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Solid-Phase Synthesis of Trisubstituted Guanidines

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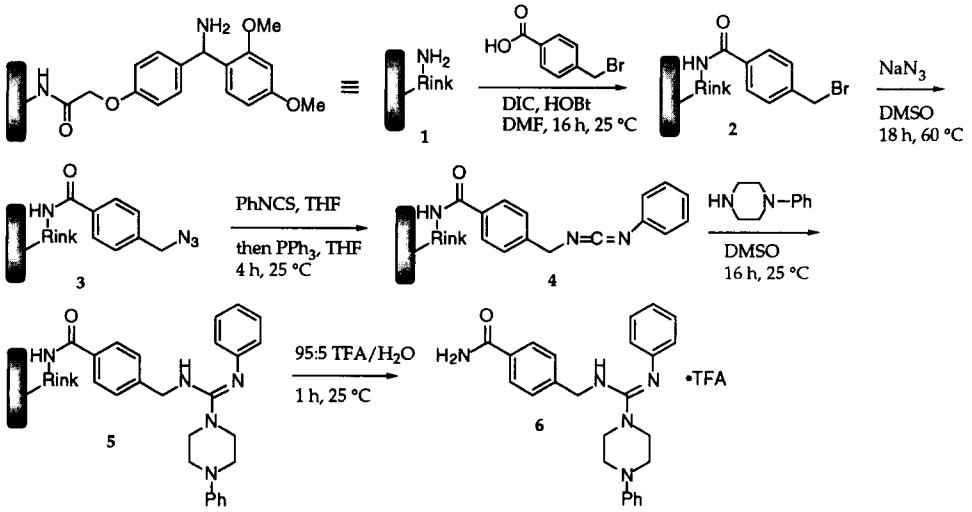
Abstract: The solid-phase synthesis of trisubsituted guanidines is reported via aza-Wittig coupling of a solid-supported alkyl iminophosphorane with an aryl or alkyl isothiocyanate to generate the corresponding solid-supported carbodiimide which is then reacted with a primary or secondary amine to afford the desired trisubstituted guanidines. © 1997 Elsevier Science Ltd.

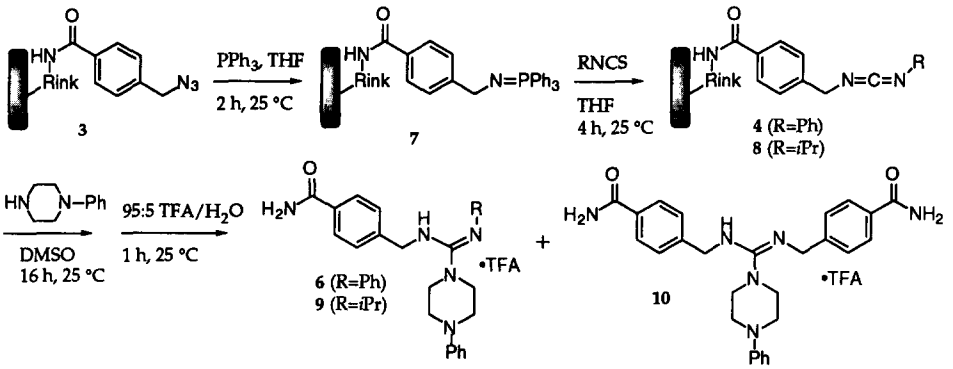
Substituted guanidines are found in many compounds of medicinal interest, spanning a multitude of therapeutic areas.[1] Guanidines have been reported recently as Histamine H1 antagonists,[2a] Histamine H2 agonists,[2a] Histamine H3 antagonists,[2a] non-competitive NMDA receptor antagonists,[2b] and taste receptor ligands.[2c] Due to this wide range of biological activities, we became interested in developing solid-phase chemistry to produce libraries of compounds containing this important functional group. There are a number of efficient solution-phase methods to prepare guanidines.[3] Based on these, we chose to explore the reaction of a polymer-bound carbodiimide with amines for several reasons: the reaction typically proceeds under very mild conditions, carbodiimides are readily accessible from iminophosphoranes,[4] and polymer-bound carbodiimides are known to be stable.[5] Furthermore, this synthetic strategy permits the independent variation of the three guanidine substituents using a large and diverse set of reactants.

Scheme 1



As illustrated in Scheme 1, our synthesis commenced with the coupling of α-bromo-*p*-toluic acid to the primary amine of a Rink-equipped macro crown[6] (**1**) with diisopropylcarbodiimide to yield the corresponding α-bromo-*p*-toluamide (**2**). Nucleophilic displacement of the bromide with azide proceeded smoothly to afford α-azido-*p*-toluamide **3**, which upon treatment with triphenylphosphine and phenyl isothiocyanate provided carbodiimide **4**, presumably via an *in situ* Staudinger reaction to generate the intermediate iminophosphorane and subsequent aza-Wittig coupling with the isothiocyanate. Reaction of the carbodiimide with *N*-phenylpiperazine yielded polymer-bound guanidine **5** which was cleaved from the solid support with TFA/H_2O (95:5) to afford trisubstituted guanidine **6** (>95% crude yield) as the TFA salt.[7] The crude material was 96% pure by reverse phase HPLC.

