Tetrahedron Letters,Vol.24,No.10,pp 1031-1034,1983 0040-4039/83/101031-04$03.00/0
Printed in Great Britain ©1983 Pergamon Press Ltd.

A SHORT AND EFFICIENT SYNTHESIS OF PHENOLCARBOXAMIDES

Aline HUSSON, Richard BESSELIEVRE and Henri-Philippe HUSSON*

Institut de Chimie des Substances Naturelles, CNRS, 91190 Gif s/Yvette (France)

ABSTRACT - The selective acylation of primary amine functions of polyamines with acylating agents derived from unprotected mono or o-dihydroxy aromatic acids is described. The key step of the method is the transient protection of the phenol groups during the preparation of hydroxy-1-piperidine active esters. This method is especially applicable to the preparation of the radiolabelled polyamine derivatives.

Over the past several years considerable effort has been directed towards the synthesis of amide derivatives of polyamines due to the role that these compounds play in biochemical processes and to their occurence as secondary metabolites in many living organisms. For example spermidine phenolamides have been found to act as iron chelators[1] whereas the biosynthesis of putrescine phenolamides has been shown to play a role in the flowering of plants[2].

The problem that is presented in the synthesis of polyamine derivatives is the selective acylation of the terminal primary amino groups. Acylation with acid chlorides or anhydrides gives mixtures of products[3]. In this area we have previously demonstrated that 1-hydroxy-piperidine active esters acylate regioselectively N^1 and N^8 primary amines of spermidine 14 in high yield without affecting the secondary amine function. The first synthesis of the 19-membered lactam ring of tetrahydrolunaridine[4] was achieved using this method as was the facile preparation of maytenine 16 [5] (scheme 3).

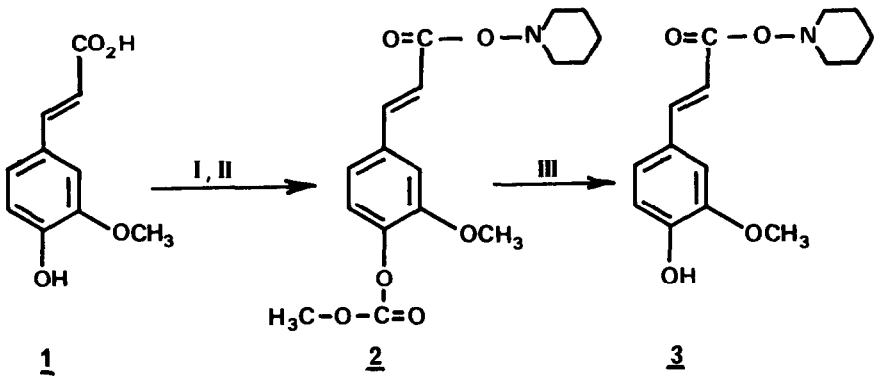
Alternate methods have subsequently been developed for the selective acylation[6] or more interestingly for chemical differentiation of the two ends of spermidine[7]. A multistep synthesis of N^1, N^8 bis-acyl spermidine derivatives 15 and 18 involving N^4 amino group protection has also been recently reported [8].

In this communication we wish to report an extension of our previous work using 1-hydroxy-piperidine esters to the synthesis of mono or bis-amide derivatives of mono or dihydroxy aromatic carboxylic acids wherein the phenolic group is unprotected. This was accomplished by transient protection of the hydroxyl group or groups during the formation of the active ester.

In this way the habitual problem of protection-deprotection of phenols was avoided which may, besides introducing supplementary steps, require conditions incompatible with the presence of other functionalities in the molecules.

Such considerations are particularly important when considering the synthesis of phenolamides radiolabelled on the aromatic ring and/or on the polyamine backbone where the use of a short and convergent route is essential.

