Rapid, effective deprotection of tert-butoxycarbonyl (Boc) amino acids and peptides at high temperatures using a thermally stable Ionic Liquid.

Sumit S. Bhawal, Rahul A. Patil and Daniel W. Armstrong

Department of Chemistry and Biochemistry, The University of Texas at Arlington, 700 Planetarium Place, Arlington, Texas 76019-0065, USA. E-mail: sec4dwa@uta.edu

General

General Procedure for Experiments

NMR Spectra
**General**: Compounds were purchased in their purest commercial quality. All materials were used as obtained, unless otherwise indicated. Column chromatography for recovery of Ionic Liquid was performed using silica gel (300-400 mesh) with Hexane/EtOAc as eluent. $^1$H NMR, $^{13}$C NMR, $^{19}$F NMR and $^{31}$P NMR experiments were performed on 500 MHz a JEOL Eclipse Plus 500 instrument. Chemical shifts were recorded with reference to residual solvent peaks (D$_2$O residue = 4.79 ppm, CDCl$_3$ residue = 7.26 ppm. ESI Mass spectroscopy was performed with Thermo Finnigan LXQ linear Ion Trap mass spectrometer, when required.

![Chemical structure](image)

$R_1$= Hexyl, $R_2$ = Tetradecyl

Trihexyl tetradecyl phosphonium bis(trifluoromethane)sulfonimide (TTP-NTf$_2$)

### General Procedures for Experiments

**Preparation of TTP-NTf$_2$:** To a solution of (40 g, 77 mmol) trihexyl tetradecylphosphonium chloride, (graciously donated by CYTEC, West Paterson, NJ, USA) in methanol (20 mL) was added (24.32 g, 84.71 mmol) LiNTf$_2$. Additional methanol was added to obtain a clear solution. The solution was slightly warm at the beginning and was stirred overnight. Methanol was removed under reduced pressure and ~200 mL CH$_2$Cl$_2$ was added to the round bottom flask. The organic layer containing the ionic liquid was transferred to the separating funnel and LiCl was extracted with (3x100 mL) deionized water. The organic layer was concentrated under reduced pressure at and dried in vacuum oven (maintained at 40 °C) over P$_2$O$_5$ for at least 36 h before use. The products were characterized by $^1$H NMR, $^{13}$C NMR, $^{19}$F and $^{31}$P NMR.

![Chemical reaction](image)

$R = H, Me, iPr, iso-Bu, s-Bu, Bzl, pyrrolidine, thiomethylethyl, 1-hydroxyethyl, 3-(1H-imidazol-4-yl), 4-amino-butyl, carboxymethyl, carboxyethyl.$

**Method A (Neat Reaction in TTP-NTf$_2$)** A mixture of (0.25 g, 0.32-1.43 mmol) N-Boc protected amino acid/peptides and TTP-NTf$_2$ (7 g, 9.16 mmol) was stirred (~150 rpm) for 5-6 h at 150 °C in a round bottom flask (50 mL) equipped with a reflux condenser. Completion of reaction was monitored by TLC using ethyl acetate/methanol (95:5) and ninhydrin as staining agent. On cooling, the reaction mixture was
transferred into separating funnel with 3x10 mL (CH$_2$Cl$_2$/water 1:1). In addition, CH$_2$Cl$_2$ (100 mL) and water (50 – 80 mL, depending on the substrate) was added to the separating funnel. The layers were allowed to separate after shaking and the organic layer (containing the ionic liquid) was removed. To the aqueous layer (containing the amino acids) fresh CH$_2$Cl$_2$ (2x 75mL) was added to ensure removal of any trace of ionic liquid remaining. The aqueous layer was evaporated to dryness to obtain the product. In most of the cases, this gave us the purified amino acid, but otherwise a final washing with ~ 5 mL isopropanol (using centrifuge) proved very effective. All the products were characterized by $^1$H NMR, $^{13}$C NMR. ESI-MS was done in some cases.

The peptides were added to TTP-NTf$_2$ and heated at 120 °C for 3 h (Scheme not shown). However, incomplete conversions and product decompositions were observed (14A-16A).

Method B (TTP-NTf$_2$ and water) To a mixture of (0.25 g, 0.32-1.43 mmol) N-Boc protected amino acid/peptides and TTP-NTf$_2$ (7 g, 9.16 mmol) was added deionized water 12-14% (based on TTP.N Tf$_2$). The resulting mixture was stirred (~200 rpm) for 2.5-6 h at 150 °C (for amino acids) and 2.5 h at 110 °C (for peptides). The remaining work-up is similar to method A. All the products were characterized by $^1$H NMR, $^{13}$C NMR. ESI-MS was done in some cases.

