Useful Reagents for Introduction of Boc and Fmoc Protective Groups to Amines: Boc-DMT and Fmoc-DMT

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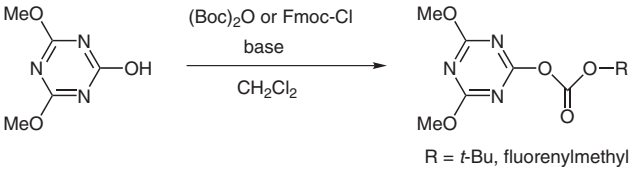
Abstract: New amino-protecting reagents, Boc-DMT and Fmoc-DMT, were prepared, and found to be useful for the introduction of Boc and Fmoc groups into amines. Both the reagents can protect various amines including amino acids in good yield in aqueous media. Since the reagents are neither unstable nor irritating, they are practically useful.

Key words: protecting groups, amines, amino acids, triazine, active carbonate ester



Scheme 1 Preparation of the N-protecting reagents containing the dimethoxytriazinyloxy group.

Recently we have introduced a novel N-protecting reagent, benzyl 4,6-dimethoxy-1,3,5-triazinyl carbonate (Z-DMT), which features a 4,6-dimethoxy-1,3,5-triazinyloxy moiety as the leaving group.[1] This reagent was developed based on the property of 2-acyloxy-4,6-dimethoxy-1,3,5-triazine, which exclusively undergoes aminolysis over methanolysis, even in methanol, as shown in dehydrocondensing reactions using 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM).[2] Various amines were protected using Z-DMT in high yields in protic solvents such as water, methanol, and their mixture, without racemization and dimerization, which are common problems observed in reactions using benzyl chloroformate (Z-Cl).[3] Furthermore, storage and handling of Z-DMT are easy, since it is non-irritating and more stable than Z-Cl. Because the reagent can be prepared by reusing 4,6-dimethoxy-1,3,5-triazin-2-ol (HO-DMT), a co-product of the condensation reaction using DMT-MM, our methodology is desirable from both environmental and economic perspectives.[4,5] In this paper, we describe the preparation of *tert*-butyl 4,6-dimethoxy-1,3,5-triazinyl carbonate (Boc-DMT; Scheme 1) and 9-fluorenylmethyl 4,6-dimethoxy-1,3,5-triazinyl carbonate (Fmoc-DMT; Scheme 1), and their usefulness as N-protecting reagents having similar characteristics as that of Z-DMT.

Boc-DMT was obtained in 68% yield as a colorless oil by treatment of HO-DMT with di-*tert*-butyl dicarbonate in dichloromethane in the presence of a catalytic amount of pyridine. The reagent is soluble in common organic solvents, such as hexane, tetrahydrofuran, acetonitrile, and methanol, but insoluble in water. As a note, the reagent can be stored over a year in a refrigerator without noticeable decomposition. Based on the reaction yields, the use of polar solvents such as methanol and acetonitrile is preferable to tetrahydrofuran for the N-protection of several aliphatic amines with Boc-DMT. The reaction with amino acid esters in methanol, which is cheaper than acetonitrile, afforded the desired products in good yields. The reactions of free amino acids were carried out in methanol–water mixtures due to the low solubility of the substrates in methanol. As shown in Table 1, all reactions were complete within an hour to afford the products in good yields.

Fmoc-DMT was obtained in 95% yield as colorless crystals by treatment of HO-DMT with 9-fluorenylmethyl chloroformate in dichloromethane in the presence of triethylamine. The reagent was found to be stable for over a year at room temperature. Although Fmoc-DMT was slightly soluble in methanol (9.5 mM), the N-protecting reactions of several amines were carried out in methanol using a suspension of Fmoc-DMT to afford the desired products in good yield within 30 minutes. However we employed acetonitrile as a solvent because the solubility of Fmoc-DMT in acetonitrile at 25 °C (331 mM) is higher than that in methanol. In the case of free amino acids, which are difficult to dissolve in acetonitrile, the use of acetonitrile–water mixtures was found to be effective. As shown in Table 1, all of the substrates were readily protected in good yields.

