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A SYNTHESIS OF BIOTIN BASED ON CYCLOADDITION OF A THIOCARBONYL YLIDE

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Abstract: The synthesis of biotin was carried out starting from N-phenylglutarimide. Key compounds are: an α-ketodithioester , its corresponding S-methylide and the cycloadduct of this ylide and fumaroyl dichloride.

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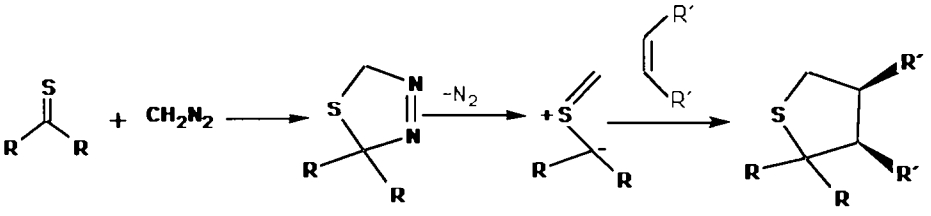
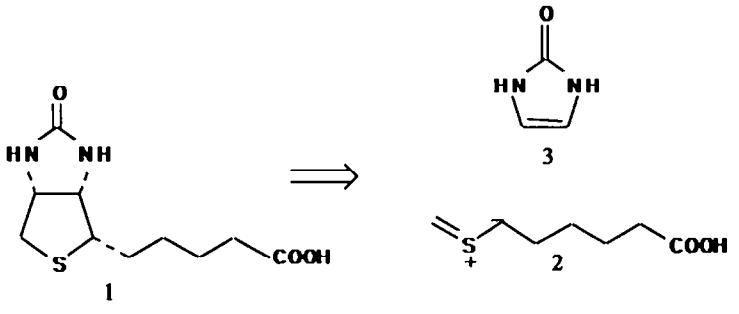
The procedure is based on the reaction of a thiocarbonyl compound with a diazoalkane[1]. This yields a thiadiazoline which on lossing its nitrogen, forms the thiocarbonyl ylide. The synthetic value of these ylides lies in the fact that they undergo fast cycloaddition with dipolarophiles, leading to tetrahydrothiophenes:



To show the synthetic value of this reaction we have carried out the synthesis of biotin[2].

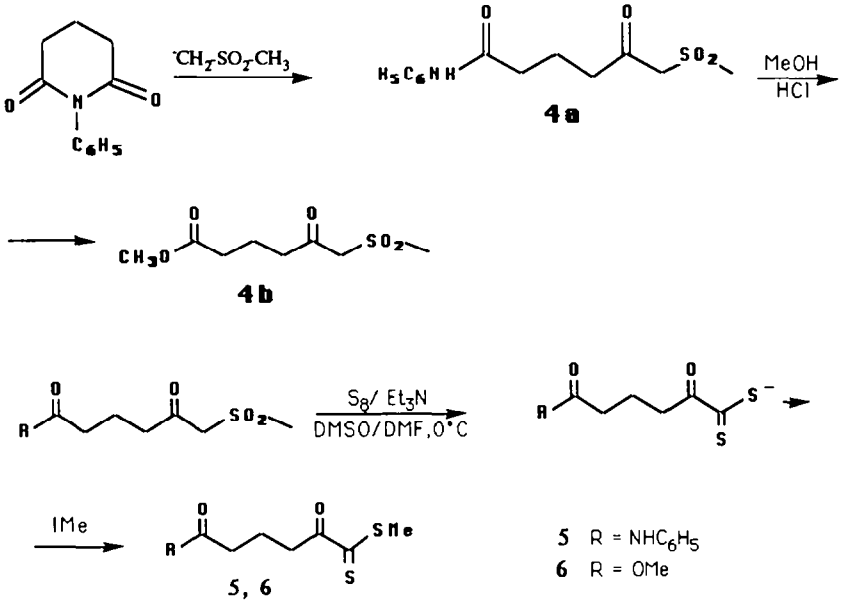
Retrosynthetic analysis shows that a thiocarbonyl ylide 2 and a dipolarophile 3 are logical precursors of biotin 1.



