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Rapid and facile Lewis acid catalysed Boc protection of amines☆

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Abstract—Efficient Boc protection of amines was carried out using $(Boc)_2O$ in the presence of a catalytic amount of $ZrCl_4$ (10 mol%) in acetonitrile at room temperature. The reaction times are very short and the yields are generally high.

1. Introduction

Among the various protecting groups used for amines, Boc protection has become a fundamental tool of modern peptide synthesis[1] and particularly of the Merrifield strategy for solid-phase peptide synthesis.[2] Owing to the instability of the corresponding *t*-butyl chloroformate and the explosive properties of *t*-butylazido formate, the $(Boc)_2O$ reagent is widely used for the introduction of the *t*-butoxycarbonyl group. Even though a variety of base mediated reaction conditions are available for Boc protection, the only reported acid (Yttria–Zirconia) mediated reaction conditions[3] need longer reaction times (3–48 h). In pursuance of our work on new synthetic methods[4] and non-natural peptides,[5] we were interested in exploring the possibility of developing Lewis acid catalysed reaction conditions for Boc protection. Herein, we report the $ZrCl_4$ catalysed Boc protection of amines with short reaction times and high yields.

$$\text{R-NH}_2 \xrightarrow[\text{CH}_3\text{CN, rt}]{(\text{Boc})_2\text{O, ZrCl}_4\text{ (10 mol\%)}} \text{R-NHBoc} \quad (1)$$

Aniline (Table 1, entry 1) and $(Boc)_2O$ in acetonitrile were treated with 10 mol% $ZrCl_4$ at room temperature to afford **1a** (95%) in 3 min. The same reaction with Yttria–Zirconia as catalyst[3] took 14 h, while it required 48 h in the absence of any catalyst. This interesting result prompted us to explore the reactivity of $(Boc)_2O$ with a variety of amines in the presence of $ZrCl_4$. Accordingly, aryl/heteroarylalkyl (entries 2 and 3), cycloalkyl (entries 4 and 5), acetoxyalkyl amines (entry 8) and secondary amines (entries 9, 10 and 11) underwent smooth Boc protection to furnish the corresponding products (Boc protected amines) in good to excellent yields (Table 1) in 3–10 min. It is worth mentioning that aminols (entries 6 and 7) on treatment with $(Boc)_2O$ in acetonitrile at room temperature chemoselectively gave **6a** and **7a** in high yields.

In a further study, amino acid esters (Table 2, entries 1, 2 and 3) were converted to the corresponding *N*-Boc esters under similar reaction conditions in 10 min and in good yields. However, the methyl ester of histidine (Table 2, entry 5) on reaction with 1 mol of $(Boc)_2O$ gave **16a** (82%) as the sole product in 10 min, while with 2 mol it gave **16b** (80%) in 15 min. The chemoselective protection of cysteine (Table 2, entry 4) gave the *N*-Boc protected derivative **15a** (81%) in 10 min. This procedure could conveniently be applied to a variety of amino acids. In a continued study, the *C*-linked carbo β-amino acid esters derived from sugars (Table 2, entries 6, 7 and 8) underwent smooth Boc protection in the presence of $ZrCl_4$ (10 mol%) in 15–25 min to give **17a**, **18a** and **19a**, respectively, in high yields. The conventional procedure [$(Boc)_2O$, Et_3N, THF] for the same transformation took more than 2 h.

In conclusion, this protocol is operationally simple, rapid and high yielding. The reaction conditions are mild and inexpensive involving the use of a readily available and environmentally friendly catalyst ($ZrCl_4$) at room temperature. The formation of side products was not observed.

