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Synthesis of DL-Isocysteine and some Derivatives from Thiomalic Acid[1]

Raul Pires and Klaus Burger*

Institut für Organische Chemie der Universität Leipzig, Talstr. 35, D-04103 Leipzig, Germany

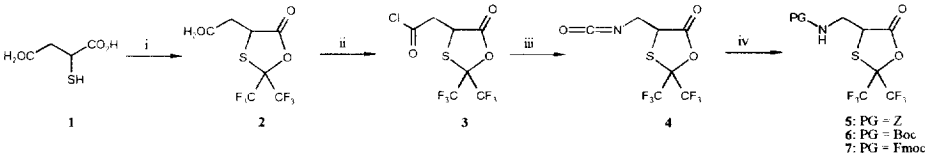
Abstract: *Thiomalic acid is transformed into isocysteine using hexafluoroacetone as protecting and activating agent. The urethanes* ***5, 6, 7*** *obtained represent N-protected, carboxylic group activated derivatives of isocysteine and are perfectly suited for further derivatizations.*

Non-proteinogenic amino acids are of current interest for the design of peptide mimetics.[2] Amino acids bearing a thiol group appear to be particularly valuable for generation of disulfide bridges and consequent imposition of conformational restrictions to the peptide backbone.[3]

In this paper we wish to report on a new synthetic approach to the non-proteinogenic amino acid isocysteine and its derivatives using hexafluoroacetone as protecting and activating agent.[4] To our knowledge, until now only one single synthesis of DL-isocysteine, employing a similar approach to ours has been published.[5]

Recently, DL-isocysteine was incorporated into a peptide inhibitor of stromelysin. The result was a highly potent inhibitor with a IC_{50} of 3 μM.[6]

Starting from commercially available DL-thiomalic acid **1**, the oxathiolanone **2** is obtained in high yield on reaction with hexafluoroacetone (Scheme 1). By this reaction, protection of the α-thiol and regioselective activation of the α-carboxylic group is achieved simultaneously, whereas the β-carboxylic group remains unaffected, ready for further regioselective functionalizations.

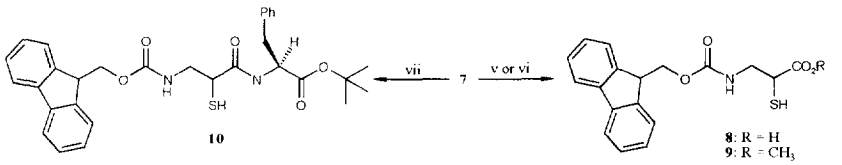


Scheme 1: i) $(CF_3)_2CO$, DMSO, 86%; ii) $SOCl_2$, reflux, 79%; iii) Me_3SiN_3, toluene, then heating, 88%; iv) benzylalcohol, $CHCl_3$, reflux, 95% (**4**→**5**); *tert.*-butanol, $CHCl_3$, reflux, 95% (**4**→**6**); 9-fluorenyl-methanol, $CHCl_3$, reflux, 71% (**4**→**7**).

The position of highest electrophilicity in the molecule is transferred from the α- to the β-carboxylic group on treatment of **2** with thionyl chloride, which affords the acid chloride **3**. Heating of **3** with trimethylsilylazide results in the formation of the isocyanate **4**[7], which represents a double activated isocysteine derivative. Addition of equimolar amounts of alcohols to the isocyanate **4** furnishes urethanes. Via this route, the common protective groups of peptide chemistry like Z, Boc or Fmoc can be introduced on reaction with benzylalcohol (**4**→**5**), *tert.*-

butanol (**4**→**6**) or 9-fluorenylmethanol (**4**→**7**), respectively (Scheme 1). Thus, fully protected and carboxylic group activated isocysteine derivatives, stable at 0°C for months and perfectly suited for further derivatizations are readily available.

Hydrolysis of **7** using a mixture of water/2-propanol (50:50, v/v) at room temperature yields Fmoc-protected isocysteine **8** (Scheme 2). Similarly, ring opening with methanol (**7**→**9**) or with phenylalanine *tert.*-butylester (**7**→**10**) is accomplished under very mild conditions giving the N-protected isocysteine methylester **9** and the dipeptide[7] **10**, respectively.



Scheme 2: v) water/2-propanol (1:1), room temperature, 35% (R = H); vi) methanol, reflux, 50% (R = CH_3); vii) Phe-O^{t}Bu, diethyl ether, 61%.

Acidolytic deprotection of **6** with 90% CF_3CO_2H provides racemic DL-isocysteine trifluoroacetate in one step. All new compounds are fully characterized by standard spectroscopical methods and elemental analyses.

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References and Notes

1. Part of this work was presented at the 4th Congress on Amino Acids, Peptides and Analogues, Vienna/Austria, Aug. 1995.
2. See for example: *Tetrahedron*, **1993**, *49*, 3433 ff; Giannis A.; Kolter Th. *Angew. Chem. Int. Ed. Engl.* **1993,** *32*, 1244; Gante J. *Angew. Chem. Int. Ed. Engl.* **1994,** *33*, 1699.
3. Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.*, **1990**, *268*, 249.
4. For a review on hexafluoroacetone as protecting and activating agent see: Pires, R.; Fehn, S.; Golubev, A.; Winkler, D.; Burger, K. *Amino Acids*, in press.
5. Gustavson, L. M; Srinivasan, A. *Synth. Commun.*, **1991**, *21*, 265.
6. Fotouhi, N.; Lugo, A.; Visnick, M.; Lusch, L.; Walsky, R.; Coffey, J.W.; Hanglow, A.C. *J. Biol. Chem.*, **1994**, *48*, 30227.
7. **4**: ^{1}H NMR ($CDCl_3$) δ 3.93 (m, 2H, C***H***$_2$); 4.44 (m, 1H, C***H***); ^{19}F-NMR ($CDCl_3$): δ 0.88 (q, J = 9 Hz, 3F, C***F***$_3$); 2.08 (q, J = 9 Hz, 3F, C***F***$_3$); **10**: ^{1}H NMR ($CDCl_3$): δ 1.44 / 1.46 (s, 9H, C(C***H***$_3$)$_3$); 1.99 / 2.05(d, J = 10 Hz, 1H, S***H***); 3.04-3.18 (m, 3H, C***H***$_2$-Phe, C***H***$_2$); 3.45-3.48 (m, 1H, C***H***$_2$); 3.54 (m, 1H, C***H***); 4.21 (m, 1H, C***H***-Fmoc); 4.41 (m, 2H, C***H***$_2$-Fmoc); 4.72 (m, 1H, C***H***-Phe); 5.52 (m, 1H, N***H***); 6.73 / 6.79 (d, J = 7 Hz, 1H, N***H***); 7.16-7.31 (m, 7H, aromatic-***H***); 7.38-7.43 (m, 2H, aromatic-***H***); 7.59-7.61 (m, 2H, aromatic-***H***); 7.76-7.78 (m, 2H, aromatic-***H***).

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