

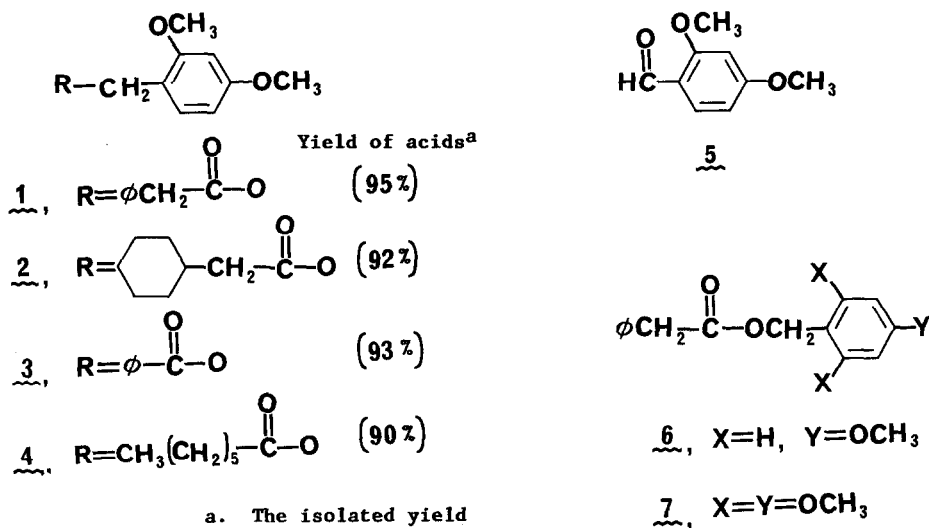
New Oxidatively Removable Carboxy Protecting Groups

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Summary: 2,6-Dimethoxybenzyl esters are readily oxidized by 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) to generate the corresponding carboxylic acids. Phenyl esters substituted with hydroxy, methoxy and dimethylamino groups are also efficiently oxidized by ceric ammonium nitrate (CAN) under pH control conditions.

Protecting groups for carboxylic acids continue to be of interest, as the restrictions placed upon them become more severe due to the high degree of functionalization of the synthetic target. The benzyl group is one of the most useful protecting groups for carboxylic acids, because it is stable to acid, alkali and a number of other usual reagents, and is readily removed by catalytic hydrogenation. The benzyl protection, however, may not be applied to the carboxylic acids having additional functional groups reducible by catalytic hydrogenation. We describe here the 2,6-dimethoxybenzyl (DMB)² functionality and phenyl ester derivatives (vide infra) which can be removed under mild oxidative conditions. Benzylic oxidation by 2,3-dichloro-5,6-dicyano benzoquinone (DDQ) has been well studied by Turner³, Oikawa⁴, and many others. It was surmised that addition of the methoxy group on the phenyl ring of the benzyl functionality would lower the oxidation potential⁵, thus facilitating the benzylic C-O bond fission under oxidative conditions.

When CH₂Cl₂ solution of 1⁶ containing a small amount of water was treated with an equimolar amount of DDQ at room temperature, a brownish green color of the initially formed charge transfer complex between the electron-donating DMB group and the electron attracting DDQ slowly faded into the light brownish yellow color. After 18 h, phenylacetic acid and 5 were isolated in excellent yield. Similarly, DDQ treatment of DMB esters 2, 3 and 4 gave the corresponding acids in high yield. Interestingly, the mono methoxybenzyl ester 6 was not affected under the same DDQ oxidation conditions. Probably the oxidation potential of 6 is not low enough to form the charge transfer complex with DDQ. On the other hand, 2,4,6-trimethoxybenzyl ester 7 was so labile that when 7 was subjected to the silica gel column purification, white 7 turned to a pink then a violet color and phenylacetic acid was produced in quantitative yield. Since the DDQ treatment occurs under mild and neutral conditions, the DMB ester will allow the presence of many other labile functionalities in the molecule at the deblocking stage.

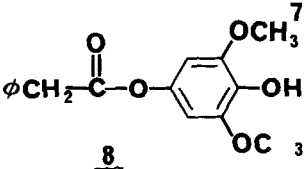
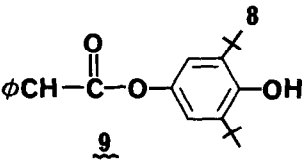
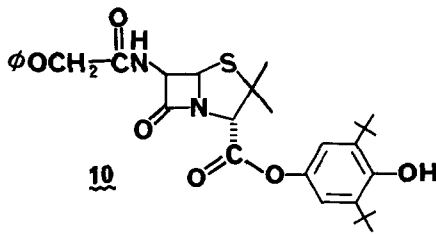
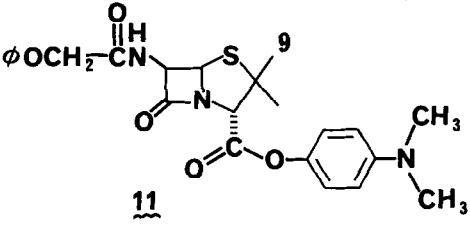


