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Synthesis of amino acid-derived thiazoles from enantiopure *N*-protected α -amino glyoxals

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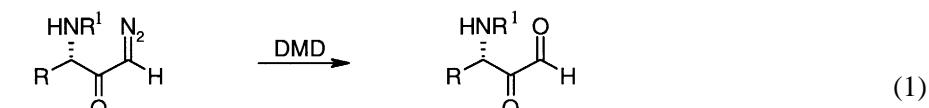
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Abstract

Several novel thiazoles with side chains derived from natural amino acids and a dipeptide have been synthesised from *N*-protected α -amino glyoxals and cysteine. © 2000 Elsevier Science Ltd. All rights reserved.

Keywords: amino acids; diazoketones; α -amino glyoxals; oxidation; thiazole synthesis.

In an earlier paper on the use of enantiopure *N*-protected α -amino glyoxals in the synthesis of heterocycles, we described convenient routes to novel imidazoles, including some histidine derivatives, from amino acids and peptides.¹ Central to the development of these routes was the discovery that *N*-protected α -amino glyoxals can be produced cleanly by oxidation of *N*-protected amino diazoketones using dimethyldioxirane (DMD) in acetone (Eq. (1)).^{2,3} These glyoxals are versatile intermediates for chemical elaboration of amino acids and peptides, which we now demonstrate in the synthesis of several novel thiazoles.



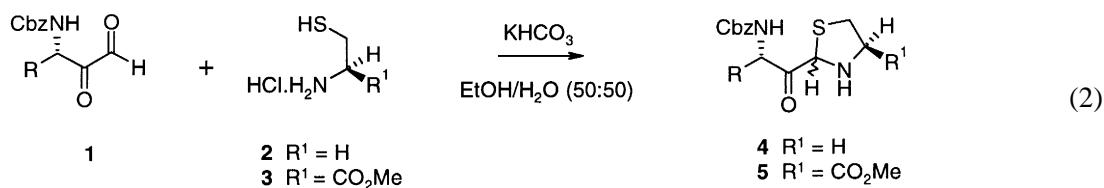
R^1 = protecting group

Enzymatic modification of peptide-based natural products include cyclisations of serine, threonine and cysteine side chains onto adjacent carbonyl groups to create five-membered heterocycles in the oxazole/thiazole series.⁴ Not only do these cyclisations alter the connectivity of the peptide backbone and electronic distribution, but they afford new recognition targets for interactions with biological targets such as DNA, RNA and proteins.⁴ The presence of such five-membered heterocyclic rings in peptide-derived compounds is of interest because of their ability to confer a wide range of therapeutic properties, including antibiotic, antiviral and antitumour activity.⁵

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It is known that glyoxylic acid condenses with mercaptoamines such as cysteine, cysteamine and penicillamine to form 1,3-thiazolidines.^{6–9} Shiori et al.¹⁰ have described the synthesis of thiazolidines from *N*-protected α -amino aldehydes and L-cysteine methyl ester which were subsequently dehydrogenated to thiazoles. Several acyl-substituted thiazoles have been prepared by Dondoni's group using a lithiated thiazole intermediate.¹¹

Initially, we considered the combination of representative *N*-protected amino glyoxals with mercaptoethylamine and L-cysteine methyl ester to form mono- and di-substituted thiazolidines **4** and **5**, respectively (Eq. (2)). Condensation reactions were conducted in aqueous ethanol containing potassium bicarbonate. As expected, both mercaptoethylamine and L-cysteine methyl ester furnished mixtures of two diastereoisomers, a new stereogenic centre having been created at the C-2 of the thiazolidine ring.



Several examples of thiazolidines, produced in >90% yield (by NMR analysis), are listed in Fig. 1.

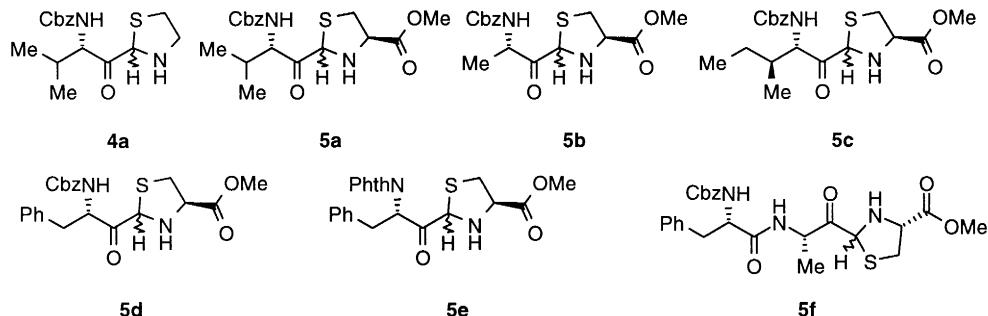


Fig. 1.

