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Picolinyl group as an efficient alcohol protecting group: cleavage with $Zn(OAc)_2 \cdot 2H_2O$ under a neutral condition

Ju Yuel Baek, Yong-Joo Shin, Heung Bae Jeon* and Kwan Soo Kim*

Center for Bioactive Molecular Hybrids and Department of Chemistry, Yonsei University, Seodaemun-gu Sinchon-dong 134, Seoul 120-749, Korea

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Abstract—As an efficient alcohol protecting group, picolinates (Pic), prepared from the corresponding alcohols using commercial picolinoyl chloride, are readily cleaved by $Zn(OAc)_2$ or $Cu(OAc)_2$, even in the presence of other common alcohol protecting groups. Moreover, the picolinyl group at C-2 position in carbohydrates can be selectively cleaved to give methyl 4,6-*O*-benzylidene-3-*O*-picolinyl-α-D-glucopyranoside and 3-*O*-picolinyl methyl-4,6-*O*-benzylidene-α-D-galactopyranoside in good yields.

In the past century, the field of organic chemistry has succeeded in developing fascinating methodologies that could accommodate the synthesis of numerous complex organic structures. However, the lack of complete control over selective functional group transformations has led to the extensive use of protecting groups (PGs). Therefore, the introduction and removal of protecting groups still plays an important role in the synthesis of polyfunctional molecules. To date, a number of PGs and their preparations and applications have been reported.[1] Nevertheless, there still remains a need for more selective, robust, and economical protecting groups.

The arrival of many PGs for hydroxyl groups has given synthetic organic chemists invaluable tools in the elaboration of complex molecules, particularly in carbohydrate chemistry. Generally, the hydroxyl groups are protected as corresponding ethers, esters, acetals, and ketals.[2] Among them, the ester functionality has been most frequently used as a temporary or persistent PG due to its relative ease in the cleavage step compared to other PGs. However, the need for basic conditions during the deprotection step has limited its applications. In this regard, we have disclosed a simple and efficient protocol using the picolinate as a novel PG that can be employed under mild and neutral conditions. Although the picolinate was found to be hydrolyzed under neutral condition,[3] it was never investigated systematically as an alcohol protecting group up to date despite its availability of easy introduction and removal.

Protected alcohols **2** and **3** were efficiently prepared by reaction of the corresponding alcohols **1** and **4** with a commercial picolinoyl chloride (1.2 equiv) and triethylamine in CH_2Cl_2 in 83–97% yields. Reactions with the primary **1a–g** and secondary alcohols **1h–k** proceeded smoothly at room temperature to give the corresponding products **2a–k**, whereas a refluxing condition was necessary for the tertiary alcohols **1l** and **1m** to afford **2l** and **2m**. Moreover, a number of different protecting groups, such as silyl ether **3a**, MEM ether **3b**, acetate **3c**, isopropylidene acetal **3d**, and benzyloxy **3e**, were tolerated under the given reaction condition.

Initial experiments regarding the chemoselective deprotection of the picolinyl group were performed with the ester **2a** to find the suitable solvent and Lewis acid (Table 1).[4] Copper(II) acetate (1.0 equiv) readily cleaved the picolinate in THF/H_2O, MeOH, or CH_2Cl_2/MeOH (entries 1–4). In particular, we noticed that as little as 5% of MeOH in the total solvent system was enough for the cleavage (entry 4). This discovery is particularly useful for scaled up reactions in which large amounts of MeOH would be of nuisance during the work-up. Additionally, the reaction is not moisture sensitive, which

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* Corresponding authors. Tel.: +82 2 2123 2640/7615; fax: +82 2 365 7608; e-mail addresses: hbj@yonsei.ac.kr; kwan@yonsei.ac.kr

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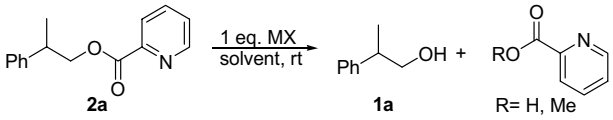
Table 1. Removal of picolinyl group under various conditions



