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Solid-Phase Synthesis of Disubstituted Guanidines

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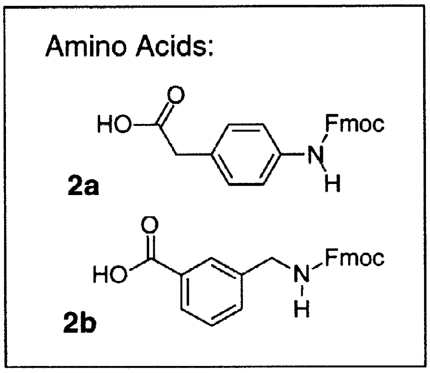
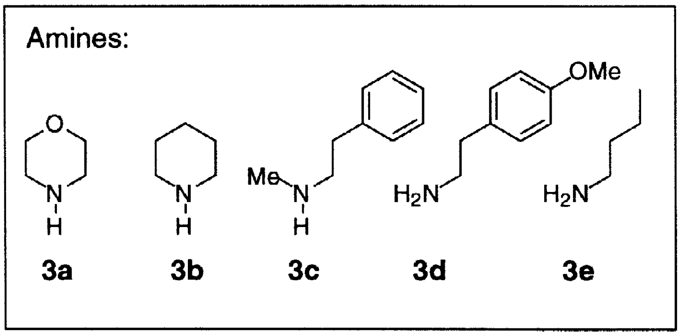
Abstract: A method for the solid-phase synthesis of disubstituted guanidines is reported. In this procedure, polymer-bound aryl or alkyl amines are converted to methyl isothioureas in three steps and treated with primary and secondary amines to form the disubstituted guanidine products.

The guanidine moiety has been incorporated into many drugs with uses covering a variety of therapeutic areas. Reported examples include guanidine containing cardiovascular, antihistaminic, antiinflammatory, antidiabetic, and antibacterial drugs.[1] Given this widespread utility, we became interested in the library generation of these compounds on the solid-phase. Several prior solid-phase syntheses of guanidines have been reported.[2-4] However, these immobilize an existing guanidine structure to the resin,[2] produce monosubstituted guanidines,[3] or involve the generation of azides.[4] As such, we set out to develop a solid-phase synthesis of guanidines that proceeds directly from amines and produces multiply substituted products in good overall yields.

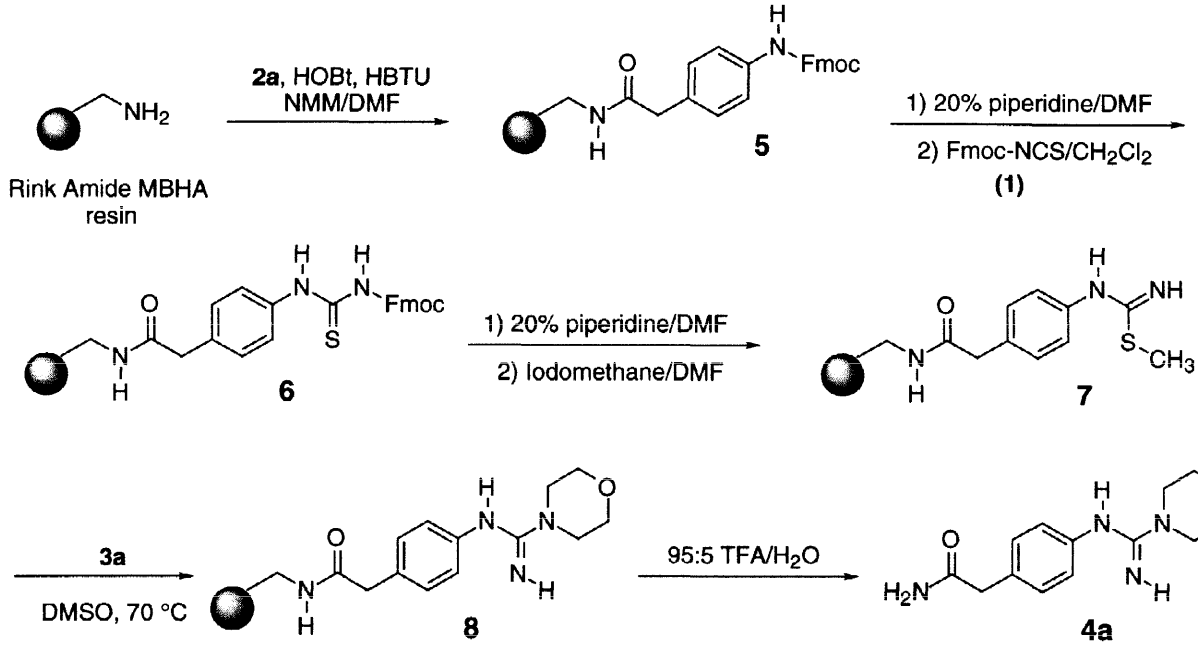
Compound **1**, fluorenylmethyloxycarbonyl isothiocyanate (Fmoc-NCS) has been reported to convert resin-bound primary and secondary amines to thioureas cleanly and in high yields.[5] As a result, routes to guanidines through intermediate thioureas should be accessible.[6] We decided to examine a particular route in which the polymer-bound thioureas are methylated to form isothioureas and subsequently treated with primary and secondary amines to generate guanidines.





