Pergamon

Tetrahedron Letters 43 (2002) 7105–7109

TETRAHEDRON LETTERS

A novel, facile methodology for the synthesis of *N*,*N*′-bis(*tert*-butoxycarbonyl)-protected guanidines using polymer-supported carbodiimide

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Received 17 June 2002; revised 8 July 2002; accepted 10 July 2002

Abstract—A novel methodology for the synthesis of guanidines from amines has been developed using polymer assisted synthesis, potentially allowing the preparation of series of compounds in a high throughput manner. The methodology comprises the use of polymer-supported carbodiimide as the activating agent for *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea with polymer-supported trisamine as a scavenger, followed by deprotection with trifluoroacetic acid. For the first time, polymer-supported carbodiimide has been utilized as an activating agent to synthesize guanidines.

The guanidine functional group is an important component in many biologically active natural products,[1] as well as medicinal agents,[2] for instance, with anti-tumour, anti-hypertensive, anti-glaucoma and cardiotonic activities, and H_2 antagonism/agonism.

As part of a lead discovery project, our work was devoted to converting a diverse set of proprietary primary and secondary amines directly into their corresponding terminal guanidines. To reach this goal in a high throughput way, it was desirable to employ solid phase methodology. Thus, a number of approaches, where the guanidylating agent is polymer-supported, have been reported in the literature. These include pyrazole carboxamidine and its derivatives,[3,4] and analogues of *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea,[5] *S*-alkyl thiourea,[6] *N*-triflyl guanidine,[7] and *N*,*N*′-bis(*tert*-butoxycarbonyl) pseudourea.[5d] However, there are some potential disadvantages by using such a strategy. These reagents must be synthetically prepared, most of them in a multi-step sequence, since they are not commercially available. Additionally, there is the need of using a large excess of starting amine to reach completion of the reaction, if an efficient subsequent cleavage, in terms of purity, is desired. This is a major issue, particularly in our case, where the amines of interest are of high synthetic value, since they are usually prepared in multi-step sequences. Furthermore, in some cases, the success of the reaction is also very substrate-dependent. Other alternatives based on solution phase approaches would need additional work-up and purification steps to obtain the final products.[8]

Herein, we report a polymer assisted synthesis (PAS) methodology[9] to obtain guanidines, which combines advantages of traditional solution phase chemistry with the application of polymeric reagents. This approach led to the desired compounds in a high throughput manner, in sufficient purity, without additional purification steps.

Among the different guanidylation methodologies reported in the literature, we focused our attention on the use of *N*,*N*′-bis-BOC-thiourea and dicyclohexylcarbodiimide,[10] since its versatility has been proven clearly in solution phase. Thus, we decided to adapt this method to a PAS environment using the activating agent in solid support, while keeping the amidine donor in solution. *N*,*N*′-Bis(*tert*-butoxycarbonyl) thiourea is readily prepared in one step,[11] in multigram scale and PS-carbodiimide is commercially available.[12] The use of PS-carbodiimide is well known in several PAS applications,[13] nevertheless, to the best of our knowledge, there are no precedents where PS-carbodiimide had been utilized for the synthesis of guanidines.

Keywords: polymer assisted synthesis; *N*,*N*-bis(*tert*-butoxycarbonyl)-protected guanidines; *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea; PS-carbodiimide; high throughput chemistry.

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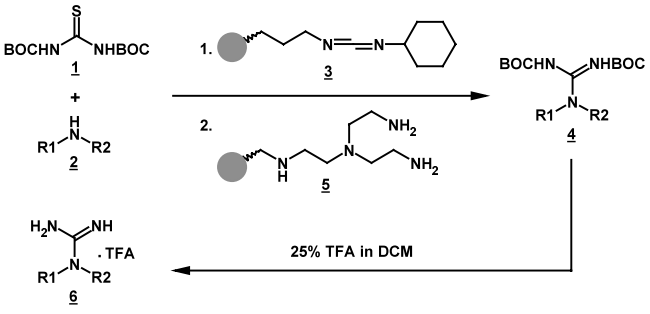
0040-4039/02/$ - see front matter
PII: S0040-4039(02)01390-4

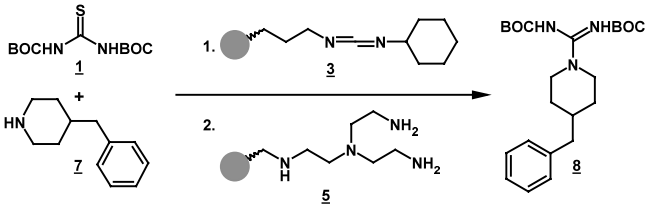
The general strategy is outlined in Scheme 1. Thus, a one-pot procedure where a mixture of the amine **2**, *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea **1** and PS-carbodiimide **3** with purification using PS-trisamine[14] **5** afforded *N*,*N*′-bis(*tert*-butoxycarbonyl) protected guanidines **4**. Subsequent deprotection under acidic conditions gave the final compounds in high purity and yield without further purification.