In summary, we have described the usefulness of two novel N-protecting reagents, Boc-DMT and Fmoc-DMT, which feature the leaving ability of a triazinyloxy group. Protecting reactions by Boc-DMT and Fmoc-DMT were completed in relatively short times (15–60 min) in aqueous media without detectable side-reactions such as dimerization and racemization.[3]

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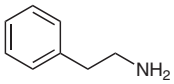
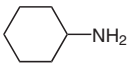
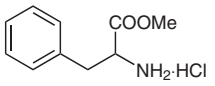
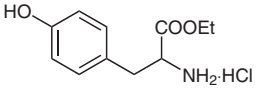
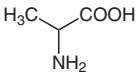
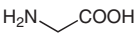
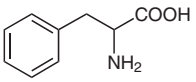
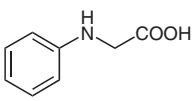
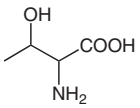
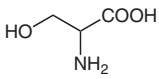
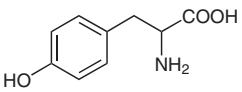
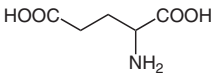
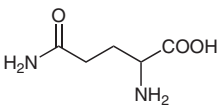
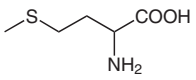
Table 1 N-Protection Reactions of Boc-DMT and Fmoc-DMT

Amine	Boc-DMT[a]			Fmoc-DMT[b]		
	Solvent[c]	Time (min)	Yield (%)[d]	Solvent[c]	Time (min)	Yield (%)[d]
	MeCN	15	91	aq MeCN	40	94
	THF MeOH MeCN	60 60 15	58[e] 73 85	aq MeCN	15	88
	THF MeCN	60 15	78[e] 98	aq MeCN	30	92
	MeOH	30	89	MeOH	30	97
	MeOH	15	91 (96)	aq MeCN	15	99
	aq MeOH	30	98	aq MeCN	75	96
	aq MeOH	30	85[f]	aq MeCN	20	96
	aq MeOH	30	88	aq MeCN	30	92
	aq MeOH	30	92	aq MeCN	65	94
	aq MeOH	30	85	aq MeCN	30	92
	aq MeOH	30	82	aq MeCN	40	89
	aq MeOH	60	79	aq MeCN	35	74
	aq MeOH	60	80 (91)	aq MeCN	75	99
	aq MeOH	60	74 (92)	aq MeCN	30	79
	aq MeOH	30	98	aq MeCN	60	94

[a] Reagent (1.5 equiv), unless noted otherwise.
[b] Reagent (1.2 equiv).
[c] aq MeOH and aq MeCN represent a mixture of H_2O–MeOH (1:1) and H_2O–MeCN (1:2), respectively.
[d] Isolated yields. The yield determined by NMR is shown in parentheses.
[e] Reagent (1.1 equiv).
[f] Reagent (2.0 equiv).

HO-DMT was prepared according to our procedures, as previously described.[4] Other chemicals and solvents were obtained from commercial sources and were used without further purifications. ^{1}H NMR spectra were taken on a Bruker DPX-400 spectrometer. Melting points were measured with a Yanaco melting point apparatus and are uncorrected. IR data were recorded on a Thermo Nicolet AVATAR 360 FT-IR instrument. Microanalyses were performed at the Center for Organic Elemental Microanalysis, Kyoto University Graduate School of Pharmaceutical Sciences.

***tert*-Butyl 4,6-Dimethoxy-1,3,5-triazinyl Carbonate (Boc-DMT)**

To a suspension of 4,6-dimethoxy-1,3,5-triazin-2-ol (HO-DMT; 10.0 g, 63.8 mmol) in CH_2Cl_2 (255 mL), at r.t. under a N_2 atmosphere, were added di-*t*-butyl dicarbonate (13.3 g, 60.7 mmol), followed by pyridine (480 mg, 6.1 mmol). After stirring for 24 h at r.t., the solvent was removed by evaporation. The residue was treated with Et_2O (200 mL), and the resulting precipitate was removed by filtration. The filtrate was concentrated, and the residual oil was purified using a short column of silica gel (90 mm diameter × 30 mm in length and activated charcoal 5 mm in length; hexane–EtOAc, 7:3) to give Boc-DMT as a colorless oil (10.6 g, 68%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 9 H, *t*-Bu), 4.05 (s, 6 H, OMe).

Anal. Calcd for $C_{10}H_{15}N_3O_5$: C, 46.69; H, 5.88. Found: C, 46.64; H, 5.87.

9-Fluorenylmethyl 4,6-Dimethoxy-1,3,5-triazinyl Carbonate (Fmoc-DMT)

To a solution of 4,6-dimethoxy-1,3,5-triazin-2-ol (HO-DMT; 668 mg, 4.3 mmol) in CH_2Cl_2 (180 mL), at r.t. under a N_2 atmosphere, were added 9-fluorenylmethyl chloroformate (1.0 g, 3.9 mmol) and Et_3N (391 mg, 3.9 mmol). After stirring for 1 h at r.t. the reaction mixture was washed with H_2O (2 × 50 mL), dried over $MgSO_4$, and concentrated. Recrystallization of the residue using EtOAc–hexane gave the desired product as colorless crystals (1.39 g, 95%); mp 100–103.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.06 (s, 6 H, OMe), 4.34 (t, *J* = 7.4 Hz, 1 H, CH), 4.57 (d, *J* = 7.4 Hz, 2 H, CH_2), 7.33 (td, *J* = 1.2, 7.5 Hz, 2 H), 7.42 (ddd, *J* = 0.6, 1.2, 7.5 Hz, 2 H), 7.64 (ddd, *J* = 0.8, 1.9, 7.5 Hz, 2 H), 7.77 (td, *J* = 0.8, 7.5 Hz, 2 H).