PII: S0040-4039(98)00373-6

Scheme 1.

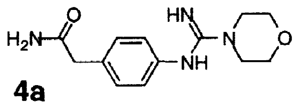
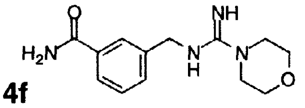
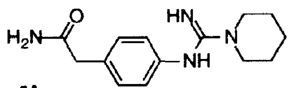
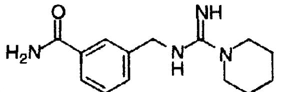
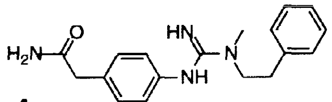
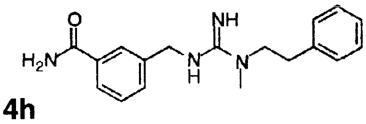
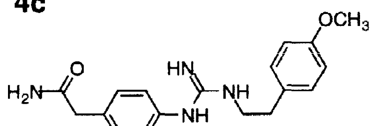
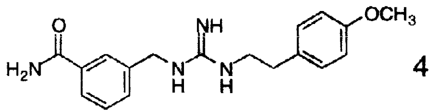
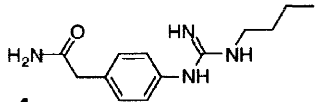
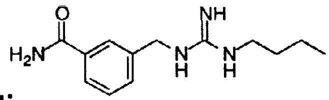


In testing this synthetic route, the amino acids **2a-b** and the amines **3a-e** were selected. The synthesis of substituted guanidines was carried out as shown for a single compound **4a** in Scheme 1.[7] The amino acid **2a**[8] was coupled to Rink amide MBHA resin[9] with HOBt/HBTU in DMF to afford **5**. This first step was performed batchwise, with the resin **5** being synthesized, washed thoroughly with DMF and methylene chloride, and dried under vacuum. After quantitation of the resin loading level,[10] an aliquot of the resin was treated with piperidine in DMF to remove the Fmoc protecting group, then exposed to Fmoc-NCS to generate the protected thiourea **6**.

Removal of the Fmoc group with piperidine in DMF followed by treatment with iodomethane generated the polymer-bound methyl isothiourea **7**. Treatment with morpholine **3a** in DMSO with heating afforded the guanidine **8**, which was cleaved from the resin with the use of 95% aqueous TFA to produce **4a**. Repetition of this procedure with **2b** and with the other amines **3b-e** produced the guanidines **4b-j**, which are shown in Table 1.