Compound **4a** is derived from mercaptoethylamine and L-*N*-Cbz-valine, while products **5a**–**5e** result from L-cysteine methyl ester and the glyoxals of L-*N*-Cbz-valine, L-*N*-Cbz-alanine, L-*N*-Cbz-isoleucine and L-phenylalanine, both *N*-Cbz and *N*-phthaloyl, respectively. Thiazolidines **5a**, **5b** and **5e** could be separated into their individual diastereoisomers by flash chromatography. Thiazolidine **5f** represents the elaboration of the dipeptide Phe-Ala.

For the purpose of continuing the synthesis to the thiazole stage (Eq. (3)), the thiazolidine mixtures could be used directly without further purification. Of the various dehydrogenation agents examined, DDQ was found to be effective, but yields were poor. Whereas activated manganese dioxide was ineffective, battery-grade manganese dioxide in benzene containing 10% pyridine did produce the thiazoles listed in Fig. 2 (yields are based on the diazoketone). However, during characterisation, thiazoles **6a**, **6b**, **6e** and **6f** were found to be optically inactive and racemisation (epimerisation in the case of **6f**) was confirmed when it was discovered from X-ray diffraction analysis¹² of the phenylalanine analogue **6e** that the space group was centrosymmetric which requires the presence of both enantiomers. The molecular structure of **6e** is shown in Fig. 3. Furthermore, the 1H NMR spectrum of **6f**, the thiazole derived from the Phe-Ala glyoxal, revealed the presence of a mixture of diastereoisomers, indicating epimerisation at the chiral centre adjacent to the carbonyl group of the Ala moiety in the side chain.

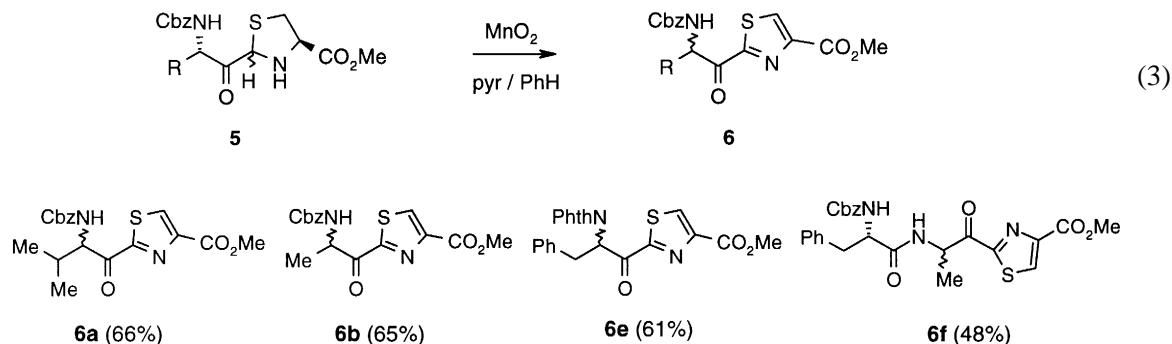


Fig. 2.

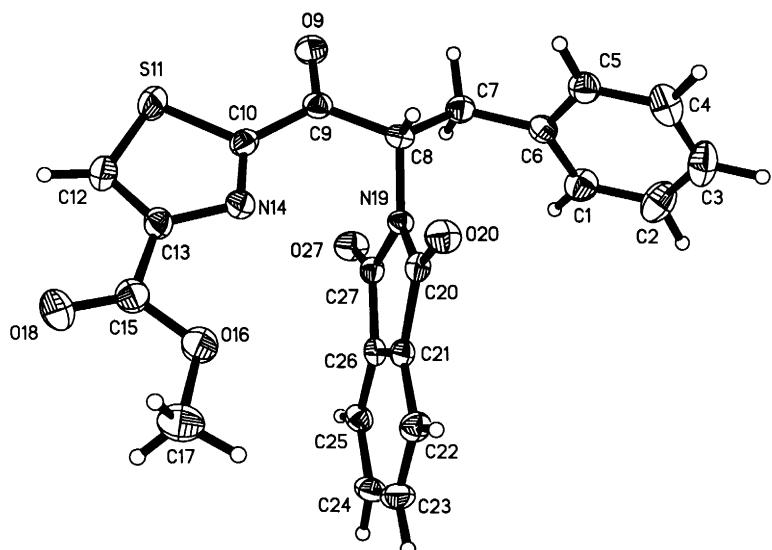
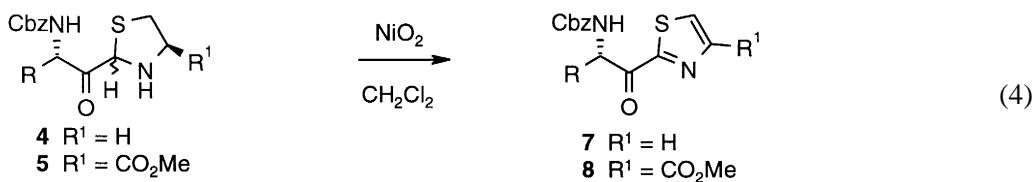