Anal. Calcd for $C_{20}H_{17}N_3O_5$: C, 63.32; H, 4.52; N, 11.08. Found: C, 63.32; H, 4.67; N, 11.01.

Reaction of Boc-DMT with Lipophilic Amines

To a solution of Boc-DMT (386 mg, 1.5 mmol) in MeCN (3.0 mL) at r.t. was added phenethylamine (121 mg, 1.0 mmol). After stirring for 15 min at r.t., the resulting precipitate was removed by filtration. The filtrate was concentrated under reduced pressure, then re-dissolved in EtOAc (30 mL), and washed with H_2O (2 × 15 mL) and brine (20 mL), successively. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure, and then purified using silica gel column chromatography (hexane–EtOAc, 85:15) to afford *tert*-butyl phenethylcarbamate (203 mg, 91%).

IR (KBr): 3349, 2977, 2931, 1693, 1523, 1365, 1249, 1170 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.43 (s, 9 H, *t*-Bu), 2.78 (t, *J* = 7.0 Hz, 2 H, $PhCH_2$), 3.29–3.43 (m, 2 H, $NHCH_2$), 4.48–4.67 (m, 1 H, NH), 7.16–7.24 (m, 3 H, Ph), 7.27–7.32 (m, 2 H, Ph).

Reactions with other lipophilic amines were carried out similarly as described above.

Reaction of Boc-DMT with Amino Acids

To a solution of glycine (0.5 mmol) in H_2O (1 mL) containing Et_3N (1.0 mmol) at r.t. was added Boc-DMT (1.0 mmol) in MeOH (1 mL). After stirring for 30 min, the reaction mixture was concentrated to remove most of the MeOH. The resulting aqueous solution was acidified to pH 3–4 using 20% citric acid, and was then extracted with EtOAc (2 × 30 mL). The combined extracts were washed with H_2O (30 mL), dried over $MgSO_4$ and concentrated. Recrystallization of the residue using EtOAc–hexane gave Boc-glycine (74 mg, 85%).

IR (KBr): 1056, 1028, 959, 883, 860, 787, 736, 677 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H, *t*-Bu), 3.86–4.02 (m, 2 H, CH_2), 5.06 (br s, 1 H, NH).

Reactions with other amino acids were carried out similarly as described above. In each case, the products were confirmed using spectroscopic data of commercial products.

Reaction of Fmoc-DMT with Amines or Amino acids

To a solution of phenylalanine (0.13 mmol) in H_2O (1 mL) containing Na_2CO_3 (0.26 mmol) at r.t. was added Fmoc-DMT (0.156 mmol) in MeCN (1 mL). After stirring for 30 min, most of the MeCN was removed by evaporation under reduced pressure. The resulting aqueous solution was acidified with 20% citric acid to pH 3–4, and then extracted with EtOAc (30 mL). The extracts were washed with H_2O (2 × 15 mL) and brine (20 mL), dried over $MgSO_4$, concentrated, and then subjected to recrystallization using EtOAc–hexane to afford Fmoc-phenylalanine (46.2 mg; 92%); mp 179–182 °C.

IR (KBr): 1676, 1538, 1435, 1341, 1230, 1038, 740 cm^{-1}.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.94 (dd, *J* = 9.5, 13.9 Hz, 1 H, $PhCH_2$), 3.21 (dd, *J* = 4.8, 13.9 Hz, 1 H, $PhCH_2$), 4.14 (br t, *J* = 7.1 Hz, 1 H, Ar_2CH), 4.22 (dd, *J* = 7.1, 10.4 Hz, 1 H, OCH_2), 4.29 (dd, *J* = 7.2, 10.4 Hz, 1 H, OCH_2), 4.42 (dd, *J* = 4.8, 9.5 Hz, 1 H, BnCH), 7.17–7.31 (m, 7 H, Ph, fluorene), 7.37 (t, *J* = 7.5 Hz, 2 H, fluorene), 7.59 (d, *J* = 7.5 Hz, 2 H, fluorene), 7.77 (d, *J* = 7.5 Hz, 2 H, fluorene).

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