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STEREOSELECTIVE SYNTHESIS OF BIOTIN PRECURSOR

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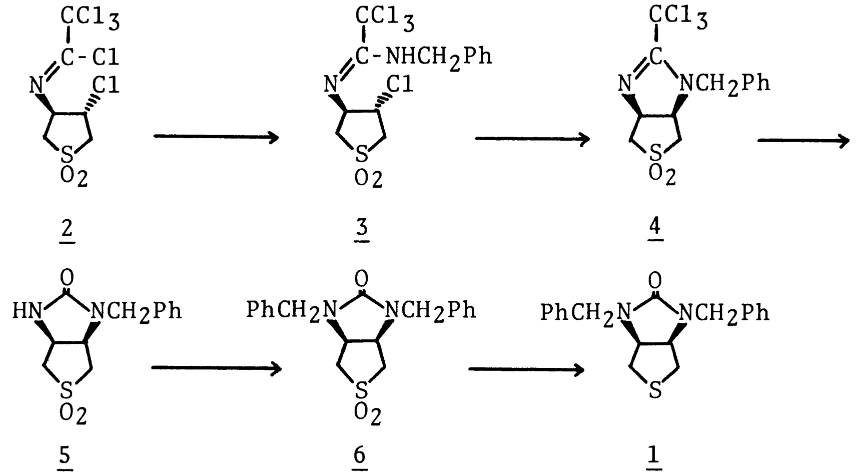
Stereoselective synthesis of N,N'-dibenzyl-cis-ureylenetetrahydrothiophene as a precursor of biotin starting from the imidoyl chloride derivative readily prepared from the reaction of 3-sulfolene with sulfuryl chloride in acetonitrile was described.

In the previous paper,1) it was reported that N,N'-dibenzyl-cis-3,4-ureylenetetrahydrothiophene(1)1,2) as a precursor of biotin2) could be easily derived by the reaction of 3,4-trans-dibromosulfolane with benzylamine, followed by the reaction with phosgene and reduction with $LiAlH_4$. However, this route to 1 was not always satisfactory, since the reaction of the dibromosulfolane with benzylamine provided the favorable cis-diamino derivative only as a minor product.

We wish to report in this paper about stereoselective synthesis of 1 starting from the imidoyl chloride compound(2) prepared from the reaction of 3-sulfolene with sulfuryl chloride in CH_3CN.

In the past, Ritter and Minieri3) reported that the reaction of the olefins with sulfuryl chloride in the presence of a radical initiator produced the corresponding 1,2-dichloro compounds in good yields and Cairns et al. have found4) that the olefins reacted with chlorine and alkanonitrile to give the corresponding imidoyl chloride derivatives in moderate yields.

Then, we have examined the reaction of 3-sulfolene with 4 equiv. of sulfuryl chloride in CH_3CN for 4 h at room temperature and found that it led the formation of imidoyl chloride compound(2) in 96% yield(Mp 141-142.5°C, lit., 136-140°C, 30%4)). Compound 2 (255 mg, 0.76 mmol) was allowed to react with 1.1 equiv. of benzylamine in the presence of 1.1 equiv. of triethylamine in THF for 2.5 h at room temperature to give 3 in 82% yield(253 mg), which was further treated with a large excess of basic alumina in CH_3CN for 2 h at room temperature to afford the cyclization product 4 in 85% yield(3-84 mg, alumina-2.55 g). On treatment of 4 (310 mg, 0.84 mmol) with 1 equiv. of 4 mol dm^{-3}NaOH in refluxing EtOH for 1.5 h,



the imino group could be effectively transformed to the amido group giving the ureylene derivative 5 in 88% yield(198 mg). N-Benzylation of 5 (154 mg, 0.58 mmol) with the aid of n-BuLi and benzyl bromide was performed in THF-HMPA(2:1) at -40°C to room temperature to afford the product 6 in 86% yield(177 mg), whose physical properties were completely in accordance with those of N,N'-dibenzyl-cis-ureylene-sulfone reported in the previous paper.$^{1)}$ Furthermore, 6 was converted to 1 in 68% yield by the treatment with 6 equiv. of $LiAlH_4$ in dry ether at -15 to -10°C for 7 h. These results show that this procedure is an effective method for the preparation of biotin.

References

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3) J. J. Ritter and P. P. Minieri, J. Am. Chem. Soc., 70, 4045 (1948).

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5) All compounds exhibited ir and pmr spectral data in accordance with assigned structure.
3: Mp 118.5-120°C; Found: C, 38.69; H, 3.54; N, 6.93%. Calcd for $C_{13}H_{14}N_2O_2SCl_4$: C, 38.64; H, 3.49; N, 6.93%. 4: Mp 177.5-179.5°C; Found: C, 42.49; H, 3.51; N, 7.56%. Calcd for $C_{13}H_{13}N_2O_2SCl_3$: C, 42.27; H, 3.56; N, 7.62%.
5: Mp 220.5-221.5°C; Found: C, 54.25; H, 5.26; N, 10.63%. Calcd for $C_{12}H_{14}N_2O_3S$: C, 54.12; H, 5.30; N, 10.52%. 6: Mp 182.5°C (lit., 184°C$^{1)}$).

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