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

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Abstract

A range of novel imidazoles, including three histidine derivatives, with chiral side chains derived from amino acids and dipeptides have been synthesised from *N*-Cbz-protected α-amino glyoxals.

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

The first synthesis of enantiopure *N*-protected α-amino glyoxals from α-amino acids and dipeptides was recently reported from this laboratory.[1,2] The key step of the synthesis was oxidation of *N*-protected α-amino diazoketones using dimethyldioxirane (DMD) in acetone (Eq. (1)).

(1)

R^1 = protecting group

These glyoxals have considerable potential as chiral educts in the chemical elaboration of amino acids and peptides and we have already shown how they can be employed in condensation reactions with various amines to produce imino ketones,[3] amino ketones,[3] and six-membered nitrogen heterocycles such as quinoxalines[1,4] and azaquinoxalines.[4] We have now explored further uses for these glyoxals in heterocycle synthesis and report here the synthesis of several amino acid and dipeptide-derived imidazoles. The presence of rigid, bifunctional structural elements such as imidazoles and other five-membered heterocyclic rings in peptide-derived compounds is of particular interest because of their ability to confer a wide range of biological properties.[5]

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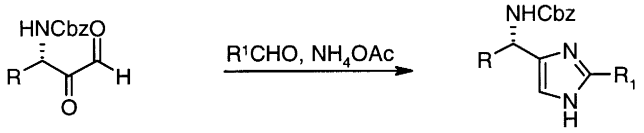
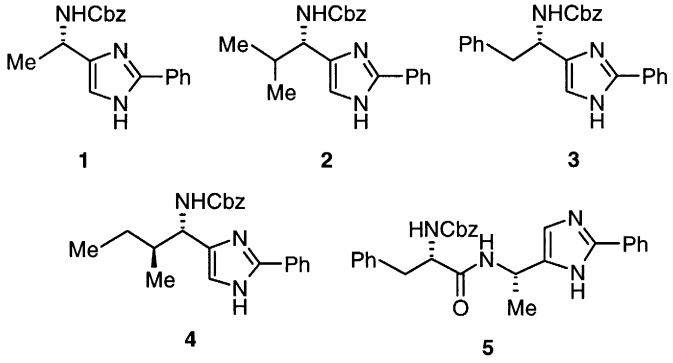
A well-tested route to imidazoles involves condensation of a 1,2-dicarbonyl compound with ammonia in the presence of an aldehyde.[6] We have found that *N*-protected α-amino glyoxals function very effectively as the dicarbonyl component in this route to imidazoles (Eq. (2)). In practice, the diazoketone was oxidised with DMD in acetone, after which the solvent was removed at reduced pressure and replaced by methanol. Ammonium acetate and the aldehyde were then added and the mixture was stirred under reflux overnight.



(2)

Application of this procedure to the glyoxals derived from *N*-Cbz-L-alanine, *N*-Cbz-L-valine, *N*-Cbz-L-phenylalanine, *N*-Cbz-L-isoleucine and the glyoxal derived from the dipeptide Phe-Ala using benzaldehyde as the aldehydic component furnished disubstituted imidazoles **1**, **2**, **3**, **4** and **5**, respectively, in 60–70% yields. The product in each case was purified by flash chromatography on silica.



The ^{1}H NMR spectra of imidazoles **1**–**5** were consistent with the assigned structures, the ring proton on C-5 of the imidazole nucleus appearing at ca. δ 6.8. The molecular structure of imidazole **1** has been confirmed by X-ray diffraction analysis (see Fig. 1).[7] The NMR spectra of imidazoles **4** and **5** indicated