L-Histidine and L-Lysine tends to form emulsions especially for method B. They were centrifuged for 5 min at around 5000 rpm (The Drucker Co., Model 614 B) to obtain the purified compound. For peptides, the water was generally removed at ~ 40-45 °C under reduced pressure.
Method C (TTP-\(\text{NTf}_2\) and TFA)  To a stirring mixture of (0.25 g, 0.32-1.43 mmol) N-Boc protected amino acid/peptides and TTP-\(\text{NTf}_2\) (7 g, 9.16 mmol) was added TFA (2 equiv, based on substrate). The resulting mixture was stirred (~150 rpm) for 7-10 min at 100 °C (for peptides) and 130 °C (for amino acids). The remaining procedure is similar to method A.

For peptides, the water was removed by either freeze drying or simply air drying at higher flow using an inverted funnel at room temperature. All the products were characterized by \(^1\text{H NMR}, \ ^{13}\text{C NMR}. \) ESI-MS was done in some cases.
**TTP-NTf₂**

Trihexyl tetradecyl phosphonium bis(trifluoromethane)sulfonimide
TTP-NTf₂\textsubscript{2} carbon

Trihexyl tetradecyl phosphonium bis(trifluoromethane)sulfonimide
TTP-NTf₂\(^{31}\)P

Trihexyl(tetradecyl)phosphonium bis(trifluoromethane)sulfonimide
TTP-NTf₂-¹⁹F

Triethyl tetradecyl phosphonium bis(trifluoromethane)sulfonimide

X : parts per Million : 19F
TTP-NTf₂ (Recovered)

TTP-NTf₂

Trihexyl tetradecyl phosphonium bis(trifluoromethane) sulfonimide
H₂N⁻\text{CO₂H}

Gly (Neat)
H₂N\(\text{C}O₂\text{H}\)

Gly (Neat)
H₂N(CONH₂)₂ Al (Neat)
Val (Neat)

$\text{H}_2\text{N} - \text{CO}_2\text{H}$

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X : parts per Million : 1H
Val (Neat)

H₂N

CO₂H

3A
H₂N
\[
\text{Leu (Neat)}
\]
H$_2$N\(\text{CO}_2\text{H}\)

Ile (Neat)

$\text{X : parts per Million : } 1\text{H}$
Phe (Neat)
Asp (Neat)
H₂N
CO₂H
Gly (Water)
Gly (Water)
2B

H₂N  CO₂H
Ala (Water)
H₂N\text{--}\text{CO}_2\text{H}

Ala (Water)
H$_2$N$\text{CO}_2$H
Leu (Water)
H$_2$NCO$_2$H

Ile (Water)
Pro (Water)
PRO (Water)
Met (Water)

**SMBetWC-2.jdf**

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Thr (Water)
H₂N
CO₂H

Thr (Water)
10B

H₂N-CO₂H
His (Water)
Lys (Water)
Asp (Water)

\[ CO_2H \]

\[ H_2N \]

\[ CO_2H \]
Asp (Water)
H-Ala-Ala-OH (water)
**H-Gly-Val-OH (water)**

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X : parts per Million : 1H
H-Gly-Val-OH (water)
SBTRIEP-3.jdf

16 B

H-Gly-His-Lys-OH (water)
H-Gly-His-Lys-OH (water)
$\text{H}_2\text{N} - \text{CO}_2\text{H}$

Ala.TFA

X : parts per Million : 1H
2C
H₂N – CO₂H
Ala, TFA

220.0 210.0 200.0 190.0 180.0 170.0 160.0 150.0 140.0 130.0 120.0 110.0 100.0 90.0 80.0 70.0 60.0 50.0 40.0 30.0 20.0 10.0 0 -10.0 -20.0

X : parts per Million : 13C
Val-TFA

X: parts per Million: 13C
Pro TFA

7C

HN
CO2H

X : parts per Million : 1H
7C

\begin{align*}
\text{HN} & \quad \text{CO}_2\text{H} \\
\text{Pro.TFA} & \\
\text{13C} & 
\end{align*}

X : parts per Million : 13C
Thr. TFA

\[ \text{OH} \]
\[ \text{H}_2\text{N}^- \text{CO}_2\text{H} \]
H-Ala-Ala-OH. TFA
H-Ala-Ala-OH, TFA
15C

H-Gly-Val-OH, TFA

X : parts per Million : 13C
H-Gly-His-Lys-OH, TFA