However, both compounds, the ylide and the dipolarophile will be troublesome in such a reaction. First, the precursor of the ylide (if the Huisgen method is to be used) is a very unstable thioaldehyde. Second, due to the low electronegativity of sulfur , thiocarbonyl ylides are Sustmann type one dipoles[3]. They only react well with electron-poor alkenes; the double bond of an imidazolone has very little chance of reacting with such a dipole; more probably, a competitive reaction such as dimerization of the ylide would be preferable [4].

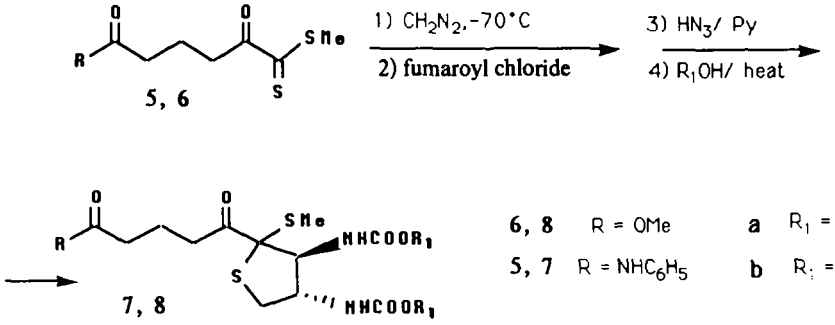
To avoid the problem of the instability of the thioaldehyde, conjugation with the non-bonding electrons of another sulfur atom can be used. The thiocarbonyl function of dithioesters is in fact stable; however cycloaddition with diazomethane then becomes so delayed compared to nitrogen extrusion of the thiadiazoline, that no synthetically useful thiocarbonyl ylide can be obtained.

Fortunately, further conjugation of the thiocarbonyl function with a ketone depresses the LUMO of the compound sufficiently to allow fast cycloaddition of diazomethane even at -80º. Synthesis of the necessary α-ketodithioester was accomplished in two steps starting from N-phenylglutarimide. This starting material is specially suitable because the necessary acid function of biotin is obtained already protected as an amide. Furthermore, the bulky aromatic ring permits easy extraction of the β-ketosulfone from the aqueous medium. A further step is necessary if the amide group has to be changed to an ester function



The commercially available fumaroyl dichloride was used as the dipolarophile, despite the fact that an erroneus stereochemistry is obtained in the cycloadduct.

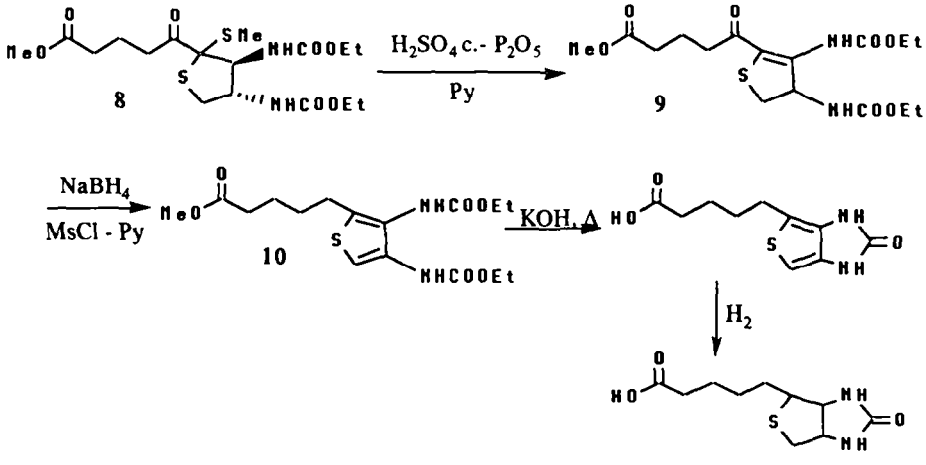
The reaction of both thiocarbonyl compounds **5** and **6** with diazomethane at -80º, followed by cycloaddition with fumaroyl dichloride, warm up, addition of hydrazoic acid, pyridine and finally MeOH or EtOH, affords a good yield of the urethanes **7** and **8**.



The urethanes already have the carbon skeleton of biotin; it is only then necessary to correct the stereochemistry of one of the nitrogen atoms, and then release the molecule from the ketone and thiomethyl groups.

