A Mild Method for the Cleavage of the 4-Picolyloxy Group with Magnesium under Neutral Conditions

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Abstract: A mild and efficient method for the selective hydrolysis of 4-picolyl esters with magnesium in methanol or water in the presence of other esters and sensitive protecting groups is described. 4-Picolyl aryl ethers and thioethers are also smoothly deprotected to give the corresponding phenols and thiophenols.

Key words: hydrolysis, 4-picolyloxy group, magnesium, protecting groups, phenols

The 4-picolyl group has been shown to be useful in the protection of carboxyl groups in organic synthesis. In the segment-condensation peptide synthesis method, segments are protected as 4-picolyl esters at the carboxyl termini.[1] In addition, in the solid-phase peptide synthesis, 4-picolyl groups have been used as key intermediates to anchor the amino acid to the polymer support.[2,3] The presence of this basic functional group also offers potential advantages for purification of products by electrophoresis[4] or ion-exchange chromatography.[5]

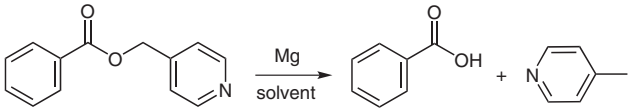
Owing to the pyridine ring, the 4-picolyl esters is stable under harsh conditions, such as in trifluoroacetic acid, hydrofluoric acid (25 °C, 20%, 1 h), and even in high concentrations of hydrochloric acid (0 °C, 2 h) or hydrobromic acid (0 °C, 2 h). 4-Picolyl esters are also stable in Et_3N (25 °C, 1 h). Due to the lack of a highly efficient and selective deprotection method, little attention has been paid to the 4-picolyl group introduced by the Young group[6] in 1968 in solution peptide synthesis. It was also reported that the 4-picolyl groups were deprotected by a light-absorbing photosensitizer.[7] An excellent yield for the free carboxylate has been obtained using visible-light-absorbing citrate-stabilized metal complexes to mediate electron transfer between dithiothreitol and an *N*-methylpicolinium ester in aqueous solution by Falvey's group.[8]

Our continued interest in peptide synthesis recently prompted us to explore the efficient deprotection of 4-picolyl esters.[9,10] Removing a protecting group by treating a compound with magnesium has good applications in organic synthesis.[11–14] We found that the hydrolysis of 4-picolyl esters using magnesium in methanol gives the corresponding products in excellent yields. The protected substrates, in most cases, released nearly quantitative yields based on converted 4-picolyl benzoate.

Magnesium in methanol was chosen as a deprotection agent for 4-picolyl esters in the present study because of the mild reaction conditions and apparent compatibility with acid-sensitive functionalities.[15,16] Using 4-picolyl benzoate as a model substrate, we have studied the effect of solvent effect on the deprotection process (Table 1). Of the solvents used, methanol was the most efficient (reaction time 4 h) and gave a high yield (Table 1, entry 1). A good yield (86%) was also achieved when water was used as solvent.

Screening of other alcohols showed that methanol is the most efficient solvent for this reaction (Table 1, entries 1–4).

Table 1 Solvent Effects in Cleavage 4-Picolyloxy Group



Entry	Solvent	Time (h)	Yield (%)[a]
1	MeOH	4	92
2	EtOH	16	30
3	*i*-PrOH	16	28
4	*t*-BuOH	16	30
5	THF	24	n.r.[b]
6	1,4-dioxane	24	n.r.[b]
7	MeOH (10%)–THF	16	90
8	MeOH (10%)–MeCN	16	95
9	H_2O (10%)–THF	16	92
10	H_2O (10%)–1,4-dioxane	16	93
11	H_2O	4	86
12	MeOH (20%)–H_2O	4	90

[a] Isolated yield.
[b] No reaction.

