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A NEW SYNTHESIS OF BIOTIN [1)]

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Summary: (+)-Biotin is prepared starting from the new intermediate 3,4-diamino-2-carbomethoxy-thiophene.

Biotin (1), one of the essential vitamins required for the human diet, is physiologically active only in one chiral form. The intricate chemistry necessary to construct the all-cis-skeleton of 1 has found considerable attention in recent time [2a, 2b].

Nevertheless many of these synthetic schemes require a large number of steps, the main disadvantage of the most important commercial process[3]. The number of operations could be obviously shortened by a synthesis starting from an aromatic precursor. However, strategies via aromatic intermediates have found little interest in the past[4] because of the inaccessibility of suitably functionalized diaminothiophenes and their corresponding hydrogenation products.

Our interest in thiophene chemistry[5] led us to a new entry into 3,4-diamino-thiophenes which could be converted to 1 in only 7 steps. The starting material 2 was synthesized in a two-step procedure[6a] from commercially available N-benzylidene aminoacetonitrile, or alternatively by a more conventional approach[7a] starting from 3-amino-2-carbomethoxy-thiophene[7b].

3,4-Diamino-2-carbomethoxy-thiophene (2) was transformed to the acylated derivative 3 with pyridine/benzoylchloride in chloroform in almost quantitative yield. With lithium aluminium hydride in tetrahydrofuran under carefully controlled conditions at 0°C a surprisingly selective reaction at the ester moiety occurred furnishing 4 in 75 % yield. The reduction of 3 with diisobutylaluminium hydride, sodium borohydride/lithium bromide or several other commonly used reducing agents gave lower yields because of competitive saponification of the labile benzamide group in 3-position or further reduction of the hydroxymethyl group. Oxidation with pyri-

dinium chlorochromate in methylene chloride gave the aldehyde 5 (80 % yield) which underwent a smooth Wittig reaction with the required C_4-synthon[8] in toluene to afford a cis/trans-mixture of 6 (91 % yield).

Now two routes to (±)-biotin are possible. Firstly hydrogenation of the side chain in methanol over 5 - 10 % Pd/C afforded 7 in quantitative yield. Similar to a literature procedure[4d], 7 was saponified (without isolation of the very sensitive diamino-intermediate) and carbonylated with phosgene to yield 70 % of aromatic biotin 8. The hydrogenation of the N-acylated derivative 8 to give 1 in good yield was recently described[9]. On the other hand it was possible to hydrogenate 6 via 7 in one step to 9 at 90 bar/100°C in acetic acid with the same catalyst (5 % Pd/C). We isolated 9 in 60 % yield and could identify as minor by-products a stereoisomer of 9, a 3,4-dihydrothiophene derivative and a desulfurized product after chromatographic separation on silica gel. The conversion of 9 to (±)-biotin was straight-forward. Saponification of 8 with barium hydroxide in water (14 h, 140°C), followed by phosgenation afforded of 1 in 75 % yield.

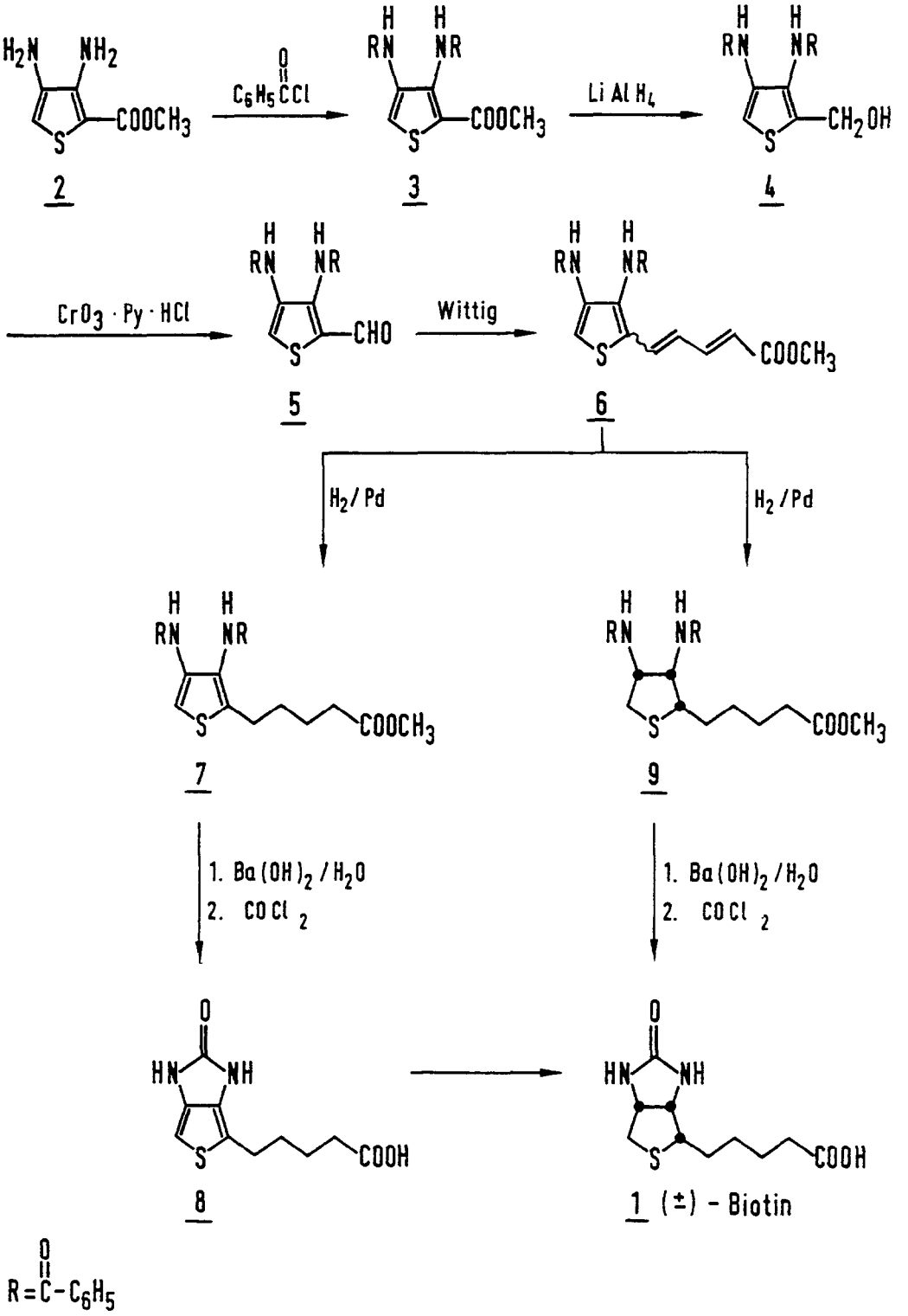
The relatively mild conditions required for the hydrogenation[9] of 9 have encouraged us to study the optimization of this important step.

