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A Novel Traceless Resin-Bound Guanidinylating Reagent for Secondary Amines To Prepare *N*,*N*-Disubstituted Guanidines

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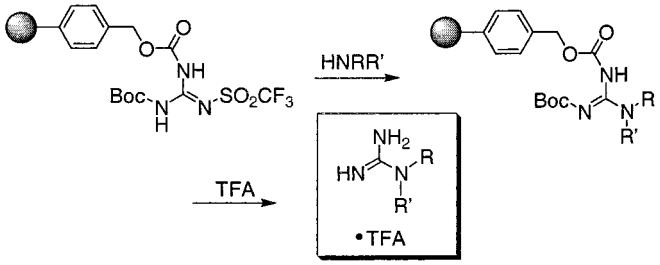
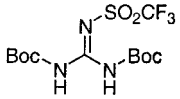
ABSTRACT



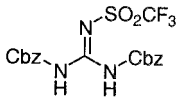
We report the development of a solid support-linked guanidinylating reagent. This reagent consists of a urethane-protected triflyl guanidine attached to the resin via a carbamate linker. It allows for rapid synthesis of guanidines from a variety of amines. It provides access to *N*-alkyl/aryl- or *N*,*N*-dialkylguanidines under mild conditions. Cleavage with 50% TFA produces target molecules in high yields and purity. The ability to guanidinylate secondary amines is a significant feature of this guanidinylating reagent.

The guanidine group is a decisive feature in many biologically active compounds.[1] Under physiological conditions, the guanidine group is protonated and therefore able to bind strongly to a substrate, ligand, or receptor via electrostatic interactions. Compounds containing the guanidine core as a functional group have been isolated from many species, such as algae, sponges, and other marine and freshwater microorganisms.[2] Many of them exhibit potent antiviral, antifungal, or neurotoxic bioactivities.

Recently our group developed novel guanidinylating reagents **1** and **2** for transformation of amines into guanidines



1



2

in solution.[3] Scheme 1 illustrates the guanidinylation of benzylamine **3** with di-Boc-triflylguanidine **1** as a model reaction.

Extensive studies of compounds **1** and **2** have shown their effectiveness in guanidinylation of primary and cyclic

(1) The list of cited references contains only very few examples of biologically active guanidine-containing molecules and is by no means complete. (a) Yamamoto, T.; Hori, M.; Watanabe, I.; Harada, K. *Chem. Pharm. Bull.* **2000**, *48*, 843−849. (b) Blondelle, S. E.; Crooks, E.; Ostresh, J. M.; Houghten, R. A. *Antimicrob. Agents Chemother.* **1999**, *43*, 106−114. (c) Chalina, E. G.; Chakarova, L. *Eur. J. Med. Chem.* **1998**, *33*, 975−983. (d) Haubner, R.; Schmitt, W.; Hölzemann, G.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7881−7891. (e) Ruoslahti, E. *Annu. Rev. Cell Dev. Biol.* **1996**, *12*, 697−715.

(2) (a) Berlinck, R. G. S. *Nat. Prod. Rep.* **1999**, 339−365. (b) Berlinck, R. G. S. *Nat. Prod. Rep.* **1996**, 377−410.

(3) (a) Feichtinger, K.; Sings, H. L.; Baker, T. J.; Matthews, K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 8432−8439. (b) Feichtinger, K.; Zapf, C.; Sings, H. L.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 3804−3805.

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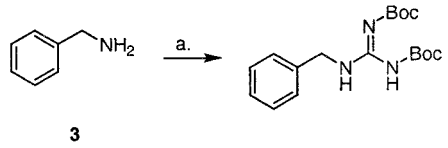
Scheme 1[a]



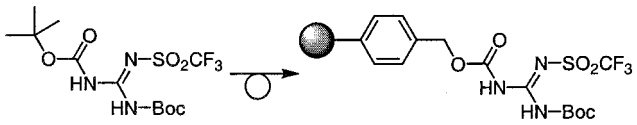
3

[a] (a) **1**, NEt_3, CH_2Cl_2, 0.5 h, rt, quantitative.

secondary amines as well as arylamines to form *N*-mono- and *N,N*-dialkylated guanidine structures under mild conditions and short reaction times and in high yields. Reagents **1** and **2** were unsuccessful at guanidinylating acyclic or sterically hindered cyclic secondary amines in solution.

We utilized features of our guanidinylating reagents **1** and **2** to construct a solid phase-based guanidinylating reagent. This was accomplished by replacing one of the urethane protecting groups of reagent **1** by a carbamate linkage to the Wang resin[4] (Scheme 2). This linkage provides the possibility of facile and traceless cleavage.

