Tetrahedron Letters No. 43, pp 3737 - 3740, 1975. Pergamon Press. Printed in Great Britain.

AMINO ACID SYNTHESIS II. AMIDOALKYLATION OF OLEFINS WITH GLYOXYLIC ACID DERIVATIVES

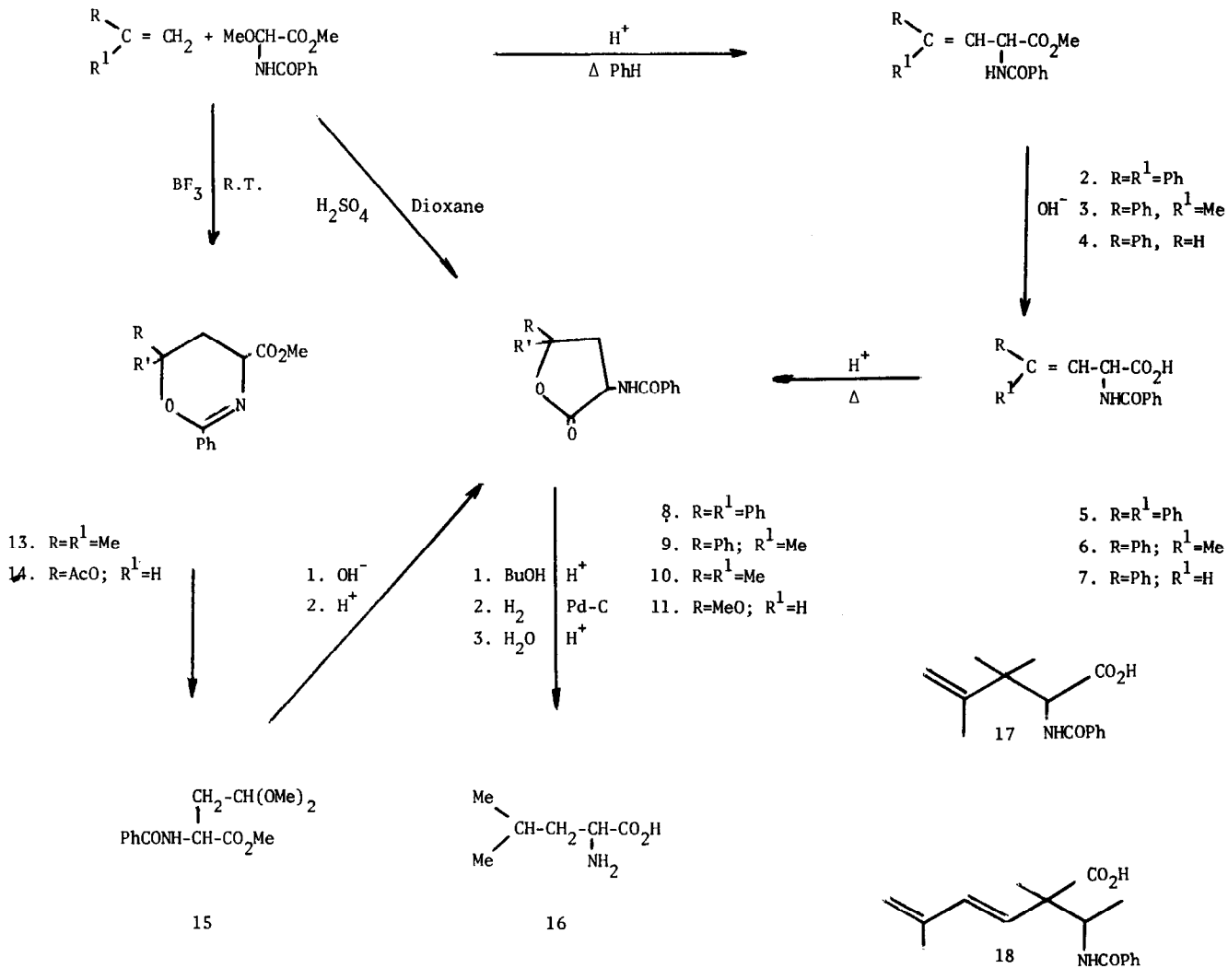
Janina Altman, Reuven Moshberg and Dov Ben-Ishai*
Department of Chemistry, Israel Institute of Technology, Haifa, Israel

(Received in UK 31 July 1975; accepted for publication 15 September 1975)

Synthetic amino acids have found applications as food additives (e.g. methionine, lysine)[2], in the synthesis of semi-synthetic penicillins and cephalosporins (Ampicillin,..)[3], as sweetening agents (aspartylphenylalanine methyl ester)[4] or as chelating agents (e.g. EDTA). We would like to report a new synthesis of leucine (16) aspartic acid (20), aspartic acid semialdehyde derivatives (11,14,15) and other unsaturated α-amino acid derivatives by the amidoalkylation of olefins with methyl α-methoxyhippurate, α-hydroxyhippuric acids and related glyoxylic acid amide adducts.[5]

Reacting 1,1-diphenylethylene, α-methyl styrene, styrene, tetramethylethylene and 2,5-dimethyl-2,4-hexadiene with methyl α-methoxyhippurate in boiling benzene and in the presence of a sulfonic acid catalyst afforded the methyl esters of the N-benzoyl unsaturated α-amino acids (2-4,17,18). The diphenyl methyl ester 2 (m.p. 163°C) which was obtained in 57% yield, was hydrolyzed to the benzamido acid 5 (m.p. 206°C) and further cyclized to the 5,5-diphenyl-α-benzamidobutyrolactone (8, m.p. 198°). By using the same procedure we have prepared the crystalline benzamido acids 6 (m.p. 193°, 51%); 7 (m.p. 212, 42°); 17 (m.p. 146, 27%) and 18 (m.p. 97°, 46%). The corresponding methyl esters were obtained as oils. The crude acid 6, was according to the nmr a mixture of two isomers. Both the 3 and the 4-pentenoic acid derivatives afforded the same butyrolactone 9 on cyclization.