To optimize the procedure, we chose 4-benzylpiperidine **7**, as a model. Experiments were carried out using different combinations of equivalents of **1** (from 1.2 to 1.5 equiv.) and **3** (from 1.5 to 3.0 equiv.) with or without the presence of base (di-isopropylethylamine, 2.0 equiv.) and two different solvents (DMF and CH_2Cl_2).

We observed that the use of a base is not necessary and does not produce any improvement in the process. Also, carrying out the reaction in DMF or CH_2Cl_2 gave similar results in this model experiment. It is interesting to note that we observed the formation of small amounts of a byproduct (tentatively assigned as bis-(*tert*-butoxycarbonyl) carbodiimide)[9a] in the reaction mixture. Thus, in order to remove such an impurity-byproduct, we added PS-trisamine **5** as a scavenger, thereby obtaining the desired *N*,*N*′-bis(*tert*-butoxycarbonyl)-protected guanidine **8** in high yield (95%, based on mass recovery) and purity (96%/86%, based on LC-MS-UV/^{1}H NMR analyses).[15] The final optimized conditions are summarized in Scheme 2. Interestingly, the presence of electron-withdrawing groups in the thiourea derivative was shown to be important to the success of the process, since the use of thiourea itself gave negative results under the same protocol.[16]



Scheme 1. One-pot synthesis–purification of deprotected guanidines.



Scheme 2. *Conditions*: (1) 1.0 equiv. 4-benzylpiperidine, 1.5 equiv. *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea, 3.0 equiv. PS-carbodiimide, DMF (or CH_2Cl_2), rt; 16 h. (2) 2.0 equiv. PS-trisamine, DMF (or CH_2Cl_2), rt; 4 h.

Fig. 1 displays a set of representative amines chosen to explore the scope and limitations of this process. The results for each amine are summarized in Table 1.

In order to test the influence of the solvent in this protocol, a duplicate set of experiments with DMF and CH_2Cl_2 were carried out. In general, the isolated yields for *N*,*N*′-bis(*tert*-butoxycarbonyl)-protected guanidines were comparable in both solvents. However, the purity of the final compounds was slightly better when CH_2Cl_2 was used. The most interesting effect was on the reaction rate. Thus, in DMF some guanidylation reactions needed times of up to 72 h for completion, while in CH_2Cl_2 required reaction times were not longer than 16 h.[17] Therefore, CH_2Cl_2 was the solvent of choice, with the additional advantage of easier removal/evaporation compared to DMF. Regarding the diversity of the commercial amines, it is worth noting that in all cases the corresponding *N*,*N*′-bis(*tert*-butoxycarbonyl)-protected guanidines were obtained in good to excellent yields and purities when CH_2Cl_2 was used as solvent. Even deactivated anilines (**2j**) or sterically hindered amines (**2l**) reacted efficiently, improving on or matching results with other guanidylation systems.[17] Further treatment of the protected guanidines with 25% TFA in CH_2Cl_2 at room temperature for 6 h, and subsequent evaporation gave the corresponding deprotected guanidines, with good yields and purities, as their corresponding TFA salts (see Table 1).[18,19]

In summary, we have developed a novel, facile methodology for the synthesis of *N*,*N*′-bis(*tert*-butoxycarbonyl)-protected guanidines, in high purity and yield, for a diverse set of amines, by using PS-carbodiimide and *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea coupled with the use of PS-trisamine. Further deprotection with TFA afforded terminal guanidines. This represents the first use of PS-carbodiimide as an activating agent for the synthesis of *N*,*N*′-bis(*tert*-butoxycarbonyl)-protected guanidines. The whole protocol has potential use in high throughput synthesis for this class of compounds.

