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A SYNTHESIS OF 2-ACYL- 3-HYDROXYTHIOPHENES

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2-Acyl-3-hydroxythiophenes have been made by the reaction of the anion of a mercaptoketone with dimethyl acetylenedicarboxylate to give a hydroxythiophene ester which is then hydrolysed and decarboxylated.

In connection with other work[1] we needed various 2-acyl-3-hydroxythiophenes. These have usually been made by the acylation of 3-butoxy-[2] or 3-methoxy-[3] thiophenes followed by dealkylation, but we found the method not to be general. An alternative method involves the condensation of methyl propiolate with mercaptoacetone[4] but the yields are very poor. Whilst the reaction of mercaptoacetone with

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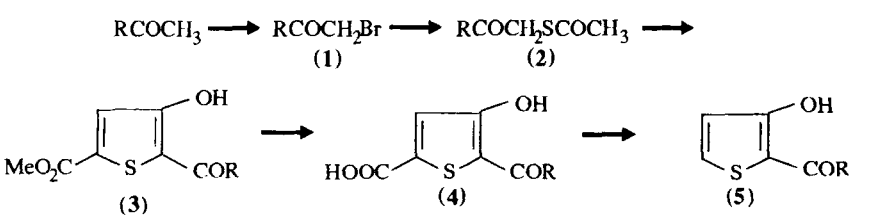
2-chloroacrylonitrile gives good yields of 2-acetyl-3-aminothiophene[5] the corresponding reaction with methyl 2-chloroacrylate always gives very poor yields of 2-acetyl-3-hydroxythiophene and sometimes the entire product is 4-methylthiophene-3-carboxylic acid. The reaction of mercaptoacetone with diethyl acetylenedicarboxylate has been shown to give ethyl 5-acetyl-4-hydroxythiophene-2-carboxylate in moderate yield[6] so we decided to investigate this reaction further. It was found that with dimethyl acetylenedicarboxylate (DMAD) the yield was substantially improved; we have now developed the general method shown below.



a, R = Me; b, R = Ph; c, R = 2-ClPh; d, R = 4-BrPh;
e, R = 3-MeOPh; f, R = 2-furyl; g, R = 2-thienyl

Whilst mercaptoacetone is easily prepared[7] and relatively stable the same would appear not to be the case for the aroylthiols $ArCOCH_2SH$. Compounds of type (**2**) were therefore prepared by the reaction of (**1**) with MeCOSH and K_2CO_3; then the anion of the

mercaptoketone was generated by the action of NaOMe and allowed to react with DMAD. The resulting esters were hydrolysed to the acids (**4**) which were decarboxylated to give the desired ketones (**5**). All the compounds prepared had the expected spectral properties save for the cmr spectrum of (**5c**). Molecular modelling[8] showed that the dihedral angle between the rings in (**5c**) is much greater than those in (**5b**) and (**5g**); however, the spectra of (**4c**) and (**3c**) are normal.

Experimental

5-Acetyl-4-hydroxy-2-methoxycarbonylthiophene (**3a**)

Mercaptoacetone[7] (16g) and DMAD (25.6g) were stirred in methanol (100ml) in an ice bath. A solution of potassium hydroxide (13.45g) in methanol (200ml) was added dropwise with stirring whereupon the temperature rose to 25°C. When the addition was complete the mixture was stirred at room temperature for 30min. The liquid was then poured into water and acidified to Congo Red with concentrated HCl. The mixture was allowed to stand for 30min in an ice bath before the yellow solid was filtered off; yield 28.78g (80%). The analytical sample was crystallised from methanol and had mp 103-105°C (lit.[9] 110-111°C) (Found: C, 49.1, H, 3.1; calc. for $C_{11}H_8O_4S$ C, 49.25, H, 3.1%, $M+H^+$ m/z 269, δ_H ($CDCl_3$) 2.48 (3H, s, COMe) 3.93 (3H, s, CO_2Me) 7.35 (1H, s, ArH) 11.13 (1H, s, OH), δ_C ($CDCl_3$) 27.78 (COMe) 52.90 (CO_2Me) 118.38 (C5) 124.20 (C3) 137.02 (C2) 161.74 (C4) 164.09 (CO) 195.86 (CO), υ_{max} (KBr) 3100 (br, OH) 1710 (CO) cm^{-1}).

