Oxidation of α-Diazoketones derived from L-Amino Acids and Dipeptides using Dimethyldioxirane. Synthesis and Reactions of Homochiral *N*-Protected α-Amino Glyoxals

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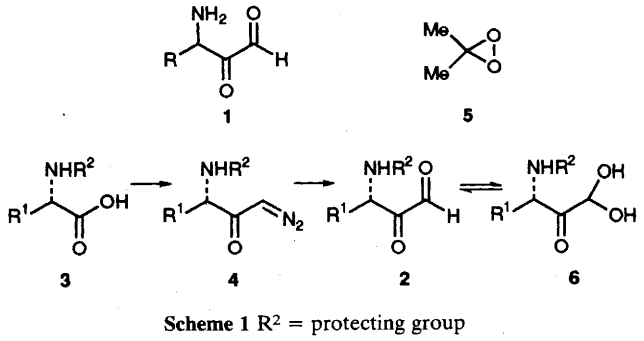
Homochiral *N*-protected α-amino glyoxals are readily accessible by oxidation of α-diazoketones derived from natural amino acids and dipeptides using dimethyldioxirane in acetone; the glyoxals can be trapped efficiently in reactions such as Wittig olefination and condensation with amines and vicinal diamines.

Without functional group protection amino glyoxals of type **1** would be expected to undergo spontaneous polymerisation. With appropriate *N*-protection they should be reasonably stable, yet amenable to a range of useful synthetic transformations through the highly electrophilic aldehyde group. They are, for example, potential precursors of hydrolytically stable pseudopeptides or peptide isosteres.[1]

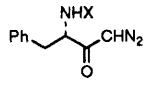
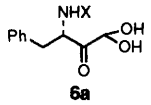
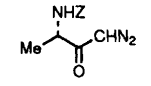
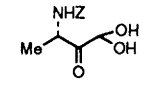
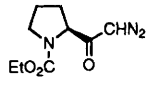
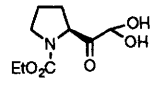
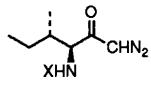
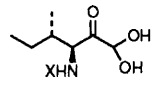
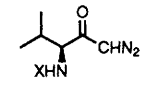
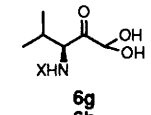
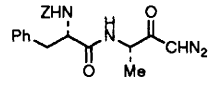
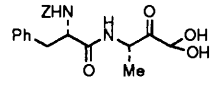
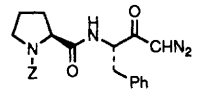
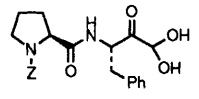
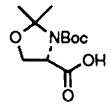
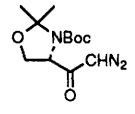
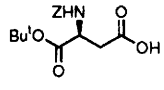
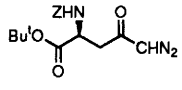
We have developed a general route (Scheme 1) to amino glyoxals in the *N*-protected form **2** from a range of L-amino acids. The route is equally applicable to any *N*-protected peptide with a free carboxylic acid group and the reaction conditions appear to tolerate most forms of N-protection. So far we have successfully employed Boc, Z, phthaloyl and ethoxycarbonyl groups. The *N*-protected amino acids and dipeptides **3** shown in Table 1 were transformed into the corresponding diazoketones **4** using standard procedures.[2] The key step in the sequence was oxidation of the diazoketones to glyoxals **2** using distilled dimethyldioxirane (DMD) **5** in acetone,[3,4] a process recently reported for simple achiral diazoketones.[5] The glyoxals were predominantly, if not exclusively, in the hydrated form **6**; no purification was necessary, there being no by-products of the oxidation other than acetone and nitrogen. Although the glyoxal hydrate **6a** derived from Z-L-phenylalanine was fully characterised,† routinely the oxidation products were not scrutinised closely other than by TLC analysis to confirm that reaction was complete.