As the cleavage of 1 into its enantiomers is an established process[10] this completes a new alternative route to (+)-biotin.

Physical Data

All compounds exhibited satisfactory elemental analysis and spectra, typical data are given below:

2: mp. 94-96°C; 3: mp. 149-151°C; 4: mp. 199-200°C; 5: mp. 179-181°C; 6 (cis-trans-mixture): mp. 236-237°C, HNMR (DMSO): δ = 10.1 (d, J = 8Hz, NH), 10.0 (d, J = 8Hz, NH) 8.2-7.8 (m, 5H, thiophene and benzene), 7.75-7.5 (m, 6H, aromatic), 7.46 and 7.26 (2d, J = 10 and 16Hz, 1H, δ-H), 6.92-6.75 (m, 1H, ß-H), 6.5-6.1 (m, 2H, α-H+ γ-H), 3.73 and 3.69 (2s, 3H, OCH_3); 7: mp. 149-151°C; 9: HNMR (DMSO): δ = 7.9-7.1 (m, 11H, aromatic, NH), 6.95 (d, J = 8Hz, 1 H, NH), 4.9-4.8 (m, H-2), 4.65-4.50 (m, H-3), 3.75 (dt, J = 7+5Hz, H-2), 3.62 (s, 3H, OCH_3), 3.60 (t, J = 7Hz, H_A-4), 2.70 (t, J = 6Hz, H_B-4), 2.30 (t, J = 7Hz, 3H, CH_2-CO_2), 1.9-1.1 (m, 6H, CH_2).


H2N NH2
COOCH3
C6H5CCl
O
H H
RN NR
COOCH3
Li Al H4
CH2OH
2
3
4
CrO3 · Py · HCl
CHO
Wittig
COOCH3
5
6
H2 / Pd
H2 / Pd
7
9
1. Ba(OH)2 / H2O
2. COCl2
1. Ba(OH)2 / H2O
2. COCl2
HN NH
O
COOH
8
1 (±) - Biotin
R = C - C6H5

References and notes

1) Dedicated to Prof. Dr. Werner Reif on the occasion of his 60th birthday

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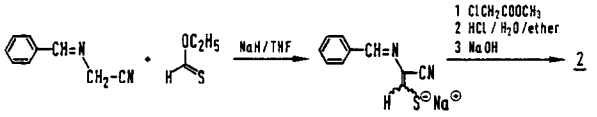
6 a) Benzylidenaminoacetonitrile was condensed with ethylthioformate[6c] in a manner analogous to the known procedures (see ref. 6b) used for the preparation of 5-substituted diamino-thiophenes. The resulting sodium salt (E/Z mixture 8 : 2) was allowed to react with methyl chloroacetate; cyclization of the intermediate using sodium methylate in methanol afforded 4-N-benzylideneamino-3-amino-2-carboxythiophene. Treatment with hydrogen chloride in wet ether and subsequent neutralization gave 2 in an overall yield of 45 %.



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7 a) 3-N-Acetylamino-2-carbomethoxy-thiophene was nitrated an -30°C in 10 parts HNO_3/90 parts H_2SO_4, yielding a 60 : 40 mixture of the 4-nitro- (mp. 113-116°C) and 5-nitroderivative (mp. 176 - 178°C). After the facile separation of these isomers by crystallisation from toluene, 2 was prepared by saponification with sodium methylate in methanol followed by hydrogenation of the nitro group.

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