Applications of the *N*-*tert*-Butylsulfonyl (Bus) Protecting Group in Amino Acid and Peptide Chemistry

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Dedicated to Professor Steven Weinreb for his scholarly contributions to organic chemistry

Abstract: The utility of the *tert*-butylsulfonyl group (Bus) for the temporary protection of amino acids and peptides is reported. Compatibility and orthogonality in the presence of other N- and O-protecting groups were studied.

Key words: *tert*-butylsulfonyl group, amino-group protection, amino acids, orthogonal N-protection

N-Protecting groups are of primary importance in the utilization of amino acids and organic molecules containing amino groups in synthesis.[1] Among the more popular N-protecting groups that can also benefit from an orthogonal deprotection strategy are the *N*-Boc, *N*-Cbz, and *N*-Fmoc groups. With the exception of the *N*-*o*-nitrophenylsulfonyl group introduced by Fukuyama,[2] other commonly available sulfonamides are not as versatile, due to the harsh conditions required for their removal. In 1997 Sun and Weinreb[3] reported the use of the *N*-*tert*-butylsulfonyl group as a new protecting group for amines. Their preparation consisted of a two-step procedure involving reaction of an amine with the commercially available *tert*-butylsulfinyl chloride, followed by oxidation of the resulting sulfinamide with a variety of oxidants to give the corresponding *tert*-butylsulfonamides in excellent overall yield. Sun and Weinreb also showed that the *N*-Bus group could be cleaved with TFA/anisole at room temperature to regenerate the amine salt in good yields.

Only limited use has been made of this versatile N-protecting group since its initial report in 1997. For example, Sharpless and coworkers[4] have shown that *tert*-butyl sulfonamide is an effective nitrogen source for catalytic aminohydroxylation and aziridination of olefins. The resulting *N*-Bus products could be cleaved to the corresponding amino alcohols and aziridines, respectively. Other applications have involved addition reactions to *N*-Bus imines[5,6] and lithiation–electrophile trapping of terminal *N*-Bus aziridines and related applications.[7] The regioselective opening of an aziridine intermediate with $CeCl_3$ during the total synthesis of chlorodysinosin A[8] was only possible with the *N*-Bus protection. Other sulfonamides led to mixture of chloro products.

Surprisingly, the utility of the *N*-Bus protecting group has not been systematically explored in amino acid and peptide chemistry. We report herein our efforts in the preparation a variety of *N*-Bus derivatives of common amino acids and peptides. We further show the combination of *N*-Bus and other common N-protecting groups, and the prospects of performing orthogonal deprotections. The results for the formation and cleavage of the *N*-Bus amino acid esters are shown in Table 1 (compounds **3a**–**g**).

We next studied the formation and cleavage of *N*-Bus derivatives of functionalized amino acids (Table 2, **5a**–**f**). Selective deprotection of *N*-Boc, *N*-Cbz, *N*-Fmoc, and benzyl ethers groups could be achieved in the presence of the *N*-Bus group (Table 2, **6a**–**f**). However, deprotection of the *N*-Bus group with TfOH in CH_2Cl_2 also cleaved *N*-Boc, *N*-Cbz, and benzyl ether groups (Table 2, **5a**–**e**). The *N*-Fmoc group was not affected under the conditions of deprotection (Table 2, **6g**).

The formation and cleavage of *N*-Bus dipeptides containing other N-protecting groups is shown in Scheme 1. L-Proline methyl ester was coupled to *N*-Bus-*O*-Bn-L-Ser (**7**) and *N*-Bus-*O*-Bn-L-Tyr (**8**), respectively, and the products were hydrogenated to the dipeptides **11** and **12**. Similar coupling with N^6-Boc-L-Lys-OMe led to the dipeptides **13** and **14**. Hydrogenolysis of the benzyl ether or deprotection of the *N*-Boc gave **15**–**18**. Dipeptides **21**–**24** were prepared from N^6-Boc (or Cbz)-L-Lys-OMe by coupling with *N*-Bus-L-Ala-OH and *N*-Bus-L-Phe-OH (**19** and **20**). Selective cleavage of the N^6-Boc or N^6-Cbz group with TFA/CH_2Cl_2 or hydrogenolysis gave **25** and **26**, respectively. The same sequence was also achieved with *N*-Bus-D-Ala-OH and *N*-Bus-D-Phe-OH to give **29**–**34** in essentially identical yields.

