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ALKYLTHIOPHENS AS VERSATILE SYNTHETIC PRECURSORS. PART I

A NEW ROUTE TO 3-THIENYL ALDEHYDES AND KETONES[†]

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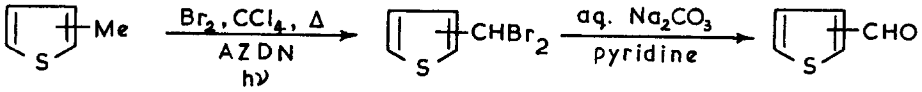
Until recently, alkylthiophens were generally expensive or non-available compounds and, apart from one or two exceptions, were of little value as synthetic intermediates. The current availability[1] of a range of inexpensive homologues (e.g. 2- and 3- methyl-, 2,4- and 2,5-dimethyl- and 2- and 3-ethyl-thiophens) in large quantities, has made a study of their chemistry of renewed interest. We herein describe a simple and effective method for their conversion to aldehydes, ketones and related derivatives.

Campaigne[2a] has shown that the action of N-bromosuccinimide on 3-methylthiophen gives reasonable yields of 3-bromomethylthiophen. This compound may be converted into the corresponding aldehyde in moderate yield by the Sommelet reaction[2b] and thence to 3-thenoic acid[2c]. This acid is also available by aqueous dichromate oxidation of 3-methylthiophen[3], while halogen-metal interconversion of 3-bromothiophen with butyllithium at low temperature offers an alternative entry to 3-substituted thiophens[4]. No other useful routes to 3-substituted thiophens are known and the above routes all have their limitations particularly for commercial exploitation.

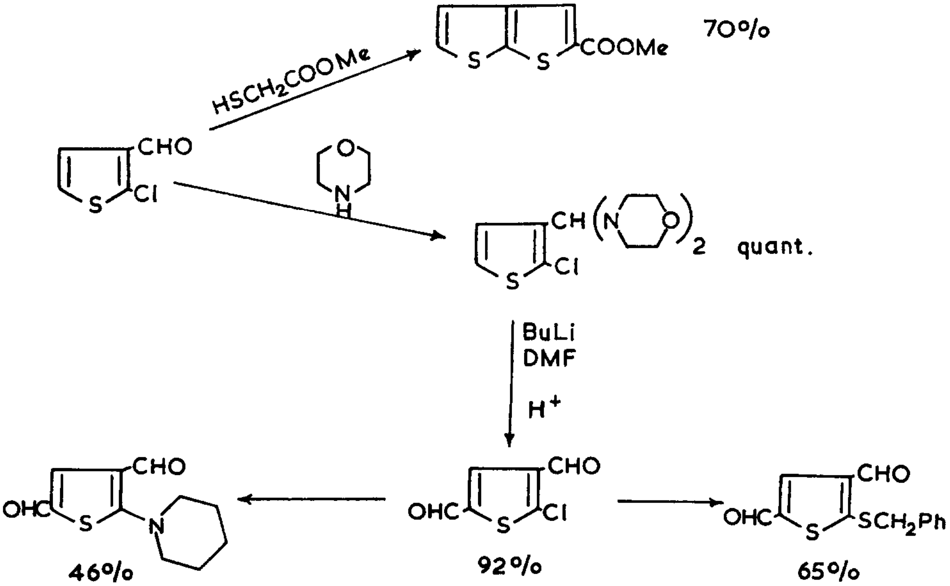
Bromination of thiophens with bromine is a rapid, efficient process of electrophilic substitution, in the α-positions first. However, we find that this reaction may be suppressed and sometimes eliminated by the action of light and a radical catalyst (azo-bis-isobutyronitrile-AZDN) during the slow addition of bromine to a refluxing solution of an alkylthiophen in carbon tetrachloride solution (Scheme 1). Side-chain substitution occurs and, depending upon the thiophen, one, two or three bromines may be introduced before extensive ring bromination competes with this attack (Table 1).

[†] Dedicated to Prof. Hans Suschitzky on his 60th birthday.



