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A Short, Scaleable Synthesis of Both Enantiomers of 2-Benzoylsulfanyl-5-phthalimidopentanoic Acid From Ornithine

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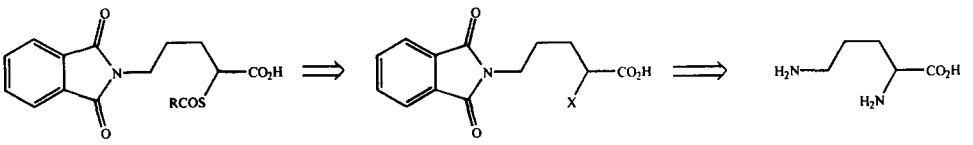
Abstract: An efficient "one-pot" synthesis of (R)- and (S)-2-bromo-5-phthalimidopentanoic acid from ornithine is described. Subsequent reaction with potassium thiobenzoate affords a concise, scaleable route to (R)- and (S)-enantiomers of 2-benzoylsulfanyl-5-phthalimidopentanoic acid, an intermediate in the synthesis of MMP inhibitors. © 1997 Elsevier Science Ltd.

In order to support a programme aimed at the development of inhibitors of zinc-dependent matrix metalloproteinase (MMP) enzymes for the treatment of arthritis and cancer, we needed large quantities of the protected α-thio acid (**1**) in both enantiomeric forms.[1,2] Our retrosynthetic analysis is outlined in scheme 1, in which the precursor α-bromo acid (**2a**) should be available from N_ε-phthaloyl ornithine (**2b**)[3] through nitrous acid deamination. In turn, compound (**2b**) should be available from ornithine (**3**) by a chemoselective protection of the ε-amino group.



(1)
a; R = Me
b; R = Ph

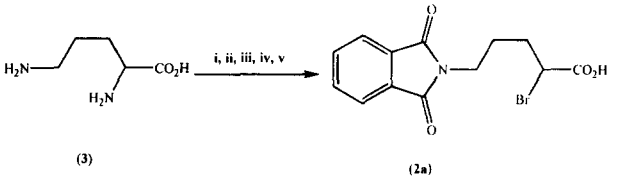
(2)
a; X = Br
b; X = NH_2
c; X = OH

(3)

Scheme 1

In this letter we report the successful implementation of our strategy and describe an efficient "one-pot" procedure for the preparation of the key α-bromo acid (**2a**). In the first instance N_ε-phthaloyl-(S)-ornithine (**2b**) was prepared by reaction of the copper salt of (S)-ornithine with *N*-carboethoxyphthalimide (CEP) followed by treatment with hydrogen sulphide as described by Nefkens for (S)-lysine.[4] Diazotisation

of (**2b**) with 48% aqueous hydrobromic acid and sodium nitrite gave the desired bromo acid (S)-(**2a**) (>99% e.e.).[5,6] The high enantiomeric excess of the product is of note given that other workers have observed up to 2% racemisation during the preparation of α-chloroacids from amino acids.[7] This process was readily adapted into a "one-pot" procdure by using an excess of hydrobromic acid to cleave the copper complex rather than the highly toxic and noxious hydrogen sulphide (scheme 2). This procedure also led us to replace the more usual sodium hydrogen carbonate in the phthalimide protection step with potassium hydroxide in order to avoid large gas evolutions during the acidification step; this seemingly trivial change requires careful pH control in order to avoid partial hydrolysis of the phthalimido moiety. A useful feature of this process is that the bromoacid (**2a**) precipitates from solution, allowing for an easy work-up of the reaction. Disappointingly this procedure could not be easily scaled-up due to excessive foaming, however the use of polypropylene glycol 2025 (PPG) as an anti-foaming agent circumvented this problem whilst still allowing the product to be harvested by filtration. After recrystallisation from toluene (to remove the PPG) the α-bromoacid (**2a**) was obtained in 35-45% overall yield from ornithine (>99% e.e.) on a 500 g scale.[8] A drawback of our "one-pot" procedure was the co-production of a small amount of the hydroxy acid (**2c**)[3] (*ca.* 2-3%) which was not removed by recrystallisation. Other recrystallisation solvents were examined although none proved superior to toluene in this respect, thus the impurity was removed at the next stage.



(3) (2a)

Scheme 2: i) $H_2O/CuSO_4$; ii) KOH; iii) CEP; iv) 48% HBr; v) $NaNO_2/KBr$

We next turned our attention towards the preparation of the protected α-thioacid (**1**). Whilst the use of cesium salts has been advocated to overcome problems with racemisation[9] the high cost of these reagents prompted us to investigate the use of potassium salts. Thus treatment of (R)-(**2a**) with potassium thioacetate in DMF furnished a pure product (S)-(**1a**) albeit of only 85% e.e.[10] Kellogg has noted that treatment of the mesylate of ethyl mandelate with cesium thioacetate in DMF furnished a racemic product, whereas the use of ethanol as solvent gave clean stereochemical inversion.[9] In a similar fashion we have found that the α-thioacetyl acid (S)-(**1a**) was obtained with 99% e.e. using potassium thioacetate and methanol as solvent. We did, however, find that the product, although apparently pure on the basis of a 400 MHz ^{1}H NMR

spectrum, was contaminated with free thiol and disulphide when analysed by HPLC;[11] this despite working under an argon atmosphere.

