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A Novel and Efficient Method for Cleavage of Phenacylesters by Magnesium Reduction with Acetic Acid

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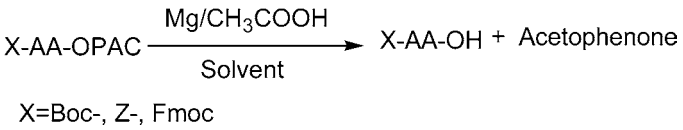
ABSTRACT



In the present study, we use magnesium turnings as a new deprotection reagent for the phenacyl group during orthogonal organic synthesis in the presence of other esters and sensitive protecting groups. By applying the new magnesium turnings/acetic acid deprotection method, phenacyl group can be more easily combined with other protecting groups that are not compatible with the zinc/acetic acid method.

Since its first use, the phenacyl group has proved to be an important reagent for protecting carboxyl functions during orthogonal organic synthesis in the presence of other esters and sensitive protecting groups (such as alkyl, benzyl esters, Boc, Z, Fmoc).[1] Phenacyl esters are generally solids that are easily prepared, purified and handled and soluble in most common solvents.The phenacyl group has been used in peptide synthesis for the temporary protection of the β- and γ-carboxy group of aspartic and glutamic acids.[2,3] In addition, in the segment condensation peptide synthesis method, the segments were protected as phenacyl esters at the carboxyl termini.[4] In solid-phase peptide synthesis, 4-(Boc-amino-acyloxymethyl)-phenylacetic acid phenacyl esters have been used as key intermediates to anchor the first amino acid to the polymer support.[5]

The phenacyl group is stable in 50% trifluoroacetic acid in methylene chloride and to HF (0 °C, 1 h),[3] as well as in high concentrations of hydrogen chloride or hydrogen bromide in acetic acid.[2] It is readily cleaved (a) by nucleophiles such as sodium thiophenoxide,[6] KCN/18-crown-6,[7] hydrazine,[8] and tetrabutylammonium fluoride,[9] (b) by hydrogenolysis with H_2/Pd−C,[2] or (c) by reduction with zinc in acetic acid[10] or with zinc with acetylacetone and pyridine.[11] It can also be removed by photolysis[12] and CuII/O^2/DMF−H_2O,[13] but these methods are somewhat too complicated to be used in synthesis.

In the course of the synthesis of Fmoc-glycyl-4-oxymethylphenoxy acetic acid as an intermediate for loading solid-phase peptide synthesis resins by the Fmoc strategy, we observed that the reduction of the intermediate compound phenacyl ester (Figure 1) either by the standard activated

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(1) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; J. Wiley & Sons: New York, 1999; pp 393−394, 728.
(2) Stelakatos, G. C.; Zervas, L. *J. Chem. Soc. C* **1966**, 1191−1199.
(3) Yang, C. C.; Merrifield, R. B. *J. Org. Chem.* **1976**, *41*, 1032−1041.
(4) Kimura, T.; Morikawa, T.; Takai, M.; Sakakibara, S. *J. Chem. Soc., Chem. Commun.* **1982**, 340−341.
(5) Mitchell, A. R.; Kent, S. B. H.; Engelhard, M.; Merrifield, R. B. *J. Org. Chem.* **1978**, *43*, 2845−2852.
(6) Sheehan, J. C.; Daves, G. D., Jr. *J. Org. Chem.* **1964**, *29*, 2006−2008.
(7) Tam, J. P.; Cunningham-Rundles, W. F.; Erickson, B. W.; Merrifield, R. B. *Tetrahedron Lett.* **1977**, 4001−4004.
(8) Kimura, T.; Takai, M.; Masui, Y.; Morikawa, T.; Sakakibara, S. *Biopolymers* **1981**, *20*, 1823−1832.
(9) (a) Ueki, M.; Kai, K.; Amemiya, M.; Horino, H.; Oyamada, H. *J. Chem. Soc., Chem. Commun.* **1988**, 414−415. (b) Namikoshi, M.; Kundu, B.; Rinehart, K. L. *J. Org. Chem.* **1991**, *56*, 5464−5466.
(10) Hendrickson, J. B.; Kandall, C. *Tetrahedron Lett.* **1970**, 343−344.
(11) Hagiwarwa, D.; Neya, M.; Hashimoto, M. *Tetrahedron Lett.* **1990**, *31*, 6539−6542.
(12) Sheehan, J. C.; Umezawa, K. *J. Org. Chem.* **1973**, *21*, 3771−3774.
(13) Ram, R. N.; Singh, L. *Tetrahedron Lett.* **1995**, *36*, 5401−5404.

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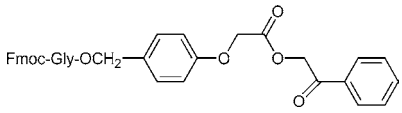


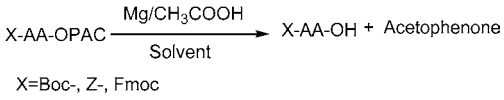
Figure 1.

zinc/acetic acid method or by the modified method was problematic. Indeed, the reaction was sluggish, and the formation of the desired product was accompanied by several byproducts. Fmoc-glycine was identified as one of these and is the result of the cleavage of the ester bond between the Fmoc-glycine and the 4-(oxymethyl)-phenoxy acetic acid

We attributed this cleavage to the significant Lewis acidity of the zinc salts generated during the reaction. To alleviate this problem, we considered reducing the phenacyl esters by utilizing a different metal that would produce, upon reduction, less acidic salts. We chose for this purpose magnesium, the common Grignard reagent, which is a more reductive reagent than zinc and generates less acidic salts.