Entry	MX	Solvent	Time (h)	Yield (%)[a]
1	$Cu(OAc)_2$	THF/H_2O = 8:2	1.7	94
2	$Cu(OAc)_2$	MeOH	0.2	96
3	$Cu(OAc)_2$	CH_2Cl_2/MeOH = 8:2	1.0	95
4	$Cu(OAc)_2$	CH_2Cl_2/MeOH = 95:5	2.0	96
5	$Cu(OAc)_2{\cdot}H_2O$	CH_2Cl_2/MeOH = 95:5	2.0	96
6	$CuCl_2$	CH_2Cl_2/MeOH = 95:5		NR[b]
7	$CuSO_4$	CH_2Cl_2/MeOH = 95:5		NR
8	$CuSO_4{\cdot}5H_2O$	CH_2Cl_2/MeOH = 95:5		NR
9	$Cu(OTf)_2$	CH_2Cl_2/MeOH = 95:5		NR
10	$Co(OAc)_2{\cdot}4H_2O$	CH_2Cl_2/MeOH = 95:5	26	90
11	$Ni(OAc)_2{\cdot}4H_2O$	CH_2Cl_2/MeOH = 95:5	26	91
12	$MgBr_2$	CH_2Cl_2/MeOH = 95:5		NR
13	$ZnBr_2$	CH_2Cl_2/MeOH = 95:5	28	90
14	$ZnSO_4$	CH_2Cl_2/MeOH = 95:5		NR
15	$Zn(OAc)_2$	CH_2Cl_2/MeOH = 95:5	2.0	96
16	$Zn(OAc)_2{\cdot}2H_2O$	CH_2Cl_2/MeOH = 95:5	1.8	96

[a] Isolated yields.
[b] No reaction until 24 h.

makes this procedure even more attractive and convenient (entries 1 and 5). Next, different Lewis acids were investigated (entries 4–16). Among them, $Cu(OAc)_2$, $Cu(OAc)_2{\cdot}H_2O$, $Zn(OAc)_2$, and $Zn(OAc)_2{\cdot}2H_2O$ displayed the best results (Table 1, entries 4, 5, 15, and 16). Further studies were carried out with $Zn(OAc)_2{\cdot}2H_2O$ since this reagent was more economically available than other reagents.

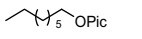
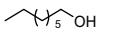
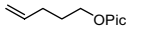
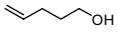
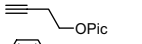
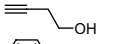
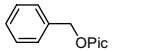
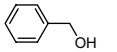
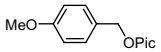
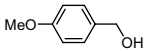
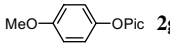
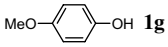
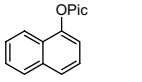
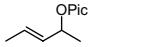
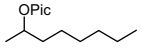
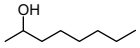
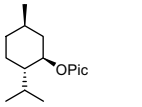
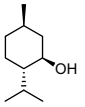
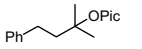
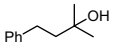
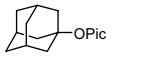
Using the optimized deprotection condition, a variety of picolinates were treated with $Zn(OAc)_2{\cdot}2H_2O$ (1 equiv) in CH_2Cl_2/MeOH (95/5) to give the parent alcohols in excellent yields (Table 2). The reaction rates were heavily dependent on the steric issue of the substrates. The deprotection of the primary alcohol derivatives **2b–g** (entries 1–6) was completed at room temperature in 1.5 h, whereas that of the secondary alcohol derivatives **2h–k** took more than 10 h at room temperature but completed in 2 h at 38 °C (entries 7–10). In the case of tertiary alcohol derivatives **2l** and **2m**, no deprotection was observed at room temperature, and thus heating at 38 °C was essential in order to realize the cleavage of the protecting group (entries 11 and 12). Additionally, we were delighted to find that the deprotection of primary and secondary alcohol derivatives can be achieved in the presence of a catalytic amount of $Zn(OAc)_2{\cdot}2H_2O$ (0.1 equiv) (Table 2, entries 1–10).

Results from the selective deprotection of the picolinyl moiety in the presence of other alcohol protecting groups are summarized in Scheme 1. The orthogonal removal of the picolinyl group is readily effected with $Zn(OAc)_2{\cdot}2H_2O$ in CH_2Cl_2/MeOH (95/5) at room temperature to afford mono-alcohols **4a–e** in excellent yields. Remarkably, the picolinyl group in **3c** was selectively removed without deteriorating the acetate, which is considered the most vulnerable ester, to give the desired product **4c** in 91% yield. Next, the selective deprotections of other protecting groups in the presence of the picolinate were performed according to the known procedures. Cleavage of *tert*-butyldimethylsilyl ether in **3a** using *n*-Bu_4NF in THF afforded **5a** in 88% yield. Removal of MEM group with $ZnBr_2$[5] and isopropylidene group with trifluoroacetic acid[6] in **3b** and **3d** provided **5b** and **5d** in 92% and 94% yield, respectively. A catalytic hydrogenation of a benzyl ether in the presence of the picolinyl group gave a rather unexpected result. Not only did this procedure debenzylate the compound **3e** but it also reduced the pyridine ring in the picolinyl group to give **6** and **7** in 25% and 75% yields, respectively. Fortunately, the benzyl group was successfully removed by using 25% $MeSO_3H$ in CH_2Cl_2 at room temperature to give **5e** in 90% yield.[7] As expected, it was difficult to remove the acetate group without hydrolyzing the picolinyl group. Removal of the acetate group of **3c** with K_2CO_3 in MeOH gave the diol **5c** in 93% yield indicating that both ester functional groups, acetate and picolinate, were cleaved under the basic condition.

