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A NEW APPROACH TO THE SYNTHESIS OF 2-SUBSTITUTED BENZOTHIOPHENS AND THEIR HETERO-ANALOGUES.

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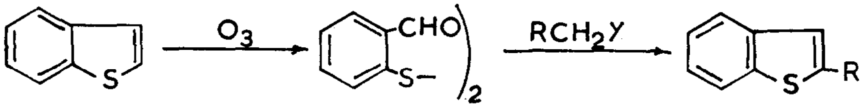
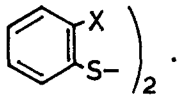
The substitution of benzothiophen by electrophiles takes place predominantly at the 3-position, while 2-substitution is possible by way of the readily prepared 2-lithio derivative[1]. However, this latter method is not convenient for many useful substituents such as aryl, nitro, amino, acyl etc. We wish to report a simple, novel, 'one-pot' method that allows the synthesis of such 2-substituted compounds, as outlined in Scheme 1.



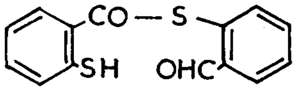
1 2 3

Scheme 1

The ozonation of benzothiophen was reported[2] to yield a mixture of the aldehyde (2) (20%), together with the corresponding acid (4) (30%) and phenol (5) (50%).



4; X = COOH
5; X = OH



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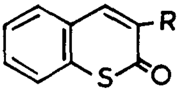

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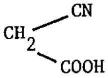
We find that the major products of ozonation (CH_2Cl_2, -78^{o}) are the aldehydes (2) and (6) (34 and 22% respectively), the latter breaking down on alkaline work-up to yield the aldehyde (2) and acid (4). The phenol is probably an artefact (Baeyer-Villiger reaction) produced by work-up according to the German method[2]. The full details of our thorough investigation into this ozonation will appear elsewhere.

Interaction of the aldehyde (2) (which need not necessarily be isolated but used directly after treatment of the ozonised benzothiophen with dimethyl sulphide[3]) with compounds containing an 'active' methyl or methylene group yields 2-substituted benzothiophens as shown in the Table. The arylacetic acids generally gave a thiocoumarin by-product (7) which was readily separated by chromatography. Since the reaction involves an oxidation step, it was sometimes found advantageous to add ½ mole benzoyl peroxide (see Table).

Table

Synthesis of 2-Substituted Benzothiophens (3) from benzothiophen/O_3 or from the aldehyde (2).

Reagent*	Method**	Product* (3) R=	Yield‡ (%)	M.p. (°C) ± 1	Remarks
$CH_2(COOH)_2$	A	COOH	77 (72)	240[4]	
$CH_2(COOH)_2$	A†	COOH	21	240	
 $CH_2(CN)COOH$	A	CN	16 (78)	oil	+ (3); R=$CONH_2$[5] m.p. 176° (40%)
CH_3NO_2	A	NO_2	29 (77)	116[6]	
CH_3NO_2	A†	NO_2	38	116	
$PhCH_2COOH$	B	Ph	60 (37)	176[7]	+ (7; R=Ph) (38%)
$PhCH_2COOH$	B†	Ph	17	176	
2-ThCH_2COOH	B	2-Th	65	156[8]	+ (7; R=2-Th) (35%)
3-ThCH_2COOH	B	3-Th	70	191	+ (7; R=3-Th) (27%)
$PhCONHCH_2COOH$	C	NHCOPh	25	174	
$AcNHCH_2COOH$	C	$NHCOCH_3$	34	223[9]	+ (7; R=NHAc) (23%)
2-CH_3Py.MeI	D	2-Py.MeI	37	171	

‡ yield in parenthesis is with ½ mole $(PhCO)_2O_2$ added to reaction mixture.

