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THIOPHENE CHEMISTRY—XXI*

ALKYLATION OF AMBIDENT IONS FROM POTENTIAL HYDROXYTHIOPHENES†

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Abstract—On treatment with R-Hal the thallium salt of 3-thiolene-2-one underwent C-alkylation in the 3-position. O-, di-, and trialkylation reactions were also observed. The effect of solvent as well as the structure of the alkylating agent on the substitution O/C-ratio has been investigated.

INTRODUCTION

IN AN earlier investigation[1] it was demonstrated that the thallium (I) salt of 3-thiolene-2-one by treatment with MeI gave 3-methyl-3-thiolene-2-one and 2-methoxythiophene in the ratio 7:1 and also higher methylated products were isolated. As the preparation of 3-methyl-3-thiolene-2-one from a synthetic point of view was very promising, we also felt prompted to study the generality of the alkylation reactions of the thallium (I) salt of 3-thiolene-2-one. In this paper we are mainly concerned with the effect of alkylating agent and the influence of solvent on the O/C-ratio of substitution.

RESULTS AND MECHANISTIC CONSIDERATIONS

A complex mixture was obtained from the alkylation of the thallium salt (II), of 3-thiolene-2-one (I). The lower-boiling part, usually containing 5–6 different products, was removed from the mixture by distillation and then fractionated by unidimensional multiple chromatography[2] (UMC) on a preparative scale. In this manner all products except VI and X were usually separated from each other.

To account for the different products formed the following mechanism is suggested (Fig 1). It is assumed that II can undergo a Tl^+(I) exchange reaction with III, VII, and IX initially formed, thereby producing VI, IX, and X on subsequent alkylation reactions. This mechanism is in accordance with the fact that the original compound (I) from which II is prepared is also found in the mixture. Alkylation at the 5-position of I is also observed by treatment of II with benzyl bromide and crotyl bromide and the ratio of substitution at positions 5 and 3 of II was as low as 0·1.

That the alkylation in the 5-position of the anion is essentially less favoured than in the 3-position is in accordance with the greater π-electron density at the 3-position relative to the 5-position of the anion,[3] indicating the greater nucleophilicity at the

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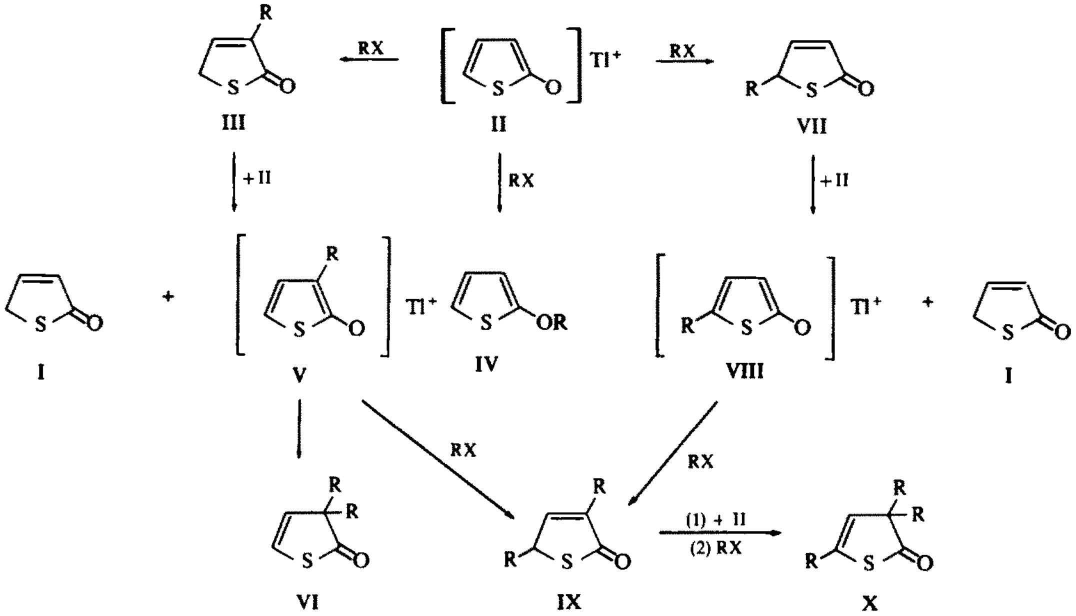


