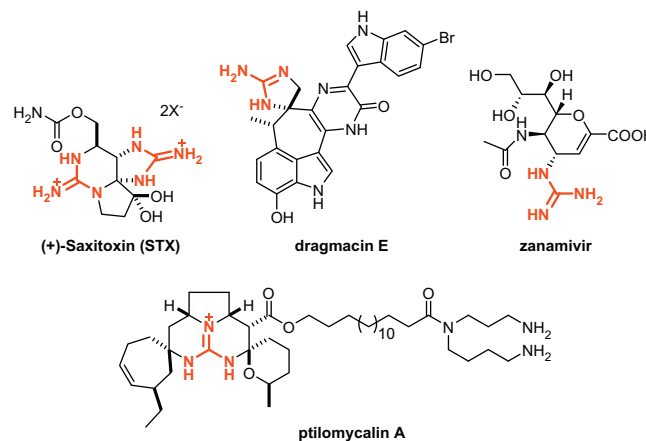
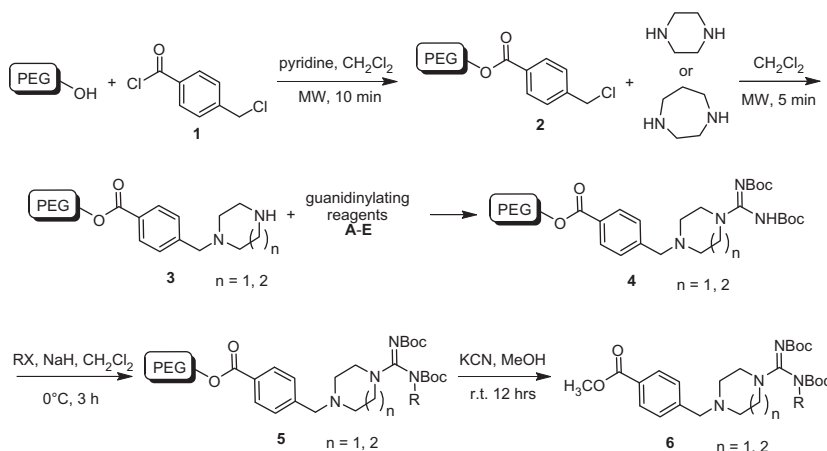


Figure 1. Various types of biologically active heterocycles containing guanidine frameworks.

give a more highly substituted guanidine are referred to as a guanidinylation. There are very few methods that are employed for the further functionalization of protected guanidines. Batey and co-workers developed a phase-transfer catalyzed alkylation of guanidines for the synthesis of substituted guanidines.¹⁶ The most commonly used method involves the reaction of guanidine with a primary or secondary alcohol under Mitsunobu conditions.¹⁷ The advent of microwave-assisted organic synthesis has contributed significantly to the development of eco-compatible methodologies to save both energy and resources.¹⁸ The polyethylene glycol

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Scheme 1. Synthesis of Boc-guanidine derivatives.

support is suitable for energy dissipation with microwaves.¹⁹ The incorporation of microwave irradiation with PEG supported organic synthesis greatly accelerates the library synthesis and simplifies the purification steps in multistep organic synthesis. In this report, we present highly efficient guanylation and guanidinylation for the synthesis of highly substituted guanidines on soluble polymer support under microwave irradiation.