*Th = thienyl. † Starting from ozonised benzothiophen instead of aldehyde (2)

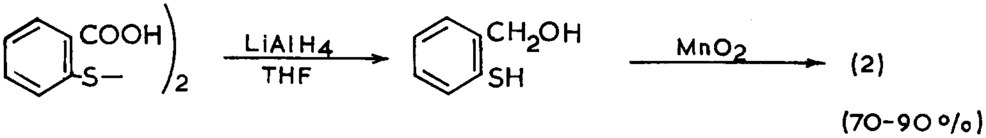
Py = pyridyl. **Method A : 4 hrs. reflux in ethanol + triethylamine.

Method B : 30 min. reflux in acetic anhydride + triethylamine

Method C : 60 min reflux in acetic anhydride + sodium acetate

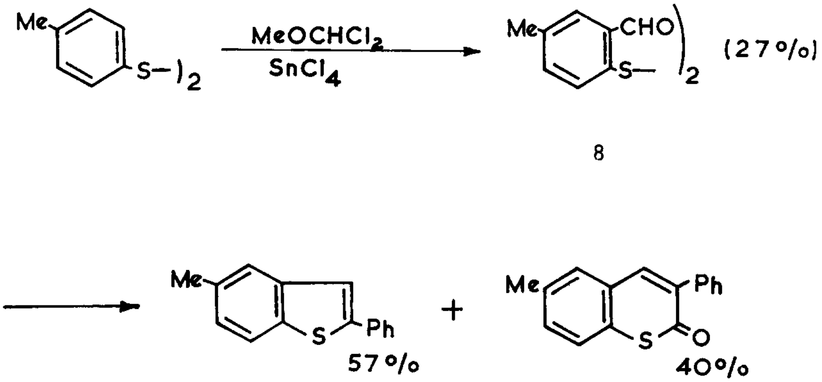
Method D : 4 hrs reflux in methanol + piperidine.

Since the aldehyde (2) was so versatile in synthesis we sought other methods to make it. The most effective is indicated in Scheme 2[10], the starting material being readily available



Scheme 2

from diazotised anthranilic acid[11]. Analogous products (e.g. 8) may be prepared (Scheme 3) which allow the synthesis of further substituted benzothiophens (e.g. 9; m.p. 157°)



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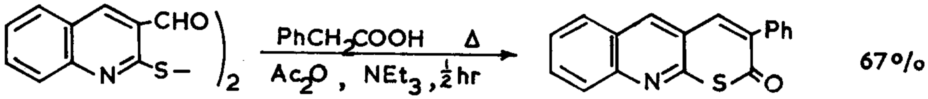
Scheme 3

Finally the use of other o-formyl disulphides or thiols is of interest. Thus while the readily made aldehyde[12] (10) gives solely the thiocoumarin (11; m.p. 223-5°), the



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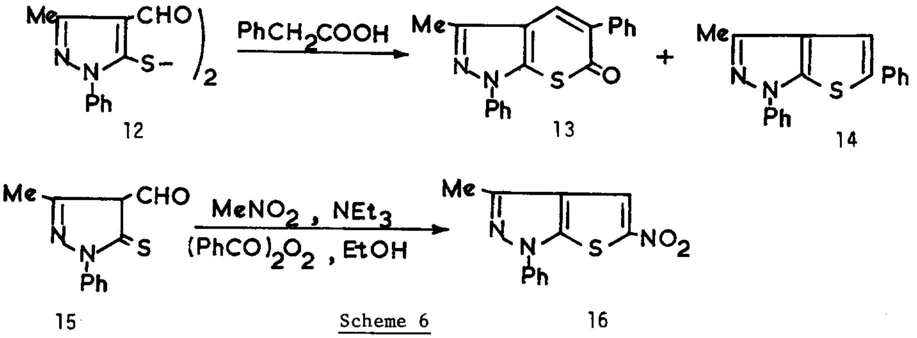
readily available pyrazole[13] (12) gave the thienopyrazole (14; m.p. 162-6°). In a similar manner the thione (15) gave the nitrothienopyrazole (16; 23%, m.p. 178°) in the presence of benzoyl peroxide (Scheme 6).



Scheme 6

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