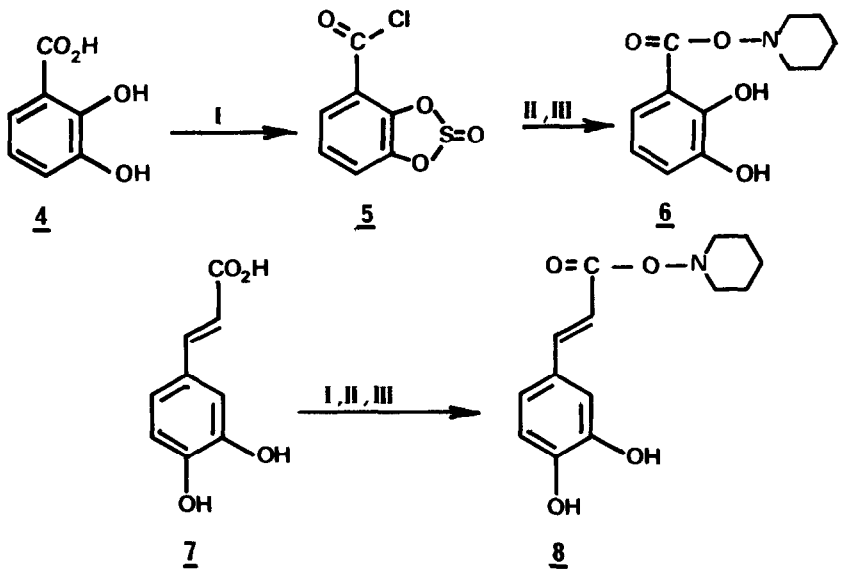
The technique used for the preparation of the active ester 3 is as follows : the reaction of ferulic acid 1 (1 equiv.) with $ClCO_2CH_3$ (2.1 equiv.) in the presence of $(C_2H_5)_3N$



1 2 3

Reagents : I, $ClCO_2CH_3$, $N(C_2H_5)_3$, CH_2Cl_2, 0°, 1 h. ; II, 1-hydroxy-piperidine, rt, 18 h. ; III, CH_3OH-NH_4OH (97-3), rt, 3 h.

SCHEME 1



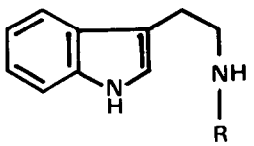
4 5 6 7 8

Reagents : I, $SOCl_2$, $(NH_2)_2CO$ catalytic, 40°, 2 h. ; II, C_6H_6, 1-hydroxy-piperidine, rt, 12 h. ; III, $NaHCO_3$, H_2O, rt, 1 h. Filtration of a CH_2Cl_2 solution on SiO_2.

SCHEME 2

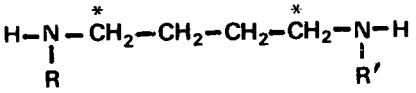
(2.1 equiv.) in CH_2Cl_2 at 0° gave an intermediate phenol methylcarbonate mixed anhydride. This product reacted with 1-hydroxy-piperidine (1.1 equiv.) affording 2 [9] (scheme 1). The phenol function was subsequently liberated by treatment of 2 with NH_4OH-CH_3OH to give 3 (Y : 90% from 1)[10].

This method could not be used for o-diphenols 4 or 7 however, as complex mixtures were obtained. For 2,3-dihydroxybenzoic acid 4 reaction with $SOCl_2$ led to the formation of the acid chloride 5 [11] (scheme 2). Reaction of 5 with 1-hydroxy-piperidine followed by sulfite hydrolysis during working up gave the desired active ester 6 (Y : 75% from 4)[12]. Similarly 3,4-dihydroxycinnamic acid 7 yielded the active ester 8 [13]. The formation of a sulfite derivative of o-dihydroxy derivatives was convenient as it provided a temporary protection of this system. The corresponding chlorosulfites of mono-hydroxy derivatives are apparently less stable as side reactions occured.



9 R = H : tryptamine

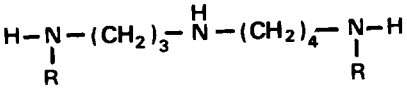
10 R = ferulyl



11 R = R' = H : putrescine

12 R = ferulyl, R' = H

13 R = R' = ferulyl



14 R = H : spermidine

15 R = benzoyl

16 R = cinnamyl

17 R = ferulyl

18 R = 2,3-dihydroxybenzoyl

SCHEME 3

Active esters 3 and 6 were found to react selectively with a number of amine substrates[14] whose corresponding amides are of biological interest. Thus, the N-ferulyltryptamine 10 [15] and the bis-ferulylamides 13 [16] and 17 [16] derived respectively from putrescine 11 and spermidine 14 (scheme 3) were synthesised [17].

Preparation of the mono-acyl derivatives of 11 or 14 has proved difficult in the past. Usually, either the bis-acyl derivatives are partially saponified [18] or a large excess of the polyamine is reacted with acyl chlorides of protected hydroxy aromatic acids. These methods are not convenient for either synthesis on a large scale or the microscale preparation of radiolabelled derivatives.

Of special interest was the preparation of ^{14}C-labelled monoferulylputrescine 12 whose biological role is being studied [19]. The reaction of 1-4 ^{14}C putrescine (100 mCi/mmol ; 0.1 mmol)[20] with 3 (0.05 mmol)[17] gave the mono-acyl derivative 12 and traces of the bis-acyl derivative 13 (along with the remaining putrescine). After paper chromatographic purification the required radioactive phenolamide 12 was isolated at its hydrochloride (Y = 26 % ; 100 mCi/mmol)[16].