Keywords: Amines; Amino acids; Carbo β-amino acids; Lewis acid catalyst; $(Boc)_2O$.
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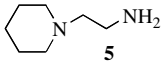
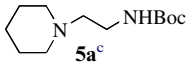
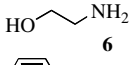
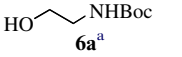
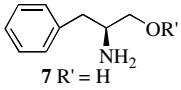
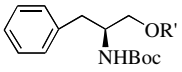
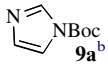
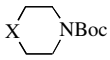
Table 1. $ZrCl_4$ (10 mol%) catalysed protection of amines

Entry	Starting material	Product	Time (min)	Yield (%)
	RNH_2	RNHBoc		
1	R = phenyl **1**	R = phenyl **1a**[a]	3	95
2	R = benzyl **2**	R = benzyl **2a**[a]	3	96
3	R = 4-pyridylmethyl **3**	R = 4-pyridylmethyl **3a**[c]	3	90
4	R = cyclohexyl **4**	R = cyclohexyl **4a**[a]	3	91
5	 **5**	 **5a**[c]	5	88
6	 **6**	 **6a**[a]	5	96
7	 **7** R' = H	 **7a**[b] R′ = H	5	90
8	**8** R′ = Ac	**8a**[c] R′ = Ac	10	85
9	 **9**	 **9a**[b]	5	92
10			5	92
	10 X = CH_2	**10a**[b] X = CH_2		
11	**11** X = O	**11a**[a] X = O	10	90

[a] See Ref. 3.
[b] Commercially available compounds.
[c] All new compounds gave satisfactory spectral and analytical data.

2. General experimental procedure

To a solution of the amine/amino acid ester (1 mmol) in acetonitrile (2 mL), $(Boc)_2O$ (1 mmol) was added dropwise followed by a catalytic amount of $ZrCl_4$ (10 mol%) at room temperature. After stirring the reaction mixture for the specified time (Tables 1 and 2), the solvent was removed under reduced pressure and the mixture diluted with water and extracted with ethyl acetate (3×5 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried (Na_2SO_4), evaporated under reduced pressure and purified the residue by column chromatography (silica gel, 60–120 mesh, 5–15% EtOAc in hexane) to furnish the pure product.

2.1. Spectral data of selected compounds

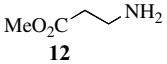
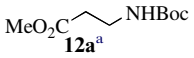
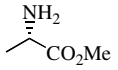
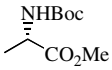
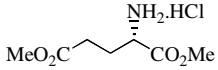
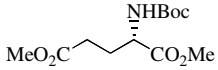
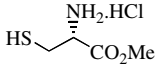
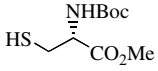
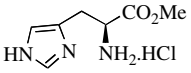
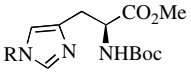
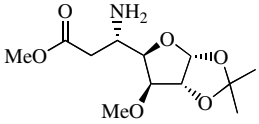
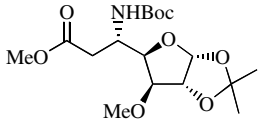
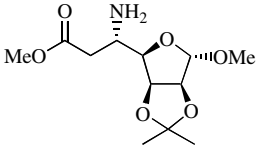
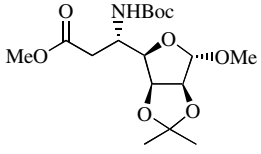
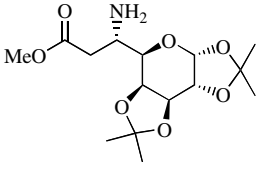
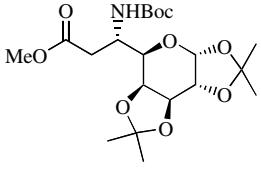
2.1.1. 4-(*N*-*tert*-Butylcarboxylate)-amino methyl pyridine (3a). White solid, mp 70–75 °C; IR (KBr): 3380, 2985, 2928, 1705, 1500, 1310, 1165, 1070, 1010 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 1.40 (s, 9H), 4.32 (d, 2H, $J = 6.6$ Hz), 5.00 (br s, 1H), 7.16 (d, 2H, $J = 5.3$ Hz), 8.55 (d, 2H, $J = 5.3$ Hz); EIMS: (*m*/*z*, %) 208 (M^+, 3), 152 (M^+-56, 73), 108 (M^+-Boc, 24), 57 (100). Anal. Calcd for $C_{11}H_{16}N_2O_2$ (208): C, 63.44; H, 7.74. Found: C, 63.47; H, 7.70.