Elimination of the thiomethyl group was accomplished by dissolving the substrate in sulfuric acid containing P_2O_5 at 0º, followed by the addition of pyridine. This reaction works better using the ester function than with the amide, which probably undergoes sulfonation due to its aromatic ring. Sulfuric acid alone produced only the exchange of the thiomethyl by a hydroxyl group; this same product is obtained if no pyridine is used before aqueous work up.

Reduction of the ketone is easily performed with $NaBH_4$, yielding an alcoholic epimeric mixture. When this material is treated with mesyl chloride in pyridine, elimination and rearrangement take place to afford the thiophen molecule **10**. Hydrolysis of the ester and cyclization of the urethanes to urea can be attained at the same time by treating the substrate with KOH/MeOH at reflux for one hour. Similar cyclizations have been reported[5]. Product **11** was isolated at a yield of 80%. Hydrogenation of this material to yield biotin has already been reported to afford good yields[6].



Experimental part

Melting points are uncorrected. All solvents and reagents were purificated by standard methods before use. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP 200 SY (200 MHz). All the ^1H and ^{13}C NMR spectra were run on $CDCl_3$ solutions, unless otherwise stated. Mass spectra were obtained on a VG TS 250 mass spectrometer under 70 eV. IR spectra were recorded on a Beckmann Acculab 8.

N-phenyl-6-methylsulfonyl-5-oxo-hexanamide ***4a*** . Dimethyl sulfone (85 g) in 170 ml of dry DMSO was treated with 27.3 g of NaH. The evolution of hydrogen took place quickly. When the reaction had moderated, the mixture was heated at 60º in water bath with stirring. The reaction was considered to be finished when no further H_2 was given off. The reaction mixture was cooled and finely powdered N-phenylglutarimide (80 g), was added carefully to maintain the temperature at 0-5ºC. After the addition was complete the reaction mixture was allowed to reach r. t. (10-15 min.), diluted with 200 ml of benzene, poured into 200 ml of NaCl saturated water and the organic phase was eliminated. The aqueous layer was treated with HCl c. until a slightly acid pH was obtained. The sulfone **4a** precipitated as a white solid affording 90 g (76%) of the desired product after recrystallization from THF. mp : 136°. IR (nujol) υ: 3300 (NH), 1690 (C=O amide), 1650, 1600, 1300, 1130, 760, 690 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.49 (2H, d, J=7.6Hz), 7.26 (2H, t, J=7.5Hz), 7.04 (1H, d, J=7.5Hz), 4.24 (2H, s), 3.02 (3H, s), 2.75 (2H, t, J=7Hz), 2.38 (2H, t, J=7Hz), 1.96 (2H, m, J=7Hz). ^{13}C NMR ($CDCl_3$) δ : 200.6 (s), 173.2 (s, C=O amide), 139.4 (s), 129.4 (d, 2C), 125.0 (d, 2C), 121.4 (d), 64.5 (t), 44.1 (t), 42.2 (q), 38.3 (t), 19.9 (t).

Methyl 6-methylsulfonyl-5-hexanoate ***4b*** . A stream of HCl was bubbled into a solution of the sulfone **4a** (8 g) in 60 ml of methanol, until saturation. The mixture was heated at reflux for half an hour. The solvent was evaporated and the crude residue was dissolved in $CHCl_3$. The ammonium salt - nearly insoluble in this solvent - was removed by filtration *in vacuo*, and the filtrate was concentrated and chromatographed on silica gel to afford 5.2 g (83%) of **4b**. mp 40° . IR (film) υ: 1730-1710 (C=O), 1300, 1130 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 3.92 (2H, s), 3.32 (3H, s, COOMe), 2.75 (3H, s, RSO_2Me), 2.44 (2H, t, J=7.0Hz), 2.03 (2H, t, J=7.1Hz), 1.54 (2H, m). ^{13}C NMR ($CDCl_3$) δ : 198.7 (s), 172.6 (s), 63.4 (t), 50.6 (q), 42.5 (t), 40.7 (q), 31.7 (t), 17.5 (t).

