Benzyl 4,6-Dimethoxy-1,3,5-triazinyl Carbonate as *N*-Protecting Reagent

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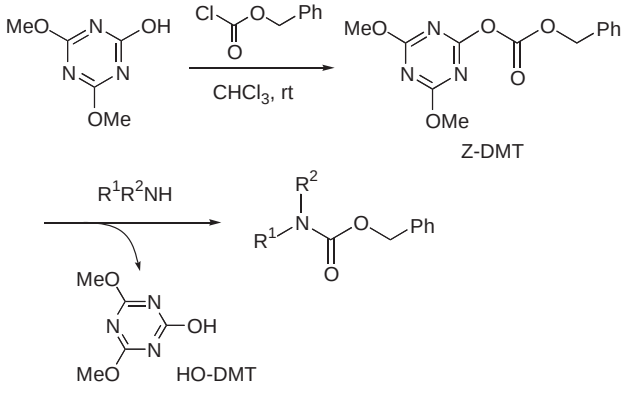
A new active carbonate ester, benzyl 4,6-dimethoxy-1,3,5-triazinyl carbonate (Z-DMT), was prepared, and found to be a useful reagent for the introduction of benzyloxycarbonyl group into amines. Since Z-DMT is neither unstable nor irritating, it is practically useful.

Among numerous *N*-protecting groups, urethane-type protecting groups represented by benzyloxycarbonyl (Z), *t*-butoxycarbonyl (Boc), and 9-fluorenylmethoxycarbonyl (Fmoc) are most widely known and used in general organic synthesis. For the introduction of Z group, benzyl chloroformate (Z-Cl) is generally used for many practical purposes because of its reactivity and costs.[1] However, the chloroformate is irritating and unstable, and serious side reactions sometimes occur leading to the formation of dipeptides during *N*-benzyloxycarbonylation of amino acids.[2] Although other benzyloxycarbonyl donors like mixed carbonates with phenols or *N*-hydroxy compounds, and various heterocycles possessing Z group have been studied, they have not found much application partly because of laborious preparation, cost, or lower reactivity of the reagents.[3] Thus, a more practical and effective reagent for benzyloxycarbonylation of amines is required.

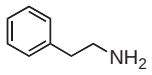
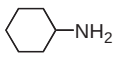
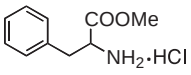
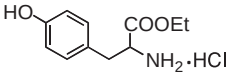
Recently, we have introduced 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMT-MM) as a new condensing reagent for the synthesis of amides or esters.[4] Most importantly, DMT-MM allows to condense carboxylic acids and amines in commercial methanol under atmospheric conditions. The reaction involves an intermediate acyloxytriazine, which exclusively undergoes aminolysis over methanolysis even in methanol. The high amide/ester selectivity can be attributed to the moderate reactivity of the triazinyl esters allowing them to be isolated.[5] Based on this fact, we expected that the ester activating ability of the dimethoxytriazinyl group is applicable to carbonate esters for protection of amino groups. In this paper we describe development of benzyl 4,6-dimethoxy-1,3,5-triazinyl carbonate (Z-DMT) as a new *N*-protecting reagent.



Scheme 1.

Z-DMT was synthesized in 87% yield by treatment of 4,6-dimethoxy-2-hydroxy-1,3,5-triazine (HO-DMT; 1 equiv) with Z-Cl (1 equiv) and triethylamine (1 equiv) in dry chloroform at rt.[6] Z-DMT is not irritating to the eye and nose, and can be stored over several months in a refrigerator without marked decomposition.

Table 1. The *N*-benzyloxycarbonylation of amines with Z-DMT

R—NH_2	Z-DMT/equiv	Solvent	Time	Yield/%
	1.1	THF	30 min	90
	1.2	THF	30 min	91
	1.2	MeOH	40 min	92
	1.2	CH_3CN	30 min	92
	1.1	THF	60 min	83
	1.2	MeOH[a]	30 min	85
	1.2	MeOH[a]	15 min	90

[a]2 eq of Et_3N was used.

Table 1 summarizes *N*-bezyloxycarbonylation of simple amines by Z-DMT. Sterically hindered cyclohexylamine or secondary amine as well as primary one readily underwent *N*-protection in good yield. HO-DMT formed as a co-product was easily removed by simple extraction with water. Since Z-DMT undergoes aminolysis faster than either hydrolysis or alcoholysis, *N*-benzyloxycarbonylation can be conducted in a protic solvent. For example, reaction of polar compounds, amino acid ester hydrochlorides, occurred smoothly in methanol.

