Tetrahedron Letters,Vol.24,No.47,pp 5211-5214,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

AN EFFICIENT SYNTHESIS OF SOME BIOLOGICALLY IMPORTANT MONOACYLATED DIAMINES

Gerhard KUNESCH

Laboratoire des Médiateurs Chimiques (INRA-CNRS,ERA 740)
F-78470 Magny-les-Hameaux,France.

ABSTRACT : Some biologically important monoacylated diamines were synthesized via azide intermediates in good yield.

Several authors have recently demonstrated the biological importance of compounds like feruloylputrescine 1 and p-coumaroylputrescine 2.

In spite of their widespread occurrence in plants[3] it is difficult to isolate these highly polar compounds from natural sources.[4] In order to define precisely the scope of their biological activity we set out to synthesize 1 and 2 . A recent publication[5] prompts us to report our results in this field.[6]

Using direct acylation procedures even a large excess of diamine invariably gives only low yields of monoamides [7,8]; e.g. radioactive feruloylputrescine was obtained in 26% yield in spite of a 2-fold excess of labeled putrescine and the product had to be purified in form of its hydrochloride using paper chromatography.[5]

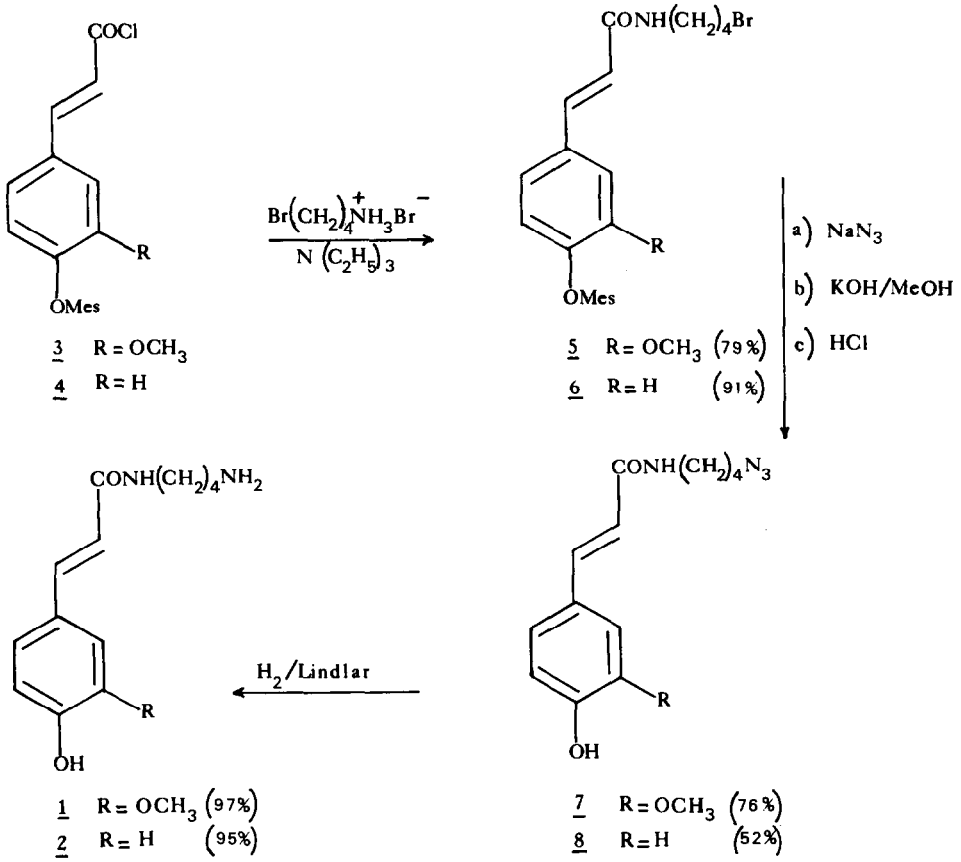
In a more systematic study of this synthetic strategy, BARRET and al.[9] isolated only 1% of monoamide after treatment of excess putrescine with benzoyl chloride. In contrast , the same authors achieved good yields of monoacylation through dynamic protection of one amino group by 18-crown-6 (64%). Similar yields were observed (50-80%) when insoluble polymer supports were used as monoblocking agents of symmetrical diamines [10].