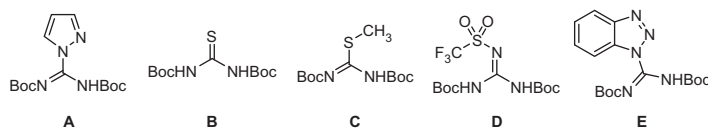
Results and discussion

A synthetic route toward the highly functionalized Boc-guanidines of piperazine and homopiperazine is described in Scheme 1. Monohydroxyl functionalized PEG (MW 5000) was employed as a soluble support for a multistep synthetic sequence. PEG is allowed to react first with di-electrophile, 4-chloromethyl benzoyl chloride under basic condition. The formation of ester bond in a refluxing condition required 48 h in dichloromethane which was brought down to 10 min under open vessel microwave irradiation leading to polymer conjugates **2** (Scheme 1). Accordingly, PEG conjugate **2** was purified by precipitation with diethyl ether. The progress of the PEG supported reaction was directly monitored through regular proton NMR spectroscopy without releasing the intermediate from the support. The piperazinyl and diazepamyl moiety are introduced to the immobilized benzyl chloride **2** by a nucleophilic substitution reaction toward the targeted guanidine skeleton. This reaction was completed in 5 min in a microwave cavity at 100 °C. It took 16 h to complete in oil-based refluxing condition to afford polymer conjugate **3**. It is noteworthy to mention that the nucleophilic substitution with piperazine or diazepamane did not cleave the ester bond of the polymer linkage site even under harsh microwave condition.

With the PEG attached benzylamine **3** in hand, we explored the viability and efficiency of the guanylation reaction with various

guanylation reagents comprising *N,N'*-di-*tert*-butoxycarbonyl-1*H*-pyrazole-1-carboxamide **A**,^{15a} *N,N'*-di-*tert*-butoxycarbonylthiourea **B**, *N,N'*-protected *S*-methylisothiourea **C**, triflylguanidine derivative **D**, and bis-Boc-benzotriazole-carboxamide **E** (Fig. 2).²⁰ The feasibility of these guanylation reagents was first attempted at room temperature. A comparison of the yields and purities of guanylation of the PEG linked cyclic diamines **3** with guanylation reagents **A–E** is shown in Figure 3. The desired guanylation adducts were unsuccessful in the case of agent **A**. However, guanylation reagents **B–E** react efficiently with PEG immobilized benzylpiperazine and benzyl diazepamane to afford Boc-protected guanidines in good yields and purities. The benzotriazole-based reagents **E** comparatively analyzed and proved to be the most efficient one as the guanylation reagent which leads to a quantitative conversion of the PEG supported amines into the guanidines in excellent yield within 6 h at room temperature. The same transformation with guanylation reagent **E** is also performed in an open vessel microwave reactor which needed only 7 min to furnish the same product to show a substantial enhancement of the reaction efficiency. The reactivities of these guanylation reagents are proposed to be dependent on the properties of leaving groups that may enhance the electrophilicity of the amidine carbon.^{20c} The mechanism of the guanylation of **3** was speculated through a highly electrophilic intermediate, bis(Boc)carbodiimide.

The next challenge was the synthesis of substituted guanidine derivatives from PEG conjugate **4** through nucleophilic substitution. To extend the scope of the present process, the PEG linked guanidine derivatives were planned to react with electrophiles to furnish extra scaffold diversity to provide highly substituted guanidine derivatives. The NH alkylation of the PEG linked guanidine **4** is expected to be laborious. Since, the NH is hindered by the Boc functionality sterically and the nucleophilicity of the nitrogen may be dispersed by the guanidine due to resonance effect. PEG supported



condition for **A**: 1.2 eq. of **A** in CH_2Cl_2 (r.t.; 8 h)
 condition for **B**: 1.2 eq. of **B** and 1.2 eq. DICI in CH_2Cl_2 (r.t.; 18 h)
 condition for **C**: 1.2 eq. of **C**, 2 eq. of HgCl_2 and 3 eq. of Et_3N in CH_2Cl_2 (r.t.; 40 h)
 condition for **D**: 1.2 eq. of **D**, and 3 eq. of Et_3N in CH_2Cl_2 (r.t.; 10 h)
 condition for **E**: 1.2 eq. of **E**, and 3 eq. of Et_3N in CH_2Cl_2 (r.t.; 6 h or MW; 7 min)

Figure 2. Reagents and conditions for the synthesis of *N,N'*-diprotected guanidines.