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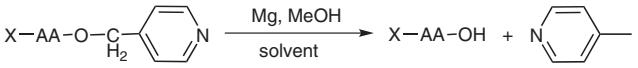
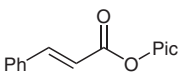
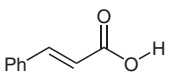
In the nonprotonic solvent, the reaction did not proceed (Table 1, entries 5, 6). However, when only 10% of methanol or water was added into the aprotic solvents, the cleavage of the 4-picolyloxy group of 4-picolyl benzoate was completed within 16 hours in the mixture of solvents, and the reaction gave benzoic acid in 85–93% yield (Table 1, entries 7–10).

Pyridin-4-ylmethanol can be coupled to carboxylic acids, protected amino acids, phenols, and benzenethiols using standard ester synthesis techniques, described in detail in the typical procedure.[17,18] We tried to reduce 4-picolyl esters of common Cbz, Boc, and Fmoc N-protected amino acids and cinnamic acid with magnesium in methanol. The results obtained are summarized in Table 2. In these reactions, the acid-sensitive Cbz and Boc groups and the basic-sensitive Fmoc group were unaffected. Deprotection of 4-picolyl cinnamate, which has a potentially reduceable α,β-unsaturated system, was unaffected when treated with magnesium in methanol, even after long reaction times (24 h at r.t., Table 2, entry 16). Thus, a remarkable specificity is observed.

Table 2 Removal of Protection for the Carboxyl Group[a]



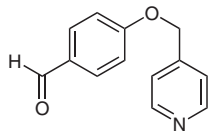
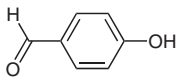
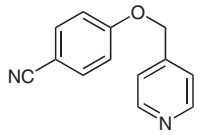
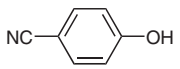
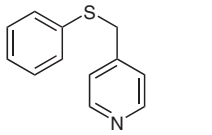
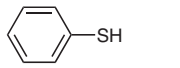
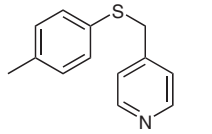
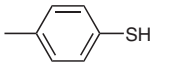
X = Boc, Cbz, Fmoc

Entry	Starting material	Product	$[\alpha]_D^{20}$ (c = 1, AcOH)	
			Reaction	Standard
1	Boc-Phe-OPic	Boc-Phe-OH	4.1	4.2
2	Boc-Val-OPic	Boc-Val-OH	–6.0	–5.9
3	Boc-Ala-OPic	Boc-Ala-OH	–24.4	–24.6
4	Boc-Asp(Bn)-OPic	Boc-Asp(Bn)-OH	–19.5	–19.8
5	Boc-Leu-OPic	Boc-Leu-OH	–23.9	–23.9
6	Boc-Ile-OPic	Boc-Ile-OH	–23.4	–23.6
7	Boc-Pro-OPic	Cbz-Pro-OH	–63.1	–63.2
8	Boc-Trp-OPic	Boc-Trp-OH	–20.9	–21.0
9	Cbz-Met-OPic	Cbz-Met-OH	–28.3	–28.4
10	Cbz-Val-OPic	Cbz-Val-OH	–4.5	–4.6
11	Cbz-Ala-OPic	Cbz-Ala-OH	–13.8	–13.9
12	Cbz-Phe-OPic	Cbz-Phe-OH	5.1	4.9
13	Cbz-Ile-OPic	Cbz-Ile-OH	–18.2	–18.3
14	Cbz-Gly-OPic	Cbz-Gly-OH	–	–
15	Fmoc-Met-OPic	Fmoc-Met-OH	–19.5	–19.4
16			–	–

[a] Starting material (2 mmol), Mg (288 mg, 12 mmol), MeOH (20 mL), r.t., 4 h.

As shown in Table 2, in all the magnesium-deprotection products the same rotation was measured indicating that no significant racemization of the amino acids occurs during these reactions. To corroborate this observation, 4-picoly ester was removed from the synthesized dipeptide Boc-(L)-Ala-(L)-Val-OPic. After Boc deprotection, the resulting free dipeptide was analyzed by HPLC. Only a small peak (0.2%) was detected at the time corresponding to the (L)-Ala-(D)-Val-OH isomer when compared to control chromatograms of (L)-Ala-(L)-Val-OH (t_R = 8.63 min) and (L)-Ala-(D)-Val-OH (t_R = 7.74 min) isomers. This fact indicates that no significant racemization took place during derivatization with 4-picoly ester and subsequent deprotection.