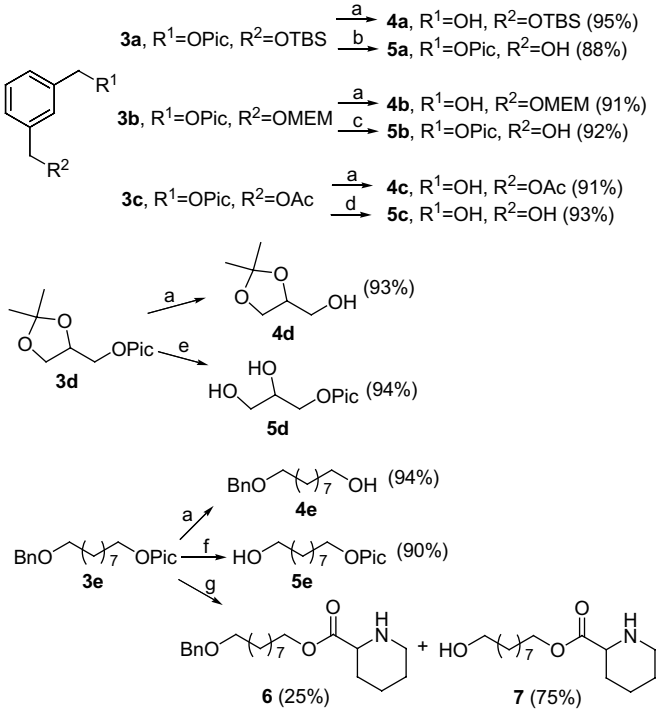
It is speculated that the cleavage of the picolinate group is initiated by chelation between the zinc metal and the picolinate carbonyl oxygen and pyridinyl nitrogen to form the intermediate **A** (Scheme 2). This would induce the picolinyl group of the intermediate **A** to become more reactive and accelerate the nucleophilic attack by neutral MeOH to release the parent alcohol and the zinc-chelated methyl picolinate **B**.

Another neighboring chelating site, namely the benzyloxy group in compounds **3f** and **3g**, could potentially increase the rate of reactions, hence providing even greater selectivity (Scheme 3). When **3f** was compared to **2n**, the

Table 2. Removal of picolinyl group using $Zn(OAc)_2{\cdot}2H_2O$ in CH_2Cl_2/MeOH (95/5)

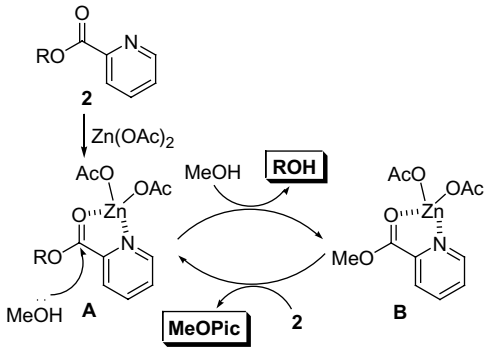
Entry	Substrate		Product		1 equiv $Zn(OAc)_2{\cdot}2H_2O$			0.1 equiv $Zn(OAc)_2{\cdot}2H_2O$		
					Temperature (°C)	Time (h)	Yield (%)[a]	Temperature (°C)	Time (h)	Yield (%)[a]
1		**2b**		**1b**	rt	1.5	95	rt	4.0	91
2		**2c**		**1c**	rt	1.5	93	rt	4.0	92
3		**2d**		**1d**	rt	1.5	97	rt	4.0	93
4		**2e**		**1e**	rt	1.5	90	rt	4.0	93
5		**2f**		**1f**	rt	1.5	94	rt	4.0	95
6		**2g**		**1g**	rt	1.5	91	rt	3.0	93
7		**2h**		**1h**	38	1.3	93	38	3.0	92
8		**2i**		**1i**	38 (rt)	1.5 (10)	92 (91)	38	3.2	95
9		**2j**		**1j**	38 (rt)	1.5 (11)	94 (92)	38	3.5	96
10		**2k**		**1k**	38 (rt)	2.0 (45)	93 (89)	38	3.8	94
11		**2l**		**1l**	38	30	92			
12		**2m**		**1m**	38	30	96			

[a] Isolated yields.

