Novel Carboxylic Acid and Carboxamide Protective Groups Based on the Exceptional Stabilization of the Cyclopropylmethyl Cation

Louis A. Carpino,* Hann-Guang Chao, Shahnaz Ghassemi, E. M. E. Mansour,† Christoph Riemer, Ralf Warrass, Dean Sadat-Aalaee, George A. Truran, Hideko Imazumi, Ayman El-Faham,† Dumitru Ionescu,‡ Mohamed Ismail, Thadeus L. Kowaleski, and Chung Hwa Han

Department of Chemistry, Box 34510, University of Massachusetts, Amherst, Massachusetts 01003-4510

Holger Wenschuh, Michael Beyermann, and Michael Bienert

Institute of Molecular Pharmacology, Alfred Kowalke Str. 4, D-10315 Berlin, Germany

Hitesh Shroff and Fernando Albericio§

Millipore Corporation, 75A Wiggins Avenue, Bedford, Massachusetts 01730

Salvatore A. Triolo, Nuria A. Sole, and Steven A. Kates

Perseptive Biosystems, Inc., 500 Old Connecticut Path, Framingham, Massachusetts 01701

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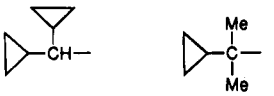
The facile solvolysis of cyclopropylmethyl substrates has long been recognized as being exceptional, an α-cyclopropyl substituent being even more effective, in many situations, than the α-phenyl residue in cationic stabilization.[1] Surprisingly, little practical application of this unusual effect has been made in spite of the fact that no moiety of lower molecular weight comes close to equaling the effect of this simple three-carbon unit. In 1977, Brady, Hirschmann, and Veber[2] examined the [(cyclopropylmethyl)oxy]carbonyl and [(1-cyclopropylethyl)oxy]-carbonyl groups as potential N-α-amino acid protectants. A deficiency of the former, noted by Veber and coworkers, is the rearrangement of a portion of the substrate under acidic deblocking conditions to the (1-cyclobutyloxy)carbonyl system with consequent partial early termination of the deblocking process.

In the present paper it is demonstrated that the secondary system **1** incorporating two α-cyclopropyl units or the tertiary system **2** having one cyclopropyl and two methyl residues give rise to two widely applicable protective systems for carboxyl and amide protection, respectively. The dicyclopropylmethyl (Dcpm) group can be used for carboxylic acid protection where selective removal is necessary in the presence of *tert*-butyl-derived or *N*-trityl side chain protection.



1 **2**

A typical example involved assembly of the protected hexapeptide acid **3**[3] from Fmoc-Tyr(*t*-Bu)-ODcpm by the rapid, continuous Fmoc/tris(2-aminoethyl)amine (TAEA) solution method of peptide synthesis.[4,5] Except for Arg, which was coupled via *N*-[[(dimethylamino)-1*H*-1,2,3-triazolo[4,5-*b*]pyridin-1-yl]methylene]-*N*-methylmethanaminium hexafluorophosphate *N*-oxide (HATU),[6] all acylations were carried out via the appropriate Fmoc amino acid fluorides[7] which were employed in the presence of base (DIEA). The final deblocking step involved short time (15 min) treatment of the Dcpm ester with 1% trifluoroacetic acid (TFA) in DCM.

Fmoc–Ile–Thr(*t*-Bu)–Arg(Pmc)–Gln(Trt)–Arg(Pmc)–Tyr(*t*-Bu)–OH

3

Comparable amide protection, useful for avoidance of dehydration, to enhance solubility or interfere with aggregation[8] can be achieved similarly. Although the Dcpm residue can be used for this purpose, its removal from nitrogen is somewhat sluggish and it is preferable to use a tertiary system, such as the dimethylcyclopropylmethyl (Dmcp) residue **2**, which provides the desired level of reactivity.[9] Table 1 collects some relevant half-times for conversion of simple *N*-alkyl derivatives to acetamide by treatment with TFA and provides comparison with analogous phenylated systems. Comparison between **5** and **6** shows the cyclopropyl system to be about 10 times more reactive than the phenyl analog. A further deficiency of phenylated systems was noted in the case of **7**, which was somewhat more reactive than **5**, namely separation from the reaction mixture of an insoluble sticky material, presumably a polymer of the corresponding olefin.[10] Under the conditions of Table 1,[12] *N*-

† On leave from the Department of Chemistry, Faculty of Science, Alexandria University, Alexandria, Egypt.

‡ On leave from the Department of Chemistry, Faculty of Chemistry, University of Bucharest, 70346 Bucharest, Romania.

§ Current address: Department of Organic Chemistry, University of Barcelona, 08028–Barcelona, Spain.

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(9) Once the *tert*-butyl residue had become established as an important oxygen protectant in the form of ethers and esters and as an amino protectant in the form of urethanes, *N-tert*-butyl amides were examined for Asn and Gln protection. The results were, however, disappointing. See: Callahan, F. M.; Anderson, G. W.; Paul, R.; Zimmerman, J. E. *J. Am. Chem. Soc.* **1963**, *85*, 201.

(10) If the deblocking is carried out in the presence of triethylsilane no polymer is formed. Instead ^{1}H NMR examination suggests formation of $(C_6H_5)_2CHCH_3$ (doublet near δ 1.61) by reductive capture of the intermediate cation.[11]

(11) Triethylsilane has been recommended as a convenient scavenger for cations liberated during the final deblocking step of Fmoc/*t*-Bu solid phase peptide synthesis. See: (a) Pearson, D. A.; Blanchette, M.; Baker, M. L.; Guindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739. (b) Mehta, A.; Jaouhari, R.; Benson, T. J.; Douglas, K. T. *Tetrahedron Lett.* **1992**, *33*, 5441. For a discussion of the propensity of various cyclopropylmethyl cations to suffer ring opening vs. scavenging by hydride ion in the presence of trisubstituted silanes, see: Carey, F. A.; Tremper, H. S. *J. Am. Chem. Soc.* **1969**, *91*, 2967.

