Reductive Acylation of α-Keto Azides Derived from L-Amino Acids using *N*-Protected L-Aminothiocarboxylic *S*-Acids

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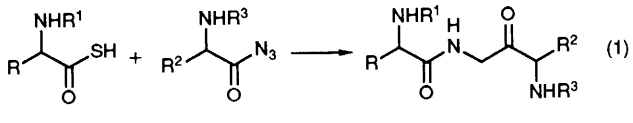
Several homochiral *N*-protected α-aminothiocarboxylic *S*-acids have been synthesised from natural amino acids and used for reductive acylation of homochiral α,α'-amino keto azides, also derived from natural amino acids.

α-Aminothiocarboxylic *S*-acids derived from *N*-protected natural amino acids have been employed as reagents for peptide segment coupling[1] and in peptide backbone modification through thioamide bond formation (endothiopeptides).[2] We have devised a new use for *N*-protected aminothiocarboxylic *S*-acids which, by analogy with thioacetic *S*-acid, is based on their ability to engage in reductive acylation. It is known, for example, that thioacetic *S*-acid combines with benzyl azide to form *N*-benzylacetamide in high yield and that the process tolerates additional functionality such as alkene or methanesulfonate in the azide.[3] We have prepared a series of *N*-protected aminothiocarboxylic *S*-acids and have studied their reactions with azides in order to assess their potential in reductive acylation, in particular of azides derived from natural amino acids [eqn. (1)].

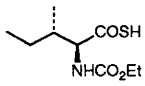
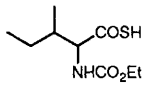
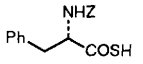
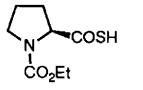
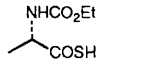
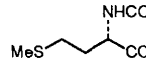
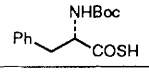


(1)

Although *N*-protected aminothiocarboxylic *S*-acids are accessible from the corresponding *N*-hydroxysuccinimide esters[1,2,4], a convenient one-pot alternative consists of treating the *N*-protected amino acid in dichloromethane with 1,1'-carbonyldiimidazole at room temperature followed by exposure (*via* a bubbler) of the solution to gaseous hydrogen sulfide for *ca.* 1 h. This procedure proved successful for several *N*-protected thiocarboxylic *S*-acids some of which are shown in Table 1. The ^{13}C NMR spectrum of each compound displayed a signal at δ 199–200 diagnostic of the carbon atom of the COSH moiety.

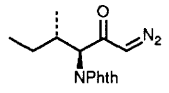
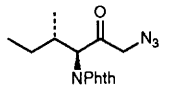
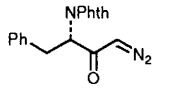
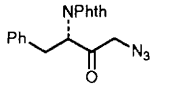
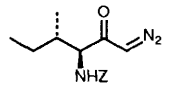
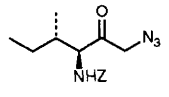
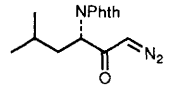
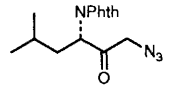
Each thio *S*-acid was treated with benzyl azide to test its efficacy in reductive acylation. As a group the compounds were rather less reactive than thioacetic *S*-acid and about as reactive as thiopivalic *S*-acid. Treatment of benzyl azide with thio *S*-acid **1** (2 equiv.) in the minimum amount of benzene at 60–70 °C for 16 h under nitrogen furnished *N*-benzylamide **8**, m.p. 162–163 °C, in 73% yield. Thio *S*-acids **2**–**7** produced the appropriate benzylamide in 73–85% yield when similarly treated. The major by-product in each case was a disulfide of general formula **9**. That these reductive acylations proceeded

Table 1 Thio *S*-acids obtained from amino acids

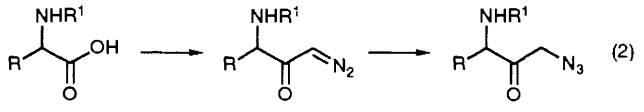
Amino acid	*S*-Acid	$[\alpha]_D^{20}$ (CH_2Cl_2)	Yield (%)
L-*N*-ethoxycarbonylisoleucine	**1** 	−10.6 (*c*, 4.0)	91
DL-*N*-ethoxycarbonylisoleucine	**2** 	—	97
L-*N*-benzyloxycarbonylphenylalanine	**3**[a] 	−10.2 (*c*, 4.0)	90
L-*N*-ethoxycarbonylproline	**4** 	−88.0 (*c*, 4.0)	96
L-*N*-ethoxycarbonylalanine	**5** 	−15.4 (*c*, 2.7)	100
L-*N*-ethoxycarbonylmethionine	**6** 	−17.8 (*c*, 4.8)	89
L-*N*-*tert*-butyloxycarbonylphenylalanine	**7** 	−21.8 (*c*, 4.5)	90

[a] Z = benzyloxycarbonyl.