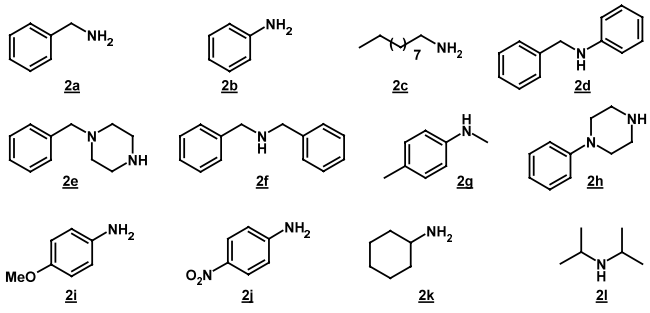


Figure 1. Set of representative amines.

Table 1.

Entry	N,N'-bis(*tert*-butoxycarbonyl)-protected guanidines (4)			Deprotected guanidines (6)[f]
	DMF[a]	CH_2Cl_2 (16 h)[c]		
	Time(h) / Purity[b] (%)	Purity[b/d] (%)	Yield[e] (%)	Purity[d] (%) (Yield)[e] (%)
2a	16/90	99/92	95	90 (97)
2b	48/83	90/94	93	92 (93)
2c	16/94	94/89	91	87 (94)
2d	72/70	74/79	93	77 (91)
2e	16/96	96/91	87	89 (90)
2f	48/93	93/88	89	87 (92)
2g	72/82	90/89	94	89 (94)
2h	16/92	92/88	90	86 (98)
2i	16/91	100/91	92	90 (95)
2j	72/10	(91/88)[g]	-	89[g] (-)
2k	48/76	89/92	95	92 (93)
2l	16/70	90/85	93	84 (98)

[a] Yields from DMF experiments ranged from 70 to 95%, and are determined based on mass recovery of crude product. [b] Purity given is determined from crude material based on area of peak corresponding to the correct molecular weight, monitored by UV detection, scanning from 200 to 450 nm. [c] Time for CH_2Cl_2 experiments was set up to 16 h and was not further optimized. [d] Purity given is determined based on ^1H NMR analysis of crude material. [e] Yield determined based on mass recovery of crude product. [f] The deprotection step was carried out from those guanidylation experiments performed in CH_2Cl_2. [g] See Ref. 17.
For typical experimental procedures see Ref. 15.

Acknowledgements

The authors wish to thank their colleagues from the Analytical Department for their support. Johnson & Johnson Pharmaceutical Research and Development (a division of Janssen-Cilag, S.A. Toledo, Spain) is also gratefully acknowledged for a Ph.D. fellowship (O.G.).

