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The carbonylhydrazone pseudopeptide link via quinonic oxidation of the peptide amino terminus

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Abstract

Oxidation of the amino terminus in α-amino acid derivatives using 3,5-di-*tert*-butyl-1,2-quinone generally failed to give the corresponding ketone, and cyclic compounds due to the nucleophilic attack of the phenol hydroxyl in the intermediate 2-aminophenol were recovered. The expected ketone was obtained by using 2,6-di-*tert*-butyl-1,4-quinone, and the condensation of the ketone and a peptide hydrazide gave the pseudopeptide carbonylhydrazone link. © 2000 Elsevier Science Ltd. All rights reserved.

A challenge in the design of bioactive peptide analogues for therapeutic purposes is to introduce separately and easily a chemical diversity both on the peptide backbone and the side substituents.[1] The modification of the peptide backbone is expected to mainly reduce enzymatic degradation and to orientate the conformational preferences by affecting the backbone–backbone interactions. The modification of the side substituents may strengthen the molecular recognition by the biological target. To this aim, one can take advantage of the chemical diversity offered by the great number of available, coded and non-coded α-amino acids, and to modify their amino or carboxylic group in order to create a non-peptidic link between α-carbons. We have considered the carbonylhydrazone link C^{α}–CO–NH–N=C^{α} as a possible amide surrogate resulting from the coupling of a hydrazide and an α-keto acid derivative.

$$R^1\text{-CO-NH-N=}CR^2\text{-CO-}R^3 \Longrightarrow R^1\text{-CO-NH-NH}_2 + O\text{=}CR^2\text{-CO-}R^3 \Longleftarrow H_2N\text{-}CHR^2\text{-CO-}R^3$$

α-Keto acids are natural metabolites derived from the α-amino acids by enzymic oxidation.[2,3] They have also been obtained from α-amino acids in three main ways: (i) hydrolysis of a

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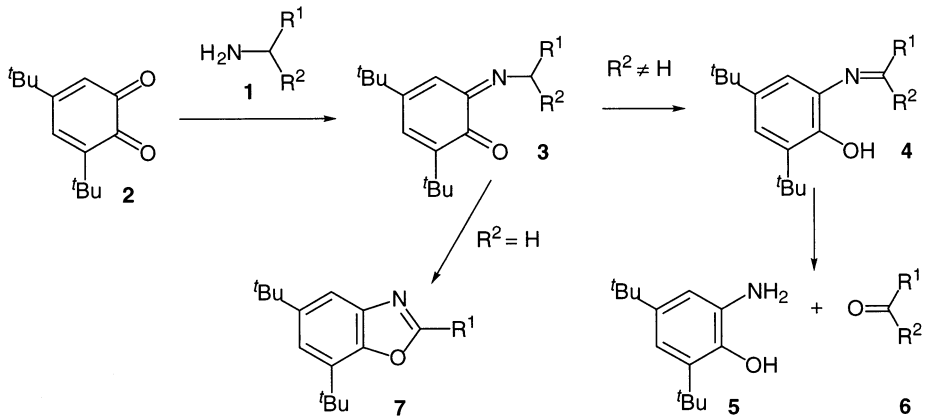
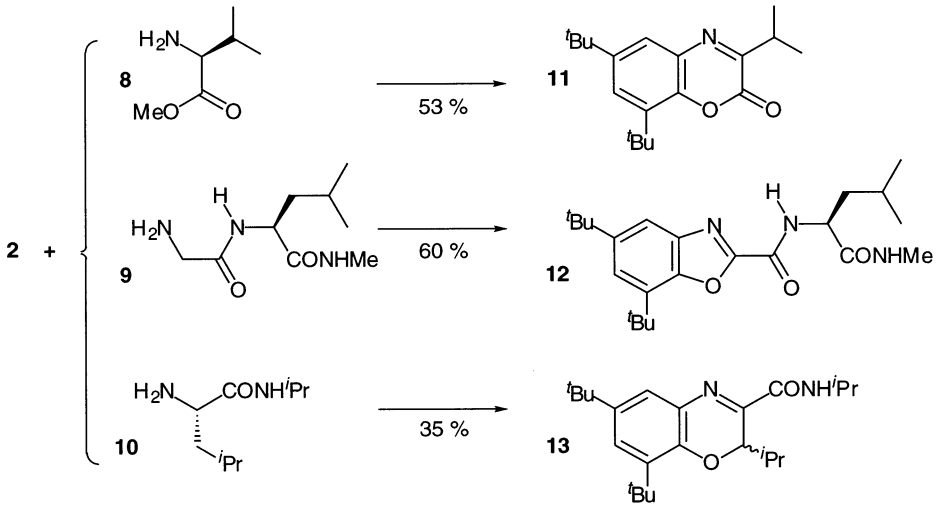
2-trifluoromethyl-1,3-oxazolone;[4] (ii) diazotation, reduction of the diazo into the corresponding hydrazone and hydrolysis of the hydrazone;[5] (iii) oxidation of the amino group into an imino group with ^{t}BuOCl/DBU, and hydrolysis of the imine.[6] However, none of the above procedures is convenient to the conversion of a peptide amino terminus into a ketone. We have therefore investigated the procedure proposed by Corey and Achiwa,[7] with direct oxidation of a primary amine **1** using 3,5-di-*tert*-butyl-1,2-quinone **2** (Scheme 1). This procedure does not apply to aldehyde formation as the cyclic side product **7** is obtained when the amino group is connected to a methylene.[7]