Orthogonal deprotections in the tripeptide series are shown in Scheme 2. Thus *N*-Bus-L-Pro-OMe (**35**) was hydrolyzed to the acid **36**, then coupled with N^6-Cbz-L-Lys-OMe to give **37**. Hydrolysis to the acid **38**, followed by coupling with N^6-Boc-L-Lys-OMe afforded **39**, which was subjected to hydrogenolysis to give **40**. Subsequent treatment with methanolic HCl gave **41**. Alternatively cleavage of the N^6-Boc group in **39** with TFA/CH_2Cl_2 gave **42**. Finally, global deprotection of *N*-Bus, *N*-Boc, and *N*-Cbz groups in **39** could be achieved to give the tripeptide methyl ester **43** in excellent yield.

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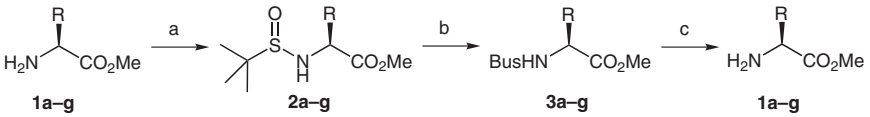
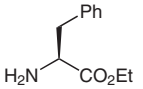
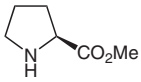
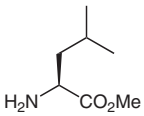
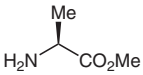
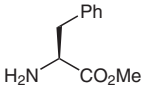
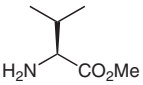
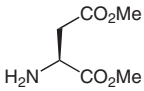
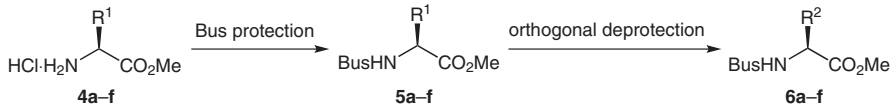
Table 1 Formation and Cleavage for *N*-Bus Amino Acid Esters[a]



Entry	Compound	*N*-Bus formation[c]		*N*-Bus cleavage	
		Compound	Yield (%)[b]	Compound	Yield (%)[b,d]
1		**3a**	84	**1a**	89
2		**3b**	82	**1b**	90
3		**3c**	82	**1c**	79
4		**3d**	77	**1d**	85
5		**3e**	88	**1e**	85
6		**3f**	77	**1f**	85
7		**3g**	72	**1g**	84

[a] *Reaction conditions*: a) *tert*-butylsulfinyl chloride, Et_3N, CH_2Cl_2, 0 °C, 1 h; b) MCPBA, CH_2Cl_2, r.t., 1 h; c) TfOH, CH_2Cl_2, anisole, 0 °C, 10 h.
[b] Yields of isolated pure product.
[c] Total yields over two steps.
[d] Enantiomeric purities were checked by HPLC and $^1H/^{19}F$ NMR spectra of Mosher amides.