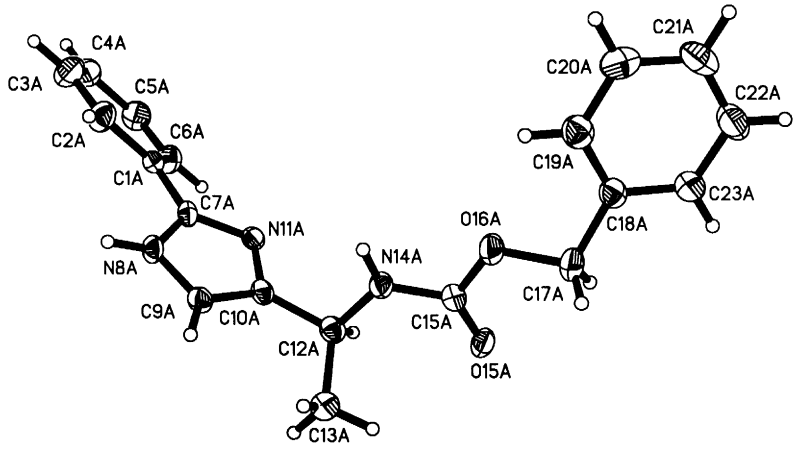
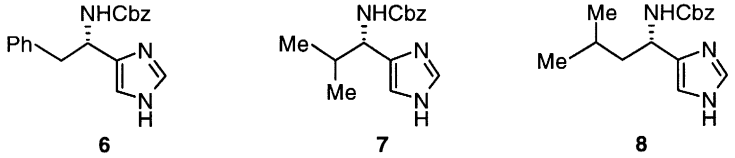


Fig. 1. Molecular structure of 2-phenyl-4-(1-(*S*)-benzyloxycarbonylamino-ethyl)-1*H*-imidazole **1** showing the atom-labelling scheme for all non-hydrogen atoms. Thermal ellipsoids at 50% level

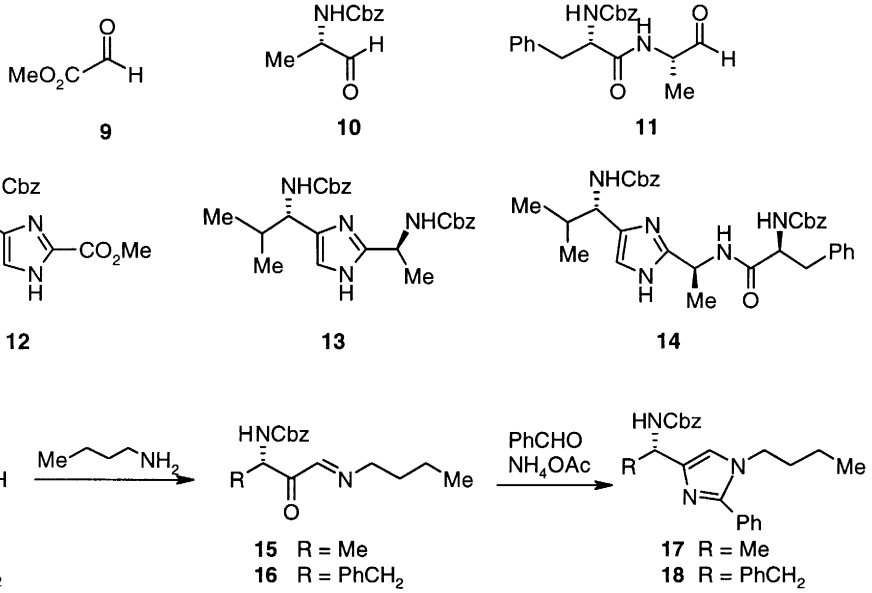
that these products were formed as single diastereoisomers from which we concluded that epimerisation did not occur in the course of the condensation reactions.

One of the attractions of this route to imidazoles is the scope for variation in the reaction components. For example, the reaction of the glyoxals derived from *N*-Cbz-L-phenylalanine, *N*-Cbz-L-valine and *N*-Cbz-L-leucine with formaldehyde as the aldehyde source led to the formation of three monosubstituted imidazoles **6**, **7** and **8**, in (80%), (76%) and (78%) yield, respectively.



6 **7** **8**

Three further variations in the aldehyde component are represented by methyl glyoxylate **9**, *N*-Cbz-L-alaninal **10** and the Phe-Ala derived aldehyde **11**, which on reaction with the glyoxal derived from *N*-Cbz-L-valine and ammonium acetate furnished imidazoles **12**, **13** and **14**, respectively. Yet another variation in imidazole synthesis is the use of a primary amine as the source of one of the ring nitrogen atoms. We have already shown that *N*-protected α-amino glyoxals form aldimines with amines such as 1-aminobutane (Scheme 1).[3]



9 **10** **11**

12 **13** **14**

R = Me
R = $PhCH_2$

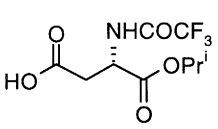
15 R = Me
16 R = $PhCH_2$

17 R = Me
18 R = $PhCH_2$

Scheme 1.