2.1.2. *tert*-Butyl 1*H*-1-imidazolecarboxylate (9a). White solid, mp 42–45 °C, lit. (Lancaster catalogue) mp 46–47 °C; IR (KBr): 3365, 2975, 2930, 1725, 1700, 1502, 1308, 1165, 1070, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (s, 1H), 7.36 (s, 1H), 7.00 (s, 1H), 1.62 (s, 9H, Boc); EIMS: (*m*/*z*, %) 169 ($M+1^+$, 8), 131 ($M+1^+-37$, 9), 96 ($M+1^+-72$, 100), 69 ($M+1^+-$ Boc, 63).

2.1.3. Methyl (3*S*)-3-[(*tert*-butoxy)carbonylamino]-3-[6-methoxy-2,2-dimethyl-(3a*R*,6*S*,6a*R*)-tetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl]propanoate (17a). $[\alpha]_D^{25}$ −26.9 (*c* 1.1, $CHCl_3$); IR (neat): 3385, 2980, 2938, 1725, 1705, 1502, 1308, 1161, 1071, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.31 (s, 3H), 1.43 (s, 9H), 1.48 (s, 3H), 2.67 (dd, 1H, $J = 7.9$, 14.6 Hz), 2.71 (dd, 1H, $J = 3.2$, 14.6 Hz), 3.37 (s, 3H), 3.68 (s, 3H), 3.68 (d, 1H, $J = 3.1$ Hz), 4.30 (m, 1H), 4.29 (m, 1H), 4.57 (d, 1H, $J = 3.8$ Hz), 5.09 (br s, 1H), 5.91 (d, 1H, $J = 3.8$ Hz); FABMS: (*m*/*z*, %) 752 ($2[M+1]^+$, 4), 376 ($M+1^+$, 23), 320 (12), 276 ($M+1^+-$Boc, 100), 218 (11), 133 (15). Anal. Calcd for $C_{17}H_{29}NO_8$ (375): C, 54.39; H, 7.79. Found: C, 54.45; H, 7.72.

2.1.4. Methyl (3*S*)-3-[(*tert*-butoxy)carbonylamino]-3-[2,2,7,7-tetramethyl-(3a*R*,5*R*,5a*S*,8a*S*,8b*R*)-tetrahydrodi-[1,3]dioxolo[5,4-*b*:4,5-*d*]pyran-5-yl]propanoate (19a). $[\alpha]_D^{25}$ −41.0 (*c* 1.0, $CHCl_3$); IR (neat): 3380, 2985, 2940, 1725, 1710, 1500, 1308, 1165, 1070, 1012 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 6H), 1.42 (s,12H), 1.48 (s, 3H), 2.75 (d, 2H, $J = 7.7$ Hz), 3.56 (s, 3H), 3.94–4.02 (m, 1H), 4.06 (q, 1H, $J = 7.7$ Hz), 4.24–4.28 (m, 2H), 4.55 (d, 1H, $J = 18.4$ Hz), 4.98 (br s, 1H), 5.48 (d, 1H, $J = 6.4$ Hz); FABMS: (*m*/*z*, %) 862 ($2M^+$, 5), 432 ($M+1^+$, 20), 376 (12), 332 ($M+1^+-$Boc, 100), 274 (11), 189 (15), 64 (25). Anal. Calcd for $C_{20}H_{33}NO_9$ (431): C, 55.67; H, 7.71. Found: C, 55.59; H, 7.65.

Table 2. $ZrCl_4$ (10 mol%) catalysed protection of amino acid esters

Entry	Starting material	Product	Time (min)	Yield (%)
1	 **12**	 **12a**[a]	10	82
2	 **13**	 **13a**[a]	10	84
3	 **14**	 **14a**[a]	10	80
4	 **15**	 **15a**[a]	10	81
5	 **16**	 **16b**[a] R = H; **16b**[a] R = Boc	10 15	82 80
6	 **17**	 **17a**[b]	25	88
7	 **18**	 **18a**[b]	15	93
8	 **19**	 **19a**[b]	20	89

[a] Commercially available compounds.
[b] All new compounds gave satisfactory spectral and analytical data.

Acknowledgement

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