Purities of the crude guanidine compounds were determined by reverse phase HPLC with monitoring at 254 nm. With the exception of compounds **4i** and **4j**, the purities as determined by HPLC were generally good (73-92%). Secondary amines produced guanidines of higher purity than did primary amines, a result not unexpected given the greater nucleophilicity of these compounds. Purified guanidines were obtained by preparative reverse phase HPLC as their TFA salts and were identified by ^{1}H NMR and electrospray MS. All compounds were obtained as colorless oils. The amount of material present was determined by ^{1}H NMR integration of guanidine solutions in DMSO-d_6 against known quantities of *p*-dimethoxybenzene.[11] Yields were calculated with the values obtained from the integrations and the loading levels of the amino acid containing resins **5**. In general, the yields of the purified products were high (64-95%), and both the immobilized aryl and alkyl amines used produced guanidines in acceptable yields. Paralleling the purity data, the use of secondary amines generally gave higher yields.

Table 1.

Product	Purity[a]	Yield[b]	Product	Purity[a]	Yield[b]
 **4a**	88	95	 **4f**	73	77
 **4b**	92	95	 **4g**	80	89
 **4c**	89	93	 **4h**	82	73
 **4d**	79	72	 **4i**	40	64
 **4e**	82	83	 **4j**	44	64

a) Determined from relative peak areas of HPLC chromatograms with monitoring at 254 nm. b) Determined by NMR integration. See footnote 11.

In conclusion, we have demonstrated a synthetic route to disubstituted guanidines from simple amines via intermediate thioureas. Polymer-bound alkyl and aryl amines could be converted to guanidines in good yields and with reasonable purity. The use of secondary amines to generate guanidines from methyl isothioureas was superior to the use of primary amines.

References and Notes:

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2. Bonnat, M; Bradley, M.; Kilburn, J. D. *Tetrahedron Lett.* **1996**, *37*, 5409. See footnote 11 in; Virgilio, A. A.; Schürer, S. C.; Ellman, J. A. *Tetrahedron Lett.* **1996**, *37*, 6961.
3. Robinson, S.; Roskamp, E. J. *Tetrahedron* **1997**, *53*, 6697. Yong, Y.F.; Kowalski, J.A.; Lipton, M.A. *J. Org. Chem.* **1997**, *62*, 1540. Kowalski, J.; Lipton, M.A. *Tetrahedron Lett.* **1996**, *33*, 5839.
4. Drewry, D. H.; Gerritz, S. W.; Linn, J. A. *Tetrahedron Lett.* **1997**, *38*, 3377.
5. Kearney, P. C.; Fernandez, M.; Flygare, J. A. *J. Org. Chem.* **1998**, *63*, 196.
6. For references about these synthetic transformations, see: Nagarajan, S.; Ho, T. L.; DuBois, G. E. *Synth. Commun.* **1992**, *22*, 1191.
7. Guanidine **4a**: Resin **5** (408 mg, 0.49 mmol/g substitution) was swollen with DMF (5 mL, 5 min, 3X) and treated with a solution of 20% piperidine in DMF (5 mL, 2.5 min, 3X) to remove the Fmoc protecting group. After washing with DMF (5 mL, 30 s, 3X) and methylene chloride (5 mL, 30 s, 5X), a 0.2 M solution of Fmoc-NCS in methylene chloride was applied (5 mL, 45 min, 1X) to form **6**. Resin **6** was washed with methylene chloride (5 mL, 30 s, 3X) and DMF (5 mL, 30 s, 3X) and subsequently treated

with 20% piperidine in DMF (5 mL, 2.5 min, 3X). After washing with DMF, a 0.2 M solution of iodomethane in DMF was added to the resin (5 mL, 1 h) and another DMF wash performed (5 mL, 30 s, 3X). In generating resin **7**, the iodomethane addition and DMF wash were repeated two more times. The resin was transferred to a 20-mL Ace pressure tube and swollen with DMSO. The DMSO was removed by means of a filtration cannula, a 2 M solution of morpholine in DMSO added, and the tube capped and heated at 80 °C for 12 h in an oil bath. The tube was cooled to room temperature and the resin **8** was transferred to a Whatman polypropylene syringe-type reaction vessel (12-mL). The resin was washed with DMF (5 mL, 30 s, 3X) and methylene chloride (5 mL, 30 s, 5X) and cleavage was executed by treatment of the resin with 95% aqueous TFA for 45 min. The cleavage solution and two subsequent rinses of the resin (5 mL 95% TFA and 5 mL MeOH) were combined and evaporated to dryness with a Speedvac. The purified compound was obtained via preparative HPLC, Dynamax-60A C_{18} column (0.1% solutions of TFA, water/acetonitrile 9:1 to 2:8 eluant gradient over 40 min, 20 mL/min flow-rate). ^1H NMR (400 MHz, DMSO-d_6) δ 9.61 (s, 1H), 8.95 (bs, 2H), 7.44 (s, 1H), 7.31 (d, J = 8 Hz, 2H), 7.13 (d, J = 8 Hz, 2H), 6.88 (s, 1H), 3.68 (t, J = 5 Hz, 4H), 3.49 (bt, J = 5 Hz, 4H), 3.36 (s, 2H). ES-MS m/z for $C_{13}H_{18}N_4O_2$: 263.3 ($M+H^+$).