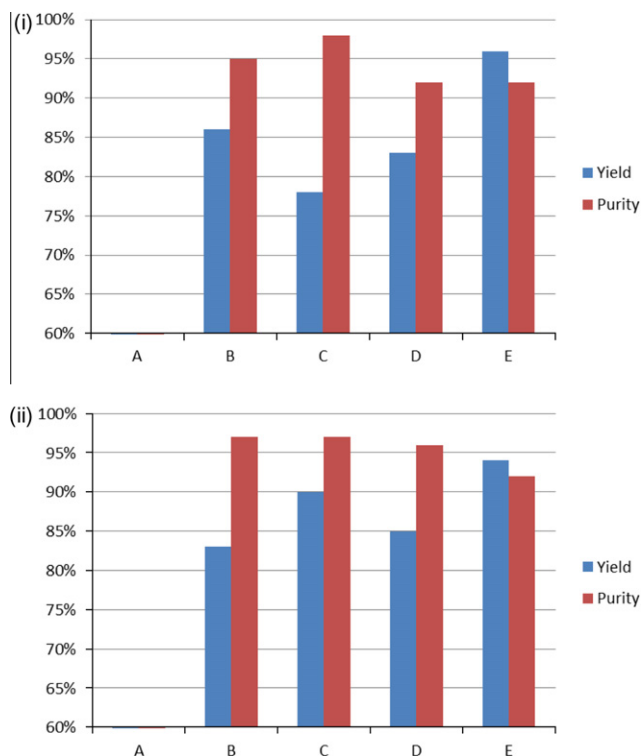


Figure 3. Yields and purities of isolated N,N'-diprotected guanidines **6** upon reaction of (i) PEG immobilized benzylpiperazine and (ii) PEG immobilized benzyl diazepane with guanylation reagents A–E.

guanidine **4** was treated with sodium hydride and electrophiles in dichloromethane. Gratifyingly, polymer supported substituted guanidine conjugate **5** was obtained in 3 h through deprotonation and nucleophilic substitution. It is worth to mention that the ester functionality of the electrophiles remains intact under the strongly basic condition during the nucleophilic substitution (entries **6d**, **6f**, **6j**, and **6l**). Compared with previous reports,^{16,17} we have demonstrated the guanidinylation protocol that is compatible with a wide range of substrates and additional phase-transfer-catalysts or coupling reagents are not needed. The cleavage of the polymer support from compound **5** was carried out by using a 1% potassium cyanide solution in methanol. The polymer was precipitated out by addition of a cold ether solution and the filtrates were concentrated to obtain polymer-free substituted guanidine derivatives **6** with high purities and yields (Table 1).²¹ The results summarized in Table 1 show some representative examples to demonstrate the successful access of guanidinylation and N-alkylation to the substituted Boc-guanidine derivatives with manifold appendages. In current synthetic approach, we have successfully integrated the advantages of PEG with microwave synthesis to afford a rapid synthesis of substituted Boc-guanidine derivatives with high purities and yields.

Conclusion

An efficient method for the alkylation of N-dicarbamate-protected guanidines using a variety of alkyl halides has been explored. Under this procedure, the acidic N-carbamate hydrogen is deprotonated using basic conditions and subsequently alkylation to yield highly functionalized guanidines. This protocol provides

Table 1
Synthesis of substituted guanidine derivatives

Entry	Amine	RX	HPLC purity ^c (%)	Isolate yield ^a (%)
6a			91	82
6b			95	86
6c			97	87
6d			79	71
6e			93	84
6f			97	87
6g			91	82
6h			89	80
6i			97	87
6j			69 (29) ^b	62
6k			88	79
6l			92	83

^a Yields were determined on weight of purified samples.

^b The yields in the parentheses represent unreacted starting material.

^c HPLC purities were determined with crude samples.

an alternate method for the alkylation of protected guanidines from those currently utilized. In addition, the need for stoichiometric amounts of costly reactive coupling reagents is circumvented. An attractive feature of this methodology is that few byproducts are generated and at the end of the reaction, simple workup followed by filtration gives high yields of the desired products. The efficiency of parallel synthesis was greatly enhanced by combining the advantages of microwave synthesis and a soluble polymer support.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.tetlet.2012.05.074>.