For a convenient purification of the monoacylated products a protection of the remaining free amino groups becomes necessary[7,9,10].

The difficulties mentioned above and the need of notable amounts of pure phenolamides for a thorough evaluation of their biological activity led us to consider a totally different approach of their synthesis as depicted in SCHEME I.

Addition of a solution of 1,4-aminobromobutane bromohydrate in anhydrous chloroform to the mesyl-protected acid chlorides 3 and 4 in the presence of a slight excess of triethylamine at room temperature (10 min) yielded 5 and 6 which could be easily transformed into the corresponding azide with NaN_3 in boiling 90% ethanol (2h). Removal of the protecting group with KOH/MeOH (r.t.,8h) followed by acidification furnished 7 and 8 which were hydrogenated in the presence of Lindlar catalyst [11](EtOH, r.t., 2h) to afford pure 1 and 2 after filtration and evaporation.

SCHEME I

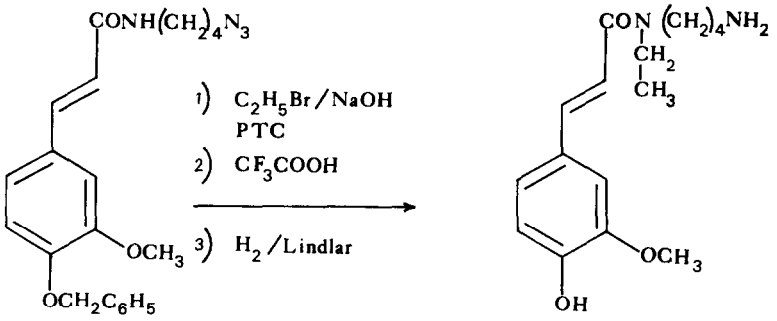


The starting materials for our pathway are easily available [12,13]. The yields are good to excellent and the desired phenolamides 1 and 2 are obtained in the final key step by cristallisation without requiring chromatographic purification.

In order to demonstrate the versatility of the above reaction sequence we synthesized 1-ethyl-1-feruylputrescine along SCHEME II from compound 9 which was prepared in analogy to 5 and 6 from benzylated ferulic acid. N-alkylation of 9 was easily achieved *via* phase-transfer catalysis [14] and the amide-blocked intermediate thus obtained was debenzylated using trifluoroacetic acid [15]. Finally, hydrogenation of the resulting azide provided the desired product 10 .

Regioselective synthesis of monoacylated spermidines and related polyamine derivatives is currently in progress in our laboratory and will be reported in due course[16].

SCHEME II



9 10

Acknowledgments : We thank the CNRS for financial support (ATP Chimie Fine n° 8182) and Mrs S.CHUILON for skilled technical assistance.

REFERENCES

1) a) C.MARTIN and J.MARTIN-TANGUY, C.R. Acad. Sc. Paris, 293 , série III, 249 (1981).
b) J.MARTIN-TANGUY, C.MARTIN, M.GALLET and R.VERNOY, C.R. Acad. Sc. Paris ,282, série D , 2231 (1976).
c) C.CABANNE, M.A.DALEBROUX, J.MARTIN-TANGUY and C.MARTIN, Physiol. Plant. 53 , 399 (1981).

2) a) J.BERLIN, K.H.KNOBLOCH, G.HOFLE and L.WITTE, J.Nat. Prod., 45 , 83 (1982).
b) J.BERLIN and L.WITTE, J. Nat. Prod., 45 , 88 (1982).

3) J.MARTIN-TANGUY, F.CABANNE, E.PERDRIZET and C.MARTIN, Phytochemistry, 17 ,1927 (1978).

4) a) A.HOLLERBACH and G.SPITELLER, Monatsh. Chem., 101 , 141 (1970).
b) A.EHMANN, Phytochemistry, 13 , 1973 (1974).