R a: Me
b: Et
c: iso-Pr
d: allyl
e: crotyl
f: $PhCH_2$
g: CH_2COOEt

FIG 1

3-position. The question of whether the two alkyl groups in VI are at the 3- or 5-positions was settled by the fact that the carbonyl absorption of VI in the IR was found at 1715–1740 cm^{-1} which is typical for the 4-thiolene-2-ones, whereas for 3-thiolene-2-ones the corresponding absorption is found at 1670–1695 cm^{-1} [4–6] The structure of X was similarly confirmed.

In the mixture, obtained by treatment of II with allyl bromide at room temperature, it was not possible by NMR to show the presence of IVd. Neither was it possible to obtain IVe by treatment of II with crotyl bromide under the same conditions, but in this case a fraction containing both IIIe and XI in the ratio 2:1 (Fig 2) could be isolated by UMC. We also isolated (by UMC) a fraction of VIIe, which contained no traces of its isomer, XII, which we assumed to have the same or almost the same R_f value as VIIe. Consequently, it is reasonable to exclude the crotyl-cation as an intermediate in the alkylation reaction as the ratio of the rearranged products XII and VIIe from alkylation at the 5-position should be expected to be almost the same as the ratio of XI and IIIe from alkylation at the 3-position. In a similar way a S_N2' and a combined S_N1–S_Ni mechanism are excluded and it thus seems reasonable to

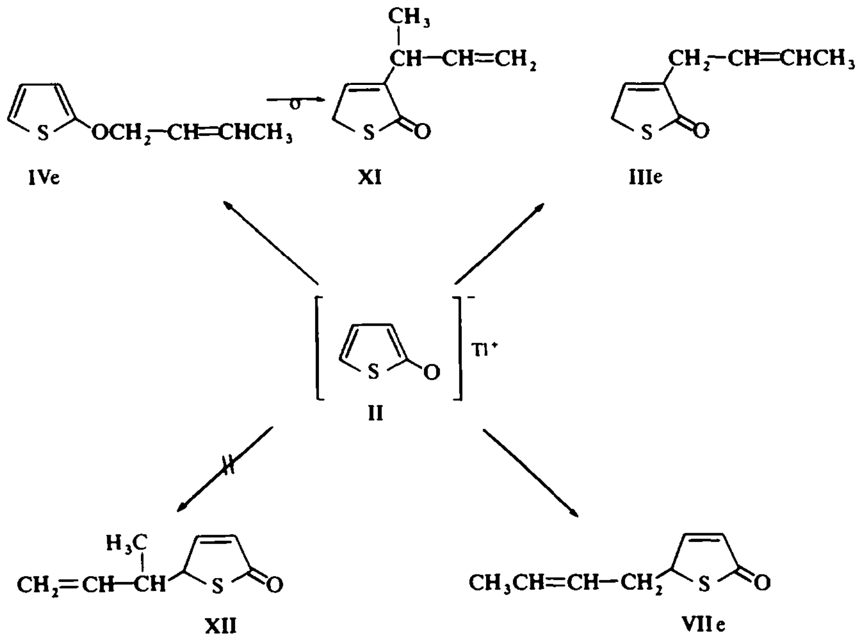


FIG 2

assume that XI is formed by a Claisen rearrangement reaction from primarily formed IVe as suggested in Fig 2. Also it is reasonable to assume compound IVe to be thermally unstable at room temperature as hitherto no one,[7] to our knowledge, has prepared it. This is further accounted for by our observation that the NMR spectra of the crude mixture did show that no ether was present. It could, however, be claimed that the reaction conditions used by us in one way or another could catalyze a Claisen rearrangement of IVe, but also this seems doubtful as treatment of allyl phenylether under the same conditions as used by us gave no Claisen rearrangement at all.