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15. **Typical experimental procedures**:
Guanidylation of model compound 4-benzylpiperidine (7): To a solution of *N*,*N*′-bis(*tert*-butoxycarbonyl) thiourea (236 mg, 0.85 mmol, 1.5 equiv.) in CH_2Cl_2 (10 mL) was added 4-benzylpiperidine (100 mg, 0.57 mmol, 1.0 equiv.) and PS-carbodiimide (Argonaut Technologies Ltd, 1.26 mmol/g, 1.34 g, 1.70 mmol, 3.0 equiv.). The mixture was shaken at room temperature for 16 h, then it was filtered and the polymer washed with CH_2Cl_2 (2×5 mL). PS-trisamine (4.2 mmol/g, 270 mg, 1.14 mmol, 2.0 equiv.) was added to the resulting solution and the mixture was shaken for 4 h. The polymer was filtered and washed with CH_2Cl_2 (2×5 mL). The solvent was evaporated under reduced pressure affording the corresponding bis-Boc protected guanidine **8** (226 mg, 95% yield). The purity of crude compound 8 was determined by LC-MS-UV analysis (MH^+=418) (96%) and confirmed by its ^{1}H NMR spectrum (86%). ^{1}H NMR (400 MHz $CDCl_3$): δ 1.28–1.41 (m, 2H), 1.41–1.54 (m, 2H), 1.46 (s, 9H), 1.50 (s, 9H), 1.64–1.70 (m, 2H), 1.70–1.82 (m, 1H), 2.55 (d, J=7.0 Hz, 2H), 2.80–2.94 (m, 2H), 7.13 (d, J=7.2 Hz, 2H), 7.20 (t, J=7.2 Hz, 1H), 7.28 (t, J=7.2 Hz, 2H), 10.15 (broad s, 1H).
*Guanidylation of amines **2a–l** and final deprotection:* To twelve tubes of a Quest 210™ synthesizer (Argonaut Technologies Ltd) was added PS-carbodiimide (1.26 mmol/g, 595 mg, 0.75 mmol, 3.0 equiv.) and CH_2Cl_2 (5.0 mL). The resin was washed/swollen for 15 min. The solvent was filtered and the process repeated twice. The resin was suspended again in CH_2Cl_2 (5.0 mL), then the corresponding amines **2a–l** (0.25 mmol, 1.0 equiv.) were added to each tube and finally *N*,*N*′-bis(*tert*-butoxycarbonyl)thiourea (103 mg, 0.37 mmol, 1.5 equiv.). The mixtures were shaken at room temperature under N_2 atmosphere for 16 h. Then, PS-trisamine (4.2 mmol/g, 120 mg, 0.50 mmol, 2.0 equiv.) and CH_2Cl_2 (1.0 mL) were added to each mixture. The shaking was continued for 16 h at room temperature. The polymers were removed by filtration, washed with more CH_2Cl_2 (2×6 mL), and the resulting solutions were evaporated under reduced pressure. The yield were determined by mass recovery, and the purity of each protected guanidine **4** were calculated by LC-MS-UV and ^{1}H NMR analyses (see Table 1). Crude protected guanidines were further treated with a solution of trifluoroacetic acid (25% in CH_2Cl_2, 5.0 mL) at room temperature for 6 h, finally, evaporation of the solvent gave the corresponding deprotected guanidines **6**. Yields and purities were calculated as mentioned above.
HPLC-UV-ESI-MS analysis was performed on a HPLC HP1100 from Agilent Technologies Ltd. and a Platform II single quadrupole mass spectrometer from Micromass Ltd. Reversed phase HPLC was done using a Zorbax XDB C-18 4.6×30 mm×3.5 μm with a 6 min gradient from 80% to 100% MeOH/AcCN containing 0.2% ammonium acetate. The mass spectrometer was operated both in positive and negative ionization scanning from 100 to 1000 a.m.u. ^{1}H NMR analysis was performed on a Bruker Avance DPX, 400 MHz.
16. Starting materials were the only products detected by LC-MS.
17. Although experiments carried out in CH_2Cl_2 for 16 h with di-isopropyl amine (**2l**) and *p*-NO_2-aniline (**2j**) improved precedent results with other guanidylating systems,[3a,4c] reaction of amine **2j** proceeded with 70% of conversion. The LC-MS-UV analysis of the crude material revealed 30% of starting amine, protected guanidine 64% and 6% of impurities. This result means a 91% purity for expected compound, if unreacted amine is not taken into account. Therefore, yields of guanidines from entry **2j** are not given.
18. The purity of deprotected guanidines was determined by ^{1}H NMR, and not by LC-MS-UV, since their high polarity gave in general remarkable peak tailing. This issue made difficult the adequate determination of the peak area corresponding to these compounds.
19. *^{1}H NMR (400 MHz $CDCl_3$) data for protected guanidines derived from entries*: **2a**: δ 1.48 (s, 9H), 1.52 (s, 9H), 4.63 (d, J=5.2 Hz, 2H), 7.25–7.40 (m, 5H), 8.58 (broad s, 1H), 11.54 (broad s, 1H). **2b**: δ 1.51 (s, 9H), 1.54 (s, 9H), 7.11 (t, J=7.4 Hz, 1H), 7.32 (t, J=7.8 Hz, 2H), 7.60 (d, J=7.8 Hz, 2H), 10.33 (broad s, 1H), 11.65 (broad s, 1H). **2c**: δ 0.88 (t, J=6.8 Hz, 3H), 1.25–1.38 (m, 14H), 1.49 (s, 9H), 1.51 (s, 9H), 1.57–1.60 (m, 2H), 3.37–3.42 (m, 2H), 8.3 (broad s, 1H), 11.5 (broad s, 1H). **2d**: δ 1.20 (s, 9H), 1.51 (s, 9H), 5.15 (s, 2H), 7.05–7.16 (m, 3H), 7.19–7.38 (m, 7H), 9.22 (broad s, 1H). **2e**: δ 1.46 (s, 9H), 1.50 (s, 9H), 2.47–2.52 (m, 4H), 3.52 (s, 2H), 3.51–3.73 (m, 4H), 7.29–7.35 (m, 5H), 10.15 (broad s, 1H). **2f**: δ 1.51 (broad s, 18H), 4.55 (s, 4H), 7.10–7.15 (m, 4H), 7.20–7.42 (m, 6H), 10.13 (broad s, 1H). **2g**: δ 1.21 (s, 9H), 1.53 (s, 9H), 2.32 (s, 3H), 3.42 (s, 3H), 7.09 (d, J=8.1 Hz, 2H), 7.15 (d, J=8.1 Hz, 2H), 9.22 (broad, s, 1H). **2h**: δ 1.48 (s, 9H), 1.51 (s, 9H), 3.22–3.28 (m, 4H), 3.62–3.85 (m, 4H), 6.88–6.96 (m, 3H), 7.24–7.30 (m, 2H), 10.24 (broad s, 1H). **2i**: δ 1.49 (s, 9H), 1.53 (s, 9H), 3.79 (s, 3H), 6.86 (d, J=8.9 Hz, 2H), 7.48 (d, J=8.9 Hz, 2H), 10.18 (broad s, 1H), 11.64 (broad s, 1H). **2j**: δ 1.53 (s, 9H), 1.55 (s, 9H), 7.85 (d, J=9.5 Hz, 2H), 8.22 (d, J=9.5 Hz, 2H), 10.77 (broad s, 1H), 11.60 (broad s, 1H). **2k**: δ 1.14–1.45 (m, 6H), 1.49 (s, 9H), 1.50 (s, 9H), 1.63–1.73 (m, 2H), 1.88–1.98 (m, 2H), 3.96–4.06 (m, 1H), 8.31 (d, J=7.4 Hz, 1H), 11.53 (broad s, 1H). **2l**: δ 1.33 (d, J=6.6 Hz, 12H), 1.47 (broad s, 18H), 3.93 (h, J=6.6 Hz, 2H), 8.29 (broad s, 1H).
^{1}H NMR (400 MHz DMSO-d_6) data for deprotected guanidines derived from entries: **2a**: δ 4.35 (d, J=6.0 Hz, 2H), 6.80–7.65 (m, 9H), 8.05 (t, J=6.0 Hz, 1H). **2b**: δ 7.24 (d, J=7.4 Hz, 2H), 7.29 (t, J=7.4 Hz, 1H), 7.45 (t, J=7.9 Hz, 2H), 7.61 (broad s, 4H), 10.07 (broad s, 1H).