Scheme 2



1 **4**

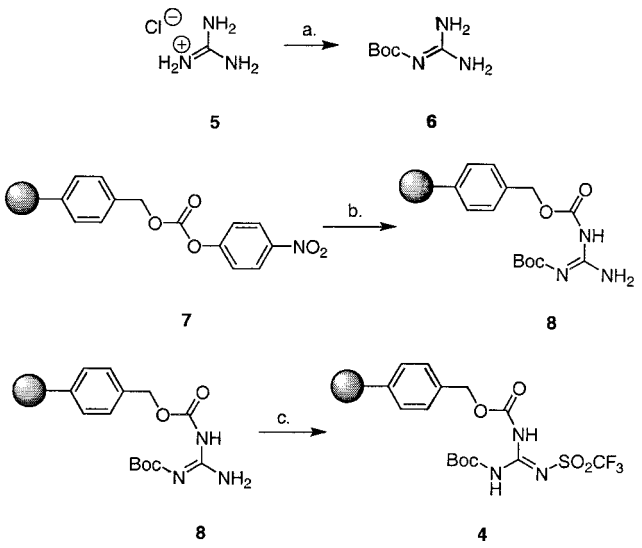
Scheme 3 illustrates the formation of resin-bound guanidinylating reagent **4**. Guanidine hydrochloride **5** was allowed to react with Boc-anhydride to form Boc-guanidine **6** in 88% yield. Subsequently, Boc-guanidine **6** was immobilized on *p*-nitrophenyl carbonate Wang resin **7** to form the protected guanidine **8**. Triflation[5] of the immobilized guanidine **8**, which resembles a diurethane-protected guanidine, resulted in the formation of resin-bound guanidinylating reagent **4**.

Elemental analysis was performed to identify the loading of resin **4**.[6] Determination of the N, S, and F content revealed a loading of 89% of the theoretical value.[7]

Resin-Bound Guanidinylations. With this guanidinylating resin, we investigated its potential for the conversion of primary[8] and secondary amines into resin-bound guanidines (Scheme 4). In this reaction, the secondary amine was

(4) Wang, S. S. *J. Am. Chem. Soc.* **1973**, *95*, 1328−1333.
(5) Rottländer, M.; Knochel, P. *Synlett* **1997**, 1084−1086.
(6) Yan, B.; Jewell, C. F., Jr.; Myers, S. W. *Tetrahedron* **1998**, *54*, 11755−11766.
(7) The contents were found to be N 2.15%, S 1.47%, and F 2.88%. From these values, a loading of 0.49 mmol/g was deduced. Starting with a resin with an initial loading of 0.6 mmol/g, this loading represents an 89% yield over two steps.
(8) Primary aliphatic and aromatic amines can be quantitatively converted to the corresponding guanidines rapidly and in high purities. However, in this paper only secondary amines will be discussed.
(9) Hamper, B. C.; Kolodziej, S. A.; Scates, A. M.; Smith, R. G.; Cortez, E. *J. Org. Chem.* **1998**, *63*, 708−718.

Scheme 3[a]



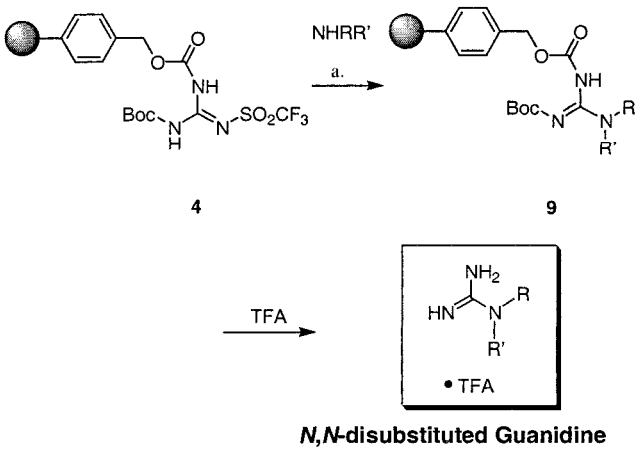
5 **6** **7** **8** **8** **4**

[a] (a) Boc_2O, NaOH, dioxane/water, 15 h, rt, 88%; (b) **6**, NEt_3, DMF, DMAP, 15 h, rt; (c) Tf_2O, NEt_3, CH_2Cl_2, 6 h, −78 °C to 0 °C.

allowed to react with the resin **4** for 24 h after which the resin was washed thoroughly and cleaved with 1:1 TFA: CH_2Cl_2 for 2−3 h. The solution was collected and the resin washed with methanol and methylene chloride. The filtrates were combined and the solvents removed under reduced pressure. Table 1 illustrates the variety of secondary amines that were subjected to resin-bound guanidinylation.