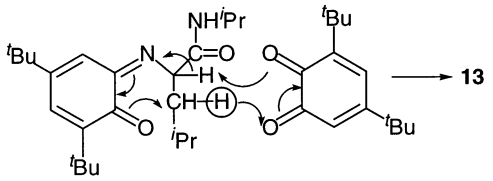
Scheme 1. Oxidation of primary amines into ketones using 3,5-di-*tert*-butyl-1,2-quinone **2**.[7,8]

Oxidation of the α-amino acid derivatives **8**–**10** using quinone **2** under Corey and Achiwa conditions failed to give the expected ketones, but the cyclic derivatives **11**–**13** (Scheme 2) obtained in medium to high yield, which were characterized by mass spectroscopy, ^{1}H NMR and element analysis.[9] Due to the nucleophilic properties of the ester carbonyl in **8**, the cyclic compound **11** was not unexpected and, on the basis of Corey and Achiwa's observations, so was



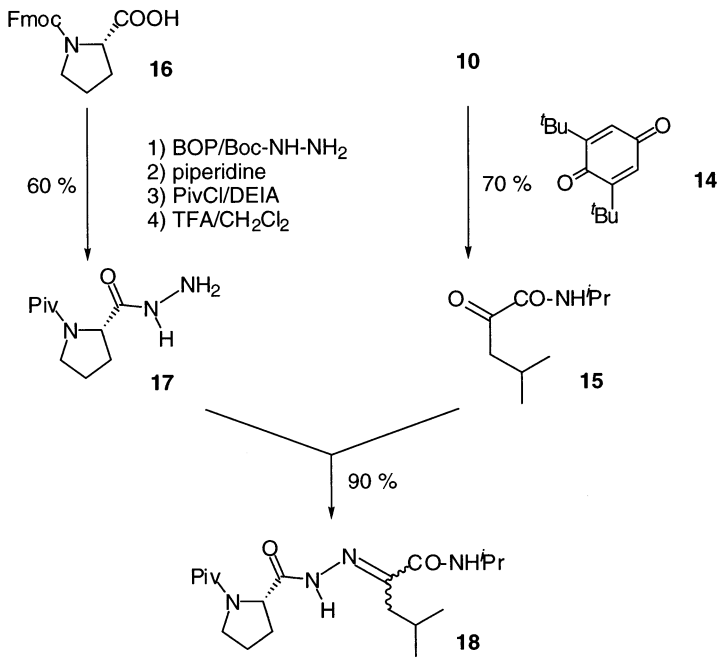
Scheme 2. Cyclic derivatives **11**–**13** obtained by oxidizing peptides **8**–**10** with 1 equiv. of 3,5-di-*tert*-butyl-1,2-quinone **2**.[8,9]

the amino methylene-containing glycine derivative **9**, which gave **12**. The mechanism of the cyclization giving derivative **13** remains questionable. A possible explanation is that a second molecule of quinone could act as a dehydrogenating agent (Scheme 3).[10] This hypothesis is partially confirmed by the fact that, in the presence of a twofold excess of quinone **2**, the final yield in **13** (70%) is twice that of the previous one.



Scheme 3. Putative mechanism for the formation of **13**

In order to avoid the cyclization step, we tested 2,6-di-*tert*-butyl-1,4-quinone **14** as an oxidizing reagent of leucine derivative **10** (Scheme 4). The reaction proceeded more slowly than with **2**, but the final yield in the expected ketone **15** was satisfactory.[11] Derivative **15** was reacted with **17** to give the pseudodipeptide **18** containing the carbonylhydrazone link.[12] The above procedure was successively applied to the oxidation of the amino terminus of H-Phe-NHiPr and H-Phe-Leu-NHiPr. The proton NMR spectrum of **18** was typical of a slow equilibrium between two conformers. As the Piv–Pro amide bond was known to exclusively adopt the *trans* conformation,[13] splitting of the signals was attributed to the equilibrated *E* and *Z* conformations



Scheme 4. Synthesis of the carbonylhydrazone dipeptide **18** by condensing a peptide hydrazide and an α-keto amide obtained by oxidation of the amino terminus in the leucine derivative **10** using 2,6-di-*tert*-butyl-1,4-quinone **14**[8]

of the N=C bond. The E/Z ratio was found to vary with the solvent (88/12 in $CDCl_3$ and 60/40 in DMSO-d_6), and the two stereomers of **18** could not be separated by chromatography.

Quinonic oxidation with 2,6-di-*tert*-butyl-1,4-quinone **14** is currently applied to the amino terminus of various peptide sequences, and the structural analysis of the resulting carbonylhydrazone pseudopeptides is in progress. Preliminary results on solvent-protection for the amide NHs in **18** indicate that the E and Z-conformers assume different conformational properties which are under investigation.