We have also found that the phenyl ester derivatives substituted with hydroxy, methoxy and dimethylamino groups are quite susceptible to the chemical oxidation (Table). Among the many oxidants, ceric ammonium nitrate (CAN) was the most general reagent for the oxidation of this class of compounds¹⁰. The oxidative removal of the phenyl esters 10 and 11 by CAN in aqueous CH₃CN were quite facile at pH=3.0 but the compounds were practically inert at pH=5.0 indicating that the oxidation power of CAN reduced as the pH of the media was raised. Since the CAN treatment occurs under mild and pH control conditions, the phenyl esters described in this communication will allow the presence of many other labile functionalities in the molecule at the deblocking stage. Finally, electrochemical reactions¹¹ might provide a viable alternative to the chemical oxidations, because they can supply a significant amount of energy (1volt=23 Kcal) under very mild conditions. This investigation is in progress in our laboratory.

Acknowledgments

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Table. Oxidative Removal of Phenyl esters

Esters	Oxidants	Yield of Acids % ^c
	CAN (no buffer) ^a CAN (pH=4.0) CAN (pH=6.0) MnO ₂ ^b	97 80 65 60
	CAN (pH=2.0)	95
	CAN (pH=3.0)	75
	CAN (pH=2.7)	69

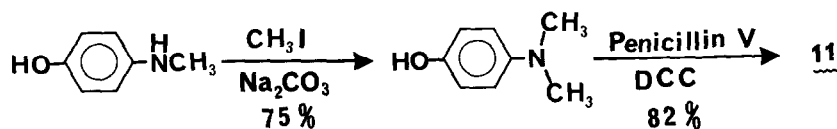
a. All CAN oxidations were carried out in CH₃CN-H₂O at 0°, for 4 h.

b. Activated MnO₂ in CH₃CN-H₂O at room temperature. c. The isolated yield.

References and Notes

- See review by E. Haslam, *Tetrahedron*, **36**, 2409 (1980); J. F. W. McOmie, *Chemistry and Industry*, No.18, 603 (1979).

2. Abbreviation: DMB=2,6-Dimethoxy benzyl
3. A. B. Turner, "Synthetic Reagents", J. S. Pizey, Ed., Wiley, New York, 1977, p 193.
4. a) Y. Oikawa and O. Yonemitsu, Heterocycles, **5**, 233 (1976); b) Y. Oikawa and O. Yonemitsu, J. Org. Chem., **42**, 1213 (1977); c) Y. Oikawa, T. Yoshioka, K. Mohri, and O. Yonemitsu, Heterocycles, **12**, 1457 (1979); d) Y. Oikawa, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., **23**, 885 (1982); e) Y. Oikawa, T. Tanaka, K. Horita, T. Yoshioka, and O. Yonemitsu, Tetrahedron Lett., **25**, 5393 (1984).
5. A. Zweig, W. G. Hodgson, and N. H. Jura, J. Amer. Chem. Soc., **86**, 4124 (1964).
6. The ester 1 was prepared by the coupling of phenylacetyl chloride and 2,6-dimethoxybenzyl alcohol (K&K Rare and Fine Chemicals) in the presence of triethylamine in CH_2Cl_2 .
7. 2,6-Dimethoxyhydroquinone was prepared by reduction of 2,6-dimethoxyquinone with $\text{Na}_2\text{S}_2\text{O}_4$ and coupled with phenylacetic acid in the presence of DCC.
8. 2,6-Di-t-butylhydroquinone was prepared by reduction of 2,6-di-t-butylquinone with $\text{Na}_2\text{S}_2\text{O}_4$ and coupled with phenylacetic acid in the presence of DCC.
9. This compound was prepared by the sequence shown below.



10. T. Fukuyama, R. K. Frank, C. F. Jewell, J. Amer. Chem. Soc., **102**, 2122 (1980).
Also, see a) W. H. Huffman, K. G. Holden, T. F. Buckley, III, J. G. Gleason, and L. Wu, J. Amer. Chem. Soc., **99**, 2352 (1977); b) D. R. Kronenthal, C. Y. Han and M. Taylor, J. Org. Chem., **47**, 2765 (1982).
11. For electrochemical oxidation of phenyl esters see: R. W. Johnson, M. D. Bednarski, B. F. O'Leary and E. R. Grover, Tetrahedron Lett., **22**, 3715 (1981).
12. All new compounds had spectroscopic properties consistent with the assigned structures.

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