Employing a specific amount of resin and knowing its loading from elemental analysis (N, S, and F), it is possible to obtain the yield by comparing ^{1}H NMR integration of the product to the integration of a known amount of an added standard (hexamethyldisiloxane).[9] Typically, the target molecules were prepared from 50 to 100 mg of resin which correlated to about 20 μmol of product. Several milligrams

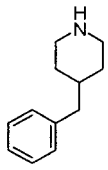
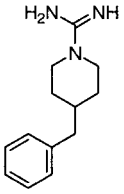
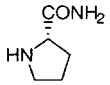
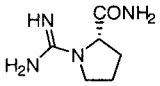
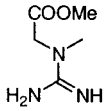
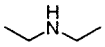
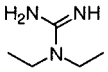
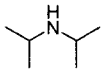
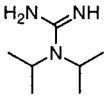
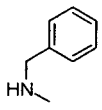
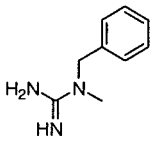
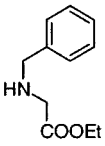
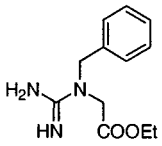
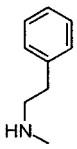
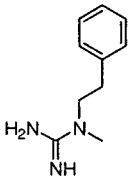
Scheme 4[a]



4 **9**

[a] (a) CH_2Cl_2, rt.

Table 1. Resin-Bound Guanidinylation of Amines Utilizing Resin **4**

entry	amine	product [a]	yield (%)
1			100
2			100
3[12]			95
4			69
5			65
6			77 (73)[11b]
7			33 (2)[11b]
8			76

[a] Isolated as TFA salt.

of the TFA salt of the final product were obtained and characterized by ^{1}H NMR and high-resolution mass spectrometry. Purities were assessed by RP-HPLC at 220 nm.

Synthesis of resin-bound guanidine structures has been reported previously.[10] Several groups have used a conceptually different approach to that reported here. These literature methods employ an immobilized amine which is allowed to react with various guanidinylating reagents to form guanidines on the solid supports. For this purpose, carbodiimides, thioureas, 1-*H*-pyrazolecarboxamidines, aminium/uronium salts, and guanidinylating reagent **1** have been used.

Methods utilizing a resin-bound guanidinylating reagent have also been reported previously.[11] One resin-bound intermediate which is commonly used involves thiourea. From that intermediate, alkyl isothioureas and carbodiimides have been prepared which serve as the guanidinylating reagents. The thiourea is attached to the solid support through a linker which may or may not be incorporated into the final target structures under the cleavage conditions.

Recently there have been reports of several immobilized guanidinylating reagents that allow traceless cleavage of the target guanidines from the solid support. Immobilization of the traceless reagents is accomplished either through an acid labile carbamate, an acyl linkage, or a thiopseudourea. These reagents are derived from a 1-*H*-pyrazolecarboxamidine or from thioureas. These methods have been shown to work well with primary and cyclic secondary amines. One report[11b] utilizing the 1-*H*-pyrazole-1-*N*-Boc-carboxamidine attached through a carbamate linker to a solid support showed reactions with two acyclic amines that correspond to our entries 6 and 7 in Table 1. The yield for entry 6 was comparable to ours, but they were only able to obtain a 2% yield for entry 7 compared to our 33% yield. The other report[11h] utilizes amines that correspond to entries 1 and 6. The authors did not provide individual yields for their final products but report yields generally greater than 85% which are comparable to the yields we obtained for entries 1 and

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(11) (a) Gomez, L.; Gellibert, F.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* **2000**, *6*, 4016−4020. (b) Patek, M.; Smrcina, M.; Nakanishi, E.; Izawa, H. *J. Comb. Chem.* **2000**, *4*, 370−377. (c) Chen, J.; Pattarawarapan, M.; Zhang, A. J.; Burgess, K. *J. Comb. Chem.* **2000**, *2*, 276−281. (d) Chang, J.; Oyelaran, O.; Esser, C. K.; Kath, G. S.; King, G. W.; Uhrig, B. G.; Konteatis, Z.; Kim, R. M.; Chapman, K. T. *Tetrahedron Lett.* **1999**, *40*, 4477−4480. (e) Wilson, L. J.; Klopfenstein, S. R.; Li, M. *Tetrahedron Lett.* **1999**, *40*, 3999−4002. (f) Dodd, D. S.; Wallace, O. B. *Tetrahedron Lett.* **1998**, *39*, 5701−5704. (g) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663−2666. (h) Josey, J. A.; Tarlton, C. A.; Payne, C. E. *Tetrahedron Lett.* **1998**, *39*, 5899−5902. (i) Drewry, D. H.; Gerritz, S. W.; Linn, J. A. *Tetrahedron Lett.* **1997**, *38*, 3377−3380.