N-phenyl-5-(methylthio)thiocarbonyl-5-oxopentanamide ***5*** . Sulfone **4a** (10g) and sulfur (2.82 g) were dissolved in DMSO (60 ml), and the solution was cooled using a water bath. The mixture was stirred vigorously and Et_3N (9 ml) was added. After stirring for 45 minutes, the reaction mixture was diluted with water (60 ml) and ice, washed three times with ether (40 ml) and the aqueous phase was treated with MeI (2.6 ml). The solution was stirred for 15 minutes, and a green solid precipitated and was filtered to afford the thiocarbonyl compound **5**. (6.64 g, 67%). mp : 78-80°. IR (nujol) υ : 3360-3000 (NH), 1690-1660, 1600, 1130 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.68 (1H, broad s, NH), 7.50 (2H, d, J=7Hz), 7.27 (2H, t, J=7Hz), 7.07 (1H, t, J=7Hz), 3.13 (2H, t, J=6.9Hz), 2.61 (3H, s), 2.41 (2H, t, J=7.2Hz), 2.06 (2H, m). ^{13}C NMR ($CDCl_3$) δ : 198 (s), 194.2 (s), 171 (s), 137.8 (s), 128.5 (d, 2C), 124 (d, 2C), 120 (d), 37.1 (t), 35.7 (t), 19.6 (t), 18.8 (q).

Methyl-5-(methylthio)thiocarbonyl-5-oxopentanoate ***6*** . The sulfone **4b** (12 g) and sulfur (4.32 g) were dissolved in a DMSO-DMF (105 ml / 35 ml) mixture. The reaction mixture was cooled using an ice-NaCl bath. Et_3N (13.3 ml) was then added slowly to maintain the temperature around 0-5ºC. After addition was complete (30 min.), stirring was continued for 45 minutes. The reaction was quenched with water (100 ml) and crushed ice and washed twice with ether (50 ml). The aqueous phase was treated with MeI (6 ml) , stirred for 10 minutes and extracted with an ether - hexane (1/1) mixture to afford 10.3 g (87%) of compound **6**.IR (film) υ : 1730, 1690 cm^{-1}.^1H NMR ($CDCl_3$) δ : 3.48 (3H, s), 2.93 (2H,

t, J=7Hz), 2.47 (3H, s, SMe), 2.22 (2H, t, J=7.1Hz), 1.78 (2H, m). ^{13}C NMR ($CDCl_3$) δ : 199.5 (s), 193.4 (s), 172.7 (s), 51.0 (q), 36.7 (t), 32.4 (t), 18.9 (t), 18.5 (q, SMe).

2-(4-(phenylcarbamoyl)butyryl)-2-methylthio-3,4-bis(methoxycarbonylamine)tetrahydrothiophen **7a**. Thiocarbonyl compound **5** (1.5 g) was dissolved in CH_2Cl_2 (35 ml) at -80°C, with stirring and under nitrogen atmosphere. The solution was titrated with an ethereal solution of diazomethane (previously cooled at -80°C) until the violet colour disappeared. 1.2 ml of fumaroyl chloride were then added dropwise by syringe and the resulting reaction mixture was allowed to warm to -60°C. The evolution of nitrogen took place at this temperature. When all the gas had been released, the solution was treated with a chloroform solution of pyridine (1.1 eq.)- hydrazoic acid (1.3 eq.) and was allowed to warm to room temperature. The reaction mixture was then washed with water, HCl and water to remove the pyridinium salt. The organic phase was dried and concentrated *in vacuo* without heating to yield a crystalline mass which was dissolved in 30 ml of methanol and heated at reflux. The reaction was monitored by TLC. When no starting material remained, the reaction mixture was concentrated *in vacuo* and chromatographed on silica gel (ether- EtOAc 7/3 as eluent) to yield the urethane (1.2 g, 50%). mp: 91°. IR (Nujol) υ : 3260 (NH), 1710, 1680, 1600, 1050 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 8.45 (1H, broad s, NH), 7.55-7.51 (2H, d, J=8Hz), 7.26 (2H, t, J=8.1Hz), 7.09-7.05 (1H, d, J=8Hz), 5.5 (1H, d, J=9Hz), 4.93 (1H, t, J=9Hz), 4.30 (1H, m), 3.66 (6H, s, 2COOMe), 3.03 (2H, m), 2.85-2.72 (2H, m), 2.41 (2H, t, J=7.1Hz), 2.03 (3H, s, SMe), 1.99 (2H, m). ^{13}C NMR ($CDCl_3$) δ : 202.1 (s, C=O), 171.0 (s, C=O amide), 156.7 (s), 156.5 (s),138.1 (s), 128.7 (d, 2C), 123.9 (d), 119.9 (d, 2C), 69.2 (s), 59.7 (d), 58.1 (d), 52.4 (q), 52.2 (q), 36.1 (t, 2C), 31.3 (t), 20.3 (t), 15.3(q, SMe).

