Tetrahedron Letters No. 51, pp 5143 - 5144.

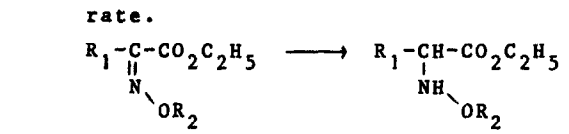
0040-4039/78/1215-5143$02.00/0

# A PRACTICAL SYNTHESIS OF N-HYDROXY-α-AMINO ACID ESTERS

J.D.M. Herscheid and H.C.J. Ottenheijm*

Department of Organic Chemistry, University of Nijmegen,
Toernooiveld, 6525 ED Nijmegen, the Netherlands

A substantial number of natural products containing one or more oxidized peptide bonds -C(O)-N(OH)- have been found in nature. These compounds act variously as potent growth factors, antibiotics, antibiotic antagonists, tumor inhibitors or cell-division factors[1]. In addition it has been suggested that N-hydroxy peptides play an important role in the biosynthesis of β-lactam antibiotics[2] and dehydro amino acids[3]. In connection with studies on epidithiodioxopiperazines, i.e. cyclic dipeptides of α-mercapto-α-amino acids in their disulfide form, we are interested in di-N-hydroxy dioxopiperazines as possible intermediates in their bio- and chemosyntheses. The precursors of choice for the preparation of di-N-hydroxy dioxopiperazines, which hitherto have been prepared only by Cook and Slater[4], seem to be the O-protected N-hydroxy-α-amino acid esters 2; acylation of free N-hydroxy-α-amino acid esters may lead to N- or O-acyl derivatives[5]. The syntheses reported so far for 2 are laborious, as they require the preparation of nitrones[6] or N- and O-blocked N-hydroxy-α-amino acids[7] as intermediates. In addition several syntheses of N-hydroxy-α-amino *acids* have been described[4,8], but these have limited application, give poor yields or are elaborate.



1 2

We wish to report a practical route for the synthesis of N-hydroxy-α-amino esters (2, $R_2$ = H) and their O-benzylated derivatives[9] (2, $R_2$ = $C_6H_5CH_2$). Obvious precursors for these compounds are the easily accessible corresponding oximes 1. The reduction of α-oximino *acids* with cyanoborohydrides to the corresponding N-hydroxy-α-amino acids is known[10]. However, this method is limited to the acids; we found that it fails with α-oximino esters or the corresponding amides. Recently, Kikugawa and Kawase[11] reported the reduction of oxims with pyridine-borane. We were able to apply this method with a slight modification for the selective reduction of α-oximino esters 1 ($R_2$ = H or $C_6H_5CH_2$) to the corresponding N-hydroxy-α-amino esters 2 ($R_2$ = H or $C_6H_5CH_2$, respectively).

A general procedure for this conversion, which proceeds in fair to good yields (see table), is as follows: A 7N ethanolic HCl solution (7 ml) was added

dropwise to a stirred solution of 1 (5 mmol) and borane-pyridine complex[12] (25 mmol) in ethanol (10 ml) at such a rate that the temperature did not exceed 40°C. Stirring was continued for one hour after which the solvent was evaporated. The residue was taken up in $CH_2Cl_2$, washed with 1N NaOH, or neutralized by stirring with an excess of solid $Na_2CO_3$ (for $R_2$ = $C_6H_5CH_2$ or H, respectively), the organic layer was dried ($Na_2SO_4$) and evaporated. Purification was done by column chromatography (Merck silica gel 60, 1-2% $C_2H_5OH$ in $CH_2Cl_2$ as eluent) to give the pure[13] N-hydroxy-α-amino acid esters 2 (see table).

Table. Conversion of 1 into 2

| | $R_1$ | $R_2$ | 2, yield(%) |
|---|---|---|---|
| A | H | H | 47 |
| B | $CH_3$ | H | 75 |
| C | $C_6H_5$ | H | - |
| D | $C_6H_5CH_2$ | H | 82 |
| E | H | $C_6H_5CH_2$ | 95 |
| F | $CH_3$ | $C_6H_5CH_2$ | 94 |
| G | $C_6H_5$ | $C_6H_5CH_2$ | - |
| H | $C_6H_5CH_2$ | $C_6H_5CH_2$ | 50 |

Compound 2c could not be prepared due to decomposition of 1c under the reaction conditions. Oxim 1G could not be reduced, whereas on reduction of 1H, 50% starting material was recovered besides 2H. This failure is difficult to explain, as the mechanism of the pyridine-borane reduction is unknown[11]. However, we are inclined to contribute it to steric hindrance. The α-oximino esters 1 were prepared from the corresponding α-keto acids, hydroxylamine hydrochloride (1A-C in 60-90% yield) or O-benzylhydroxylamine hydrochloride (1E-G in 90-100% yield) and p-TosOH in $C_2H_5OH$ with azeotropic removal of water. Nitrosation[14] of benzylmalonic ester gave compound 1D, which was converted into 1H in 84% yield by alkylation.

As pyridine-borane does not reduce other functional groups[11], O-benzylated α-oximino acid derivatives 1 ($R_2$ = $C_6H_5CH_2$), having a fully protected hydroxylamino function, can now be regarded as valuable synthons in the preparation of N-hydroxy peptides. Work is in progress to use these synthons for the preparation of di-N-hydroxy dioxopiperazines.

REFERENCES AND FOOTNOTES

1. J.H. Wiesburger and E.K. Weisburger, Pharmacol. Rev. 25, 1 (1973); H. Maehr, Pure Appl. Chem. 28, 603 (1971); J.B. Neilands, Science 156, 1443 (1967).
2. A.I. Scott, S.E. Yoo, S.-K. Chung and J.A. Lacadie,Tetr. Letters,1137 (1976).
3. U. Schmidt, Pure Appl. Chem. 49, 163 (1977).
4. A.H. Cook and C.A. Slater, J. Chem. Soc., 4130 (1956).
5. T. Kolasa and A. Chimiak, Tetrahedron 30, 3591 (1974).
6. T. Polonski and A. Chimiak, J. Org. Chem. 41, 2092 (1976).
7. T. Kolasa, A. Chimiak and A. Kitowska, J. Prakt. Chem. 317, 252 (1975).
8. L. Neelakantan and W.H. Hartung, J. Org. Chem. 23, 964 (1958); T. La Noce, E. Bellasio and E. Testa, Ann. Chim. (Rome) 58, 393 (1968); E. Buehler and G.B. Brown, J. Org. Chem. 32, 265 (1967).
9. The benzyl group was chosen on the basis of arguments given by T. Kolasa and A. Chimiak, ref. 5.
10. A. Ahmad, Bull. Chem. Soc. Japan 47, 1819 (1974); B.L. Moller, I.J. McFarlane and E.E. Conn, Acta Chem. Scand. B 31, 343 (1977).
11. Y. Kikugawa and M. Kawase, Chem. Letters, 1279 (1977).
12. Commercially available from Aldrich.
13. Satisfactory spectral data were obtained of all these oily compounds.
14. J.C. Shivers and C.R. Hauser, J. Amer. Chem. Soc. 69, 1264 (1947).

(Received in UK 6 October 1978)