Table 2 Formation and Cleavage of Functionalized Amino Acid Esters



R^1 = N-protected amino acid, R^2 = N-unprotected amino acid

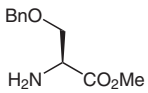
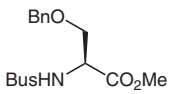
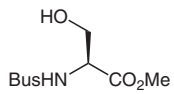
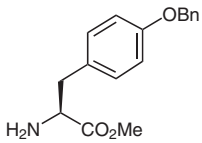
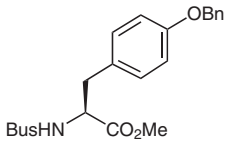
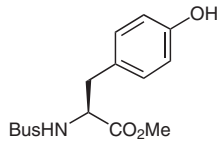
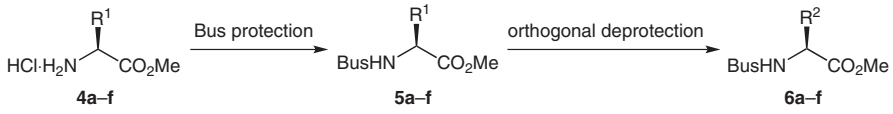
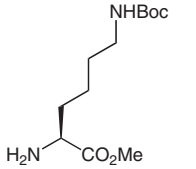
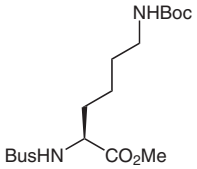
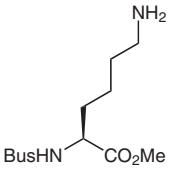
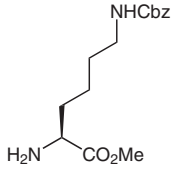
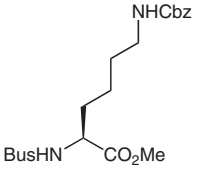
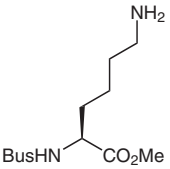
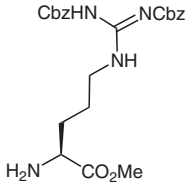
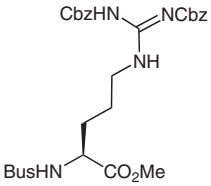
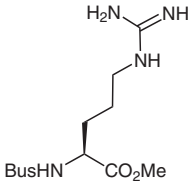
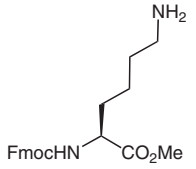
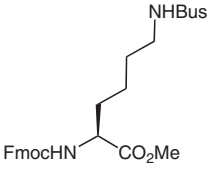
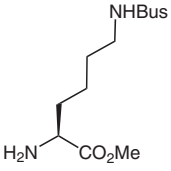
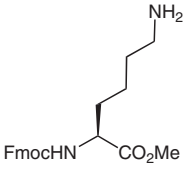
Entry	Compound		Bus formation			Orthogonal cleavage	
			Compound	Yield (%)[a]		Compound	Yield (%)[a]
1	**4a**		**5a**		78	**6a**	 97[b]
2	**4b**		**5b**		80	**6b**	 97[b]

Table 2 Formation and Cleavage of Functionalized Amino Acid Esters (continued)



