Pergamon

Tetrahedron Letters 39 (1998) 5701–5704

TETRAHEDRON LETTERS

Solid-Phase Synthesis of *N,N'* Substituted Guanidines[a]

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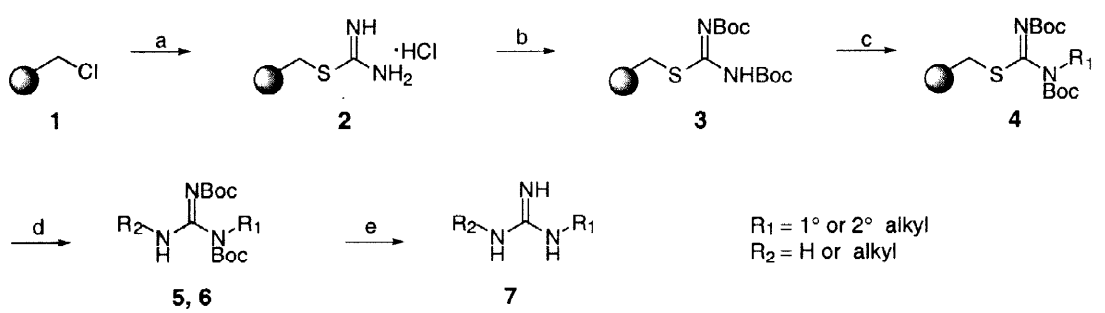
Received 23 April 1998; accepted 22 May 1998

Abstract: An efficient method for the solid-phase synthesis of substituted guanidines is presented. A variety of alcohols react with resin-bound N,N'*-bis*(t*-butoxycarbonyl)thiopseudourea under Mitsunobu conditions to give the corresponding alkylated thiopseudoureas. The guanidines are liberated from the resin upon exposure to ammonia or primary amines.*

The guanidine moiety is an important feature in many biologically active compounds.[1] Whilst there are many methods known for the preparation of guanidines in solution phase,[2,3] there have been limited reports of a disubstituted guanidine synthesis using solid-phase chemistry techniques.[4] Although the published reports allow for the generation of reasonable diversity, they are limited in scope in that they necessitate the use of a resin-bound amine or azide as the starting scaffold. We previously reported the solution phase synthesis of mono-*N*-alkylated guanidines from alcohols using the Mitsunobu protocol,[2,5] and herein disclose a similar approach for the preparation of guanidines using a solid support. Our approach uses resin-bound *N,N'*-bis(*t*-butoxycarbonyl)thiopseudourea as the masked guanidine scaffold and allows for the parallel synthesis of mono-*N*-alkylated guanidines as well as *N,N'* bisalkylated guanidines in high yield and high purity.

Scheme 1



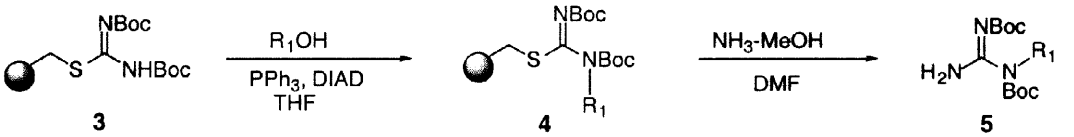
Reagents: (a) thiourea, DMF, 75°C, 20 h; (b) Boc_2O, *i*-Pr_2EtN, CH_2Cl_2, 40 h; (c) R_1-OH, PPh_3, DIAD, THF, 20 h; (d) NH_3, MeOH, DMF, 20 h, rt. or R_2NH_2, DMF, 80°C, 20 h; (e) TFA, CH_2Cl_2.

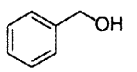
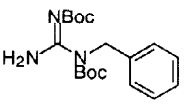
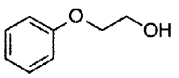
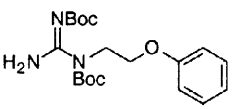
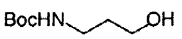
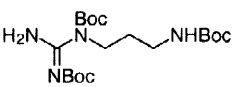
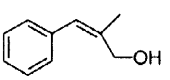
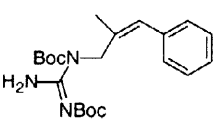
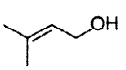
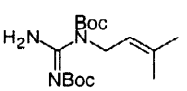
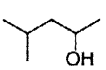
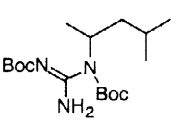
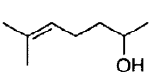
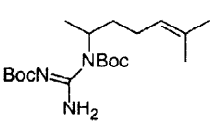
Treatment of Merrifield resin (**1**) with excess thiourea (5-10 mol. equiv.) results in the formation of resin bound thiouronium salt **2**.[6,7] Subsequent protection of the nitrogens of **2** to afford **3** was achieved using a 4-6 fold excess of Boc_2O in the presence of excess *i*-Pr_2EtN. The reaction of bis(*t*-butoxycarbonyl)thiopseudourea **3** with alcohols in the presence of Ph_3P and DIAD gave *N*-alkylated resin bound intermediate **4**. The Mitsunobu reaction is general for most primary and secondary alcohols including benzylic and allylic alcohols. Typically, for one