α-Bromoketones (**1**).

Phenacyl bromide was a commercial product; (**1e - 1f**) were made by bromination of the corresponding ketone in dichloromethane solution. (**1f**) was prepared by bromination with copper(II) bromide[10] as follows: copper(II) bromide (111.5g, 0.5 mole) in ethyl acetate (150ml) was heated to reflux then a solution of 2-acetylthiophene (37.8g, 0.3 mole) in chloroform (100ml) was added. After the mixture had been refluxing for 4h the liquid had become amber coloured and the evolution of HBr had ceased. The mixture was cooled and the precipitated copper(I) bromide was filtered off. The filtrate was stirred for 10min with charcoal, filtered and evaporated; the product weighed 39.3g (96%). As with all the bromoketones it was used immediately without further treatment.

α-Mercaptoacetylketones (**2**).

A solution of thiolacetic acid in ethanol was stirred for 30min at room temperature with anhydrous potassium carbonate, then a solution of the α-bromoketone in a suitable solvent was added over 5min. Stirring was continued at room temperature until TLC ($SiO_2/CHCl_3$) showed that all the ketone had been consumed. The mixture was filtered, the residue was washed with ethanol or acetone (if the latter had been the solvent for the ketone), and the combined washings and filtrate were evaporated on the rotary evaporator. Details of the quantities employed and of the final work-up are given in Table 1 and its footnotes.

Table 1

Preparation of α-mercaptoacetyl ketones (2)

Cpd	MeCOSH g/Mole	K_2CO_3 g/Mole	EtOH ml	$RCOCH_2Br$/Solvent* g/Mole	ml	Stir time h	Work-up
2b	0.76/0.01	1.38/0.01	25	1.94/0.01	A, 10	3	b
2c	0.76/0.01	1.38/0.01	25	2.33/0.01	A, 10	1	a
2d	3.8/0.05	4.0/0.025	50	13.9/0.05	C, 50	3	b
2e	7.6/0.1	13.8/0.1	50	22.9/0.1	B, 50	1	c
2f	0.76/0.01	1.38/0.01	25	1.89/0.01	A, 10	2	a
2g	0.76/0.01	1.38/0.01	25	2.05/0.01	C, 15	4	b

*A = EtOH B = Me_2CO C = 1:1 A+B

Work-up notes:-

a. Partitioned CH_2Cl_2-H_2O, organic solution washed (H_2O 3x, brine), dried ($MgSO_4$), evaporated, product distilled

b. Triturated with light petroleum (bp 60-80°C), recrystallised from the same solvent (charcoal)

c. As a, but with Et_2O instead of CH_2Cl_2

Table 2

Yields, Mp's/Bp's and analyses of (2)

Cpd	Yield %	Mp °C Bp °C/mmHg	Molecular Formula	Found % C	Found % H	Required % C	Required % H
2b	91	46-48*	$C_{10}H_{10}O_2S$	61.7	5.2	61.9	5.2
2c	82	181-183/0.05	$C_{10}H_9ClO_2S$	52.0	3.8	52.5	3.9
2d	84	70-71	$C_{10}H_9BrO_2S$	43.7	3.3	44.0	3.3
2e	87	158-160/0.5	$C_{11}H_{12}O_3S$	59.3	5.5	58.9	5.4
2f	84	130-132/0.3**	$C_8H_8O_3S$	52.5	4.5	52.2	4.3
2g	85	63-64	$C_8H_8O_2S_2$	48.4	4.1	48.0	4.0