4a–f **5a–f** **6a–f**

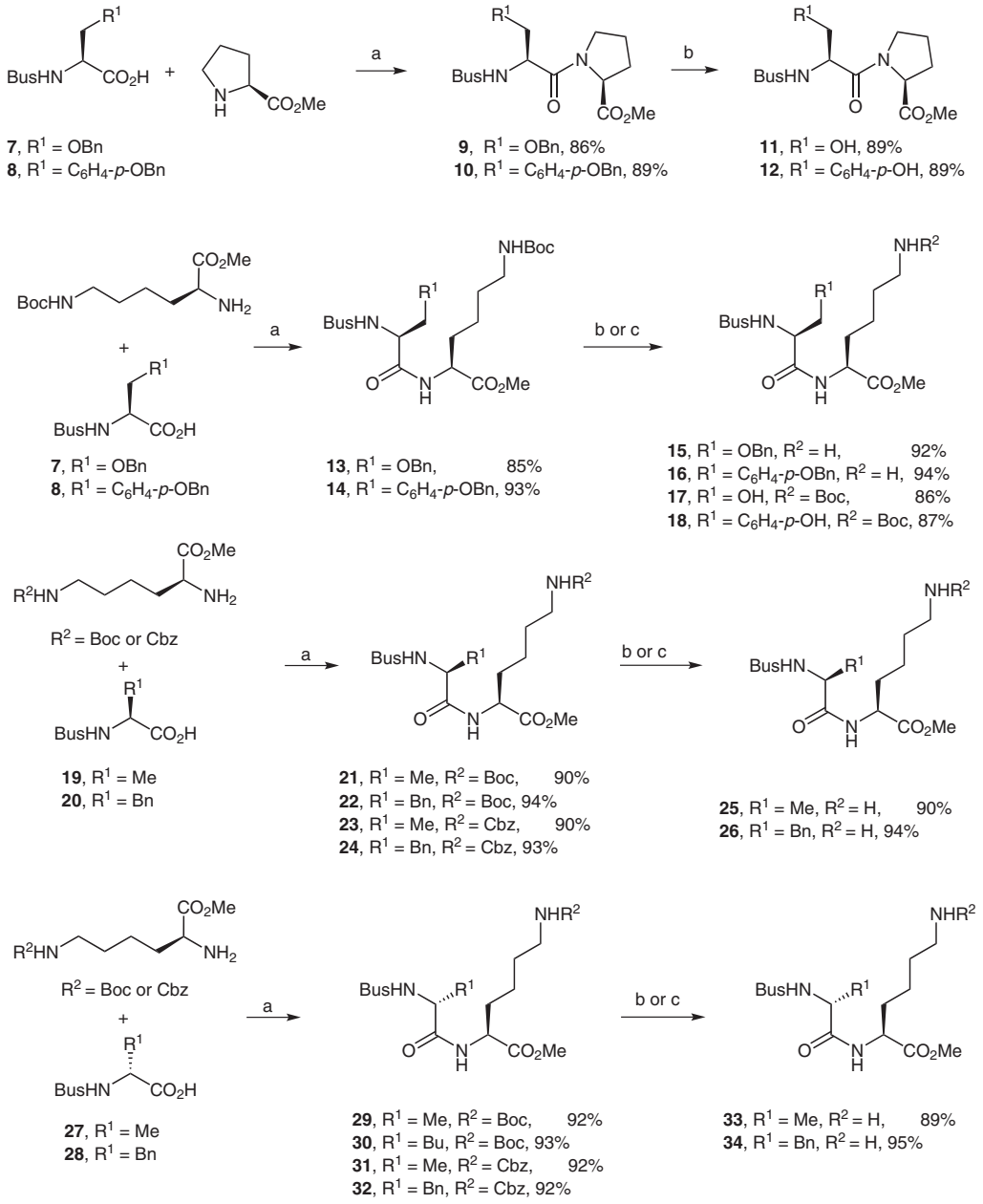
R^1 = N-protected amino acid, R^2 = N-unprotected amino acid

Entry	Compound		Bus formation			Orthogonal cleavage		
			Compound		Yield (%)[a]	Compound		Yield (%)[a]
3	**4c**		**5c**		80	**6c**		97[c]
4	**4d**		**5d**		76	**6d**		97[b]
5	**4e**		**5e**		76	**6e**		95[b]
6	**4f**		**5f**		81	**6f**		92[d]
						6g		89[e]

[a] Yields of isolated pure product.
[b] Conditions: 20% wt% $Pd(OH)_2$, H_2, MeOH, r.t., 2–3 h.
[c] Conditions: 5 equiv TFA, CH_2Cl_2, r.t., 8 h.
[d] Conditions: piperidine (5 mol%), DMF, r.t., 8 h.
[e] Conditions: TfOH, CH_2Cl_2, anisole, 4 °C, 6 h.

In conclusion, protection of amino groups as *N*-Bus sulfonamides in amino acid and peptide chemistry can be achieved in a two-step procedure involving reaction of the amine with the commercially available *tert*-butylsulfinyl chloride, followed by oxidation of the resulting sulfinamide in excellent overall yields. The *N*-Bus group can be cleaved to regenerate the corresponding amine in 0.1 N TfOH–CH_2Cl_2–anisole at 0 °C for 10 hours.

A variety of *N*-Bus-protected amino acids in conjunction with other protecting groups can be used to form dipeptides and tripeptides. Our studies show that the original conditions[3] required for the *N*-Bus-group cleavage, also cleaved the *N*-Boc, *N*-Cbz, and *O*-Bn groups. The *N*-Fmoc is stable during the deprotection of the *N*-Bus derivatives to regenerate the corresponding amine with an excellent yield. Selective and orthogonal deprotection of *N*-Boc, *N*-Cbz, *N*-Fmoc, and *O*-Bn groups and methyl esters could be achieved in the presence of the *N*-Bus protecting group without detectable racemization.[9–11] Based on these observations, the *N*-Bus group should find extensive utility in amino acid and peptide chemistry.



