A Mild and Inexpensive Procedure for the Synthesis of *N*,*N*′-Di-Boc-Protected Guanidines

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Abstract: A novel and efficient synthetic procedure for converting a diverse set of amines to *N*,*N*′-di-Boc-protected guanidines is described. The methodology comprises the use of cyanuric chloride (TCT) as activating reagent for di-Boc-thiourea. The employ of inexpensive TCT instead of classical $HgCl_2$ eliminates the environmental hazard of heavy-metal waste without appreciable loss of yield or reactivity. This protocol provides an alternative route for the guanylation of amines from those currently employed.

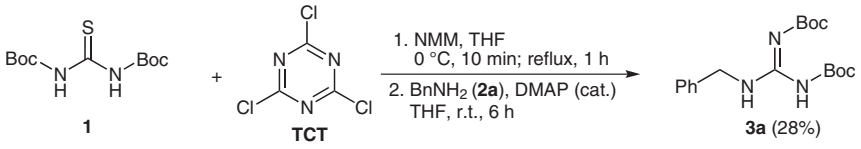
Key words: cyanuric chloride, TCT, guanidine, *N*,*N*′-di-Boc-protected guanidines, guanylating reagent

The guanidine moiety is an important structural motif, which often occurs in many biologically and pharmaceutically relevant compounds.[1] Recent studies have disclosed that guanidine-containing molecules exhibit antiviral, antifungal, and antitumorous activities.[2] The wide range of biological activities found for guanidines are mainly due both to the high stability of the protonated guanidine and to the hydrogen-bond mediated interaction of guanidinium ions.[3] In fact, under physiological conditions, the guanidine framework is fully protonated due to its strongly basic character, a detail that is essential to understand specific noncovalent ligand–receptor interactions.[4] Taking into account the growing importance of guanidine derivatives in the field of medicinal chemistry, there is significant interest in new methods to synthesize guanidines. Typical synthetic routes to guanidines involve the reaction of a primary or secondary amine with an electrophilic guanylating reagent.[5] To date, a variety of such agents have been documented for this conversion, including cianamide,[6] pyrazole-1-carboxamidine derivatives,[7] *O*-methylisourea hydrogen sulfate,[8] diprotected triflylguanidines,[9] and protected thioureas as well as *S*-methylisothioureas derivatives, which need to be activated by toxic Hg salts[10] or by Mukaiyama's reagent.[11] However, some shortcomings and limitations[12] inherent in using these guanylating reagents have led to the development of milder, efficient, and environmentally benign methodologies, though not all are devoid of disadvantages. Most procedures run into difficulties at the purification step, usually compounded by the high basicity of guanidines. The employ of more activated carbamate-guanylating reagents allows for the direct synthesis of protected guanidines introducing several advances[13] in the guanylation of amines. Unlike free guanidines, protected guanidines are less polar and basic, and unreacted amines can be easily removed by washing with an acidic aqueous solution.

In continuation of our interest in the preparation of amidines[14] and guanidines,[15] we herein report an eco-friendly, efficient, and inexpensive synthesis of *N*,*N*′-di-Boc-protected guanidines making use of di-Boc-thiourea as guanylating agent, and 2,4,6-trichloro-1,3,5-triazine[16] (TCT, cyanuric chloride) as initial activating[17] reagent (promoter).[18]

In order to find the best reaction conditions, we have performed the guanylation reaction using benzylamine as model target. Preliminary efforts were mainly focused on the evaluation of the optimum amount of TCT with different solvents. In the first instance, the reaction was accomplished by treating di-Boc-thiourea **1** with an equimolar amounts of TCT and three equivalents of *N*-methylmorpholine (NMM) in anhydrous THF (Scheme 1). The activated thiourea was successively reacted with benzylamine **2a** and NMM[19] in the presence of a catalytic amount of 4-(*N*,*N*-dimethylamino)pyridine[20] (DMAP) until completion. The product **3a** was isolated in low yield (28%) after aqueous workup and an exceptionally tedious column chromatographic purification.[21]

After a careful analysis of reaction products, we have discovered the formation of alkyamino-substituted triazines



