Pergamon

Tetrahedron Letters, Vol. 35, No. 11, pp. 1651-1652, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $6.00+0.00

0040-4039(94)E0151-M

The (±)-1-(4-Methoxyphenyl)ethyl Ester as a Carboxyl Protecting Group

Michael S. Bernatowicz,* Hann-Guang Chao, and Gary R. Matsueda

The Bristol-Myers Squibb Pharmaceutical Research Institute
P. O. Box 4000, Princeton, New Jersey 08543-4000 USA

Abstract: Unhindered carboxylic acids were converted to their (±)-1-(4-methoxyphenyl)ethyl (Mpe) esters in good yields by condensation with (±)-1-(4-methoxyphenyl)ethanol under mild conditions. The Mpe esters were rapidly and quantitatively cleavable by either 1% TFA in CH_2Cl_2 or 10% DCA in CH_2Cl_2, conditions which leave Boc, t-butyl ester and ether intact. An Mpe ester was removed by hydrogenolysis much more slowly than the analogous benzyl ester.

This laboratory recently reported on the utility of the (±)-1-(4-methoxyphenyl)ethyloxycarbonyl (Mpeoc)[1,2] group for protection of the δ-amino group of ornithine in the solid phase synthesis of arginine peptides by specific guanylation of ornithine residues with 1H-pyrazole-1-carboxamidine.[3] The ease with which the Mpeoc group was completely cleaved under mild acid conditions (1% by vol. TFA in CH_2Cl_2 or 3% DCA in CH_2Cl_2) without cleavage of Boc or t-butyl ester or ether protection suggested that the (±)-1-(4-methoxyphenyl)ethyl (Mpe) ester counterpart could be similarly useful for selective carboxyl group protection. Although many different types of esters are available for carboxyl group protection,[4] the potentially unique acid lability possible for the Mpe ester could make it particularly well suited for certain synthetic applications.

To test these hypotheses a variety of Mpe esters were prepared by condensation of equimolar amounts of carboxylic acids and (±)-1-(4-methoxyphenyl)ethanol[5] (MpeOH) using one equivalent of DCC and 0.1 equivalent of DMAP in THF.[6] Results of the esterification reactions are summarized in Table 1. In all cases, except for the hindered trimethylacetic acid derivative, pure Mpe esters[7] were obtained in good yields without chromatographic purification. Condensation of trimethylacetic acid with MpeOH under such conditions was slow even at room temperature giving rise to N-trimethylacetyl-N,N'-dicyclohexylurea as an undesired side product (>23% of theoretical isolated) and necessitating purification of Mpe ester **3** by silica gel chromatography eluting with ethyl acetate in hexanes. It is noteworthy that Mpe esters were found to be stable

Table 1. Results of Esterifications of Carboxylic Acids by MpeOH / DCC / DMAP (cat.) in THF.

Carboxylic acid	Mpe ester entry	Reaction time (h) (4 °C → room temp)	Yield (%)
cyclohexyl	**1**	17	93
benzoic	**2**	24	91
trimethylacetic	**3**	27	28
Boc-L-Tryptophan	**4**	17	87

to silica gel chromatography, extractive work up with aqueous acid (5% $KHSO_4$), and glacial acetic acid.

Initial small scale experiments showed that Mpe esters **1-3** were quantitatively cleaved by 1% (v/v) TFA (10 equiv.) in CH_2Cl_2 within 5 min at room temp to produce their precursor acids as evidenced by TLC and MS data. Milder acid conditions (DCA in CH_2Cl_2) were also investigated. It was found that 10% DCA (20 equiv.) in CH_2Cl_2 was required to produce the desired cleavage within 15 min at room temp.[8] In a

preparative scale experiment (1.35 mmol) Mpe ester 2 was treated with 1% TFA as described and pure benzoic acid was isolated (100% yield) after extractive work up. Also isolated separately was the labile TFA-OMpe ester (Fig.1.) as a colorless oil which, on standing overnight at room temperature, eliminated TFA yielding a deep blue oil which gave an NMR spectrum consistent with cationic polymeric decomposition products. These results agree with Mpe group cleavage taking place as depicted in Figure 1.