The aldimines **15** and **16** derived from the glyoxals of *N*-Cbz-L-alanine and *N*-Cbz-L-phenylalanine and 1-aminobutane, respectively, were combined with benzaldehyde and ammonium acetate to form *N*-alkyl imidazoles **17** and **18** in unoptimised yields of 31 and 28%, respectively.

We have also applied aspects of this methodology to a glyoxal synthesised from L-aspartic acid. This application is of particular interest in that it offers the possibility of synthesising histidine derivatives from aspartic acid. The known doubly protected aspartic acid derivative[8] **19** was readily transformed, via diazoketone **20**, into glyoxal **21**. Three separate condensation combinations of **21** and ammonium acetate with benzaldehyde, methyl glyoxalate and aldehyde **11** were examined and found to yield histidine derivatives **22**, **23** and **24**, respectively, in moderate yields.



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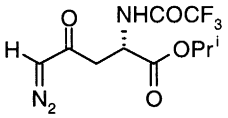

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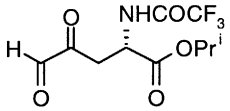

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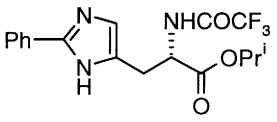

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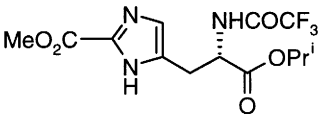

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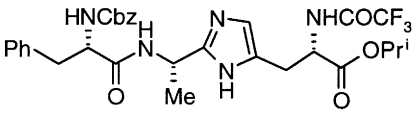

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In conclusion, these studies further demonstrate the versatility of *N*-protected α-amino glyoxals in the synthesis of novel polyfunctional heterocycles.

1. Typical experimental procedure for 2-phenyl-4-(1-(*S*)-benzyloxycarbonyl amino-ethyl)-1*H*-imidazole (1)

N-Cbz-L-alanine diazoketone (100 mg, 0.4 mmol) was oxidised using DMD (8.6 mL, 0.07 M) in acetone at room temperature. After 10 min the solvent was removed in vacuo and replaced by methanol (20 mL). NH_4OAc (308 mg, 4 mmol) and benzaldehyde (0.12 mL, 1.2 mmol) were added. The mixture was stirred at reflux overnight then cooled to room temperature after which the solvent was evaporated. The crude reaction mixture was then taken up in CH_2Cl_2, washed with saturated $NaHCO_3$, H_2O and brine, dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure to yield the crude imidazole. Purification was carried out by flash chromatography on silica using EtOAc:hexane (50:50) as eluant to give imidazole **1** as a white solid (91 mg, 71%); mp 152–154°C. Found: C, 70.8; H, 5.9; N, 12.9%. $C_{19}H_{19}N_3O_2$ requires C, 71.0; H, 5.9; N, 13.1%. $[\alpha]_D^{20}$ –31.7 (c 1.04, $CHCl_3$); ν_{max} (KBr)/cm^{-1} 3316, 1716, 1699, 1653; ^{1}H NMR (500 MHz, $CDCl_3$) 1.55 (3H, d, J=6.8 Hz, C*H*$_3$CH(NH)), 4.88 (1H, m, CH$_3$C*H*(NH)), 5.09, 5.15 (2H, 2×d, J=12.2 Hz, PhC*H*$_2$OCO), 5.36 (1H, br s CH(N*H*)), 6.88 (1H, s, C=C*H*NH), 7.35 (8H, m, Ar*H*), 7.76 (2H, d, J=7.3 Hz, Ar*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 14.21, 44.27, 66.93, 125.29, 128.05, 128.16, 128.56, 128.67, 128.86, 130.29, 136.51, 146.73, 156.52, 171.14; m/z 321 (M^+), 91(PhCH$_2$ 100).

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7. Crystallographic data for the structure of compound **1** 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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