As shown in Table 2, reaction of various amino acids also took place in good yields in either water or aqueous methanol.[7] When Z-Cl is used for the protection of amino acids, dimerization *via* the activation of the carboxyl group often becomes a serious side reaction.[8] By contrast, in the benzyloxycarbonylation of glycine with Z-DMT, the dimerization did not occur to a discernible extent (< 1%). Since HO-DMT is the co-product formed in dehydrating condensation using DMT-MM as well as in the present reaction, Z-DMT salvaging HO-DMT is economical and environmentally friendly, and therefore, a useful and stable alternative to Z-Cl.

Table 2. The protection of amino acids

Amino acid	Solvent[a]	Z-DMT /equiv	Base /equiv	Yield /%
Ala	H_2O	1.1	Et_3N; 1.1	94
Gly	H_2O	1.0	Et_3N; 1.1	95
Phe	H_2O	1.0	Et_3N; 1.0	70
Phe	H_2O	1.5	Et_3N; 1.1	88
Phe	aq. MeOH	1.5	$NaHCO_3$; 1.5	92
N-phenylGly	H_2O	1.0	Et_3N; 1.0	74
Thr	aq. MeOH	1.5	$NaHCO_3$; 2.0	82
Thr	aq. MeOH	1.5	Et_3N; 2.0	79
Ser	aq. MeOH	1.5	$NaHCO_3$; 2.0	88
Tyr	aq. MeOH	1.5	Et_3N; 3.0	80
Met	aq. MeOH	1.5	$NaHCO_3$; 2.0	87[b]
Glu	aq. MeOH	1.0	Et_3N; 2.0	70
Gln	aq. MeOH	1.2	Et_3N; 2.0	67

[a]The concentration of aq. MeOH was prepared to ca. 50%.[7] [b]n.m.r. yield.

References and Notes

1 ''Amino Acid Derivatives,'' ed. by G. C. Barrett, Oxford University Press, New York (1999), pp 7-19.

2 S. Romani, L. Moroder, G. Bovermann, and E. Wünsch, *Synthesis*, **1985**, 738.

3 E. Wünsch, W. Graf, O. Keller, W. Keller, and G. Wersin, *Synthesis*, **1986**, 958. See also references therein.

4 a) M. Kunishima, C. Kawachi, J. Morita, K. Terao, F. Iwasaki, and S. Tani, *Tetrahedron*, **55**, 13159 (1999). b) M. Kunishima, C. Kawachi, K. Hioki, K. Terao, and S. Tani, *Tetrahedron*, **57**, 1551 (2001).

5 a) J. E. Kaminska, Z. J. Kaminski, and J. Gora, *Synthesis*, **1999**, 593. b) Z. J. Kaminski, *J. Prakt. Chem.*, **332**, 579 (1990).

6 For the synthesis of Z-DMT: freshly distilled Z-Cl (904 mg, 5.30 mmol) was added to a solution of HO-DMT (1.0 g, 6.36 mmol) and triethylamine (536 mg, 5.30 mmol) in chloroform (200 mL) at rt. After stirring for 1 h at rt, the solution was washed three times with water (100 mL) and dried over magnesium sulfate and evaporated. The title compound was obtained as colorless viscous oil (1.34 g, 87% yield). The reagent was used for following experiments without further purification.

7 For general procedures for *N*-protection: to a solution of an amino acid (0.5 mmol) in water (1 mL) containing triethylamine (1.0 mmol), Z-DMT (0.75 mmol) in methanol (1 mL) was added at rt. After stirring for 1 h, most of the methanol was evaporated and the resulting aqueous solution was acidified with 1 N hydrochloric acid to pH 1 to 2. The aqueous solution was extracted with ethyl acetate, and the combined extracts were washed with water, dried, and evaporated. The amino acid derivatives were isolated by either recrystallization or column chromatography.

8 a) ''Peptide–Structure and Functions, Proc. 8th Am. Peptide Symp. 1983,'' ed. by V. J. Hruby and D. H. Rich, Pierce Chem. Company, Rockford, Illinois 1984, pp 55–64. b) S. Iguchi, K. Kawasaki, and Y. Okada, *Int. J. Peptide Protein Res.*, **30**, 695 (1987).