Solvent effects

Solvent effects on product distribution on alkylation of II were the same as those observed with other comparable ambident anion systems.[9,10] Thus the ratio (O/C) of O-alkylation and alkylation at the 3-position of II was increased with increasing polarity of aprotic solvent (Table 1). It is noted that EtOH due to hydrogen bonding to oxygen completely prevents ethylation at the oxygen atom. It should also be observed that the relative yields of di- and triethylated products are almost unaffected by the solvent used except for EtOH, which gave an increase of di- and triethylated products.

Rather surprisingly there was no solvent effect on the O/C ratio (Table 2) when benzyl- or crotyl bromide were used as the alkylating agent. It has been claimed by Tieckelmann *et al.*,[10,11] that a relatively small solvent effect on alkylation of ambident anions is consistent with a reaction which proceeds through a transition state, which

TABLE 1. SOLVENT EFFECTS ON ETHYLATION OF THE THALLIUM (I) SALT OF 3-THIOLENE-2-ONE (in %)

Products \ Solvent	DMF	MeCN	Pet[a]	EtOH
O/C	1·25	0·46	0·20	0
O-Ethyl	50	24	13	0
3-Ethyl	40	52	65	64
3,3-Diethyl	2	3	1	4
3,5-Diethyl	2	4	5	8
3,3,5-Triethyl	2	3	2	4
3-Thiolene-2-one	4	14	14	20

[a] Petroleum ether

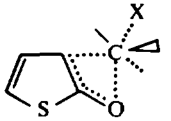


FIG 3

produces the two possible products. This transition state is shown for the anion of I in Fig 3. According to this theory the large solvent effect on the O/C ratio for alkylation with EtBr should in this case indicate a mechanism quite different from the one for benzyl- and crotyl bromides. However, according to the formula

$$\Delta \ln k = -\frac{\Delta V^{\ddagger}}{RT}\Delta P_i{}^{12}$$

where $\Delta V^{\ddagger}$ is the volume of activation and P_i is the internal pressure of the solvent used, it is indicated that if the volume of activation is equivalent for O- and C-alkylation, no solvent effect on the O/C ratio should be expected. So it is possible to have the same mechanism in all cases if we assume that the volumes of activation for O- and C-alkylation are almost equal using benzyl- and crotyl bromide as the alkylating agent, but unequal using EtBr.

Structure of the alkylating agent

Not unexpectedly, a number of authors[8,9] have noted that increased steric requirements of the alkyl group interfere more seriously with C- than with O-alkylation. In this investigation the heterocyclic ambident anion II gave an increased O/C ratio for Me- < Et- < i-PrI (Table 2), fully in accordance with earlier findings.[8,9] It is also

TABLE 2. PRODUCT DISTRIBUTION IN ALKYLATION OF II (in %)