Scheme 1 *Reagents and conditions*: a) EDC, HOBt, 2,6-lutidine, DMF–CH_2Cl_2 (1:4), r.t., 4 h; b) 20% wt% $Pd(OH)_2$/C, H_2, MeOH, r.t., 1 h; TFA–CH_2Cl_2 (1:10), r.t., 4 h.

References and Notes

(1) (a) Llobet, A. I.; Alvarez, M.; Albericio, F. *Chem. Rev.* **2009**, *109*, 2455. (b) Ribiere, P.; Declerck, V.; Martinez, J.; Lamaty, F. *Chem. Rev.* **2006**, *106*, 2249. See also: (c) Kocienski, P. J. *Protecting Groups*; Thieme: New York, **2000**. (d) Greene, T. W.; Wuts, P. G. M. *Protecting Groups in Organic Synthesis*; J. Wiley and Sons: New York, **1999**.

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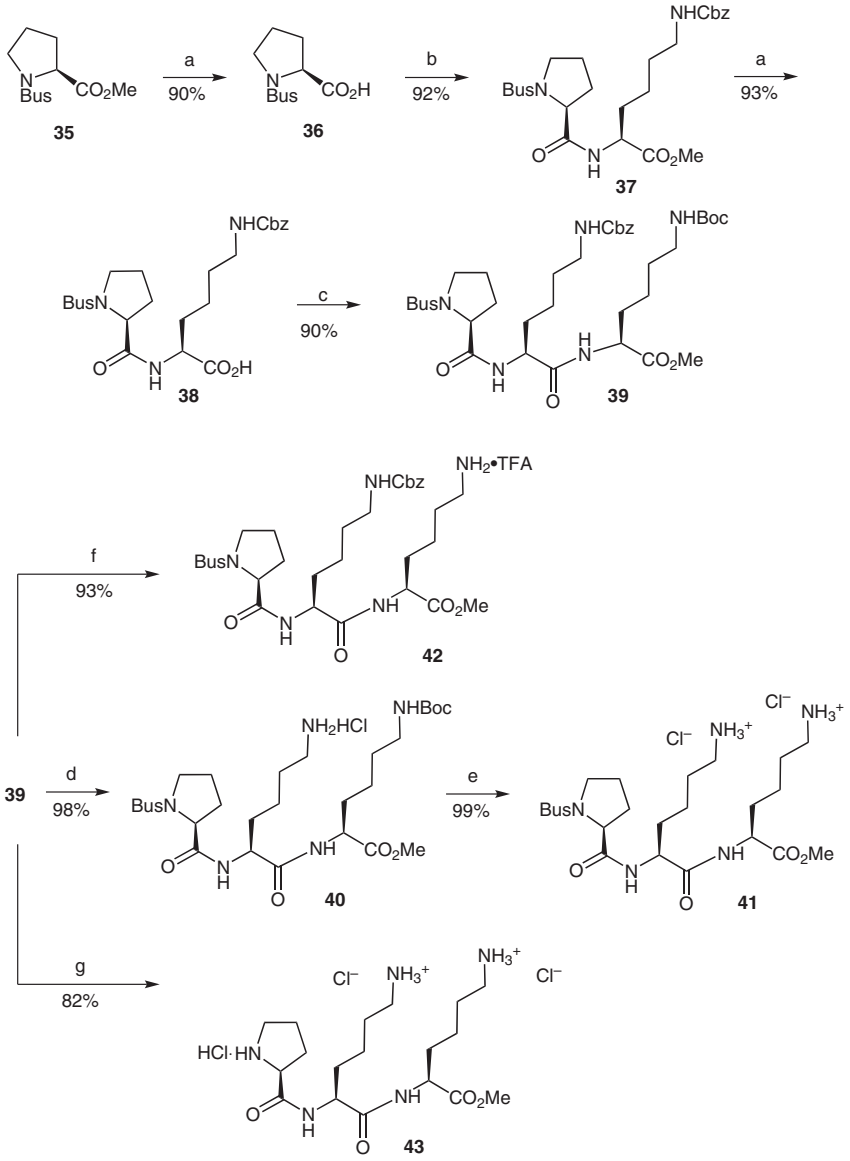
(9) **General Procedure for the Formation of *tert*-Butylsulfonamides**
A solution of L-phenylanine ethyl ester hydrochloride (**1a**, 58 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was cooled to 0 °C and treated with Et_3N (0.35 mL, 2.5 mmol), followed by dropwise addition of *tert*-butylsulfinyl chloride (62 μL, 0.5