0040-4039/98/$19.00
PII: S0040-4039(98)01197-6

molar equivalent of the resin bound thiopseudourea, 5 equivalents of alcohol and 5 equivalents of the azodicarboxylate-PPh_3 complex are sufficient for complete alkylation. The mono-*N*-alkylated guanidines were liberated from the resin as the bis(*t*-butoxycarbonyl)-protected[8] derivatives **5** by exposure of **4** to excess methanolic NH_3 in DMF. Typical yields and purities for the mono-*N*-alkylated products are listed in Table 1.

Table 1



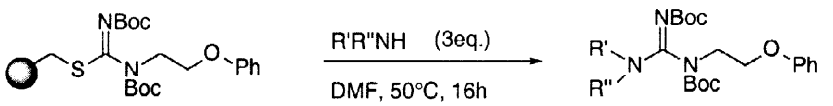
Entry	R_1OH	Product (5)		Yield (%)[a,b]	HPLC Purity (%)[c]
1			(5a)	88	>95
2			(5b)	100	>95
3			(5c)	88	>95
4			(5d)	92	>95
5			(5e)	95	100
6			(5f)	85	90
7			(5g)	85	86

[a]Purified yields, based on resin loading established by NH_3 cleaved unsubstituted bis(*tert*-butoxycarbonyl)guanidine. [b]Compounds purified using reverse-phase preparative HPLC using H_2O-MeOH (0.1% TFA) solvent mixture. [c] Purity of crude product based on analytical HPLC detection at 220 nm.

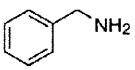
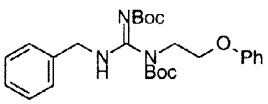
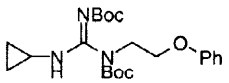
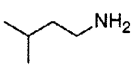
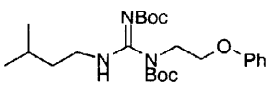
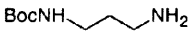
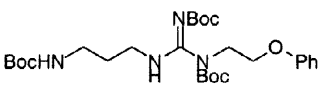
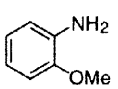
The resin bound bis(*t*-butoxycarbonyl)-*N*-alkylthiopseudoureas (**4**) react with amines in a similar manner to the 1,3-bis(*t*-butoxycarbonyl)-*S*-alkyl-2-thiopseudourea guanylating agents in solution phase reactions. Table 2 outlines the guanylation reaction using resin **4b**. The corresponding internal *N,N'*-substituted guanidines (**6**) were liberated cleanly using an excess of 1° amine (3-5 equiv.) at 50°C in DMF. Under these conditions, primary

amines reacted with **4** to give only a single product in high purity and high yield.[9] As anticipated, we observed no reaction of **4** with anilines, and secondary amines such as piperidine gave a complex mixture with only a trace of the desired product. It has been reported that reaction of *S*-alkylthiopseudoureas with secondary amines and anilines usually requires the presence of "soft" cationic salts such as silver or mercury salts.[3a,b]

Table 2



4b **6**

Entry	R'R"NH	Product (6)		Yield (%)[a]
1			**(6a)**	90[b]
2			**(6b)**	92
3			**(6c)**	92
4			**(6d)**	96
5		trace	**(6e)**	—
6		no rxn	**(6f)**	—

[a]Isolated yields, purified by reverse-phase preparative HPLC. [b]Yield based on the guanidine-TFA salt, after *t*-Boc deprotection.

In summary, a novel and an efficient route to the preparation of substituted guanidines using solid-phase chemistry has been developed. This procedure allows for a high level of diversity using parallel array or combinatorial synthesis. The initial Mitsunobu step allows for the use of either 1° or 2° alcohols to generate the first point of diversity. Subsequent treatment of the resin bound *N*-alkylated thiopseudoureas with ammonia or 1° amines liberates guanidines with the second point of diversity.

References and Notes

(a) Presented in part (by OBW) at IBC's Fifth Annual International Symposium "Peptidomimetics & Small Molecule Design," March 5-6, 1998, Philadelphia, PA.

(1) Greenhill, J. V.; Lue, L. In *Progress in Medicinal Chemistry*, Ellis, G. P.; Luscombe, D. K. Eds.; Elsevier Science: New York, 1993; Vol. 30, Chapter 5.

(2) Dodd, D. S.; Kozikowski, A. P. *Tetrahedron Lett.* **1994**, *35*, 977.

