



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

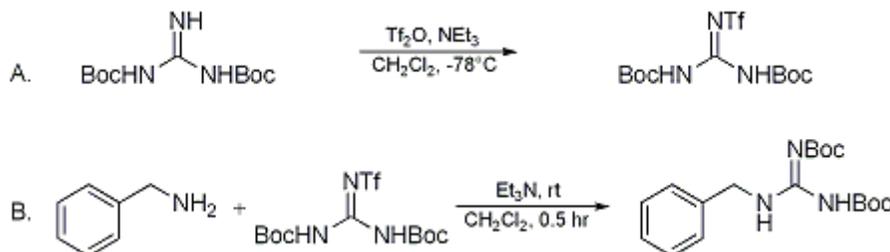
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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PREPARATION AND USE OF *N,N'*-DI-BOC-*N''*-TRIFLYLGUANIDINE

[Carbamic acid, [[(trifluoromethyl)sulfonyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester]



Submitted by Tracy J. Baker, Mika Tomioka, and Murray Goodman¹.
Checked by Dustin J. Mergott and William R. Roush.

1. Procedure

A. N,N'-di-Boc-*N''*-triflylguanidine. A 250-mL, two-necked, round-bottomed flask equipped with a 10-mL pressure-equalizing dropping funnel sealed with a rubber septum, gas inlet, and a large football-shaped Teflon-coated magnetic stirring bar is purged with nitrogen (Note 1). The flask is charged with *N,N'*-di-Boc-guanidine (7.5 g, 29 mmol, Note 2), dichloromethane (100 mL, Note 3), and triethylamine (5.0 mL, 36 mmol, Note 4). The temperature of the mixture is equilibrated to -78°C using a dry ice/isopropyl alcohol bath. Triflic anhydride (5.9 mL, 35 mmol, Note 5) is added dropwise through the dropping funnel over a period of 20 min, and the resulting mixture is allowed to warm to -20°C over 4 hr (Notes 6, 7). A 2 M aqueous sodium bisulfate solution is added to the mixture at -20°C , such that the reaction temperature does not rise above -10°C , and the resulting layers are stirred vigorously for 5 min (longer stir times lead to decreased yields). The layers are immediately separated, and the aqueous phase is extracted with dichloromethane (3×50 mL). The combined organic layers are washed with 2 M aqueous sodium bisulfate (80 mL), brine (50 mL), dried (MgSO_4), filtered and concentrated under reduced pressure. The crude material is purified by flash column chromatography (Note 8) and dried under reduced pressure to afford *N,N'*-di-Boc-*N''*-triflylguanidine (10 g, 90%, mp 124°C , Notes 9, 10).

B. N,N'-Bis(*tert*-butoxycarbonyl)-*N''*-benzylguanidine. An oven-dried, 50-mL, round-bottomed flask equipped with a magnetic stirring bar is charged with *N,N'*-di-Boc-*N''*-triflylguanidine (1.00 g, 2.55 mmol) and dichloromethane (13 mL, Notes 11, 12). Benzylamine (0.31 mL, 2.8 mmol, Note 13) is added in one portion via syringe at room temperature. After 30 min, the mixture is transferred to a 60-mL separatory funnel and washed with 2 M aqueous sodium bisulfate (10 mL) and saturated sodium bicarbonate (10 mL). Each aqueous layer is extracted with dichloromethane (2×10 mL). The combined organic phases are washed with brine (10 mL), dried (MgSO_4), filtered and concentrated under reduced pressure to afford *N,N'*-di-Boc-*N''*-benzylguanidine in quantitative yield (0.89 g, Notes 14, 15).

2. Notes

- All glassware was flame-dried and cooled in a desiccator charged with anhydrous calcium sulfate. Once completely cooled, the glassware was quickly assembled and purged with nitrogen.
- N,N'*-di-Boc-guanidine [1,3-bis(*tert*-butoxycarbonyl)guanidine, 98%] was purchased from Aldrich Chemical Company, Inc. (catalog #: 49,687-1) and used as received. Alternatively, *N,N'*-di-Boc-guanidine can be easily synthesized from guanidine hydrochloride and di-*tert*-butyl dicarbonate according to the literature procedure.²
- Dichloromethane (Fisher Scientific Company) was predried with calcium chloride and freshly distilled under argon from calcium hydride prior to use.