Alkylating agent	Solvent[a]	II (g)	I	III	IV	VI	VII	IX	X	O/C (IV/III)	b.p.
MeI[1]	Pet	30	5	37	5	½		2	½	0·14	
EtI	Pet	20	7	30	6	1		2	1	0·20	60–120°/15 mm
EtI	MeCN	20	10	36	16	2		3	2	0·44	50–110°/10 mm
EtI	DMF	24	2	21	26	1		1	1	1·24	55–115°/13 mm
EtI	EtOH	20	8	27	0	2		4	2	0	90–120°/15 mm
iso-PrI	Pet	55	2	19	14			2		0·74	70–103°/13 mm
$C_6H_5CH_2Cl$	Pet	19		19	5	½				0·26	80 190°/0·2 mm
$C_6H_5CH_2Br$	Pet	20		31	5	9	7[d]			0·16	80–190°/0·2 mm
$C_6H_5CH_2Br$	CH_3CN	20		29	4	3	4[d]			0·14	80–190°/0·4 mm
$CH_2{=}CHCH_2Cl$	Pet	30	11	40		3		2	1		90–140°/12 mm
$CH_2{=}CHCH_2Br$	Pet	30	17	51		12		3			90–140°/12 mm
$CH_3CH{=}CHCH_2Br$	Pet	36	8	29	13[b]		2[e]	3[c]		0·45	30–120°/0·4 mm
$CH_3CH{=}CHCH_2Br$	DMF	35	3	19	9[b]		3[e]	5[c]		0·47	40–140°/0·6 mm
$EtOOCCH_2Br$	Pet	24	12	14	10					0·71	40–160°/0·4 mm

[a] Pet = petroleum ether (b.p. 60–80°); DMF = dimethylformamide

[b] Isolated as XI

[c] Mixture of IXe and 3-(1′ methyl-allyl)-5-crotyl-3-thiolene-2-one (XIII) (2:1)

[d] See ref. 4, $R_f = 0{\cdot}06^{II}$ and $0{\cdot}18^{IV}$ (Table 3)

[e] NMR spectrum of VIIe: 6·25 δ (H^3), 7·45 δ (H^4), 4·44 δ (H^5), ~2·5 δ (C^5H), $J_{34} = 6{\cdot}1$ Hz, $J_{35} = 1{\cdot}9$ Hz and $J_{45} = 2{\cdot}6$. $R_f = 0{\cdot}14^{III}$ (Table 3)

well-known that the allyl and benzyl halides produce increased C-alkylation. All these facts can be summarized in the statement that relatively high O-alkylation rates correlate with low S_N2 reactivity. That is in accordance with what we found for benzyl bromide which gave an O/C ratio as low as 0·1, but using ethyl bromoacetate and crotyl bromide, which we have assumed to have high S_N2 reactivities the O/C ratios were considerably higher (Table 2). At this stage of the investigation it is immature to draw conclusions, but at least the correlation between the O/C ratio and the S_N2 reactivity of the alkylating agent has to be questioned.

Effect of leaving group

Virtually all recent studies[8,9] have come to the conclusion that for a high O/C ratio the preferred leaving group (among the halides) should be Cl^-. The halides are here arranged in order of the highest O/C ratio formed by alkylation:

$$Cl^- > Br^- > I^-$$

We also investigated the validity of this statement for alkylation of II with benzyl chloride and benzyl bromide. The found O/C ratios were 0·26 and 0·16, respectively, in full accordance with the above-mentioned statement.

Acylation

Treatment of II with acetyl chloride gave 2-thienyl acetate in 91% yield and no other products were observed. According to the theory of hard and soft acids and bases (HSAB) no other products could be expected as acetyl chloride is considered a hard acid, which should react exclusively at the hard oxygen atom of II.[9]

CONCLUSION

We have found for alkylation reactions of the thallium (I) salt of 3-thiolene-2-one that the effects of solvent, alkylating agent and leaving group on the O/C ratio are almost the same as found for other salts. But the applicability of using thallium ethoxide as a base in alkylation reactions may not be underestimated as in this way it may be possible to isolate stable salts of an anion, which are not easy to handle under the usual conventional conditions for alkylation.

EXPERIMENTAL

NMR spectra were recorded in $CDCl_3$ at 60 MHz on a Varian A-60 spectrometer. The chemical shifts are expressed in ppm from TMS ($\delta = 0$). Numerical AB and ABX analyses have been carried out on the thiophene ring protons of VI and IV, respectively. In all other cases the analyzed spin pattern is considered to be approximately first order. UMC was carried out on Kieselgel $PF_{254+366}$ (Merck) support (20 × 40 cm and 3 mm thick); the light petroleum (b.p. 37–50°) was distilled before use. R_f values were obtained from the pure products using the same support (0·3 mm thick) and solvent for elution. B.ps are uncorrected. Analyses were made by Løvens kemiske Fabrik, Copenhagen.