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8. The following abbreviations are used: BOP, benzotriazol-1-yl-oxy-tris(dimethylamino) phosphonium hexafluorophosphate; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DIEA, diisopropylethylamine; PE, petroleum ether; Piv, pivaloyl; TFA, trifluoroacetic acid.
9. **11**: R_f=0.30, PE/5% EtOAc; MS: m/z 302.14 [M+1]; ^{1}H NMR ($CDCl_3$, 200 MHz, rt): 1.34 (d, 6H, J^3=6.9 Hz), 1.37 (s, 9H), 1.50 (s, 9H), 3.44 (m, 1H), 7.50 (d, 1H, J^4=2.2 Hz), 7.61 (d, 1H, J^4=2.6 Hz); element analysis: calcd %C (75.71), %H (9.03), %N (4.65); found %C (75.27), %H (9.21), %N (4.65). **12**: R_f=0.30, PE/20% EtOAc; MS: m/z 402.20 [M+1]; ^{1}H NMR ($CDCl_3$, 200 MHz, rt): 0.99 (d, 6H, J^3=6.6 Hz), 1.39 (s, 9H), 1.52 (s, 9H), 1.78 (m, 3H), 2.85 (d, 3H, J^3=4.7 Hz), 4.64 (m, 1H), 6.28 (b, 1H), 7.43 (d, 1H, J^4=1.1 Hz), 7.62 (d, 1H, J^4=1.1 Hz), 7.65 (s, 1H); element analysis: calcd %C (68.80), %H (8.79), %N (10.46); found %C (68.78), %H (9.05), %N (10.22). 13: R_f=0.30, PE/10% EtOAc; MS: m/z 373.17 [M+1]; ^{1}H NMR ($CDCl_3$, 200 MHz, rt): 0.95 (d, 3H, J^3=6.9 Hz), 1.02 (d, 3H, J^3=6.9 Hz), 1.24 (d, 3H, J^3=6.2 Hz), 1.26 (d, 3H, J^3=6.6 Hz), 1.31 (s, 9H), 1.40 (s, 9H), 2.21 (m, 1H), 4.15 (m, 1H), 5.31 (d, 1H, J^3=5.1 Hz), 7.18 (d, 1H, J^4=2.6 Hz), 7.23 (d, 1H, J^4=2.6 Hz), 7.33 (s, 1H); element analysis: calcd %C (74.13), %H (9.75), %N (7.52); found %C (73.61), %H (9.75), %N (7.05).
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11. To a solution of 2,6-di-*tert*-butyl-1,4-quinone **14** (484 mg, 2.2 mmol) in MeOH (6 ml) under nitrogen was added at rt to **10** (344 mg, 2 mmol) in MeOH (2 ml). Advancement of the reaction was followed by tlc and needed 72 h for completion. Water (10 ml) was added and pH was adjusted to 3 by addition of crystallized oxalic acid dihydrate. The mixture was maintained under stirring until complete hydrolysis as shown by tlc, and water (10 ml) was added. The ketone **15** was extracted with Et_2O and purified by flash chromatography on silica gel: 239 mg, 70% yield. **15**: R_f=0.30, PE/10% EtOAc; ^{1}H NMR ($CDCl_3$, 200 MHz, rt): 0.94 (d, 6H, J^3=6.6 Hz), 1.19 (d, 6H, J^3=6.6 Hz), 2.16 (m, 1H), 2.79 (d, 2H, J^3=6.6 Hz), 4.04 (m, 1H), 6.74 (b, 1H).
12. To a solution of **15** (172 mg, 1 mmol) in MeOH (10 ml) under nitrogen at rt was added under stirring **17** (213 mg, 1 mmol) in MeOH (2 ml). The mixture was maintained under stirring for 12 h, and tlc indicated completion of the coupling. MeOH was evaporated under reduced pressure, and the residue was taken up with water. The carbonylhydrazone pseudodipeptide **18** was extracted with Et_2O and purified by flash chromatography on silica gel: 330 mg; 90% yield. **18**: R_f=0.30, PE/50% EtOAc; MS: m/z 367.4 [M+1]; ^{1}H NMR ($CDCl_3$, 200 MHz, rt), conformers I (88%) and II (12%): 0.96 (d, 3H, J^3=6.6 Hz), 1.00 (d, 3H, J^3=6.6 Hz), 1.17 (d, 3H, J^3=6.6 Hz), 1.18 (d, 3H, J^3=6.6 Hz), 1.28 (s, 9H), 1.80 (m, 2H), 2.05 (m, 2H), 2.43 and 2.53 (ABX, 2H, J^2=13.0 Hz, J^3=7.7 and 8.0 Hz), 2.63 (m, 1H), 3.70 (m, 2H), 4.09 (m, 1H), 4.84 (m, 1H, I), 5.30 (m, 1H, II) 6.61 (d, 1H, II, J^3=7.3 Hz), 7.17 (d, 1H, I, J^3=8.0 Hz), 8.42 (s, 1H, II), 11.04 (s, 1H, I); element analysis: calcd %C (62.27), %H (9.35), %N (15.29); found %C (62.22), %H (9.33), %N (15.45).
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