(3) For a more thorough list of references on methods for the preparation of guanidines, see: (a) Kent, D. R.; Cody, W. L.; Doherty, A. M. *Tetrahedron Lett.* **1996**, *37*, 8711. (b) Miel, H.; Rault, S. *Tetrahedron Lett.* **1998**, *39*, 1565. (c) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933.

(4) (a) Drewry, D. H.; Gerritz, S. W.; Linn, J. A. *Tetrahedron Lett.* **1997**, *38*, 3377. (b) Kearney, P. C.; Fernandez, M.; Flygare, J. A. *Tetrahedron Lett.* **1998**, *39*, 2663.

(5) (a) Mitsunobu, O.; Yamada, M.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935. (b) Mitsunobu, O.; Eguchi, M. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 3427. For recent reviews on C-N bond forming reactions using the Mitsunobu protocol, see (c) Hughes, D. L. *Org. Prep. Proc., Int.* **1996**, *28*, 127. (d) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

(6) (a) Obrecht, D.; Abrecht, C.; Grieder, A.; Villalgordo, J. M. *Helv. Chim. Acta* **1997**, *80*, 65. (b) Gayo, L. M.; Suto, M. J. *Tetrahedron Lett.* **1997**, *38*, 211.

(7) (a) Typical procedure: A mixture of Merrifield resin (2.5 g, 2.35 mmol; Cl load of 0.94 mmol/g) and thiourea (0.94 g, 11.8 mmol) in DMF (25 mL) was heated at 75°C for 16 h. The resin was washed successively with DMF (4 x 50 mL), THF (3 x 50 mL), MeOH (3 x 50 mL), and CH_2Cl_2 (3 x 50 mL). The resin was dried under high vacuum for 10 h. The resin and Boc_2O (3.0 g, 14.0 mmol) were slurried in CH_2Cl_2 (50 mL) and treated with $(i\text{-Pr})_2EtN$ (4.1 mL, 24 mmol) over 5 min, and were subsequently gently shaken for 40 h. The resin was washed using the sequence of solvents described above and dried under high vacuum for 10 h. A 250 mg sample of resin in dry THF (4 mL) was treated with sat. NH_3 in MeOH (0.5 mL) and shaken for 12 h to liberate bis(*t*-butoxycarbonyl)guanidine (45 mg, 92% based on starting Merrifield resin) as the only product, thus establishing the resin load of bis(*t*-butoxycarbonyl)isothiourea to be 0.7 mmol/g. To a mixture of resin **3** (250 mg, 0.175 mmol), PPh_3 (175 mg, 0.875 mmol) and 2-phenoxyethanol (110 µL, 0.875 mmol) in dry THF (3 mL) was added DIAD (175 µl, 0.85 mmol). The reaction was gently shaken for 14 h, and the resin was washed as described above and air dried. To a portion (100 mg) of the resin in dry DMF (3 ml) was added sat. NH_3-MeOH solution (300 µL, excess). The reaction mixture was shaken for 15 h. The cleaved material was isolated and the resin rinsed with THF (2 x 1 mL); the solvent was removed *in vacuo* to give **5b** (24 mg, 100%, assumed loading of 0.7 mmol/g) with HPLC purity >98%. A second batch of the resin-bound phenoxyethylisothiourea (100 mg) was suspended in DMF (2 mL) and was treated with benzylamine (3 eq.) at 50°C for 16 h. The resin was filtered and rinsed with THF (2 x 1 mL) and the solvent was removed *in vacuo*. The product was dissolved in CH_2Cl_2 (3 mL) and the contaminating excess amine was scavenged using 4 fold excess of isocyanate resin at 30°C for 12 h to give **6a** (27 mg, 90%) in >90% HPLC purity. (b) Compounds were characterized using ^1H NMR, HPLC, LC/MS and when possible by comparison with authentic samples prepared using alternative methods.

(8) The *t*-Boc groups can be removed after isolation of the *t*-Boc-protected compounds using 50% TFA in CH_2Cl_2. As an example, **5b** was deprotected in quantitative yield and in >98% purity (HPLC). Some of the bis(*t*-butoxycarbonyl)guanidines were found to be relatively unstable to trace amount of acid or prolonged storage at rt. In some instances, partial deprotection of one of the *t*-Boc-groups was effected by the presence of 0.1% TFA in the preparative HPLC eluting solvent, when left at rt for a few hours.

(9) The reaction takes a slighly different course when the guanylations were carried out in THF at 85°C using 5 equivalents of amine over 20 h. We observed, by LC/MS, the formation of 5-10% of the *N*-(*N*'-*t*-butoxycarbonylamidino)ureas, where one of the *t*-butyloxy groups was also displaced with the amine. This was particularly evident with benzylamine. Fortunately, this side reaction can be suppressed by carrying out the guanylation at 50°C in DMF. Synthesis of similar *N*-(*N*'-*t*-butoxycarbonylamidino)ureas by reacting *N,N*'-bis(*t*-butoxycarbonyl)guanidines with amines at elevated temperatures has recently been reported.[3b]