General alkylation procedure. The amount of freshly prepared thallium salt[1] (see Table 2) was treated with excess alkyl halide using 400 ml of solvent indicated in Table 2. The mixture was heated at 60–80° until the colour of the thallium salt had changed (usually after 20 hr). The solution was filtered and the solvent evaporated (using DMF as solvent, the filtered solution was poured onto a mixture of water and ether and extracted with ether). The residue was distilled (b.p. is seen in Table 2). Separation on UMC gave the yields indicated in Table 2.

If no different R_f values are indicated in Tables 3–7 of the two products obtained in one experiment,

TABLE 3. ANALYSIS, NMR SPECTRA AND PHYSICAL CONSTANTS OF III AND XI

	Analysis						NMR						b.p.	n_D^{25}	R_f[a]
	Calc. %			Found %											
	C	H	S	C	H	S	C^3H	H^4	H^5	$J_{C^3H—H^4}$	$J_{C^3H—H^5}$	J_{45}			
IIIb	56·24	6·29	24·97	56·62	6·29	24·30	2·33	7·25	3·97	1·5	2·0	2·9	101°/9 mm	1·5346	0·32[IV]
IIIc	59·14	7·09	22·52	59·35	7·12	22·24	2·67	7·14	3·93	1·2	1·4	2·9	112°/12 mm	1·5232	0·38[IV]
IIId	59·99	5·75	22·83	59·97	5·82	22·64	3·00	7·23	3·96	1·4	1·9	2·8	124°/14 mm	1·5493	0·13[II]
IIIe[b]	62·32	6·54	20·76	62·37	6·66	20·57	2·93	7·16	3·93	1·5	2·0	2·9	90°/0·4 mm		0·28[III]
IIIf	69·46	5·30	16·83	69·53	5·42	16·78	3·56	6·94	3·83	1·5	1·8	2·8	150°/0·4 mm	1·6028	0·10[II], 0·26[IV]
IIIg	51·61	5·41	17·19	51·53	5·45	17·00	3·34	7·53	4·06	1·2	1·5	2·8	126°/0·5 mm	1·5212	0·08[IV]
XI[b]	62·32	6·54	20·76	62·37	6·66	20·57	~3·3	7·16	2·94	1·0	1·2	3·0	90°/0·4 mm		0·28[III]

[a] The roman letters indicate the ratio of ether and light petroleum ether mixture used for eluation, I (1:50), II (1:20), III (1:10), and IV (1:5)

[b] IIIe and XI were not separated from each other

they were obtained as a mixture. The ratio of the two products of that mixture was then calculated by NMR.

2-*Acetoxy-thiophene*. To 23 g of freshly prepared Tl(I)-salt of 3-thiolene-2-one in 250 ml dry ether 6 g of acetylchloride were added dropwise under external cooling (ice-bath). After reflux for 2 hr the thallium salt was filtered and extracted with ether. The ether was evaporated, and the residue distilled; b.p.[15] 85–86°, n_D^{25} = 1·5213, yield 9·8 g (91%). λ_{max}^{EtOH} (log ε_{max}) 236 (3·83). (Found: C, 51·18; H, 4·48; S, 22·21. $C_6H_6O_2S$ requires: C, 50·71; H, 4·26; S, 22·52%).