Scheme 1 Guanylation reaction by using an equimolar amount of TCT promoter

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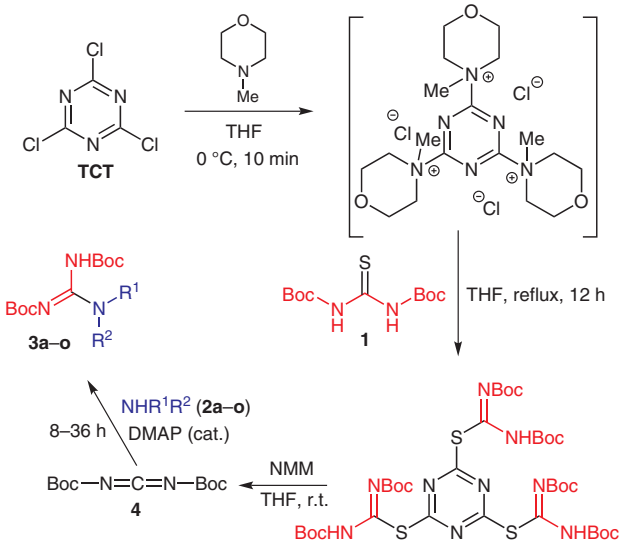
as major, undesirable side products along with many other unidentified byproducts.

In order to improve the conversion of amine **2a** into protected guanidine **3a**, we have successively carried out our guanylation reaction reducing the amount of TCT by two-thirds. At one, this ratio di-Boc-thiourea/TCT[22] (3:1) has shown a positive effect on the reactivity, and the desired product **3a** was achieved in 95% yield without any noticeable unpleasant side products.[23] The course of the reaction (8 h) was conveniently monitored by TLC analysis, and isolation of the final product involved simple aqueous workup[24] procedure and purification through a short silica gel chromatography column.

In order to test the influence of the solvent in this protocol, we have duplicated the target experiment both in DMF and CH_2Cl_2. Interestingly, a significant decrease in the reaction rate and chemical yield was observed carrying out the guanylation reaction in CH_2Cl_2[25] but it was also substantial in DMF.[26] Use of 1,2-dimethoxyethane as solvent has shown a decreased conversion of benzylamine **2a** into the corresponding guanidine, adversely affecting the isolated yield of **3a** (51%). The replacement of THF with different solvents in the second step of guanylation reaction did not allow any improvement. Among the solvents tested, THF was found the best in terms of chemical yield and purity.

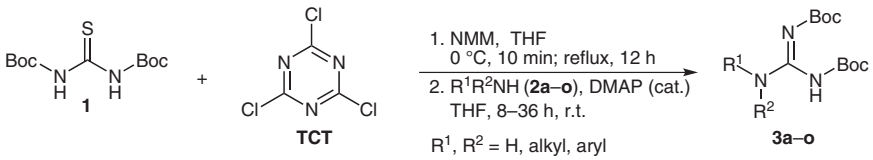
To investigate the scope and limitations of this procedure, a series of structurally and electronically diverse amines were subjected to reaction with TCT and carbamate-protected thiourea **1**. The results and some experimental details are illustrated in Table 1. Several conclusions can be reached from the analysis of these data. In all cases investigated, the guanidinylation of unhindered primary aliphatic (Table 1, entry 1–3 and 8–10) and cyclic secondary amines (Table 1, entries 13 and 14) with reagent **1** is extremely facile and proceed in high yield (>90%, based on mass recovery) and purity (>95%, based on LC-MS and ^{1}H NMR analyses). We also observed that the method is applicable to several aromatic amines (Table 1, entry 4–7), and only the electron-poor 4-nitroaniline **3f** gave somewhat lower yield. Difficulties were only observed with protected guanidine **3k** and **3l**, which were obtained in low yields, presumably due to steric interaction of *tert*-butylamine (Table 1, entry 11) and diisopropylamine (Table 1, entry 12).[27] Any attempts to increase the yield by prolonging reaction time and heating the reaction mixture proved unsuccessful. The majority of the guanidines isolated were pure enough for immediate spectroscopic characterization. Chemical identity was established by ^{1}H NMR, ^{13}C NMR, and elemental analysis in order to ensure that the reaction procedure has been successfully accomplished.[28] Using these optimized conditions, we have also investigated the guanylation of the amino group of a L-α-amino acid methyl ester (Table 1, entry 15). The results indicate that the guanylation reaction proceeds cleanly and in good yield providing ready access to protected L-guanidino methyl ester[29] with retention of stereochemistry.[30]

Based on literature precedents,[31] we suppose that TCT promotes the removal of H_2S from the thiourea **1** giving a bis-Boc-carbodimide intermediate **4** (nonisolable under this conditions) as reactive species (Scheme 2). The amine then adds to the carbodiimide to yield the corresponding guanidine.[32]



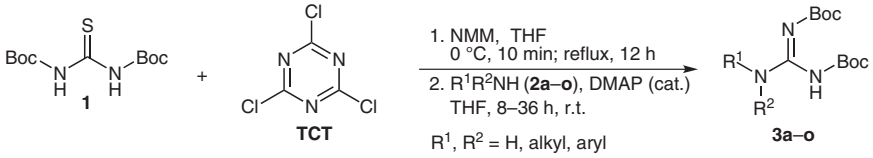
Scheme 2 Proposed mechanism for the TCT-promoted guanylation of di-Boc-protected thiourea **1** with a set of different amines **2a–o**