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- General procedures for synthesis of 6*: (All microwave experiments performed in CEM discover microwave system at the frequency of 2450 Hz and 0–300 W power in open vessel system.) The polymer support (PEG 5000; 10.0 g, 1.0 equiv, 2.0 mmol) in toluene (25 mL) was treated with 4-(chloromethyl) benzoyl chloride **1** (567.0 mg, 1.5 equiv, 3.0 mmol) in toluene (25 mL) and pyridine (791.0 mg, 5.0 equiv, 10.0 mmol) under microwave irradiation at 200 W for 10 min to afford amide **2**. The reaction mixture was diluted with slow addition of excess cold ether (50 mL). The precipitated amide conjugate was filtered through a fritted funnel, washed with ether, and then dried. Piperazine (4.31 g, 5.0 equiv, 50.0 mmol) or Homopiperazine (5.01 g, 5.0 equiv, 50.0 mmol) were added to a solution of **2** (10.31 g, 1.0 equiv, 2.0 mmol) in dichloromethane. The reaction mixture was stirred under microwave irradiation at 120 W for 5 min and after completion; the reaction mixture was passed through a thin layer of celite to remove salt. The solution was concentrated by rotary evaporation and diluted with slow addition of an excess of cold ether. The precipitated conjugate was filtered through a fritted funnel and washed with ether to afford **3**. *N,N'*-di-*tert*-butoxycarbonyl-1*H*-benzo[d][1,2,3]triazole-1-carboximidamide (0.47 g, 1.3 equiv, 1.3 mmol) was added to a solution of **3** (5.20 g, 1.0 equiv, 1.0 mmol) in dichloromethane (30 mL). After stirring for 10 min, triethylamine (0.30 g, 3.0 equiv, 3.0 mmol) was added and it was treated under microwave irradiations at 150 W for 7 min. The solution was concentrated by rotary evaporation and diluted with slow addition of an excess of cold ether. The precipitated guanidine conjugate was filtered through a fritted funnel and washed with ether to afford **4**. To a solution of **4** (1.09 g, 1.0 equiv, 0.2 mmol) and alkyl halide (3.0 equiv, 0.6 mmol) in dichloromethane (10 mL) under nitrogen, sodium hydride (0.024 g, 5.0 equiv, 1.0 mmol) was added and the reaction mixture was stirred at 0 °C for 3 h. After completion, the reaction mixture was washed with cold ether. The precipitate was filtered and dried well to furnish the PEG bound guanidine **5** in excellent yield. To a solution of **5** in methanol (10 mL), KCN (0.1 g) was added and stirred for 48 h. After the quenching procedure, the crude products **6** were obtained. The filtrate was dried and subjected to HPLC analysis which depicts high purity. The title compounds **6** were obtained in good to excellent overall yield after column chromatography purification. *Compound 6e*: ¹H NMR (300 MHz, CDCl₃) δ 7.91 (d, *J* = 8.4 Hz, 2H), 7.81 (m, 4H), 7.49 (m, 3H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.25 (b, 1H), 3.89 (m, 4H), 3.07 (m, 6H), 2.63 (b, 2H), 2.05 (b, 2H), 1.55 (s, 9H), 1.48 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 167.3, 160.0, 154.1, 152.8, 134.2, 133.7, 133.4, 130.0, 129.3, 129.1, 128.8, 128.4, 128.0, 127.7, 126.7, 126.6, 115.8, 115.0, 82.3, 79.9, 62.6, 52.5, 51.4, 28.8, 28.6; IR (neat): 2922, 2851, 1721; MS (FAB-MS) *m/z*: 617 (M+H)⁺; HRMS: calcd for C₃₅H₄₄N₄O₆ *m/z*: 616.3261; found 617.3341 (M+H)⁺.