TABLE 4. NMR SPECTRA AND PHYSICAL CONSTANTS OF IV[a]

	NMR[b]							b.p.	n_D^{25}	R_f
	H^3	H^4	H^5	OCH	J_{34}	J_{35}	J_{45}			
IVb[c]										0·45^{I}, 0·67^{IV}
IVc[d]	6·02	6·66	6·51	4·32	3·6	1·6	5·9	60°/10 mm	1·4997	0·69^{III}, 0·80^{IV}
IVf[e]	6·21	6·64	6·48	3·53	3·7	1·5	5·8			0·35^{I}, 0·57^{II}
IVg[f]	6·27	6·67	6·57	4·56	3·7	1·6	5·8	81°/0·2 mm	1·5055	0·38^{IV}

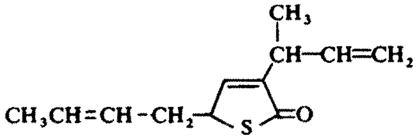
[a] See Table 3
[b] ABX analysis
[c] See ref. 13
[d] (Found: C, 59·33; H, 7·27; S, 22·83. $C_7H_{10}OS$ requires: C, 54·14; H, 7·09; S, 22·52%).
[e] The fraction of IVf contained dibenzylsulfide, confirmed by NMR and m/e = 214
[f] (Found: C, 51·55; H, 5·65; S, 16·75. $C_8H_{10}O_3S$ requires: C, 51·61; H, 5·41; S, 17·19%)

TABLE 5. NMR SPECTRA AND PHYSICAL CONSTANTS OF VI AND X[a]

	NMR						R_f
	H^4	H^5	C^3H	C^5H	J_{45}	$J_{H^4-C^5H}$	
VIb	5·75	6·70	~1·6		7·7		0·33^{I}, 0·67^{IV}
VId[b]	5·84	6·63	2·38		7·7		0·52^{II}
VIf[c]	5·83	6·22	d		7·7		0·32^{II}
Xb	5·36		~1·6	2·48		1·5	0·33^{I}, 0·67^{IV}
Xd	5·54		2·37	3·17		1·5	0·52^{II}

[a] See Table 3
[b] (Found: C, 66·33; H, 6·95; S, 17·00. $C_{10}H_{12}OS$ requires: C, 66·65; H, 6·71; S, 17·76%).
[c] Recrystallized from benzene–light petroleum ether; m.p. = 124°. (Found: C, 77·22; H, 5·69; S, 11·83. $C_{18}H_{16}OS$ requires: C, 77·12; H, 5·75; S, 11·41%)
[d] The methylene protons showed an AB spectrum; ν = 2·86 and 3·10 δ, J_{gem} = 13·3 c/s

TABLE 6. ANALYSIS, NMR SPECTRA AND PHYSICAL CONSTANTS OF IX AND



(XIII)*

	Analysis						NMR									n_D^{25}	R_f
	Calc. %			Found %													
	C	H	S	C	H	S	H^4	H^5	C^3H	$J_{H^4-C^3H}$	$J_{H^5-C^3H}$	J_{45}	$J_{H^5-C^5H}$	C^5H			
IXb	61·52	7·75	20·52	60·75	7·80	19·80	7·07	4·27	2·31	1·4	1·6	2·8		~1·9	1·5116	$0·44^{IV}$
IXc							7·01	4·23	~2·7	1·2	1·4	2·8	5·2	~2·1		$0·58^{IV}$
IXd	66·65	6·71	17·76	66·31	6·93	17·29	7·11	4·36	~3·0	1·4	1·8	2·7		~2·5	1·5324	$0·24^{II}$
IXe	69·21	7·74	15·37	69·08	7·84	15·24	7·04	4·25	2·92					~2·5		$0·46^{III}$
XIII									3·23							

* See Table 3

TABLE 7. UV SPECTRA (EtOH)

	ν_{max}	log ε	ν_{max}	log ε
IIIb	224	3·93	259	3·39
IIIc	224	3·90	260	3·41
IIId	225	3·82	262	3·33
IIIf			260	sh
IIIg	221	3·86	263	3·11
IVc	243	3·61		
IVg	239	3·69		
VId	212	3·69	277	2·89
VIf	219	4·08		
IXb	226	3·90	265	3·31
IXd	228	3·84	265	sh

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