Scheme 2



The one-pot procedure developed for the conversion of azide **3** to carbodiimide **4** via tandem Staudinger and aza-Wittig reactions merits further discussion. Our initial attempts to effect this tranformation utilized a two-step procedure as shown in Scheme 2, in which the iminophosphorane **7** was synthesized discretely and then reacted with phenyl or isopropyl isothiocyanate. After *N*-phenylpiperazine treatment and subsequent cleavage from the solid support, a complex mixture containing predominantly two products was obtained[8]: the desired trisubstituted guanidine (**6** or **9**), and another guanidine (**10**) which contained *two* α-substituted *p*-toluamide groups and *no* isothiocyanate R group, even though control studies established that an isothiocyanate is required for its synthesis. The formation of **10** presumably proceeds via a [2+2] addition between carbodiimide **4** (or **8**) with a neighboring polymer-bound iminophosphorane and subsequent elimination of triphenylphosphine phenylimide (or isopropylimide) to generate the symmetrical carbodiimide which leads to **10**. In an attempt to remove this undesired side product, we varied the solvent, temperature, phosphorus ligands, and concentrations of triphenylphosphine and isothiocyanate, with limited success. We reasoned that if the desired reaction of the solid-bound iminophosphorane with the isothiocyanate was diffusion controlled, then pre-equilibration of the solid-supported azide **3** with isothiocyanate prior to the Staudinger reaction might suppress the formation of the symmetrically substituted carbodiimide intermediate. Indeed, when we *reversed the order of addition* such that isothiocyanate and then triphenylphosphine were added in a one-pot procedure, the formation of **10** was abolished, as shown in Table 1.

Table 1: The effect of the order of addition on the yield of guanidines **6** and **9**.

Entry	Isothiocyanate	Conditions[a]	Guanidine (Area%)[b]	Area % of Side Product 10[b]
1	PhNCS	A	**6** (36%)	16%
2	PhNCS	B	**6** (96%)	0%
3	*i*PrNCS	A	**9** (15%)	45%
4	*i*PrNCS	B	**9** (63%)	0%

[a]Conditions: (A) 0.5M PPh_3 in THF, 2h, then RNCS (neat), 4h. (B) 0.5M RNCS in THF, 15min, then PPh_3 (solid), 4h.[7] [b]Area percent calculated from reverse phase HPLC[7] spectra (254 nm).

Utilizing the experimental conditions established for the synthesis of guanidines **6** and **9**, we next explored the steric and electronic requirements of the halocarboxylic acid, isothiocyanate and amine reactants. The amines we examined were largely insensitive to steric and electronic effects, but interesting trends were observed for the halocarboxylic acid and isothiocyanate reactants. As shown in Figure 1, halocarboxylic acids with carbonyl groups in close proximity to the halide failed to afford the desired guanidine. The observed unreactivity might be the consequence of the stabilization of the iminophosphorane intermediate by the proximal electron-donating amide carbonyl, a hypothesis supported by the observation that, unlike its lower homologs, 6-bromohexanoic acid provided the corresponding guanidine in good yield and purity.

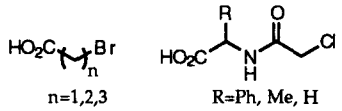


Figure 1. Representative halocarboxylic acids which failed to give desired guanidine products.

The behavior of the isothiocyanate reactants was relatively straightforward, as shown in Figure 2, in that sterically or electronically demanding isothiocyanates did not provide the desired guanidine product. In general, alkyl isothiocyanates provided products of lower purity than aryl isothiocyanates (see Table 1, entries 2 and 4). The source of the impurities has not been established.

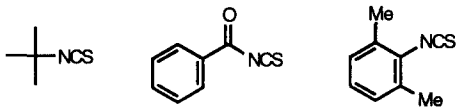


Figure 2. Representative isothiocyanates which failed to give desired guanidine products.

The present work demonstrates the viability of solid-supported iminophosphoranes for the synthesis of trisubstituted guanidines. The utility of iminophosphoranes in solution-phase synthesis is well documented,[9] and suggests that a polymer bound iminophosphorane would be a valuable intermediate.[10] Our further studies in this area will be reported in due course.