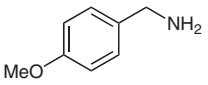
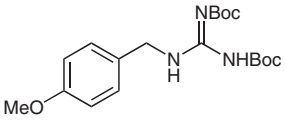
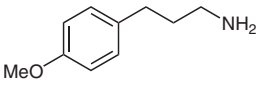
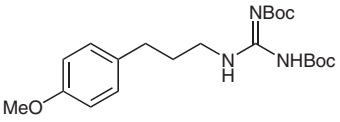
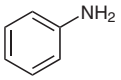
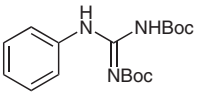
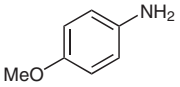
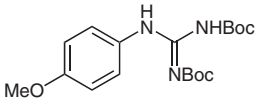
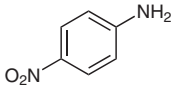
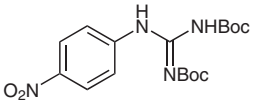
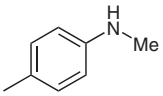
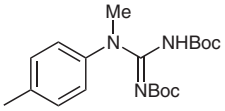
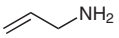
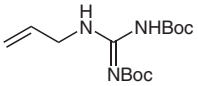
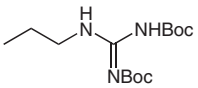
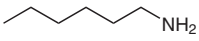
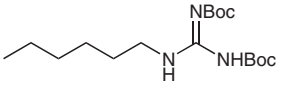
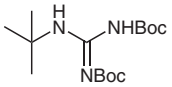
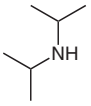
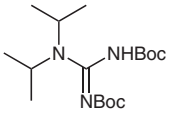
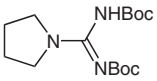
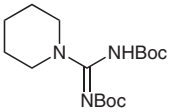
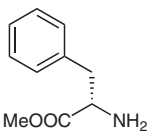
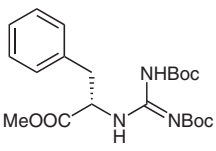
Table 1 Conversion of Several Amines to Di-Boc-protected Guanidines Using Cyanuric Chloride (TCT) as Activating Agent



Entry	Amine	Time (h)	Product[a]	Yield (%)[b]
1	**2a**	8	**3a**	95

Table 1 Conversion of Several Amines to Di-Boc-protected Guanidines Using Cyanuric Chloride (TCT) as Activating Agent (continued)



Entry	Amine		Time (h)	Product[a]		Yield (%)[b]
2	**2b**		8	**3b**		97
3	**2c**		9	**3c**		94
4	**2d**		12	**3d**		69
5	**2e**		12	**3e**		74
6	**2f**		24	**3f**		32
7	**2g**		24	**3g**		47
8	**2h**		8	**3h**		93
9	**2i**		9	**3i**		94
10	**2j**		12	**3j**		88
11	**2k**		18	**3k**		27
12	**2l**		36	**3l**		21
13	**2m**		8	**3m**		94
14	**2n**		8	**3n**		91
15	**2o**		12	**3o**		83

[a] All the products were characterized by ^{1}H NMR, ^{13}C NMR, and HRMS or elemental analysis.
[b] Overall isolated yield.

In conclusion, we have developed a novel and efficient synthetic procedure for converting a diverse set of amines into *N*,*N*′-di-Boc-protected guanidines. The reaction consists of an attack of primary and secondary amines on di-Boc-thiourea activated by a very cheap promoter (TCT). This protocol provides an alternative route for the guanylation of amines from those currently employed. An attractive feature of this methodology is that the reaction occurs under mild conditions, and without producing any significant side and/or environmental hazardous products. Furthermore, at the end of the reaction, a simple aqueous workup followed by filtration through a short plug of silica gel affords the desired products pure and in moderate to high yields.

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(12) Many of these reagents present difficulties such as toxicity, odour, moisture-sensitivity, harsh reaction conditions, and long reaction time.

(13) The application of reagents containing two urethane-type protecting groups is beneficial since two electron-withdrawing groups in positions conjugated with the reaction center increase the electrophilicity and the solubility of the guanylating agent.

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(17) Generally, the conversion of protected thiourea into a guanidine requires initial activation.

(18) In particularly, we were interested in replacing the traditional activating Mukaiyama reagent with the readily available cyanuric chloride for the guanylation of di-Boc-protected thiourea.