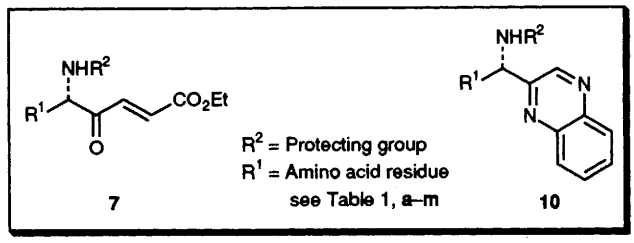


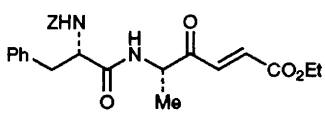
Scheme 1 R^2 = protecting group

† *Selected data* (*J* values in Hz): **6a**: ^{1}H NMR (300 MHz; CD_3COCD_3) δ 2.92 (1H, dd, J_1 14.0, J_2 9.7, $PhCH_2$), 3.39 (1H, dd, J_1 14.1, J_2 4.2, $PhCH_2$), 4.94 [1H, m, CH(N)CO], 5.00 (2H, s, OCH_2Ph), 5.36 [1H, m, $CH(OH)_2$], 5.82 [2H, d, *J* 7.9, $CH(OH)_2$], 6.66 (1H, d, *J* 7.9, NH), 7.18–7.30 (10H, m, Ar-H). **7b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.31 (3H, t, *J* 7.1, OCH_2CH_3), 1.41 [9H, s, $(CH_3)_3C$], 3.00 (1H, dd, J_1 14.0, J_2 6.4, $PhCH_2$), 3.16 (1H, dd, J_1 13.9, J_2 6.3, $PhCH_2$), 4.25 (2H, q, *J* 7.1, OCH_2CH_3), 4.79 [1H, dd, J_1 13.4, J_2 6.5, CH(N)CO], 5.18 (1H, d, *J* 7.3, NH), 6.76 (1H, d, *J* 15.8, $CH{=}CHCO_2Et$), 7.10–7.31 (6H, m, Ar-H and $CH{=}CHCO_2Et$). **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.79 [3H, d, *J* 6.9, $(CH_3)_2CH$], 0.95 [6H, d, *J* 6.4, $(CH_3)_2CH$], 1.00 [3H, d, *J* 6.7, $(CH_3)_2CH$], 1.24 (3H, t, *J* 7.0, OCH_2CH_3), 1.59 (2H, m, NCH_2CH_2), 1.66 [1H, m, $(CH_3)_2CHCH_2$], 2.24 [1H, br m, $(CH_3)_2CH$], 3.69 (2H, m, NCH_2), 4.11 (2H, q, *J* 7.0, OCH_2CH_3), 5.16 [1H, m, CH(N)CO], 5.50 (1H, br d, *J* 8.7, NH), 7.67 (1H, s, CH=N). **10a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.16 (1H, dd, J_1 13.4, J_2 8.0, $PhCH_2$), 3.40 (1H, dd, J_1 13.6, J_2 5.7, $PhCH_2$), 5.13 (2H, dd, J_1 18.6, J_2 12.3, OCH_2Ph), 5.35 [1H, dd, J_1 14.0, J_2 7.8, CH(N)CO], 6.21 (1H, d, *J* 7.8, NH), 6.98 (2H, m, Ar-H), 7.19 (4H, m, Ar-H), 7.36 (4H, d, *J* 4.1, Ar-H), 7.76 (2H, m, Ar-H), 8.06 (2H, dd, J_1 18.1, J_2 7.4, Ar-H), 8.38 (1H, s, CH=N). **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 [3H, d, *J* 6.9, $(CH_3)_2CH$], 1.00 [3H, d, *J* 6.7, $(CH_3)_2CH$], 2.06 [1H, m, $(CH_3)_2CH$], 3.35 (2H, d, *J* 12.9 NCH_2CH_2N), 3.57 (2H, d, *J* 12.3, NCH_2CH_2N), 4.45 [1H, m, CH(N)CO], 5.10 (2H, s, OCH_2Ph), 5.79 (1H, d, *J* 8.1, NH), 7.35 (5H, s, Ar-H), 7.78 (1H, s, CH=N).