The bis-(2,3-dihydroxybenzoyl) amide 18 [1] derived from spermidine 14 and the macrocyclic tris-(2,3-dihydroxybenzoyl) amide enterobactin [21] are interesting natural ferric ion sequestring agents. The short synthesis of 18 (Y : 55%)[16] using same methodology as above demonstrated that other iron chelators or analogues could be prepared in such conditions avoiding the inconvenient phenol deprotection (enterobactin is relatively unstable).

REFERENCES AND NOTES

1 - G.T. TAIT, Biochem. J., 1975, 146, 191.

2 - J. MARTIN-TANGUY, F. CABANNE, E. PERDRIZET and C. MARTIN, Phytochemistry, 1978, 17, 1927 and references therein cited.

3 - E. SCHLITTLER, U. SPITALER, N. WEBER, Helv. Chim. Acta, 1973, 56, 1097.

4 - H.-P. HUSSON, C. POUPAT, B. RODRIGUEZ and P. POTIER, Tetrahedron, 1973, 29, 1405.

5 - H.-P. HUSSON, C. POUPAT and P. POTIER, C. R. Acad. Sc., Paris, 1973, 276, 1039.

6 - Y. NAGAO, K. SENO, K. KAWABATA, T. MIYASAKA, S. TAKAO and E. FUJITA, Tetrahedron Lett., 1980, 21, 841.

7 - B. GANEM, Acc. Chem. Res., 1982, 15, 290.

8 - R.J. BERGERON, K.A. Mc GOVERN, M.A. CHANNING, P.S. BURTON, J. Org. Chem., 1980, 45, 1589; R.J. BERGERON, P.S. BURTON, K.A. Mc GOVERN and S.J. KLINE, Synthesis, 1981, 732.

9 - 2 : mp 135°C (ethyl acetate-hexane) ; MS m/e (relative intensity) : 335 ($M^{+\cdot}$, 6), 235 (100), 191 (36) ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 3.87-3.9 (2s, 2 OCH_3), 6.35 (d, 1H, J_{AB} trans = 16 Hz), 7.68 (d, 1H, J_{AB} trans = 16 Hz)

10 - 3 : mp 112°C(acetone) ; MS m/e (relative intensity) : 277 ($M^{+\cdot}$, 6) 177 (100) ; ^1H NMR ($CDCl_3$, 60 MHz, TMS δ = 0) : 3.85 (s, OCH_3) 6.15 (d, 1H, J_{AB} trans = 16 Hz), 7.55 (d, 1H, J_{AB} trans = 16 Hz).

11 - F.L. WEITL and K.N. RAYMOND, J. Am. Chem. Soc., 1979, 101, 2728.

12 - 6 : mp 154°C(CH_2Cl_2) ; MS m/e (relative intensity) : 237 ($M^{+\cdot}$, 18) 137 (100).

13 - 8 : amorphous ; MS m/e (relative intensity) : 263 ($M^{+\cdot}$, 3) 180 (40), 163 (100) ; ^1H NMR ($CDCl_3$, CD_3OD, 400 MHz, TMS δ = 0) : 1.7-1.8 (m, 6H), 2.88 (s, 4H), 6.16 and 7.54 (2 d, J_{AB} = 16 Hz).

14 - As 1-hydroxy-piperidine active esters are not reactive with alcohols or phenols self condensation side reactions did not present a problem.

15 - A. EHMANN, Phytochemistry, 1974, 13, 1979.

16 - All known compounds have been fully characterized and their spectral data are in accord with their assigned structures.

17 - Typically a THF solution of the amine was refluxed under nitrogen in the presence of 1 or 2 equiv. of active ester for 18 h. The solvent was then removed in vacuo to give a residue which was, if necessary, purified using the appropriate chromatographic methods [2,18].

18 - S. MIZUSAKI, Y. TANABE, M. NOGUCHI and E. TAMAKI, Phytochemistry, 1971, 10, 1347.

19 - F. CABANNE, M.A. DALEBROUX, J. MARTIN-TANGUY and C. MARTIN, Physiol. Plant., 1981, 53, 399.

20 - For experimental convenience the radioactive putrescine is released from its dihydrochloride with an equivalent amount of 0.1 N NaOH in the reaction mixture.

21 - J.R. POLLACK and J.B. NEILANDS, Biochem. Biophys. Res. Commun., 1970, 38, 989.

(Received in France 13 December 1982)