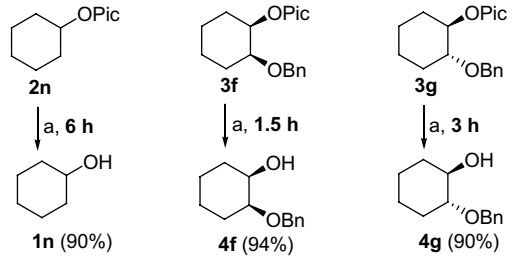


Scheme 1. Selective cleavage of the picolinate and other alcohol protective groups. Reagents and conditions: (a) $Zn(OAc)_2{\cdot}2H_2O$ (1 equiv), CH_2Cl_2/MeOH (95/5), rt, 2 h; (b) *n*-Bu_4NF (2 equiv), THF, rt, 1 h; (c) $ZnBr_2$ (5 equiv), CH_2Cl_2, rt, 10 h; (d) K_2CO_3 (1 equiv), MeOH, 0 °C, 1 h; (e) TFA (0.1 equiv), THF/H_2O (4/1), rt, 1.5 h; (f) 25% $MeSO_3H/CH_2Cl_2$, rt, 7 h; (g) Pd/C (0.1 equiv), H_2, 1 atm, EtOAc, rt, 2 h.

rate of deprotection was significantly increased due to the presence of the benzyloxy group in the molecule. More interestingly, the *cis*-positioned benzyloxy group in **3f** had a greater impact on the rate of deprotection

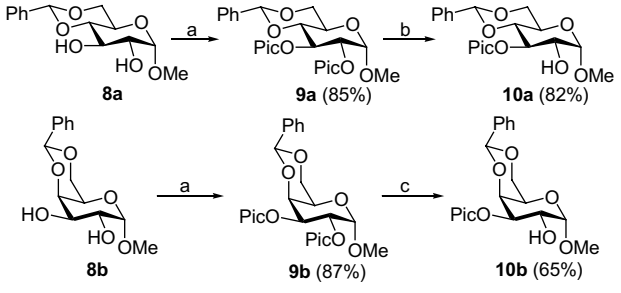


Scheme 2. Proposed deprotection mechanism.



Scheme 3. Reaction time dependence of deprotection. Reagents and conditions: (a) $Zn(OAc)_2{\cdot}2H_2O$ (1 equiv), CH_2Cl_2/MeOH (95/5), rt.

compared to the *trans*-positioned benzyloxy group in **3g**. This selective deprotection is highly desirable in carbohydrate chemistry[8] because α 1→2 linked disaccharides are key subunits of numerous biologically potent oligosaccharides, antigens, antibiotics, glycoproteins, and glycolipids.[9] The synthesis of 2,3-dipicolinate **9a** and **9b** from methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **8a** and α-D-galactopyranoside **8b** was carried out readily with 2.5 equiv picolinoyl chloride in good yields (Scheme 4). The regioselective cleavage of picolinate group at the C-2 position of **9a** and **9b** has been achieved using $Zn(OAc)_2{\cdot}2H_2O$ in THF/H_2O (5/1 or 4/1)[10] at low temperature to afford 3-*O*-picolinyl protected methyl 4,6-*O*-benzylidene-α-D-glucopyranoside **10a** and α-D-galactopyranoside **10b** in 82% and 65% yield, respectively, because of the anchimeric assistance of *cis*-OMe group at the C-1 position for zinc-chelation.



Scheme 4. Selective deprotection of C-2 position in glucose and galactose. Reagents and conditions: (a) picolinoyl chloride (2.5 equiv), TEA (5 equiv), DMAP (0.4 equiv), CH_2Cl_2, rt, 3 h; (b) $Zn(OAc)_2{\cdot}2H_2O$ (1 equiv), THF/H_2O (5/1), −10 °C, 5 h; (c) $Zn(OAc)_2{\cdot}2H_2O$ (1 equiv), THF/H_2O (4/1), −5 °C, 4.5 h.

In conclusion, we found that picolinate, prepared from the corresponding alcohols using picolinoyl chloride, is an efficient alcohol protecting group and is readily cleaved by $Zn(OAc)_2{\cdot}2H_2O$ even in the presence of other common alcohol protecting groups. Moreover, we demonstrated that the picolinyl group at C-2 position can be selectively cleaved to give methyl 4,6-*O*-benzylidene-3-*O*-picolinyl-α-D-glucopyranoside **10a** and α-D-galactopyranoside **10b** in good yields.

Acknowledgements

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4. Typical procedure for deprotection of **2a**: A solution of **2a** (48 mg, 0.20 mmol) and $Zn(OAc)_2{\cdot}2H_2O$ (44 mg, 0.20 mmol) in CH_2Cl_2 (1.9 mL) and MeOH (0.1 mL) was stirred for 100 min at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was washed with 1 N aqueous HCl solution (5 mL × 2) and brine to remove methyl picolinate, then it was dried over $MgSO_4$, and concentrated to give the pure parent alcohol **1a** (26 mg, 96%).
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10. The reaction in CH_2Cl_2/MeOH (95/5) at 0 °C gave the diol **8a** or **8b** as a major product after 2 h, even with 0.1 equiv $Zn(OAc)_2{\cdot}2H_2O$.