(12) **Table 1**, entry 3. Guanidine hydrochloride **5** (7.5 g, 78.5 mmol) was allowed to react with Boc_2O (13.71 g, 62.9 mmol) for 15 h in a mixture of 40 mL of aqueous NaOH (4M) and 80 mL of dioxane at room temperature to form *N*-Boc-guanidine **6**. The *N*-Boc-guanidine **6** (2.39 g, 15 mmol, 5 equiv) was allowed to react with *p*-nitrophenyl carbonate Wang resin **7** (5 g, 3 mmol) in DMF for 15 h in the presence of triethylamine (2.1 mL, 5 equiv) and a catalytic amount of DMAP. The resin **8** was rinsed and dried thoroughly prior to subsequent triflation with trifluoromethane sulfonic anhydride (2.52 mL, 5 equiv) which was added at −78 °C. The reaction was allowed to warm to 0 °C, filtered, and thoroughly rinsed with MeOH and DCM to yield resin **4**. Resin **4** (87 mg, 42 μmol) was allowed to react with H-Sar-OMe (43 mg, 10 equiv) for 20 h and subsequently washed with MeOH and DCM. Treatment with 2 mL of a 1:1 mixture of DCM and TFA for 3 h liberated the guanidine from the solid support (95% yield). ^{1}H NMR (DMSO-d_6, 400 MHz, δ) 4.26 (s, 2H), 3.69 (s, 3H), 2.95 (s, 3H). HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_5H_{11}N_3O_2$ 146.0924, found 146.0919.

6. Entry 8, the structure of which is comparable to entry 6 in size and steric demands, shows the formation of the substituted guanidine in a yield equal to entry 6.

The *N*,*N*′-dialkylguanidines represent another family of target structures reported in the literature which must be distinguished from our target molecules. In these compounds, the two alkyl substituents are attached to two different nitrogens.[13] These structures were prepared by allowing an immobilized alkyltriazene to react with a set of isothiocyanates to form dialkyl thioureas. These thioureas were used as guanidinylating reagents, allowing them to react with several primary amines in the presence of mercury or silver salts to produce resin-bound *N*,*N*′-dialkyl- or *N*,*N*′,*N*″-trialkylguanidines. These target structures are significantly different from the *N*,*N*-disubstituted guanidines reported in this paper.

With regard to our resin-bound guanidinylating reagent **4**, entries 1 and 2 are cyclic secondary amines which are known to be excellent reactants for guanidinylation in solution as well as on solid support. Sarcosine methyl ester can be readily transformed into creatine methyl ester (entry 3) in high yield. The key observation from our results comes from entries 4 and 5. Attempts to obtain these target structures in solution by allowing reagent **1** to react with diethyl- or diisopropylamine failed. However, Lipton and coworkers report the synthesis of the di-Boc-protected derivative of entry 5.[10b] By allowing diisopropylamine to react with 4-nitro-1-*H*-pyrazole-1-[*N*,*N*′-bis(*tert*-butoxycarbonyl)]carboxamidine in solution, they obtained the diurethane-protected *N*,*N*-diisopropylguanidine in 64% yield. When allowed to react with the resin-bound guanidinylating reagent **4**, *N*,*N*-diethyl- and *N*,*N*-diisopropylguanidine are formed in good yields, the latter in essentially the same yield as reported by Lipton.[10b]

Conclusions. We have developed a novel, traceless resin-bound guanidinylating reagent. This reagent allows us to convert primary and secondary amines into resin-bound guanidines. Secondary amines, which have been shown to be difficult to guanidinylate with previously developed guanidinylating reagents, can now be transformed readily into guanidines.

We report a set of secondary amines which have been subjected to our resin-bound guanidinylating reagent to form immobilized guanidines. The target molecules are formed under mild conditions, reasonable reaction times, and moderate to high yields. Utilizing the Wang linker, we are able to cleave these *N*-alkyl- and *N*,*N*-dialkylguanidines from the linker in a traceless manner.

We have prepared a series of guanidines from cyclic and acyclic secondary amines. Specifically, the acyclic amines cannot be readily accessed by synthesis in solution utilizing guanidinylating reagents. Furthermore, some of the prepared guanidines have either not been synthesized previously on solid support or have been obtained in low yields or in a nontraceless fashion, i.e., with additional substituents. Results from Table 1 indicate the capabilities of this resin-bound guanidinylating reagent.

Currently, we are studying the scope of our resin-bound guanidinylating reagent utilizing a broad variety of additional amines in a combinatorial approach. We intend to introduce diversity onto the guanidine moiety by allowing the immobilized guanidines to react with different alcohols under Mitsunobu conditions. Incorporation of the guanidine group into heterocyclic target molecules will be another focus of the use of this reagent. The results of these investigations will be reported in due course.

Acknowledgment. The authors thank Juliann Kwak and Nicole Smith (UCSD) for helpful discussions. We thank NIGU-Chemie GmbH, Germany, for financial support.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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