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SYNTHESIS OF DIHYDROTHIOPYRANS BY INTRAMOLECULAR WITTIG REACTION

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Abstract : The reaction of cyclopropylphosphonium salts with α-mercapto ketones, using the reported conditions for the reaction of an ω-functionalised carbonyl compound, failed to give the expected thiopyrans. An alternative procedure, which allowed the synthesis of sensitive compounds is provided.

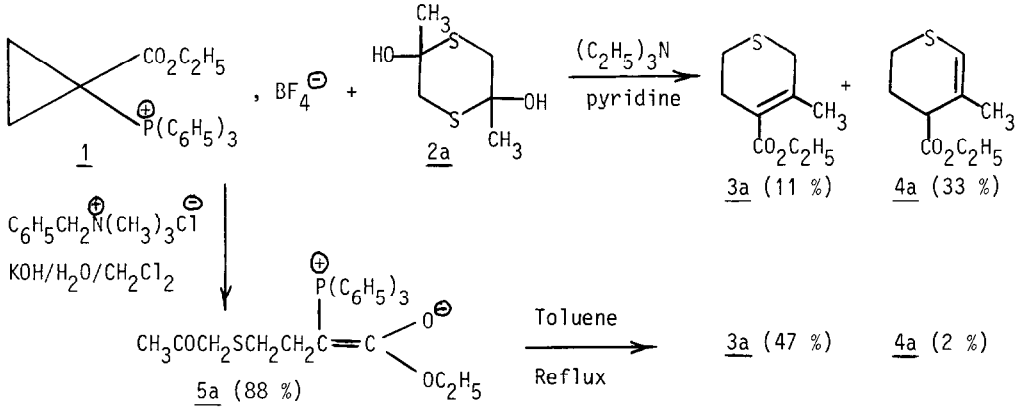
Intramolecular Wittig reaction is a well documented annelation process (1). Although there is no report of such a reaction between ω-mercapto ketones and (1-ethoxycarbonylcyclopropyl) phosphonium fluoroborate 1 (3), this seemed a viable method for the synthesis of derivatives of 3-substituted 5,6-dihydro 2H-thiopyran 4-carboxylic acid.

Synthesis of 3-methyl compound 3a (Scheme I).

When 2a was reacted with 1 using previously reported conditions (2,3) (e.g. pyridine/Et_3N/ reflux) a mixture of 3a and 4a (in a ratio of 1/3 based on NMR)(4) was obtained (yield 44 %). It is probable that the isomerisation of 3a to 4a occured in the alkaline conditions of the reaction mixture, which are required for the first step of the process (cyclopropane opening) but not for the second step (Wittig cyclisation). Thus we thought we might overcome this isomeration by proceeding in a stepwise manner.

By stirring at 20°C a mixture of 1 (0,5 M), 2a (0,5 M), KOH (1,25 M) and benzyltrimethylammonium chloride (0,025 M) in a mixture of CH_2Cl_2 (2 l) and water (1,5 l), 5a was obtained as an orange oil (88 %) which was subsequently heated in refluxing toluene to yield a mixture of 3a and 4a in a 95/5 ratio (4).

Scheme I

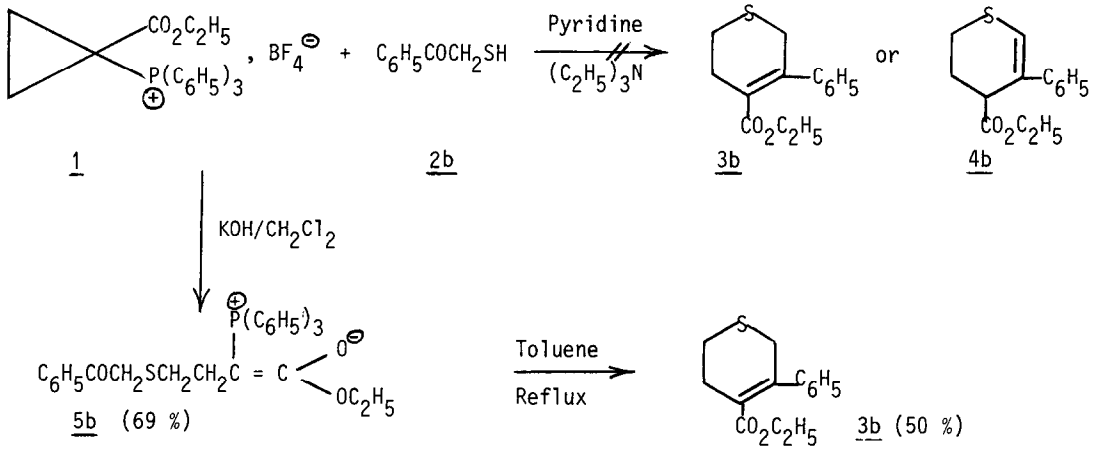


Synthesis of the 3-phenyl compound 3b (Scheme II).

When 2b was reacted with 1 under the previously reported conditions (2,3) a complex mixture was obtained. It was again demonstrated that the use of phase transfer conditions enabled the synthesis to proceed in the expected manner : 2b (0,246 M) and 1 (0,234 M) in 1,4 l of CH_2Cl_2 were stirred in the presence of KOH pellets (0,234 M). After work-up, 5b (69 %) was obtained (M.P. 149°C, AcOEt)(5). Then 5b was refluxed in toluene yielding 3b (50 %) (M.P. 62°C, diisopropylether)(6).

The following features may be pointed out : a) liquid-liquid phase transfer reaction did not proceed satisfactorily ; b) there was no need for a phase transfer catalyst ; c) 4b was not formed in a measurable amount probably because 5b (recrystallised) was purer than 5a (oil).

Scheme II.



These two examples describe an alternative process to synthesize cyclic coumpound from 1 when the target compound is sensitive to basic medium (3a) or when the starting material is rather unstable (2b).

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Notes and references.

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(4) 3a ^{1}H-NMR, 350 MHz, $CDCl_3$, δppm : 1,3 and 4,2 (CH_3CH_2) 2,8(broad s, 3H) 3,15 (broad s,2H)
4a ^{1}H-NMR, 350 MHz, $CDCl_3$, δppm : 1,3 and 4,2 (CH_3CH_2) 1,8 (s, 3H) 5,9 (broad s, 1H)

(5) 5b ^{1}H-NMR, 350 MHz, $CDCl_3$, δppm : 0,5 (t, 3H) 2,3 to 2,7 (m, 6H) 3,7 (q, 2H) 7,3 to 7,8 (m, 20H)

(6) 3b ^{1}H-NMR, 350 MHz, $CDCl_3$, δppm : 0,8 and 3,85 (CH_3CH_2) 2,2 to 2,35 (m, 4H) 3,45 (broad s, 2H) 7,2 to 7,4 (m, 5H).

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