2c: δ 0.86 (t, $J=6.8$ Hz, 3H), 1.14–1.36 (m, 14H), 1.39–1.52 (m, 2H), 3.08 (dt, $J=6.8$ Hz, $J=7.5$ Hz, 2H), 6.60–7.53 (broad s, 4H), 7.60 (broad s, 1H). **2d**: δ 4.95 (s, 2H), 7.18–7.47 (m, 10H), 7.59 (broad s, 4H). **2e**: δ 3.05–3.46 (m, 8H), 4.36 (s, 2H), 7.45–7.55 (m, 5H), 7.75 (broad s, 4H). **2f**: δ 4.60 (s, 4H), 7.20–7.27 (m, 4H), 7.31–7.37 (m, 2H), 7.37–7.44 (m, 4H), 7.65 (broad s, 4H). **2g**: δ 2.35 (s, 3H), 3.25 (s, 3H), 7.22–7.40 (m, 8H). **2h**: δ 3.18–3.28 (m, 4H), 3.54–3.64 (m, 4H), 6.83 (t, $J=7.4$ Hz, 1H), 6.98 (d, $J=7.8$ Hz, 2H), 7.24 (t, $J=7.8$ Hz, 2H), 7.56 (broad s, 4H). **2i**: δ 3.77 (s, 3H), 7.00 (d, $J=8.9$ Hz, 2H), 7.18 (d, $J=8.9$ Hz, 2H), 7.36 (broad s, 4H). **2j**: δ 7.46 (d, $J=9.0$ Hz, 2H), 8.01 (broad s, 4H), 8.28 (d, $J=9.0$ Hz, 2H), 10.49 (broad s, 1H). **2k**: δ 1.07–1.38 (m, 5H), 1.50–1.60 (m, 1H), 1.61–1.73 (m, 2H), 1.75–1.89 (m, 2H), 3.41–3.27 (m, 1H), 6.65–7.44 (broad s, 4H), 7.58 (d, $J=8.3$ Hz, 1H). **2l**: δ 1.24 (d, $J=6.8$ Hz, 12H), 3.93 (h, $J=6.8$ Hz, 2H), 7.03 (broad s, 4H). **8**: δ 1.07–1.21 (m, 2H), 1.55–1.67 (m, 2H), 1.74–1.88 (m, 1H), 2.54 (d, $J=7.0$ Hz, 2H), 2.87–2.99 (m, 2H), 3.74–3.90 (m, 2H), 7.17 (d, $J=7.0$ Hz, 2H), 7.20 (t, $J=7.2$ Hz, 1H), 7.28 (t, $J=7.2$ Hz, 2H), 7.35 (broad s, 4H).