Acknowledgements

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References

1. Greenhill, J.L; Lue, P. In *Progress in Medicinal Chemistry*, Ellis, G.P; Luscombe, D.K. Eds.; Elsevier Science: New York, 1993; Vol. 30, Chapter 5.
2. (a) Stark, H.; Krause, M.; Arrang, J.-M.; Ligneau, X.; Schwartz, J.-C.; Schunack, W. *Bioorg. and Med. Chem. Lett.* **1994**, *4*, 2907. (b) Reddy, N.L.; Hu, L.-Y.; Cotter, R.E.; Fischer, J.B.; Wong, W.J.; McBurney, R.N.; Weber, E.; Holmes, D.L.; Wong, S.T.; Prasad, R.; Keana, J.F.W. *J. Med. Chem.* **1994**, *37*, 260. (c) Sulikowski, M.M.; Kim, K.; Sulikowski, G.A.; Nagarajan, S.; Linthicum, D.S. *Bioorg. and Med. Chem. Lett.* **1995**, *5*, 2875.
3. For leading references, see: Nagarajan, S.; Ho, T. L.; DuBois, G. E. *Synth. Commun.* **1992**, *22*, 1191.
4. (a) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proc. Int.* **1992**, *24*, 209. (b) Molina, P.; Vilaplana, M.J. *Synthesis* **1994**, 1197.
5. (a) Desai, M.C.; Stramiello, L.M.S. *Tetrahedron Lett.* **1993**, *34*, 7685. (b) Chucholowski, A.; Masquelin, T.; Obrecht, D.; Stadlwieser, J.; Villalgordo, J.M. *Chimia* **1996**, *50*, 525.
6. Macro crowns were purchased from Chiron Mimotopes Pty. Ltd., Clayton, Victoria, Australia. See Maeji, N.J.; Bray, A.M.; Valerio, R.M.; Wang, W. *Pept. Res.* **1995**, *8*, 33.
7. Representative experimental procedure for the synthesis of **6**: To a Fmoc-deprotected Rink-equipped MA/DMA macro crown (loading: 7.2 μmoles) in a glass vial was added α-bromo-*p*-toluic acid and HOBt (0.5 mL of a 0.5 M solution of each reagent in DMF), then diisopropylcarbodiimide (39 μL) and the resulting suspension was shaken overnight. The crown was filtered and washed with DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). The crown was then added to 0.5 mL of a 1.0 M solution of sodium azide in DMSO and the resulting suspension was heated at 60°C overnight. Upon cooling to room temperature, the crown was filtered and washed with water (1 x 1 mL), DMF (3 x 1 mL), followed by alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). The crown was placed in a glass vial and phenyl isothiocyanate (0.5 mL of a 0.5 M solution in THF) was added and the resulting clear suspension was shaken at room temperature for 15 minutes. Triphenylphosphine (65 mg) was added and the resulting suspension was shaken for 4 hours at room temperature. The crown was filtered and washed with alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x), then added to a vial containing *N*-phenylpiperazine (0.5 mL of a 0.5 M solution in DMSO) and the resulting suspension was shaken overnight. The crown was filtered and washed successively with DMSO (1 x 1 mL), DMF (2 x 1 mL), then alternating THF (1 mL) and CH_2Cl_2 (1 mL) washes (3 x). The crown was placed in a 1 dram vial and treated with TFA:H_2O (95:5) for one hour. The crown was removed and the resulting solution was concentrated *in vacuo* to afford guanidine **6** (3.8 mg, >95% crude yield) as the TFA salt. The crude material was 96% pure by reverse phase HPLC [Rainin Dynamax® C-18 column, 1.0 mL/min flow rate, 10% CH_3CN/H_2O-100% CH_3CN (.1% TFA) gradient over 20 minutes]. Absorbance was measured at 254nm.
8. Compound **9**: ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.33 (t, *J* = 5.1 Hz, 1H, BnNH$^+$), 8.06/7.47 (2 x br s, 2H, C(O)NH_2), 7.98/7.95/7.51/7.48 (AB quartet, *J* = 8.2 Hz, 4H, H(2)/H(6) & H(3)/H(5)), 7.73 (d, *J* = 8.6 Hz, 1H, i-Pr-NH$^+$), 7.31 (t, *J* = 7.9 Hz, 2H, H(3') & H(5')), 7.03 (d, *J* = 8.3 Hz, 2H, H(2') & H(6')), 6.89 (t, *J* = 7.2 Hz, 1H, H(4')), 4.56 (d, *J* = 5.3 Hz, 2H, CH_2Ph), 3.59/3.30 (2 x m, 8H, piperazine 4 x CH_2N). Compound **10**: ^{1}H-NMR (DMSO-d_6): δ (ppm) 8.50 (t, *J* = 5.1 Hz, 2H, 2 x NH$^+$), 8.06/7.48 (2 x br s, 4H, 2 x C(O)NH_2), 7.94/7.91/7.43/7.40 (AB quartet, *J* = 8.0 Hz, 8H, 2 x H(2)/H(6) & 2 x H(3)/H(5)), 7.30 (t, *J* = 8.0 Hz, 2H, H(3') & H(5')), 7.04 (d, *J* = 8.1 Hz, 2H, H(2') & H(6')), 6.89 (t, *J* = 7.2 Hz, 1H, H(4')), 4.56 (d, *J* = 5.1 Hz, 4H, 2 x CH_2Ph), 3.59/3.30 (2 x m, 8H, piperazine 4 x CH_2N).
9. (a) Eguchi, S.; Matsushita, Y.; Yamashita, K. *Org. Prep. Proced. Int.* **1992**, *24*, 209. (b) Molina, P.; Vilaplana, M.J. *Synthesis* **1994**, 1197.
10. Goff, D.A.; Zuckerman, R.N. *J. Org. Chem.* **1995**, *60*, 5744.

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