Table 3 Removal of the Protecting Groups for the Phenols and Benzenethiols

Entry	Starting material	Product	Yield (%)
1			88
2			89
3			90
4			92

In our ongoing efforts to explore this Mg/MeOH methodology, we found it to be very effective for deprotecting 4-picolyl ethers. Preliminary experiments have given very satisfactory results (Table 3).[18] Thus, aryl ethers and thioethers are smoothly deprotected to give the corresponding phenols and thiophenols.

In summary, a simple and efficient method for the cleavage of the 4-picolyloxy group by treatment with magnesium in methanol has been developed. The reaction does not produce byproducts other than the salts generated. Finally, the deprotection reaction can be performed in H_2O or MeOH. We anticipate its widespread applicability and usefulness in organic synthesis.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synlett and can be cited using the following DOI: 10.4125/pd0022nd.

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(17) *Protective Groups in Organic Synthesis*, 3rd ed.; Green, T. W.; Wuts, P. G. M., Eds.; Wiley: New York, **1999**, 373–377.
(18) **Typical Procedure A: Protection**
A solution of *N*-Boc-L-alanine-L-valine (0.864 g, 3 mmol), 4-picolyl chloride hydrochloride (0.50 g, 3 mmol), and Et_3N (0.606 g, 6 mmol) in DMF (10 mL) was heated at 90 °C for 3 h, till TLC showed the absence of 4-picolyl chloride. The solvent was distilled off, and EtOAc (10 mL) was added to the residue. The solution was washed with sat. $NaHCO_3$ (3 × 10 mL), H_2O (2 × 10 mL), and brine (10 mL), and then dried over $MgSO_4$. After evaporation of the solvent, the dark brown solid was purified by column chromatography using EtOAc–PE (1:1). The filtrate was evaporated in vacuo, and the product was purified by column chromatography using EtOAc–PE (1:1). Yield 0.852 g (75%); $[\alpha]_D^{20}$ –24.6 (*c* 1, DMF). ESI-MS: *m/z* = 380.2 $[M + H]^+$, 402.2 $[M + Na]^+$. ESI-HRMS: *m/z* calcd for $[C_{19}H_{29}N_3O_5 + H]^+$: 380.2185; found: 380.2181; *m/z* calcd for $[C_{19}H_{29}N_3O_5Na]^+$: 402.2005; found: 402.2002. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, *J* = 7.0 Hz, 3 H), 0.95 (d, *J* = 7.0 Hz, 3 H), 1.35 (d, *J* = 6.9 Hz, 3 H), 1.44 (s, 9 H), 2.20–2.24 (m, 1 H), 4.23 (s, 1 H), 4.61 (t, *J* = 5.0, 9.0 Hz, 1 H), 5.18 (s, 2 H), 5.28 (d, *J* = 7.9 Hz, 1 H), 7.26–7.30 (m, 2 H), 8.61 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.5, 18.9, 28.1, 30.9, 49.8, 57.0, 64.7, 80.0, 121.8, 140.2, 149.9, 155.6, 171.3, 172.7.
Typical Procedure B: Deprotection
To a solution of picolyl *N*-Boc-L-alanine-L-valinate (0.76 g, 2 mmol) in MeOH (20 mL) magnesium turnings (288 mg, 12 mmol) were added. After stirring for 4 h at r.t. the reaction mixture was filtered. The filtrate was concentrated in vacuo, and the residue was diluted with 5% $NaHCO_3$ (10 mL) and EtOAc (10 mL), and the organic layer was extracted with 5% $NaHCO_3$ (2 × 10 mL). The aqueous extract was acidified to pH 2–3 with sat. $KHSO_4$ and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (2 × 10 mL), dried with Na_2SO_4, and filtered. The residue was purified by silica gel column chromatography using EtOAc–PE. Yield 0.518 g (90%); $[\alpha]_D^{20}$ 8.7 (*c* 1, $CHCl_3$).