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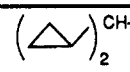
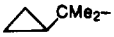
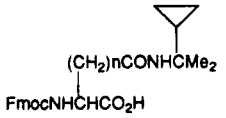
Table 1. Approximate Time Course for Deblocking of CH_3CONHR in Neat Trifluoroacetic Acid [a]

Compound No.	R	$t_{1/2}$ (min)
4		19
5		1-2
6	$C_6H_5CMe_2$–	15
7	$(C_6H_5)_2CMe$–	< 1

[a] The amide (50 mg) is added to 0.6 mL of TFA at room temperature and the deblocking followed by ^1H NMR spectroscopy. In the TFA medium the methyl group of acetamide appeared near δ 2.1, upfield from that of the various substituted acetamides.

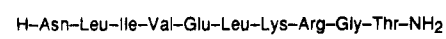
(cyclopropylmethyl)-, *N-tert*-butyl-, *N-tert*-adamantyl-, and *N*-(1-methyl-1-cyclohexyl)acetamide showed no reactivity for periods up to 24 h.

Application of the Dmcp residue in solid phase syntheses of peptides containing Asn and Gln was demonstrated in a number of cases via utilization of intermediates **8a** and **b**, respectively.



8a, n=1
8b, n=2

Examples include the ACP decapeptide,[16] bombesin,[17] and Briand's peptide **9**.[18] In the case of **9**,

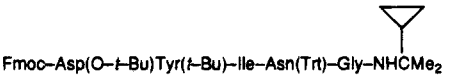


9

use of ω-*N*-tritylasparagine is problematic since deblocking of *N*-terminal Asn is sluggish in TFA.[18] In contrast, the Dmcp residue was removed rapidly from both the internal and N-terminal positions for both Asn and Gln.

A similar advantage of **8a** over the analogous ω-trityl derivative was observed when the new fluoride-based coupling reagent tetramethylfluoroformamidinium hexafluorophosphate (TFFH)[19] was used for synthesis of the acyl carrier decapeptide (ACP). Introduction of asparagine via Fmoc-Asn(Trt)-OH/TFFH gave a significant amount of the des(Asn)ACP nonapeptide, whereas with Fmoc-Asn(Dmcp)-OH/TFFH none of this byproduct was observed.

Use of the Dmcp group as C-terminal amide protectant also facilitated the direct synthesis of peptide amides by the Fmoc/TAEA rapid solution synthesis. Previously, peptide amides were obtained indirectly by this technique via initial assembly of an ester and subsequent ammonolysis.[5] The Dmcp-protected amide function resembles an ester in enhancing the solubility of the growing peptide amide in the organic phase. An example is the synthesis of the protected form **10** of the C-terminal



10

ACP pentapeptide amide in 61% yield via no-base coupling[20] of Fmoc amino acid fluorides. Complete deblocking with removal of the Fmoc function by piperidine followed by all side chain *tert*-butyl and trityl residues and the Dmcp function by TFA gave a peptide amide of excellent quality as established by HPLC and MS analysis. The HPLC and MS analysis indicated that no trace of the Dmcp residue or any rearrangement product thereof remained attached to any portion of the resulting peptide amide.[21,22]

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Supporting Information Available: Experimental details and characterizing data for all compounds (66 pages).

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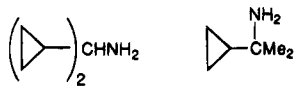
(12) Compounds **4** and **5** were obtained from the two amines **i** and **ii**.



i **ii**

Although both **i**[13] and **ii**[14] are known, convenient methods for their synthesis were developed in the present work. Both were obtained by $LiAlH_4$ reduction of the corresponding azides which were synthesized by reaction of the corresponding alcohols with hydrazoic acid generated *in situ* from NaN_3 and trichloroacetic acid in $CHCl_3$. For the method see: (a) Coombs, M. M. *J. Chem. Soc.* **1958**, 3454. (b) Leffler, J. E.; Zupancic, J. J. *J. Am. Chem. Soc.* **1980**, *102*, 259. Any such acid-catalyzed reaction of a cyclopropylmethyl substrate with retention of the three-membered ring requires careful choice of nucleophile and reaction conditions to avoid conversion to homoallyl derivatives by facile ring opening processes.[15]

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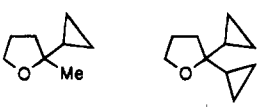
(21) Rearrangement of the Dmcp residue by ring opening, as described for the analogous primary system[2] is unlikely. For a recent discussion of the problems of retention of *tert*-butyl or other cationic residues during acidic deblocking reactions, see: Sole, N. A.; Barany, G. *J. Org. Chem.* **1992**, *57*, 5399.

(22) One of the original motivations for examination of the various cyclopropylmethyl systems described in this paper was the possibility that internal scavenging might have been expected to avoid or reduce the need for external scavengers. Thus in the presence of water, acidic treatment of dicyclopropyl methyl carbinol yields **iii**[23] and tricyclopropyl carbinol yields **iv**.[24] Whether analogous derivatives are actually formed during the deblocking of the Dmcp group remains to be determined.



iii **iv**

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