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The Redox-Sensitive, Colored N-3-(3′,6′-Dioxo-2′,4′,5′-Trimethylcyclohexa-1′,4′-Diene)-3,3-Dimethylpropionyl (Q) Amino-Protecting Group

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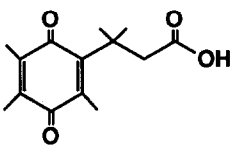
Abstract: Amino acids bearing the title (Q) protecting group undergo coupling without racemization via the mixed anhydride technique. Selective deblocking occurs via $Na_2S_2O_4$.

Among amino-protecting groups which are cleaved under reductive conditions, the benzyloxycarbonyl (Z) group occupies a special position from both a historical[1] and a practical[2] point of view. Deblocking is achieved cleanly by hydrogenolysis over a palladium catalyst. Because such catalysts are readily poisoned, initiation of the deblocking process is sometimes unpredictable and the use of highly purified reaction components is advised.[3] Furthermore, the technique cannot be used, except under special circumstances,[4] if the substrate bears a divalent sulfur moiety. Thus, for application to the synthesis of peptides, specific amino acids such as methionine or cysteine must be avoided.

Where redox-sensitive deblocking is advantageous it would be useful to have a protective function not subject to such limitations. A system which fulfills this requirement can be derived from quinone acid **1** which



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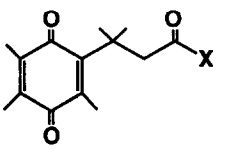
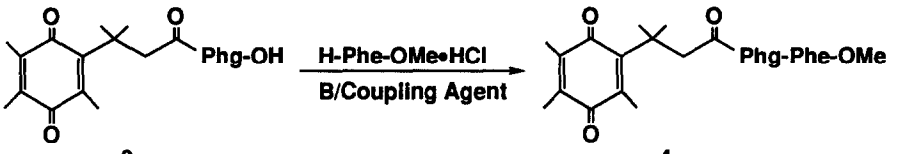


2

has previously been described in connection with the potential redox-controlled release of bioactive materials under physiological conditions.[5] Simple amides and esters (**2**, X = NR_2, OR) were shown to undergo non-hydrolytic release of the corresponding amine or alcohol under mild reductive conditions. In view of the general stability of quinone acid **1** and its derivatives, these compounds have been selected as potentially significant amino-protecting functions in organic synthesis. Among other advantages, the yellow or orange color of materials bearing this protectant allows for easy monitoring during interconversions or purification steps.

In considering possible applications to the specific case of peptide synthesis, it should be noted that amides derived from **1** represent classical *acyl* rather than *carbamyl* protectants and therefore the question of racemization during the coupling step arises, it being generally observed that the coupling of amino acids

protected by acyl functions leads to racemization via the incursion of oxazolone intermediates.[6] Initial model studies were carried out with α-phenylglycine (Phg) since this amino acid is not only highly sensitive toward racemization but the loss of chirality is readily visualized by ^{1}H NMR analysis.[7] Although dipeptide **4**, derived



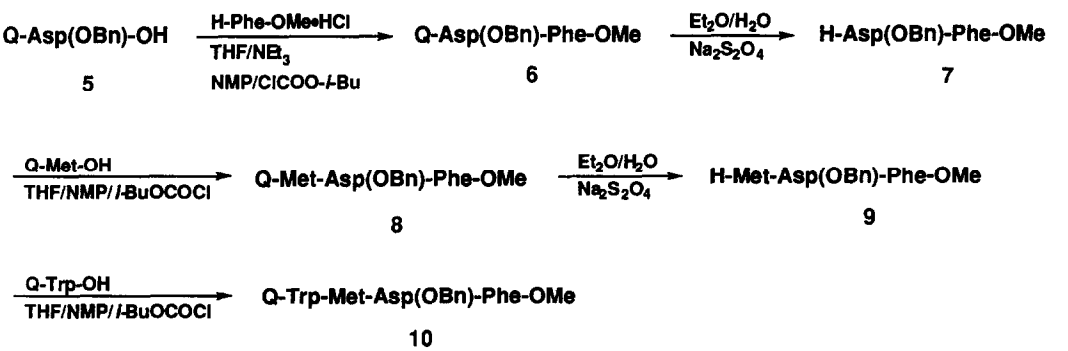
3 **4**

from **3** in the presence of DCC, was extensively racemized (13% of the DL-form), application of the mixed anhydride technique[8] using *i*-butyl chloroformate and N-methylpiperidine led to the formation of less than 0.55% of the DL-isomer.[9] A second racemization test which sums the loss of chirality throughout a complete coupling cycle involving preparation of the quinone-protected phenylalanine (**3**, Phg replaced by Phe), its coupling to leucine methyl ester, deblocking and finally N-benzoylation. Again no significant racemization (< 0.55%) was detected at the phenylalanine residue.[9]

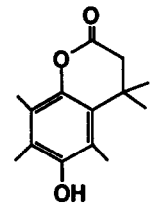
Quinone-protected amino acid **3** appeared to be stable indefinitely in pure TFA, a commonly-used reagent for BOC-deblocking. With 20% piperidine in DMF (FMOC deblocking conditions) **3** was stable for periods up to 4 h. Although normal quinones are readily subject to attack by nucleophiles, the presence of four alkyl substituents presumably acts to moderate any such reactions in the case of **3**.[10]