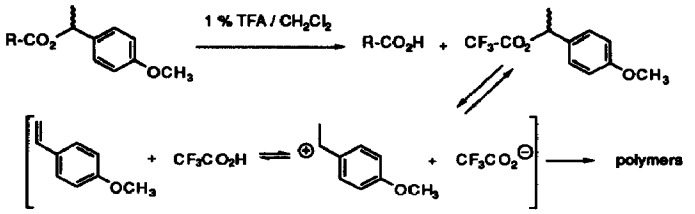

Figure 1. Cleavage of Mpe esters by TFA in CH_2Cl_2.

Previous experience with the Mpeoc group[2] has shown that the reactive products generated upon Mpe removal by acid are capable of alkylating the nucleophilic indole ring of Trp. This alkylation side reaction observed for Mpe ester **4** was almost completely eliminated when 20% (w/v) skatole was employed as scavenger[9] in the 10% DCA (30 equiv.) / CH_2Cl_2 cleavage reagent. A 63% yield[10] of pure Boc-Trp-OH was isolated when ester **4** was cleaved for 15 min at room temp under these acid / scavenger conditions.

The reactivities of Boc-Mpe ester **4** and its benzyl ester counterpart (Boc-Trp-OBzl) were compared under similar catalytic hydrogenolysis conditions (10% Pd-C cat., slight positive pressure of H_2 in gas balloon, in MeOH (for **4**) or 30% EtOAc in MeOH, room temp). Mpe ester **4** was nearly completely cleaved only after 23 h under these conditions, in contrast, Boc-Trp-OBzl was completely cleaved to give the same product (Boc-Trp-OH) in less than 10 min. The dramatic difference in reactivity observed here suggests that benzyl esters may be selectively removable in the presence of Mpe esters by catalytic hydrogenolysis.

Acknowledgement: The authors are grateful to Anne M. Starrett for high resolution MS data.

REFERENCES AND NOTES

1. Abbreviations used: Boc = *tert*-butyloxycarbonyl, Bzl = benzyl, cat. = catalytic amount, DCA = dichloroacetic acid, DCC = N, N'-dicyclohexylcarbodiimide, DMAP = 4-dimethylaminopyridine, EtOAc = ethyl acetate, EtOH = ethanol, Mpe = 1-(4-methoxyphenyl)ethyl, Mpeoc = 1-(4-methoxyphenyl)ethyloxycarbonyl, MeOH = methanol, MS = mass spectroscopy, TFA = trifluoroacetic acid, THF = tetrahydrofuran, TLC = thin layer chromatography, Trp = Tryptophan.
2. Bernatowicz, M. S.; Matsueda, G. R. A Novel Fmoc-protected Ornithine Derivative Useful for the Synthesis of Arginine Peptides by a Guanylation Approach. In *Peptides: Proceedings of the 13th American Peptide Symposium;* Hodges, R. S. Ed.; ESCOM, Leiden, the Netherlands (in press).
3. Bernatowicz, M. S.; Wu, Y.; Matsueda, G. R. *J. Org. Chem.* **1992**, *57*, 2497-2502.
4. For a compendium of esters useful for carboxyl group protection see Greene, T. W. *Protective Groups in Organic Synthesis;* John Wiley and Sons, Inc. New York, 1981; pp. 152-186, and references therein.
5. (±)-1-(4-Methoxyphenyl)ethanol was readily prepared in >95% yield by reduction of 4-methoxyacetophenone (Aldrich, Milwaukee WI) with $NaBH_4$ in EtOH.
6. Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475-4478.
7. Purity and authenticity of all reported Mpe esters were established by ^1H NMR, mass spectroscopy, and TLC. Accurate mass (FAB MS) data (calcd.; found): **1** (M+•), (262.1569; 262.1561), **2** (M+•), (256.1100; 256.1097), **3** (M+•), 236.1413; 236.1420), **4** $(M+H)^+$, (439.2232; 439.2245).
8. Mpeoc protection of the δ-amino group of ornithine was cleaved more rapidly with 3% DCA in CH_2Cl_2.
9. Other less effective scavengers examined were (highest to lowest efficacy): 1,3-dimethoxybenzene, veratrole, and xanthene. Under these DCA mediated cleavage conditions these scavengers, unlike skatole, slowed the cleavage rate about 4-fold. In no case was removal of the Boc group observed even after 60 min treatment with 10% DCA.
10. The modest yield was largely attributable to loss of product during extraction of the large amount of scavenger.

(*Received in USA* 20 *October* 1993; *revised* 21 *December* 1993; *accepted* 11 *January* 1994)