These results prompted us to investigate the use of potassium thiobenzoate which we have found to give excellent results. Thus, upon treatment of (S)-(**2a**) with potassium thiobenzoate in DMF at 10-15°C the (R)-α-thiobenzoyl acid (**1b**) was obtained in 68% yield and 99% e.e.;[12] similarly (R)-(**2a**) was converted into (S)-(**1b**) in 85% yield and 97% e.e.[13] In separate experiments we have found that racemisation by excess nucleophile takes place readily in contrast to Kellogg's results with cesium thiobenzoate[9,14] and in our experience careful temperature control is the critical factor in obtaining high e.e. product. For example we have noted that the reaction is markedly exothermic and when a reaction was allowed to obtain a temperature of 35°C the resultant product only had an e.e. of 60%. A further advantage of α-thiobenzoyl derivatives, as noted by Kellogg, is that they are usually crystalline, indeed both (R)-(**1b**) and (S)-(**1b**) may be recrystallised from toluene without racemisation.

In summary we have developed short, scaleable syntheses of (R)-(**1b**) and (S)-(**1b**) from (S)- and (R)-ornithine respectively. The route features a novel "one-pot" preparation of the key intermediate α-bromoacid (**2a**) which avoids the use of noxious hydrogen sulphide to cleave the copper complex. Of particular note is the facile conversion of the bromoacid (**2a**) into the α-thiobenzoyl acid (**1b**) with clean stereochemical inversion using potassium thiobenzoate, thus avoiding the need for expensive cesium salts.

References and Notes

1. Baxter, A.D.; Bhogal, R.; Bird, J.; Buckley, G.M.; Gregory, D.S.; Hedger, P.C.; Manallack, D.T.; Massil, T.; Minton, K.J.; Montana, J.; Neidle, S.; Owen, D.A. and Watson, R.J. *Bio-organic and Medicinal Chem. Lett.*, in press.
2. Baxter, A.D.; Bird, J.; Bhogal, R.; Massil, T.; Minton, K.J.; Montana, J. and Owen, D.A. *Bio-organic and Medicinal Chem. Lett.*, **1997**, *7*, 897.
3. Horiuchi, Y.; Akita, E. and Ito, T. *Agr. Biol. Chem.*, **1976**, *40*, 1649.
4. Nefkens, G.H.L.; Tesser, G.I. and Nivard, R.J.F. *Recueil*, **1960**, *79*, 688.
5. Racemic (**2a**) has previously been prepared by bromination of 5-phthalimidopentanoic acid; Gaudry, R. and Berlinguet, L. *Can. J. Chem.*, **1950**, 245.
6. E.e. assay for (**2a**): Chiralpak AD, eluant heptane: IPA: TFA (80:20:1), flow rate 1 ml/min., 254 nm (R)-(**2a**) 10 min., (S)-(**2a**) 12 min.
7. Koppenhoefer, B. and Schurig, V. *Org. Syn. Coll. Vol.VIII*, 159.

8. *Preparation of (S)-2-bromo-5-phthalimidopentanoic acid (2a)*: In a 20 L flange flask (S)-ornithine (500 g, 2.97 mol.) was dissolved in demineralised water (2.5 l) and copper(II) suphate pentahydrate (370 g, 1.49 mol.) added. After stirring for 30 minutes the pH was adjusted to 9 with 8N potassium hydroxide (*ca.* 550 ml) and carboethoxyphthalimide (650 g, 2.98 mol) added. After 2-3 minutes the pH began to drop and was maintained in the range 8.2 - 8.6 by autotitration of 8N potassium hydroxide. The mixture was left to stir overnight, the flask cooled to below 20°C and the copper complex destroyed by addition of 48% aqueous hydrobromic acid (2530 g) and PPG 2025 (100 ml). Potassium bromide (350 g, 2.98 mol.) was added, followed by additional 48% aqueous hydrobromic acid (750 g). The contents of the flask were cooled below 10°C and a solution of sodium nitrite (460 g, 6.63 mol.) in demineralised water (1000 ml) added over 3 hours. The reaction mixture was allowed to stir for 1 hour at 10-15°C and the product harvested by vacuum filtration. The crude product was washed well with demineralised water (4 x 2000 ml) and pulled as dry as possible at the pump. The crude product was dried in a vacuum oven at 60°C to constant weight to yield crude (**2a**) (515.2 g, 53%). The product is *ca.* 70% pure with the main contaminant being PPG.

   Crude (**2a**) (624.3 g) was dissolved in toluene (1872 ml) by heating to reflux and stirred at reflux for 60 minutes. The solution was cooled to below 10°C and the product collected by filtration. The cake was washed twice with toluene (100 ml) and dried in a vacuum oven at 45°C to yield (**2a**) (425 g, 68%; 36% from ornithine).

9. Strijtveen, B. and Kellogg, R.M. *J. Org. Chem.*, **1986**, *51*, 3664.

10. E.e assay for (**1a**):Chiracel OD, eluant heptane: IPA: TFA (90:10:1), flow rate 1 ml/min., 254 nm, (R)-(**1a**) 26.2 min. and (S)-(**1a**) 22.7 min.

11. Zorbax SB, C18, eluant 50% MeCN/50% H_2O (adjusted to pH 2.5 with orthophosphoric acid), flow rate 1 ml/min., 220 nm.

12. E.e. assay for (**1b**) (methyl ester; prepared by treatment of the acid with TMSdiazomethane): Chiralpak AD, eluant heptane: IPA (95:5), flow rate 1 ml/min., 210 nm, (R)-(**1b**) 53.8 min. and (S)-(**1b**) 46.4 min.

13. New compounds were fully characterised.

14. Other workers have also observed racemisation by excess nucleophile: Owen, L.N. and Rahman, M.B. *J. Chem. Soc.* (C), **1971**, 2432.

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