4. Triethylamine (Aldrich Chemical Company, Inc.) was predried with potassium hydroxide and freshly distilled under argon from calcium hydride prior to use.
5. Triflic anhydride (trifluoromethanesulfonic anhydride, ϵ 98%) was purchased from Fluka Chemika and used as received.
6. The reaction mixture turned yellow-orange upon addition of triflic anhydride.
7. The submitters allowed the reaction to warm to -5°C prior to quenching with bisulfate solution, and obtained the product in 90% yield. They noted that if the reaction mixture was allowed to warm above -5°C or stir longer than 4 hr, N,N'-di-Boc-N"-triflylguanidine degrades to N-mono-Boc-N"-triflylguanidine. The checkers obtained yields of 71-85% when this procedure was followed exactly. However, if the reaction was quenched at -20°C , with care not to allow the internal temperature to rise above -10°C during the quench or to stir longer than 5 min following the quench, the checkers obtained yields of 93-96%.
8. A column (5 cm in diameter) of silica gel (J. T. Baker, 233-400 mesh, 250 g, dry-packed) was equilibrated with 20% hexanes in dichloromethane. The crude material dissolved in a minimal amount of chloroform was loaded on the column and eluted with 20% hexanes in dichloromethane. Fractions were collected in 15×160 mm test tubes.
9. The compound has the following characteristics: ^1H NMR (0.6 M, DMSO- d_6 ; 500 MHz) δ : 1.46 (s, 18 H, CH_3), 11.06 (br s, 2 H, NH) ; ^{13}C NMR (0.6 M, DMSO- d_6 ; 125 MHz) δ : 27.5 (6C), 83.4 (2C), 119.1 (q, $J_{\text{CF}} = 320$ Hz), 150.1 (2C), 152.3 ; IR (neat film/NaCl plate) cm^{-1} : 1202, 1343, 1557, 1622, 1739, 1788, 3300 ; FAB-MS m/z (relative intensity) 414 (M+Na) $^+$, 392 (M+H) $^+$, 336, 280, 236 . Anal. Calcd for $\text{C}_{12}\text{H}_{20}\text{F}_3\text{N}_3\text{O}_6\text{S}$: C, 36.83; H, 5.15; N, 10.74; F, 14.56; S, 8.19. Found: C, 36.93; H, 5.21; N, 10.66; F, 14.80; S, 8.33.
10. The submitters report that the production scale of N,N'-di-Boc-N"-triflylguanidine can be increased ten-fold as long as Note 7 is followed.
11. Reagent grade dichloromethane may be used without further purification.
12. Guanidinylation of less reactive amines may require triethylamine (1.1 eq.) freshly distilled from calcium hydride.
13. Benzylamine (Aldrich Chemical Company, Inc., 99%) is stored over potassium hydroxide and used without further purification.
14. The spectral data of N,N'-di-Boc-N"-benzylguanidine matched that reported in the literature.³ The sample has the following characteristics: ^1H NMR (CDCl_3 , 500 MHz) δ : 1.42 (s, 9 H, CH_3), 1.45 (s, 9 H, CH_3), 4.57 (d, 2 H, $J = 5.2$, CH_2 Ph), 7.21-7.20 (m, 5 H, arom.), 8.55 (br s, 1 H, NH), 11.50 (br s, 1 H, NH) ; ^{13}C NMR (CDCl_3 , 125 MHz) δ : 28.0 (3C), 28.2 (3C), 45.0, 79.3, 83.1, 127.5, 127.7 (2C), 128.7 (2C), 137.1, 153.1, 156.0, 163.5 ; IR (KBr) cm^{-1} : 1560, 1626, 1654, 1741 ; FAB-MS m/z (relative intensity) 350 (M+H) $^+$, 238, 194, 91 ; high resolution mass spectrum, calcd for $\text{C}_{18}\text{H}_{27}\text{N}_3\text{O}_4$: m/z 349.2002, found 349.1997. The product was greater than 95% pure as determined by ^1H NMR spectral analysis.
15. The production of N,N'-di-Boc-N"-benzylguanidine can be increased ten-fold or more.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