Fig. 3. A view of 2-[3'-phenyl-2'-(*S*)-*N*-phthaloyl-amino-1'oxo propyl]-4-methoxycarbonyl thiazole **6e** showing the atom-labelling scheme for all non-hydrogen atoms. Thermal ellipsoids at 50% level

Although little used, nickel peroxide is known to act as a dehydrogenation agent in the formation of thiazoles from thiazolidines,^{13,14} and it was decided to explore this reagent as a substitute for manganese dioxide. With the methoxycarbonyl substituted thiazolidines derived from cysteine, **5c**, **5d** and **5f**, dehydrogenation occurred smoothly with nickel peroxide in dichloromethane at room temperature over 2 days to afford thiazoles **8c**, **8d** and **8f**, respectively (Fig. 4). Significantly, these products, unlike their counterparts from manganese dioxide mediated oxidation, were formed without racemisation. This was readily established from the ¹H NMR spectra of **8c** and **8f**, which indicated the presence of single diastereoisomers, unlike **6f**. However, nickel peroxide did not bring about complete dehydrogenation of the monosubstituted thiazolidine **4a**. The product here was dihydrothiazole **7a**.



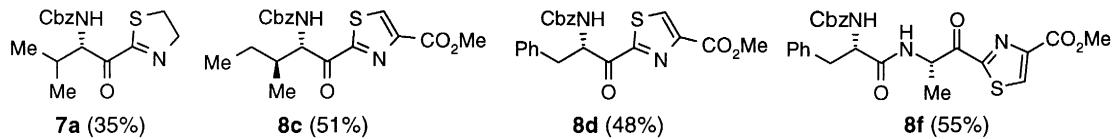


Fig. 4.

In conclusion, we have demonstrated an effective method, using amino glyoxals as intermediates, for the elaboration of amino acids and peptides into versatile heterocyclic products.

1. Typical experimental procedure for 2-[3'-phenyl-2'-(S)-benzyloxycarbonyl-amino-1'-oxo propyl]-4-methylcarboxylate thiazole (8d)

N-Cbz-L-Phe diazoketone (300 mg, 0.93 mmol) was oxidised using DMD (13.3 mL, 0.07 M) in acetone at r.t. and the glyoxal was isolated after removal of solvent at reduced pressure. The glyoxal was dissolved in EtOH (10 mL) and added to an aqueous solution of L-Cys-methyl ester (10 mL, 0.16 g, 0.93 mmol) and KHCO₃ (93 mg, 0.93 mmol) was added. The solution was allowed to stir at room temperature for 4 h. The solution was concentrated to half its volume, saturated with NaCl and extracted with CHCl₃ (3×10 mL), dried over anhydrous Na₂SO₄ and the solvent was removed under reduced pressure to give the crude thiazolidine. The crude thiazolidine was taken up in CH₂Cl₂ and NiO₂ (0.76 g, 8.36 mmol) and allowed to stir at room temperature for 2 days. The NiO₂ was filtered through Celite and the solvent evaporated under reduced pressure to yield the crude thiazole. Purification was carried out by flash chromatography on silica using 40:60 EtOAc:hexane as eluant to give **8d** as a white solid (0.2 g, 51%); mp 121–122°C. Found: C, 62.1; H, 4.7; N, 6.5%. C₂₂H₂₀N₂O₅S requires C, 62.2; H, 4.7; N, 6.6%. [α]_D²⁰ +14.7 (c 0.93, CHCl₃); ¹H NMR (500 MHz, CDCl₃) 3.25 (1H, dd, J₁=13.9 Hz, J₂=6.5 Hz, PhCH₂HCH), 3.43 (1H, dd, J₁=14.1 Hz, J₂=5.0 Hz, PhCH₂HCH), 4.00 (3H, s, CO₂CH₃), 5.05, 5.10 (2H, 2×d, J=12.3 Hz, PhCH₂OCO), 5.50 (1H, br d, J=7.4 Hz, PhCH₂CH(NH)), 5.80 (1H, m, PhCH₂CH), 7.05, 7.22, 7.35 (10H, m, ArH), 8.47 (1H, s, SCH=CN); m/z 424 (M⁺).

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12. Crystallographic data for the compound **6e** in this paper have been deposited in the Cambridge Crystallographic Data Centre. Copies of the available material can be obtained, free of charge, on application to the CCDC, 12 Union Rd, Cambridge, CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).
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