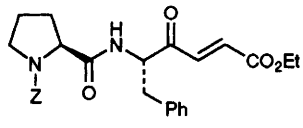
Table 1 Preparation of α-amino-glyoxals

Amino acid	Diazoketone	Glyoxal hydrate
N-X-L-Phenylalanine		
3a X = Z **3b** X = Boc	**4a** **4b**	**6a** **6b**
N-Z-L-Alanine		
3c	**4c**	**6c**
N-Ethoxycarbonyl -L-proline		
3d	**4d**	**6d**
N-X-L-Isoleucine		
3e X = Z **3f** X = Boc	**4e** **4f**	**6e** **6f**
N-X-L-Valine		
3g X = EtO_2C **3h** X = Phthaloyl **3i** X = Z	**4g** **4h** **4i**	**6g** **6h** **6i**
N-Z-L-Phe-Ala		
3j	**4j**	**6j**
N-Z-L-Pro-Phe		
3k	**4k**	**6k**
		
3l	**4l**	**6l**
		
3m	**4m**	**6m**

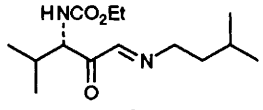




7j



7k



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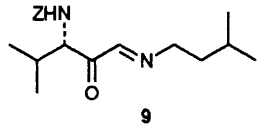

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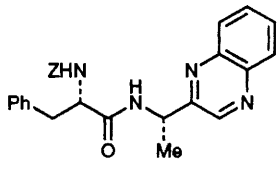
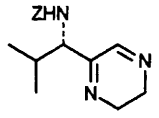


10j



11

These glyoxal hydrates can be used directly in a variety of transformations which not only confirm their identity, but which open up new routes to homochiral molecules from amino acids and peptides. For example, the acetone solution resulting from DMD oxidation of diazoketone **4a** (1 equiv.) was treated with ethyl(triphenylphosphoranylidene)acetate (1 equiv.) at room temperature for 30 min to afford the (*E*)-unsaturated ester **7a** in 86% yield.

In a similar manner, diazoketones **4b–4m** were transformed via glyoxal hydrates into (*E*)-unsaturated esters **7b–7m**, respectively, in 85–94% yields, the process with diazoketones **4j** and **4k** illustrating its application to chemical modification of dipeptides **3j** and **3k**. This combined oxidation–olefination strategy should be capable of extension to the synthesis of δ-amino-γ-methylsulfonyloxy-α,β-enoates which are useful precursors of (*E*)-alkene *N*-protected dipeptide isosteres.[6]

Prior to condensation of primary amines with glyoxal hydrates the solvent acetone was removed at reduced pressure and replaced with anhydrous dichloromethane and magnesium sulphate. Monofunctional amines produced imines in excellent yield, illustrative examples being imines **8** and **9**, from isopentylamine and glyoxal hydrates **6g** and **6i** respectively. With 1,2-diamines condensation led to nitrogen heterocycles. For example, treatment of glyoxal hydrates **6a–6i** in ethanol with 1,2-diaminobenzene furnished optically active quinoxalines **10a–10i**, respectively in >90% yield; in the dipeptide series glyoxal hydrate **6j** produced quinoxaline **10j**. Cyclisation also occurred with 1,2-diaminoethane, glyoxal hydrate **6i** furnishing dihydropyrazine **11**.

In conclusion we have shown that glyoxal hydrates are useful intermediates in the chemical modification of natural amino acids and dipeptides. That these various condensation reactions of the hydrates proceeded without detectable amounts of racemization could be established by conducting a comparative series of reactions with the L-isoleucine derived glyoxal **6f** and its DL-counterpart. ^1H NMR analysis of the products of the former revealed that the product in each case constituted a single diastereoisomer.

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