* lit.[11] mp 42-43°C

** Solidified on standing, mp 47-48°C

Table 3
Proton nmr ($CDCl_3$) and ir spectra of (2)

Cpd	$COCH_2$	$COCH_3$	R	ν_{max} cm^{-1}
2b	4.44	2.38	7.20-7.62, 3H, m, H3-5 7.82-8.22, 2H, m, H2/H6	1680, 1600 [a]
2c	4.29	2.36	7.28-7.42, 3H, m, H3-5 7.55-7.59, 1H, m, H6	1690, 1590 [a]
2d	4.39	2.40	7.62, 2H, d, H2, J = 8.6 Hz 7.84, 2H, d, H3, J = 8.6 Hz	1680, 1580 [b]
2e	4.34	2.35	7.07-7.11, 1H, m, H4 7.31-7.54, 3H, m, H2,5,6	1700, 1595 [a]
2f	4.23	2.40	6.58, 1H, dd, H4 7.32, m, 1H, d, H3, J = 3.3 Hz 7.65, 1H, d, H5, J = 1.98 Hz	1690, 1670, 1640 [b]
2g	4.30	2.40	7.00-7.20, 1H, m, H4 7.58-7.90, 2H, m, H5 + H3	1690, 1670 [b]

[a]Liquid film [b]KBr disc

Table 4
Carbon-13 ($CDCl_3$) nmr spectra of (2)

Cpd	CO	CH_2	SCO	CH_3	R
2b	194.1	36.6	193.1	30.1	1, 135.5; 2+6, 3+5, 128.7, 128.4 4, 133.7
2c	196.2	39.8	194.1	30.0	1, 137.9; 2, 131.0; 3, 130.0; 4, 132.3; 5, 127.0; 6, 130.4
2d	194.0	36.3	192.4	30.2	1, 134.3; 2+6, 130.0; 3+5, 132.1; 4, 129.0
2e	193.9	36.7 (OMe, 55.4)	192.9	30.1	1, 136.8; 2, 112.7; 3, 159.9; 4, 120.1; 5, 129.7; 6, 121.0
2f	193.9	35.6	182.0	30.1	2, 151.4; 3, 118.6; 4, 112.6; 5, 147.2
2g	193.8	36.4	186.1	30.1	2, 142.4; 3, 133.0; 4, 128.3; 5, 134.7

Methyl 5-acyl-4-hydroxythiophene-2-carboxylates (**3**).

To a solution of sodium methoxide [from 0.23g (0.01g-atom) of Na] in dry methanol (25ml) was added rapidly, at room temperature and with magnetic stirring, a solution of the *S*-acetylmercaptoketone (**2**) (0.01 mole) in the same solvent (10ml). After 15min DMAD (1.42g, 0.01 mole) was added and stirring was continued until TLC (SiO_2/ $CHCl_3$) showed that all the *S*-acetyl compound was consumed. The mixture was added to water, the solution acidified to Congo Red with 4M HCl and the product was isolated either by filtration followed by air-drying of the residue (method A) or by extraction into dichloromethane and evaporation of the washed [H_2O (2x), brine] and dried ($MgSO_4$) solution (method B). In all cases the product was crystallised from methanol (charcoal). Details of the individual preparations are shown in Table 5.

5-Acyl-4-hydroxythiophene-2-carboxylic acids (**4**).

The esters were hydrolysed by boiling them under reflux with 2M NaOH (*ca.* 12ml/g) for 2 h and the acids were isolated by precipitation with concentrated HCl.

The yields, analyses and spectral properties of the acids are collected in Tables 9 - 11.

2-Acyl-3-hydroxythiophenes (**5**).