To prove our hypothesis, we tried reducing phenacyl esters of common Z, Boc and Fmoc N^{α}-protected amino acids by magnesium turnings in a variety of solvents and with acetic acid as proton donor (Scheme 1).[14] The results obtained are

Scheme 1



summarized in Table 1. All isolated yields were more than 80%; the products were of high purity (>95%) and were characterized by elemental analysis and ^{1}H and ^{13}C NMR.

Of the solvents used, methanol was the most efficient (reaction time 60 min). When DMF was used more time was needed for full deprotection (120 min). Because some Fmoc amino acid phenacyl esters are insoluble in methanol, we used a mixture of MeOH/DMF (8:2) with no significant increase of deprotection time (75 min).

No racemization has been reported to date in the removal of phenacyl esters by the zinc/acetic acid method. In the present study, the deprotection products by magnesium turnings have the same specific rotation as the original compounds. Thus, racemization is not a problem. To

(14) **Typical Procedure.** To a solution of protected amino acid (2 mmol) in MeOH/DMF (8:2, 15 mL) were added acetic acid (1.5 mL, 24 mmol) and magnesium turnings (300 mg, 13 mmol). The solution was stirred for 60−100 min (checked by TLC; $CHCCl_3$/MeOH = 9:1) at room temperature. The reaction mixture was filtered, and the filtrate was concentrated in vacuo. The residue was diluted with 5% $NaHCO_3$ (10 mL) and ether/EtOAc (1:1, 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 saturated $KHSO_4$ and extracted with EtOAc (2 × 10 mL). The organic layer was washed with brine (2 × 10 mL), dried with sodium sulfate, and filtered. The filtrate was evaporated in vacuo, and the product was crystallized with petroleum ether (40−60).

Table 1. Removal of Protecting Group with Magnesium

			$[\alpha]^{25}_{D}$ (deg) (*c* 1, DMF)	
entry	starting material	product[a]	rxn	std
1	Boc Phe OPac	Boc Phe OH	−20.3	−20.8
2	Boc Asp(Bn) OPac	Boc Asp(Bn) OH	−20.1	−19.8
3	Boc Val OPac	Boc Val OH	−10.2	−10.0
4	Boc Leu OPac	Boc Leu OH	−29.5	−29.8
5	Boc Pro OPac	Boc Pro OH	−46.2	−46.0
6	Boc Glu(Bn) OPac	Boc Glu(Bn) OH	−16.6	−16.3
7	Boc Asn OPac	Boc Asn OH	−7.5	−7.6
8	Z Phe OPac	Z Phe OH	−37.8	−38.0
9	Fmoc Phe OPac	Fmoc Phe OH	−38.7	−39.0
10	FmocGlu(Bu)OPac	Fmoc Glu(Bu) OH	−19.1	−19.0
11	Fmoc Ala OPac	Fmoc Ala OH	−19.3	−19.2
12	FmocLys(Boc)OPac	Fmoc Lys(Boc) OH	−6.4	−6.6
13	Fmoc Val OPac	Fmoc Val OH	−17.9	−17.5
14	Fmoc Ser(Bu) OPac	Fmoc Ser(Bu) OH	−2.6	−2.4
15	Fmoc Tyr(Bu) OPac	Fmoc Tyr(Bu) OH	−30.1	−30.0
17	Fmoc Trp OPac	Fmoc Trp OH	−29.6	−29.5
18	Fmoc Met OPac	Fmoc Met OH	−30.8	−31.2

[a] MeOH/DMF (8:2) was used as solvent.

corroborate this observation, phenacylester was removed from the synthesized dipeptide Boc-(L)-Phe-(L)-OPac. After Boc deprotection, the resulting free dipeptide was analyzed by HPLC. No peak was detected at the time corresponding to the (L)-Phe-(D)-LeuOH isomer compared to control chromatograms of (L)-Phe-(L)-LeuOH (t_R = 13.908 min) and (L)-Phe-(D)-LeuOH (t_R = 16.702 min) isomers. This fact indicates that no racemization took place during derivatization with phenacyester and subsequent deprotection.

Finally, Fmoc-glycyl-4-oxymethylphenoxy acetic acid was prepared in high yield (87%) and purity by magnesium turnings reductive cleavage of its corresponding phenacyl ester (Figure 1). No detection of the side product Fmoc-Glycine was observed by TLC under these conditions.

In conclusion, we proved that magnesium is a more convenient reagent than zinc for the deprotection of the phenacyl temporary protecting group. Magnesium turnings need no activation before use, and the generated salts are soluble and do not produce side products by cleaving acid-sensitive ester bonds. Finally, the deprotection reaction can be performed in organic solvents such as DMF and MeOH and in the absence of water. By applying the magnesium turnings/acetic acid deprotection method, phenacyl group can be more readily combined with other protecting groups that are not compatible with the zinc/acetic acid method.

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Supporting Information Available: Experimental procedures and spectroscopic and analytical data for all compounds described. This material is available free of charge via the Internet at http://pubs.acs.org.

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