(19) The use of NMM or Et_3N proved to be crucial to reaction success. Without a base, the reaction did not take place.

(20) Adding a catalytic amount of DMAP we have detected an increased reaction rate.

(21) The Boc protecting group was then removed by treatment with 3 M anhyd methanolic HCl, to yield the guanidine as the HCl salt in 96% isolated yield.

(22) The ability to use only 0.33 equiv of the TCT as guanylating agent is advantageous since it minimizes reagent consumption and byproduct generation compared to the Mukaiyama reagent and *S*-methylisothioureas derivatives. Moreover our method does not give off toxic gaseous side product such as methyl mercaptan that is generated using *N*,*N*′′-bis-Boc-*S*-methylisotiourea as guanylating reagent (see ref. 10a–c).

(23) **Representative Procedure for the Synthesis of *N*,*N*′′-Di-Boc-protected Guanidines: *N*,*N*′-Bis(*tert*-butoxycarbonyl)-*N*′′-benzylguanidine (3a)**
To a solution of cyanuric chloride (185 mg, 1.0 mmol) in dry THF (20 mL), *N*-methylmorpholine (303 mg, 330 μL, 3.0 mmol) was added at 0 °C under argon and with vigorous stirring. A white suspension was formed to which a solution

of the *N*,*N*′-di-Boc-thiourea 1 (830 mg, 3.0 mmol) and *N*-methylmorpholine (606 mg, 660 μL) in anhydrous THF (20 mL) was added, and the stirring was continued at reflux temperature for 12 h. The slurry was cooled to r.t. and to this mixture, benzylamine **2a** (482 mg, 491 μL, 4.5 mmol) and DMAP (10 mg) were added, and the stirring was run for additional 8 h at r.t. The reaction was judged to be complete by TLC analysis. After completion of the reaction, solid material was collected by suction, followed by successive washing with a minimal amount of THF, and the filtrates were combined and concentrated. The residue was dissolved in CH_2Cl_2, and the resulting solution was washed successively with H_2O, HCl (1 N), $NaHCO_3$ (sat. solution), and then with brine. The organic layer was dried over anhyd Na_2SO_4, passed through short a silica gel column (hexane–EtOAc = 8:2), and the solvent removed under reduced pressure to give **3a** (1.0 g, 95%) pure as an off-white solid; mp 125–126 °C [lit.:[7b] mp 126–127 °C]. TLC: R_f = 0.46 (hexane–EtOAc = 8:2). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.47 (s, 9 H), 1.51 (s, 9 H), 4.59 (d, *J* = 5.2 Hz, 2 H), 7.20–7.39 (m, 5 H), 8.43 (br s, 1 H), 11.41 (br s, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.9, 28.3, 44.9, 80.5, 82.9, 127.8, 128.2, 129.0, 137.2, 152.9, 156.4, 163.4. ESI-HRMS: *m/z* $[M + H]^+$ calcd for $C_{18}H_{28}N_3O_4$: 350.2080; found: 350.2092. Anal. Calcd for $C_{18}H_{27}N_3O_4$: C, 61,87; H, 7,79; N, 12,03. Found: C, 61.71; H, 7.95, N, 11.92.

(24) The triazine ring is weakly basic therefore a dilute acid wash is able to remove any byproduct as well as any excess reagent from the reaction mixture. *Reagents for High-Throughput Solid-Phase Organic Synthesis,* In *Handbook of Reagents for Organic Synthesis*; Wipf, P., Ed.; Wiley: Sussex, **1999**, 72–74.

(25) Performing the model reaction in CH_2Cl_2 we have recovered the desired protected guanidine **3a** in very low yields (<5%).

(26) TCT react DMF to give an insoluble Vilsmeier–Haack-type specie, which precipitates: De Luca, L.; Giacomelli, G.; Porcheddu, A. *Org. Lett.* **2002**, *4*, 553; under these conditions, we observed a partial removal of Boc-protective group, and the formation of several side products in the crude reaction mixture..

(27) Unchanged reagents were present still after 36 h at r.t.

(28) All the analytical data are consistent with those described in the literature.

(29) Identified by matching all the analytical data with those described in literature, see: Balakrishnan, S.; Zhao, C.; Zondlo, N. J. *J. Org. Chem.* **2007**, *72*, 9834.

(30) In the reaction of TCT/di-Boc-thiourea **1** with phenylalanine methyl esther **2o**, we have not observed significant racemization of the stereogenic center as revealed by the optical rotation value of the products **3o** if compared with that reported in the literature (ref. 29).

(31) (a) Ho, K.-C.; Sun, C. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1517. (b) See also ref. 5c.

(32) The exact intermediates for this TCT-promoted guanylating reaction formation are unknown.