5) A.HUSSON, R.BESSELIEVRE and H.P.HUSSON, Tetrahedron Letters, 24 , 1031 (1983).

6) G.KUNESCH, S.CHUILON, C.MARTIN and J.MARTIN, French Patent n° 8209932(June 6th,1982).

7) A.GUGGISBERG, P. van der BROEK, M.HESSE, F.SCHNEIDER and K.BERNAUER, Helv. Chim. Acta, 59 , 3013 (1976).

8) A.HEESING and R.ECKARD, Chem. Ber. 103 , 534 (1970).

9) A.G.M.BARRETT, A.LARA and S.TOGRAIE, J.C.S. Chem. Comm., 1980, 300.

10) D.M.DIXIT and C.C.LEZNOFF, J.C.S. Chem. Comm., 1977 , 798.

11) E.J.COREY, K.C.NICOLAOU, R.D.BALANSON and Y.MACHIDA, Synthesis, 1975 , 590.

12) M.HUMORA and J.QUICK, J. Org. Chem., 44 , 1166 (1979).

13) N.L.DRAKE and J.A.GARMAN, J. Am. Chem. Soc. 71 , 2425 (1949).

14) A.KOZIARA and S.ZAWADZKI, Synthesis, 1979 , 527.

15) J.P.MARCH, Jr and L.GOODMAN, J. Org. Chem., 30 , 2491 (1965).

16) Yields have not been optimized. The physical properties and spectral data of 1, 2, and 10 are as follows :

Ferulylputrescine 1 : $C_{14}H_{20}O_3N_2$. Calc.% :C 63.61, H 7.63, N 10.6 ; found% :C 63.42, H 7.70, N 10.44 ; F = 163-165° (EtOH/H_2O) ; ^1H - NMR (CD_3OD, 60 MHz) : δ 1.65 ppm (m, 4H), 2.74 (m, 2H), 3.33 (m, 2H), 3.89 (s, 3H) 6.48 (d, 1H, J = 16Hz), 6.76 - 7.11 (3 aromatic protons), 7.49 (d, 1H, J = 16Hz) ; IR(KBr) : ν_{CO} = 1640 cm^{-1} ; mass spectrum : M^+ at $^m/_z$ = 264, base peak at $^m/_z$ = 177 ($C_{10}H_9O_3^+$).

p - Coumarylputrescine 2 : $C_{13}H_{18}O_2N_2$ - Calc.% :C 66.64, H 7.74, N 11.96 ; found% :C 66.49, H 7.79, N 11.82 ; F = 105 - 107° (EtOH/H_2O) ; ^1H - NMR (DMSO - d_6, 400 MHz) : δ 1.53 ppm (m, 4H), 2.77 (m, 2H), 3.16 (m, 2H), 6.41 (d, 1H, J = 16Hz), 6.80 (d, 2H, J = 10Hz), 7.31 (d, 1H, J = 16Hz), 7.38 (d, 2H, J = 10Hz) ; IR (KBr) : ν_{CO} = 1655 cm^{-1} ; mass spectrum : M^+ at $^m/_z$ = 234, base peak at $^m/_z$ = 147 ($C_9H_7O_2^+$).

1 - Ethyl - 1 - ferulylputrescine 10 : $C_{16}H_{24}O_3N_2$. Calc.% : C 65.72, H 8.27, N 9.58 ; found : C 65.58, H 8.40, N 9.51 ; Yellow oil ; ^1H - NMR ($CDCl_3$, 90MHz) : δ 1.13 ppm (t, 3H, J = 7Hz), 1.53 (m, 4H), 2.90 (m, 2H), 3.33 (m, 2H), 3.66 (, 2H, J = 7Hz), 2.83 (s, 3H), 6.62 (d, 1H, J = 15 Hz), 6.80 - 7.25 (3H), 7.58 (d, 1H, J = 15Hz) ; IR (film) : ν_{CO} = 1640 cm^{-1} ; mass spectrum : M + 1 at $^m/_z$ = 333.

(Received in France 24 June 1983)