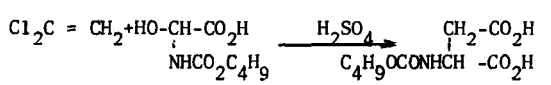
Isobutylene reacted with the methyl α-methoxyhippurate to give the oxazine 13, or the benzamidolactone 10 depending on the reaction conditions.[6] In ether solution and in the presence of boron trifluoride etherate the oily oxazine 13 was obtained in 53% yield together with the unsaturated ester (14%) of type 2. In dioxane-sulfuric acid solution isobutylene afforded 5,5-dimethyl-α-benzamidobutyrolactone (m.p. 176°, 45%).[7] The same lactone was obtained in 73% yield by reacting α-hydroxyhippuric acid with isobutylene in dioxane-sulphuric acid solution. Under the same experimental conditions we have obtained from α-hydroxy-N-benzyloxycarbonylglycine[5] and isobutylene, 5,5-dimethyl-α-benzyloxycarbonylaminobutyrolactone (m.p. 94°, 65%).[8]


R
C = CH2 + MeOCH-CO2Me
R1
NHCOPh
H+
Δ PhH
C = CH-CH-CO2Me
HNCOPh
BF3 R.T.
H2SO4 Dioxane
OH- 2. R=R1=Ph
3. R=Ph, R1=Me
4. R=Ph, R=H
CO2Me
O
N
Ph
NHCOPh
H+
Δ
C = CH-CH-CO2H
NHCOPh
13. R=R1=Me
14. R=AcO; R1=H
1. OH-
2. H+
1. BuOH H+
2. H2 Pd-C
3. H2O H+
8. R=R1=Ph
9. R=Ph; R1=Me
10. R=R1=Me
11. R=MeO; R1=H
5. R=R1=Ph
6. R=Ph; R1=Me
7. R=Ph; R1=H
CO2H
17
NHCOPh
CH2-CH(OMe)2
PhCONH-CH-CO2Me
15
Me
CH-CH2-CH-CO2H
Me
NH2
16
CO2H
18
NHCOPh

The lactone 10 was opened with n-butanol in the presence of β-naphthalene sulfonic acid to give a mixture of butyl esters of β,γ and γ,δ dehydro-N-benzoylleucine. Catalytic hydrogenation of the crude mixture followed by acid hydrolysis gave the amino acid in 70% yield (based on the lactone). The two isomeric unsaturated esters were also separated and converted to the α-benzamido acids. The β,γ-dehydrobenzoylleucine melted at 132° and the γ,δ isomer melted at 134°.

Vinyl acetate reacted with methyl α-methoxyhippurate in benzene solution and in the presence of boron trifluoride to give the oily methyl ester of 5,6-dihydro-6-acetoxy-2-phenyl-1,3-oxazine-4-carboxylic acid (14). The acetoxyoxazine which is a derivative of aspartic acid semialdehyde was converted, on treatment with methanolic sulfuric acid, to the methyl ester dimethylacetal of N-benzoylaspartic acid semialdehyde (15). The latter was further converted to 5-methoxy-α-benzamidobutyrolactone on treatment with aqueous base followed by acidification with aqueous phosphoric acid. Both the oxazine 14 and lactone 11 were obtained as mixtures of two stereomers. The oxazines 14, were separated on a florisil column to give a crystalline product (m.p. 64°) and an oil. The lactones were separated by fractional crystallization from ethyl acetate-hexane and melted at 183° and 147°.

α-Hydroxy-N-butoxycarbonylglycine (19) which was prepared from glyoxylic acid and butyl carbamate (m.p. 76°) in analogy to the preparation of the benzyl derivative,[5] was found to react in sulfuric-acetic acid mixture with 1,1-dichloroethylene to give in one step N-butoxycarbonyl aspartic acid (20, 47%). The product which melted at 114° was identical with an authentic sample prepared from aspartic acid and n-butyl chloroformate. All the new compounds described above had satisfactory analyses and showed characteristic infrared, nmr and mass spectra.



19 20

References

1. For paper I in the series see D. Ben-Ishai, I. Satati and Z. Berler, Chem. Commun., 1975, 349.
2. A.M. Altschul, Nature, 248, 643 (1974). C&EN Dec. 24 page 18 (1973).
3. Penicillins and cephalosporins. Their Chemistry and Biology. Chapter 12.E.A. James, Editor, Academic Press, New York (1972).
4. R.H. Mazur, J.M. Schlatter and A.H. Goldkamp, J. Amer. Chem. Soc., 91, 2684 (1969).
5. U. Zoller & D. Ben-Ishai, Tetrahedron, 31, 863 (1975).
6. H.E. Zaugg, Synthesis, 49 (1970) and refs. cited.
7. J. Fillman and N. Albertson, J. Amer. Chem. Soc., 70, 171 (1948). H.L. Goering, S.J. Cristol and K. Dittmer, J. Amer. Chem. Soc., 70, 3312 (1948).
8. H. Faulstich and H. Trischmann, Ann., 741, 55 (1970).