Scheme 1

Conversion of the methylthiophens into their dibromomethyl derivatives followed by hydrolysis with aqueous sodium carbonate and a trace of pyridine offers an easy route to thienyl aldehydes, which are readily separated from any of the other products by steam-distillation and subsequent distillation of the products. This method is useful for 3-thenaldehyde and the method of choice for 2-chloro-3-thenaldehyde which is a useful synthetic intermediate (Scheme 2) and will be reported on fully elsewhere.



Scheme 2

TABLE 1

Products from the bromination of methylthiophens

Methyl thiophens (MT)	Br_2 (M)	Products (%)				CHO (%)
		CH_2Br	$CHBr_2$	CBr_3	ring-Br*	
3-MT	1	47	19	-	10	
"	2	28	58	-	13	30(2.5M Br_2)
"	3	6	12	7	73	
2-Cl-3-MT	2.1	2.5	85	-	10	70
2-Br-3-MT	1	66	12	-	-	
"	2	13	36	-	38	35
2,5-Br_2-3MT	1	80	20	-	-	m
"	2	15	78	-	-	78(as morpholine aminal,[6] m.p. 173(d)°)
2-MT	2	16	-	-	83 (2-Br-5-CH_2Br)	
2-Cl-5-MT	1	96	-	-	-	
	2	35	65	-	-	

*total yield of a mixture of ring and ring+side-chain brominated products.

2,5-Dibromo-3-dibromomethylthiophen is a perfectly stable distillable liquid and is of considerable interest as an intermediate (b.p. 128°/0.1-0.2 mm, m.p. 25°C).

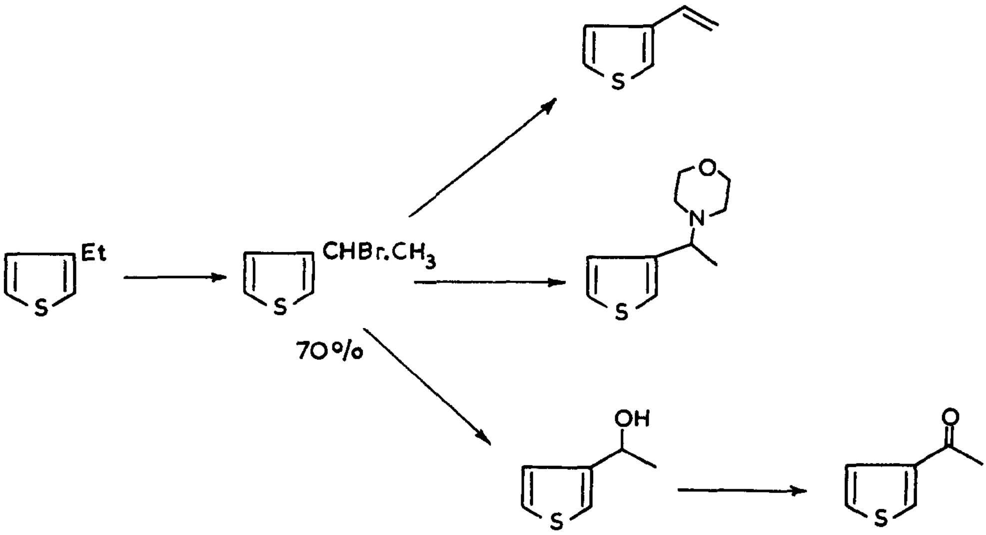
TABLE 2

Products from the bromination of 2,5-dimethylfuran and-thiophen 

X	Br_2 (M)	Products (%)		
		CH_2Br	$(CH_2Br)_2$	$CH_2Br/CHBr_2$
O	0.6	38	-	-
	1.2	68	21	-
	1.8	50	50	-
S	1	70	-	-
	2	8	80	-
	3	-	20	60

2,5-Dimethylthiophen and 2,5-dimethylfuran under the above conditions both react successively with bromine at one methyl group then the other, this route being useful for 2,5-bis(bromomethyl)thiophen synthesis (Table 2).

3-Ethylthiophen is especially of interest since the action of 1 mole of bromine gives 3-bromoethylthiophen in 70% yield (Scheme 3). Distillation of this product from quinoline gives 3-vinylthiophen in high yield while hydrolysis and oxidation[4] yields 3-acetylthiophen, again in good yield.



Scheme 3

We thank Synthetic Chemicals Ltd. for a grant and gift of chemicals.

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