In order to demonstrate the value of a quinone-based protecting group subject to reductive deblocking, the protected tetragastrin sequence **10**[11] was synthesized as outlined in Scheme I. Catalytic hydrogenolysis of **6** in

Scheme I



the presence of acetic acid removed both the quinone acid protectant and the benzyl group to give dipeptide acetate **11** along with by-product lactone **12**. Selective deblocking of only the quinone acid residue was effected



H-Asp-Phe-OMe•HOAc

11

12

by treatment of **6** with sodium dithionite (15 min, RT, Et_2O-H_2O), thus allowing assembly to continue. Without removing by-product **12** treatment with quinone acid-protected methionine gave tripeptide **8**. Following coupling, by-product **12** was easily removed due to its ready solubility in solvents such as ethyl acetate and the fact that it can be extracted into dilute sodium hydroxide. Solution of the lactone in NaOH is accompanied by ring opening since, upon acidification, quinone acid **1**, rather than the lactone itself, separates. Recovery is high (~ 90%) and the acid can be recycled.

Treatment of protected tripeptide **8** with $Na_2S_2O_4$ as noted above gave **9** which was converted directly to protected tetrapeptide **10** by coupling with Q-protected tryptophan. Tetrapeptide **10** was obtained in the form of light orange crystals, mp 128-131°C, and characterized fully by IR, ^1H NMR and elemental analysis.[12]

ACKNOWLEDGMENT

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12. All isolated new compounds gave satisfactory elemental analyses (C, H, N ± 0.3%) and consistent IR and ^{1}H NMR spectral data. Selected characterization data: (a) **Q-Phg-OH**: mp 122-123°C; α_D^{24} = +112 (c = 0.2, EtOH); (b) **Q-D-Phg-OH**: mp 122-123°C; α_D^{24} = -114.8 (c = 0.2, EtOH); (c) **Q-Phe-OH**: mp 60-62°C; α_D^{24} = +65.6 (c = 0.2, $CHCl_3$); (d) **Q-D-Phe-OH**: mp 59-61°C; α_D^{24} = -65.5 (c = 0.2, $CHCl_3$); (e) **Q-Asp(OBn)-OH**: mp 137.5-138°C; α_D^{24} = +7.0 (c = 0.2, EtOH); (f) **Q-Met-OH**: mp 140-142°C; α_D^{24} = +45.5 (c = 0.2, EtOH); (g) **Q-Trp-OH**: mp 170.5-171.5°C; α_D^{24} = +23.0 (c = 0.2, EtOH); (h) **Q-Phe-Leu-OMe**: mp 125-126°C; α_D^{24} = -7.0 (c = 0.2, EtOAc); ^{1}H NMR ($CDCl_3$) δ 0.9 (d, 6, $(\underline{CH_3})_2CH$), 1.3 (s, 3, gem-Me_1), 1.4 (s, 3, gem-Me_2), 1.5 (m, 3, $CH\underline{CH_2}CH$, $(CH_3)_2\underline{CH}CH_2$), 1.95 (s, 6, 4′- and 5′-Me's), 2.1 (s, 3, 2′-Me), 2.82 (s, 2, 2-CH_2), 3.0 (d, 2, $CH_2C_6H_5$), 3.68 (s, 3, MeO), 4.5 (m, 1, $NH\underline{CH}CH_2$), 4.57 (m, 1, $NH\underline{CH}CH_2$), 6.02 (m, 2, NH), 7.15-7.3 (m, 5, phenyl); IR (KBr) 3290 (NH), 1745 (ester C=O), 1630 cm^{-1} (amide and quinone C=O); (i) **Protected Tetrapeptide 10**: mp 128-131°C (dec); α_D^{24} = +29.5 (c = 0.2, EtOAc); ^{1}H NMR ($CDCl_3$) δ 1.3 (s, 3, gem-Me_1), 1.38 (s, 3, gem-Me_2), 1.78 (q, 2, $CH\underline{CH_2}CH_2$), 1.9 (s, 9, 4′,5′-Me's and MeS), 2.1 (s, 3, 2′-Me), 2.25 (t, 2, $CH_2\underline{CH_2}S$), 2.6-3.3 (m, 8, 2-CH_2, $CH\underline{CH_2}CO$, $CH\underline{CH_2}C{=}C$ and $CH\underline{CH_2}C_6H_5$), 3.68 (s, 3, MeO), 4.36 (q, 1, $NH\underline{CH}CH_2C_6H_5$), 4.56 (q, 1, $NH\underline{CH}CH_2CH_2$), 4.71 (quintet, 2, $NH\underline{CH}CH_2CO$ and $NH\underline{CH}CH_2C{=}C$), 5.1 (s, 2, CH_2O), 6.25 (d, 1, $\underline{NH}CHCH_2CH_2$), 6.45 (d, 1, $\underline{NH}CHCH_2C_6H_5$), 6.95-7.4 (m, 16, aryl, NH), 7.7 (d, 1, $\underline{NH}CHCH_2C{=}C$), 8.27 (broad s, 1, NHC=C); IR (KBr) 3300 (NH), 1730 (ester C=O), 1635 cm^{-1} (quinone and amide C=O).

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