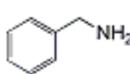
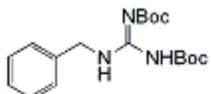
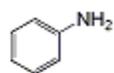
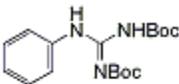
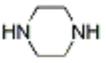
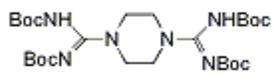
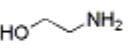
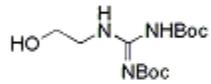
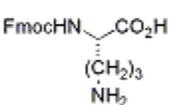
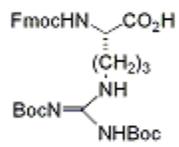
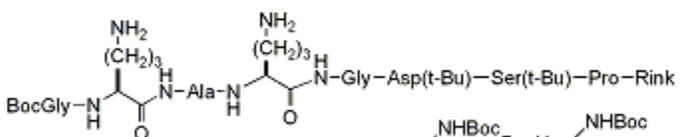
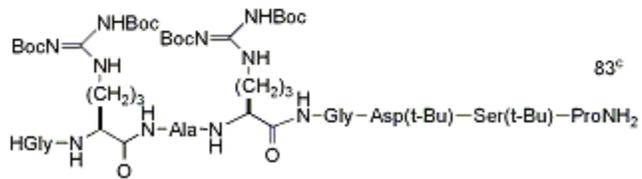
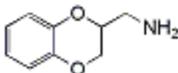
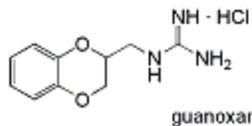
Both natural and nonnatural guanidine-containing molecules have important biological activity ranging from antimicrobial, antiviral, and antihypertensive to neurotoxic.⁴ Hence, the conversion of amines to guanidines has been a significant synthetic endeavor for many years. The present method, using N,N'-di-Boc-N"-triflylguanidine for the guanidinylation of amines is the most efficient and general approach for most applications in solution and on solid phase.^{2, 5}

To date, the most commonly used reagents for the guanidinylation of amines are derivatives of protected thioureas in the presence of the Mukaiyama reagent,³ pyrazole-1-carboxamides,⁶ and S-alkylisothiureas.⁷ Protected thioureas in conjunction with the Mukaiyama reagent have displayed the most versatile usage. This combination has been successful in the conversion of sterically demanding and resin-bound amines to protected guanidines.³ However, this method is limited to the use of highly

polar aprotic solvents such as dimethylformamide because of the solubility properties of the Mukaiyama reagent. Guanidinylations with pyrazole-1-carboxamides,⁶ and S-alkylisothioureas⁷ are sluggish in comparison to *N,N'*-di-Boc-*N''*-triflylguanidine and are incompatible with solid phase application.

The simple preparation of *N,N'*-di-Boc-*N''*-triflylguanidine from a commercially available source and its straightforward isolation make this reagent extremely attractive. Guanidinylation using *N,N'*-di-Boc-*N''*-triflylguanidine is effective for amines both in solution and on solid phase.^{2, 5} These reactions may be carried out in a variety of solvents with dichloromethane and chloroform being the most common; however, reaction rates slow with increase in solvent polarity. The use of protected thioureas with the Mukaiyama reagent seems to be superior for guanidinylations of sterically hindered and less reactive amines, but simple product isolation and experimental setup of the *N,N'*-di-Boc-*N''*-triflylguanidine method make this the reagent of choice for most applications. Some representative examples are compiled in the Table.^{2, 5}

TABLE
GUANIDINYLATION OF AMINES IN SOLUTION AND ON SOLID PHASE USING
N,N'-DI-BOC-*N''*-TRIFLYLGUANIDINE

Entry	Amine	Product	Yield (%)
1 ^a			100
2 ^a			89
3 ^b			100
4 ^b			100
5 ^a			82
6			83 ^c
7		 guanoxan · HCl	94 ^d

^aReference 2. ^bReference 5a. ^cTotal yield of peptide after cleavage from resin. Reference 5a.

^dTotal yield of guanoxan · HCl after guanidinylation and Boc removal. Reference 5b.

References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

N,N'-Di-Boc-N"-triflylguanidine:
N,N'-Bis(tert-butoxycarbonyl)-N"-trifluoromethanesulfonylguanidine:
Carbamic acid, [[(trifluoromethyl)sulfonyl]carbonimidoyl]bis-, bis(1,1-dimethylethyl) ester (14);
(207857-15-6)

N,N'-Di-Boc-guanidine:
1,3-Bis(tert-butoxycarbonyl)guanidine:
Carbamic acid, carbonimidolybis-, bis(1,1-dimethylethyl) ester (13); (154476-57-0)

Triflic anhydride:
Methanesulfonic acid, trifluoro-, anhydride (8,9); (358-23-6)

N,N'-Di-Boc-N"-benzylguanidine:
N,N'-Bis(tert-butoxycarbonyl)-N"-benzylguanidine:
Carbamic acid, [[(phenylmethyl)imino]methylene]bis-, bis(1,1-dimethylethyl) ester (13); (145013-06-5)

Benzylamine (8);
Benzenemethanamine (9); (100-46-9)

Guanidine hydrochloride:
Guanidine, monohydrochloride (9); (50-01-1)

Di-tert-butyl dicarbonate:
Formic acid, oxydi-, di-tert-butyl ester (8);
Dicarbonic acid, bis(1,1-dimethylethyl) ester (9); (24424-99-5)