3,4-bis(ethoxycarbonylamine)-2-4-(phenylcarbamoyl)butyryl)-2-methylthiotetrahydrothiophen **7b** . 20 ml of an ethereal solution of diazomethane were dissolved in a CH_2Cl_2- hexane (1/1) mixture and cooled to -90°C. The mixture was then titrated with a solution of the thiocarbonyl compound **5** in CH_2Cl_2 until a colourless suspension was obtained. 2 g of the dithioester were consumed. Fumaroyl chloride (1.6 ml) was then added and the reaction mixture was allowed to warm to -60°C. The evolution of nitrogen took place slowly. When no bubbles of gas were visible, the mixture was treated with hydrazoic acid (1.3 eq)- pyridine (1.1 eq), and the temperature was raised to 0°C. The solution was washed with HCl, water and $NaHCO_3$, and the organic phase was dried and concentrated *in vacuo*. When the volume had diminished to 30 ml, 20 ml of absolute ethanol were added and the mixture was heated at reflux. The reaction was monitored by TLC and when it had finished, the solvent was removed to afford a crude residue that was purified by chromatography on silica gel. (2.3 g, 65%).mp: 75°. IR (Nujol) υ : 3400-3260 (NH), 1730-1660 (C=O), 1600 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.55-7.51 (2H, d, J=8Hz), 7.26 (2H, t, J=8Hz), 7.07 (1H, t, J=8Hz), 5.41-5.36 (1H, d, J=10Hz), 4.80 (1H, t), 4.13-4.06 (4H, m), 3.12-2.65 (4H, m), 2.40 (2H, t), 2.03 (3H, s, SMe), 1.90 (2H, m), 1.21 (6H, t). ^{13}C NMR ($CDCl_3$) δ : 202.1 (s), 171.1 (s), 158.4 (s), 158.2 (s), 138.1 (s), 128.7 (d, 2C), 124.0 (d), 120.0 (d, 2C), 69.4 (s), 61.5 (t), 61.1 (t), 59.6 (d), 58.1 (d), 36.1 (t, 2C), 31.5 (t), 20.5 (t), 15.4 (q), 14.4 (q, 2C).

3,4-bis(ethoxycarbonylamine)-2-methylthio-2-(4-(methoxycarbonyl)-butyryl)tetrahydrothiophen **8** . 75 ml of an ethereal solution of diazomethane were dissolved in hexane (200ml) and cooled to -90°. The reaction mixture was then titrated with a solution of the thiocarbonyl compound **6** in CH_2Cl_2. 8.5g of compound **6** were consumed. Fumaroyl chloride (1.6ml) was then added and the reaction was allowed to warm to -60°. Evolution of nitrogen took place at this temperature. The reaction mixture was then treated with a chloroform solution of hydrazoic acid (1.3eq.) and pyridine (1.1eq.) and the temperature was raised to 0°. The mixture was washed with water and $NaHCO_3$ and the organic phase was concentrated *in vacuo* until the volume had reduced to 100 ml. Absolute ethanol (60ml) was then added and the solution was refluxed until no more nitrogen was evolved. After evaporation and chromatography, the following compound was isolated (11.3 g, 67%). IR (film) υ : 3280 (NH), 1730-1680 (C=O), 1530, 1260 cm^{-1}. ^1H NMR ($CDCl_3$) δ

: 5.62-5.57 (1H, d, NH), 5.30-5.22 (1H, d, NH), 4.75 (1H, t), 4.30-4.17 (1H, m), 4.10-3.90 (4H, m), 3.62 (3H, s), 3.12-2.62 (4H, m), 2.32 (2H, t), 2.02 (3H, s), 2.00-1.80 (2H, m), 1.21-1.14 (6H, m). ^{13}C NMR ($CDCl_3$) δ : 201.5 (s), 173.2 (s), 156.1 (s, 2C), 69.0 (s), 61.3 (t), 60.9 (t), 59.6 (d, 2C), 36.1 (t), 32.8 (t), 31.5 (t), 19.6 (t), 15.3 (q), 14.3 (q, 2C).