Scheme 2 *Reagents and conditions*: a) $LiOH·H_2O$, $MeOH–H_2O$, 4 °C, 10 h; b) N^6-Cbz-L-lysine methyl ester, 2,6-lutidine, EDC, HOBt, $DMF–CH_2Cl_2$ (1:4), r.t., 4 h; c) N^6-Boc-L-lysine methyl ester, EDC, 2,6-lutidine, HOBt, r.t., $DMF–CH_2Cl_2$ (1:4), 4 h; d) H_2, 20% wt% $Pd(OH)_2$/C, MeOH, r.t., 1 h; e) 1.25 M HCl, MeOH, r.t., 4 h; f) $TFA–CH_2Cl_2$ (1:10), r.t., 4 h; g) CF_3SO_3H, CH_2Cl_2, anisole, 0 °C, 12 h.

mmol) in CH_2Cl_2 (1 mL). The reaction mixture was stirred at 0 °C until TLC showed consumption of the starting material (1 h). Upon completion, sat. aq $NaHCO_3$ (5 mL) were added, and the layers separated (note: acidic washes should be avoided as *tert*-butylsulfinamides **2a** are known to be unstable at low pH). The organic layer was then dried over Na_2SO_4 and concentrated under reduced pressure. Flash column chromatography (EtOAc–hexane, 3:2) afforded pure sulfinamide **2a** which was directly taken up in CH_2Cl_2 (5 mL), and treated with MCPBA (58 mg, 0.34 mmol) at 0 °C. After the oxidation was complete by TLC (at r.t. for 1 h), the mixture was diluted with a mixture of sat. aq $NaHCO_3$ (5 mL) and sat. aq Na_2SO_3 (5 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic extracts were combined, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–hexane, 1:1) to afford *tert*-butylsulfonyl-L-phenylalanine ethyl ester (**3a**, 66 mg, 84% over 2 steps) as a colorless solid.

(10) **General Procedure for the Cleavage of *tert*-Butylsulfonamides**

To a solution of anisole (0.22 mL, 2.0 mmol) and *tert*-butylsulfonyl-L-alanine methyl ester (**3d**, 45 mg, 0.2 mmol) in CH_2Cl_2 (3 mL) was slowly added TfOH (0.2 N in CH_2Cl_2, 3 mL) at 0 °C. The solution was stirred at 0 °C for 2 h, then warmed to 4 °C for 10 h (TLC monitoring, EtOAc–hexane, 2:3), then H_2O (6 mL) was added. The aqueous layer was neutralized with DOWEX Monosphere 550A (OH^- form) anion-exchange resin at 0 °C until pH 8.5, then MeOH (6 mL) was added, and the resin was filtered. The filtrate was combined and acidified with aq 1 M HCl (3 mL). The aqueous layer was frozen and lyophilized to afford L-alanine methyl ester hydrochloride salt(**1d**) (24 mg, 85%), as a colorless oil.

(11) Enantiomeric and diastereomeric purities were determined by HPLC and $^{1}H/^{19}F$ NMR spectra of Mosher amides. For example: Mosher amides: phenylalanine (de >99.9%) and alanine (de >99.9%) Column: AD-RH 150 × 4.6 mm; dipeptides: **21** (de >99.9%), **22** (de >99.9%), **29** (de >99.9%), and **30** (de = 99.86%), column: AS-RH 150 × 4.6 mm; **23** (de = 95.66%) and **31** (de = 96.24%), column: OJ-R 150 × 4.6 mm; **23** (de = 95.50%) and **31** (de = 92.22%), column: C-18 250 × 4.6 mm.