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A NEW SYNTHESIS OF THIOPHENES

By

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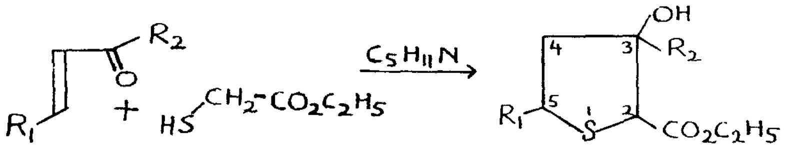
In connection with our study of thiophene derivatives as potential anti-cancer agents,[1] we have undertaken a programme of synthesis of substituted thiophenes. We wish now to report a new general method for the preparation of 2-carboethoxythiophenes carrying alkyl and/or aryl substituents in one or more of the remaining 3, 4 and 5 positions. The esters on hydrolysis and decarboxylation may be expected to yield the relevant substituted thiophenes. The compounds reported presently and those that appear synthesisable by the new route are not directly accessible by known methods.[2]

Condensation of ethyl mercaptoacetate with methyl vinyl ketone in the presence of piperidine yielded in one step 2-carboethoxy-3-hydroxy-3-methyl-tetrahydrothiophene (I) as a colourless liquid, b.p. 90-2° (bath temp.)/2 mm (yield, 80%). Alternatively the mannich base from acetone, formaldehyde and dimethylamine could be substituted for methyl vinyl ketone in the above synthesis whereby (I) was obtained in 61% yield.

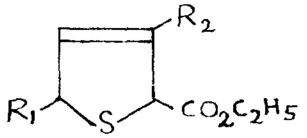


I, R_1 = H; R_2 = CH_3

II, R_1 = R_2 = C_6H_5

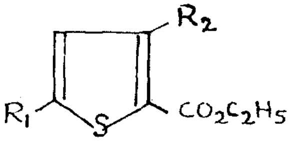
III, R_1 = C_6H_5; R_2 = CH_3

Dehydration of the tetrahydrothiophene (I) with polyphosphoric acid afforded the 2,5-dihydrothiophene (IV). The nmr spectrum indicated the position of the double bond in (IV). The nmr spectrum of the crude dehydration product also showed the presence to a small extent of thiophene and tetrahydrothiophene protons. The dihydrothiophene (IV) thus undergoes disproportionation in presence of polyphosphoric acid (cf. similar dispropbionation of $\triangle^3$-thiachromenes[3]).



(IV), R_1 = H; R_2 = CH_3

(IVa), R_1 = R_2 = C_6H_5



(V), R_1 = H; R_2 = CH_3

(Va), R_1 = R_2 = C_6H_5

(Vb), R_1 = C_6H_5; R_2 = CH_3

Dehydrogenation of (IV) with either diphenyl disulphide or chloranil yielded 2-carboethoxy-3-methylthiophene (V) as a colourless liquid, b.p. 78-80° (bath temp.)/2 mm. (yield, 70%). Hydrolysis of (V) gave 2-carboxy-3-methylthiophene, m.p. 147°, (yield, 73%) which proved identical with an authentic specimen of the acid prepared by an alternative route.[4]

Interaction of benzalacetophenone and ethyl mercaptoacetate likewise gave 2-carboethoxy-3,5-diphenyl-3-hydroxy-tetrahydrothiophene (II) as a colourless liquid (yield, 77%), b.p. 175-185° (bath temp.)/0.02 - 0.03 mm., which solidified on cooling.

Crystallization of the product from petroleum ether (b.p. 40-60°) gave colourless needles, mp. 108°. Dehydration of (II) by treatment with polyphosphoric acid gave 2-carboethoxy-2,5-dihydro-3,5-diphenylthiophene (IVa) (yield, 90%). The latter crystallized from petroleum ether (b.p. 60-80°) in white rhombic prisms, mp. 110°. The position of the double bond was indicated by its nmr spectrum.

Dehydrogenation of (IVa) by means of chloranil afforded 2-carboethoxy-3,5-diphenylthiophene (Va) (colourless flat needles from petroleum-ether (b.p. 60-80°) mp. 81-82°) (yield, 78%).

Condensation of benzalacetone and ethyl mercaptoacetate as above finally yielded 2-carboethoxy-3-methyl-5-phenylthiophene (Vb) as a colourless crystalline solid mp. 48° (yield, 60%).

The UV, IR and nmr spectra and analytical data for the compounds described in the paper are in conformity with the structures assigned.

Other variants of the above synthesis involving other mannich bases, α,β-unsaturated ketones and α,β-unsaturated aldehydes are being explored and full details of the work will be reported shortly elsewhere.

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