Table 2 α-Keto azides obtained from α-diazoketones[a]

α-Diazoketone	α-Keto azide	$[\alpha]_D^{20}$ (CH_2Cl_2)	Yield (%)[b]
10 	**14** 	−57.8 (*c*, 5.2)	71
11 	**15** 	−13.2 (*c*, 4.0)	70
12 	**16** 	+15.8 (*c*, 1.5)	68
13 	**17** 	−24.4 (*c*, 5.3)	94

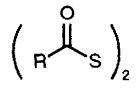
[a] Phth = phthaloyl; Z = benzyloxycarbonyl. [b] Overall yields for both reactions.


(2)

without detectable amounts of racemization was established by comparing the ^1H NMR spectrum of the amide obtained from benzyl azide and thio *S*-acid **1** with that obtained with the DL-counterpart of the thio *S*-acid **2**, which revealed that the former amide constituted a single diastereoisomer.

Our principal interest in exploring the use of these thio *S*-acids in reductive acylation was the possibility of using as substrates α-keto azides derived also from natural amino acids, a combination capable of producing novel peptide mimics. Such keto azides are accessible from α-amino acids *via* diazoketones in the sequence shown in eqn. (2).

The **10–13** series of *N*-protected α-diazoketones in Table 2 were prepared from the appropriate *N*-protected L-amino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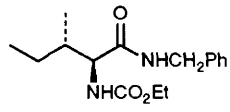
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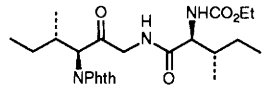
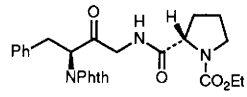
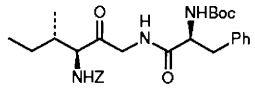
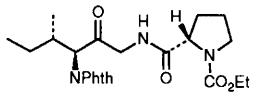
acids *via* acyl chloride or mixed anhydride formation, followed by exposure to ethereal diazomethane. Treatment of the α-diazoketones with hydrogen bromide (1 equiv.) in dry diethyl ether at room temperature furnished the α-bromo ketones and exposure of the latter to sodium azide in dry dimethyl sulfoxide completed the synthesis of the α-keto azides **14–17** (Table 2), both stages proceeding in excellent yields. ^1H NMR chiral shift studies employing [Eu(hfc)$_3$] {tris [3-heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)} established that these azides were formed free of racemization.

Table 3 Amides obtained from selected thio *S*-acids (Table 1) and α-keto azides (Table 2)[a]

Thio *S*-acid	α-Keto azide	Amide		$[\alpha]_D^{20}$ (CH_2Cl_2)	Yield (%)
1	**14**	**18**		−56.4 (*c*, 2.4)	72
4	**15**	**19**		−78.4 (*c*, 3.8)	76
7	**16**	**20**		−2.1 (*c*, 3.2)	72
4	**14**	**21**		−80.9 (*c*, 4.8)	74

[a] Phth = phthaloyl; Z = benzyloxycarbonyl.

The availability of several thio *S*-acids and α-keto azides opens up the way to a variety of peptide-like structures. Not all of the many possible combinations implicit in Tables 1 and 2 have been tested experimentally, but preliminary studies (Table 3) suggest that reductive acylation is a quite general process, proceeding smoothly under the conditions described above for benzyl azide. For example, thio *S*-acid **1** combined with keto azide **14** to afford amide **18**, m.p. 145–146 °C, in 72% yield, while thio *S*-acid **7** reductively acylated the isoleucine derived azide **16** to afford amide **20**, m.p. 150–151 °C. Similarly, the **4** + **15** and **4** + **14** combinations in Table 3 furnished amides **19** and **20**, respectively. Yields refer to analytically pure products whose structures are fully supported by ^{1}H NMR spectral data. The extension of this process to reductive acylation of peptide-derived azides is under study.

We thank Glaxo Group Research Ltd. for a postgraduate studentship to M. B. O'S.

Received, 15th September 1992; Com. 2/04942B

References

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