8. *Fluorenylmethyloxycarbonyl aminophenylacetic acid* (**2a**): Aminophenylacetic acid (15.2 g, 100 mmol) was dissolved with heating into 100 mL DMF. After the solution reached a temperature of 75 °C, fluorenylmethyloxycarbonyl chloride (12.9 g, 50 mmol) was added in several portions. After the addition was complete, the solution was stirred at 75 °C for 30 min and cooled to room temperature. The addition of 300 mL 1 N aqueous HCl caused the crude product to precipitate out of solution as an off-white powder. The precipitate was collected by filtration, washed with water, and dried under vacuum. Recrystallization of the crude material from acetone/chloroform resulted in the isolation of the purified product (15.8 g, 42 mmol) in 84% yield as white needles. ^1H NMR (400 MHz, acetone-d_6) δ 10.65 (bs, 1H), 8.81 (bs, 1H), 7.85 (d, J = 7.5 Hz, 2H), 7.71 (d, J = 7.6 Hz, 2H), 7.49 (d, J = 6.2 Hz, 2H), 7.40 (t, J = 7.1 Hz, 2H), 7.31 (t, J = 7.4 Hz, 2H), 7.23 (d, J = 8.5 Hz, 2H), 4.47 (d, J = 6.8 Hz, 2H), 4.28(t, J = 6.8 Hz, 1H), 3.56 (s, 2H). ^{13}C NMR (400 MHz, acetone-d_6) δ 172.86, 154.34, 144.97, 142.43, 138.83, 130.56, 130.10, 128.53, 127.91, 125.98, 120.81, 119.21, 66.97, 47.95, 40.58. ES-MS m/z for $C_{23}H_{19}NO_4$: 374.1 ($M+H^+$).
9. Purchased from Novabiochem.
10. Loading levels of these resins were determined by UV spectroscopic quantitation of the dibenzofulvene product released from samples of the resin treated with 20% piperidine in DMF. See Ramage, R.; Stewart, A. J. S. *J. Chem. Soc. Perkin Trans 1*, **1993**, 1947.
11. While somewhat unorthodox for solid-phase synthesis, such determinations are routine in the field of host-guest chemistry and are generally accurate to within 5% of the actual value. See: Petti, M. A.; Shepodd, T. A.; Barrans, R. E. Jr.; Dougherty, D. A. *J. Am. Chem. Soc.*, **1988**, *110*, 6825. Given the mg quantities of oily material produced, and the uncertainties that would be incurred by converting the materials either to crystalline picrate salts or hydroscopic free bases, we believe the use of this technique here is justified. The integrations were carried out as follows: The purified guanidines were dissolved in 2 mL of DMSO-d_6. A 50 µL volume of a 2 M reference solution of *p*-dimethoxybenzene in DMSO-d_6 was added to each of the samples and proton NMR spectra recorded. A 5 second delay was added between scans. The amount of guanidine present was determined by a comparison of integral peak heights of the guanidine and the reference compound. The method was tested with samples of known quantity of 2-nitrophenylacetic acid and 4-aminophenylacetic acid. For 2-nitrophenylacetic acid: determined: 0.25 mmol, actual: 0.24 mmol. For 4-aminophenylacetic acid: determined: 0.23 mmol, actual: 0.23 mmol.