3,4-bis(ethoxycarbonylamine)-2-(4-(methoxycarbonyl)butyryl)-4,5-dihydrothiophen 9 . Urethane **8** (2g) was dissolved in CH_2Cl_2 (80ml) and cooled in an ice-salt bath prior to dropwise addition of an H_2SO_4(10ml)/P_2O_5 (4g) solution. When addition was complete, a solution of pyridine (32ml) in CH_2Cl_2 (15ml) was then dropped in such a way that the temperature was kept under 5º. The reaction mixture was stirred for ten minutes more, acidified with 2N HCl , extracted and washed several times with water. The solvent was removed by distillation under reduced pressure to afford a residue which was chromatographed with hexane-ether (2/3), isolating the unsaturated compound **9**. (1.3g, 73%). mp : 85-86° . IR (Nujol) υ : 3270 (NH), 1720, 1670, 1130 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 6.00 (1H, t), 4.20-4.13 (4H, m), 3.68 (3H, s), 3.53-3.40 (1H, dd), 3.15-3.08 (1H,d), 2.66-2.52 (2H, m), 2.38 (2H, t), 1.95 (2H, q), 1.27 (3H, t), 1.24 (3H, t). ^{13}C NMR ($CDCl_3$) δ: 197.5 (s, C=O), 173.2 (s), 155.4 (s), 151.9 (s), 143.4 (s), 114.8 (s), 62.0 (t), 63.1 (t), 56.8 (d), 41.5 (t), 36.2 (t), 32.8 (t), 18.7 (t), 14.3 (q), 14.1 (q).

3,4-bis(ethoxycarbonylamine)-2-(4-methoxycarbonyl butyl)thiophen 10. Compound **9** (900mg) was dissolved in THF (10ml) and treated with $NaBH_4$ (300mg). The reaction was monitored by TLC. When no starting material remained, the solution was poured into HCl 2N, extracted with ether and washed with water. The organic phase was dried and the solvent removed by concentrating *in vacuo* to afford a crude residue which was purified by chromatography on SiO_2, isolating the alcohol as an epimeric mixture (800mg). 128mg of this material were dissolved in pyridine (3ml). Mesyl chloride (100mg) was then added and the mixture was stirred for 30 minutes. Water was then added to hydrolyze the mesyl chloride. Work up with EtOAc and 2N HCl, afforded thiophen **10** (105mg, 86%). mp: 85-87º. IR (Nujol) υ : 3300 (NH),1730, 1710, 1550, 1250 cm^{-1}. ^1H NMR ($CDCl_3$) δ : 7.15 (1H, broad s), 4.22-4.18 (4H, m), 3.66 (3H, s), 2.75-2.62 (2H, m), 2.40-2.25 (2H, m), 1.75-1.57 (4H, m), 1.32-1.26 (6H, t). ^{13}C NMR($CDCl_3$) δ : 173.7 (s,), 155.3 (s), 154.0 (s), 136.4 (s), 131.6 (s), 123.2 (s), 105.9 (d), 61.8 (t), 61.3 (t), 51.3 (q), 33.6 (t), 29.7 (t), 26.9 (t), 24.2 (t), 14.4 (q).

2,3,4,5-tetradehydrobiotin 11. Thiophen **10** (100mg) was dissolved in MeOH (10ml)/KOH(1,3g). The reaction mixture was refluxed for 1 hour. The alkaline solution was first extracted with water and ethyl acetate to remove impurities. The aqueous phase was then acidified with 2N HCl , and extracted with ethyl acetate. The solvent was evaporated to afford a compound with the same physical properties as those already described[5].

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