The acid was heated in quinoline solution with the copper species

Table 5
Preparation, yields and mp's of the methyl 5-acyl-4-hydroxy-thiophene-2-carboxylates (3)

Cpd	Stir Time (h)	Isolation method	Yield %	Mp °C
3b	2	B	87	102-103
3c	4	B	80	92-93
3d	1	A	87	134-135
3e	1	B	83	102-103
3f	3	A	82	158-159
3g	2	B	81	119-120

Table 6
Analyses of (3)

Cpd	Molecular Formula	Found %		Required %	
		C	H	C	H
3a	$C_7H_6O_4S$	45.0	3.1	45.2	3.2
3b	$C_{13}H_{10}O_4S$	59.5	3.9	59.5	3.8
3c	$C_{12}H_7ClO_4S$	51.0	2.5	50.6	2.5
3d	$C_{13}H_9BrO_4S$	45.4	2.9	45.7	2.6
3e	$C_{14}H_{12}O_5S$	57.8	4.1	57.5	4.1
3f	$C_{11}H_8O_4S$	51.6	3.1	52.4	3.1
3g	$C_{11}H_8O_4S_2$	49.1	3.1	49.3	3.1

shown in Table 12 for the time and temperature specified. After cooling, the mixture was poured into 4M HCl/ether and filtered through kieselguhr. The filter cake was washed with ether and the washings and filtrate were combined. The upper layer was separated,

Table 7
Proton nmr ($CDCl_3$) and ir (KBr) spectra of (3)

Cpd	OH	CO_2Me	ThH	R	ν_{max} cm^{-1}
3a	11.13	3.98	7.35	2.48, Me	1715, 1610
3b	12.01	3.92	7.38	7.38-7.66, 3H, m, H3'-5' 7.80-8.06, 2H, m, H2'/6'	1722, 1600
3c	11.16	3.89	7.42	7.38-7.51, 4H, m, H3'-6'	1722, 1610
3d	11.87	3.93	7.44	7.68, 2H, d, H2, J = 8.6 Hz 7.84, 2H, d, H3, J = 8.6 Hz	1718, 1600
3e	11.94	3.92	7.44	7.26-7.54, 4H, m, H2'+4'-6' 3.88, OMe	1715, 1620
3f	12.02	3.94	7.39	6.66, 1H, m, H4 7.49, 1H, d, H3, J = 3.96 Hz 7.74, 1H, s, H5	1710, 1590
3g		3.95	7.40	7.2, 1H, m, H4 7.7-8.1, 2H, m, H3+5	1720, 1575

Table 8
Carbon-13 nmr spectra ($CDCl_3$) of (3)*

Cpd	C2	C3	C4	C5	COR	CO_2Me	R
3a	137.0	124.2	161.7	118.4	195.9	164.1	Me, 27.8
3b	139.1	124.2	166.6	116.4	191.7	161.8	1', 137.7; 2'/6', 128.4; 3'/5', 128.8; 4', 133.0
3c	140.0	124.1	165.6	118.7	191.3	161.6	1', 137.1; 2', 131.0; 3', 128.4; 4', 132.1; 5', 126.8; 6', 130.6
3d	139.3	124.3	166.9	116.0	190.6	161.7	1', 136.4; 2'/6', 129.9; 3'/5', 132.2; 4', 128.2
3e	139.2	124.2	166.7	116.5	191.6	161.8	1', 139.0; 2', 113.0; 3', 159.9; 4', 119.4; 5', 129.9; 6', 120.7 MeO, 55.5
3f	140.0	123.6	167.5	114.6	177.2	162.0	2', 151.2; 3', 119.1; 4', 113.1; 5', 147.4
3g	138.4	124.2	166.9	115.3	182.0	161.7	2', 142.2; 3', 132.7; 4', 128.6; 5', 134.7

* All OMe peaks appear at δ 52.9-53.0

Table 9

Yields, mp's and analyses of 5-acyl-4-hydroxythiophenecarboxylic acids (**4**)

Cpd	Yield	Mp	Molecular	Found %		Required %	
	%	°C	Formula	C	H	C	H
4a	80	223-225	$C_7H_6O_4S$	45.0	3.1	45.2	3.2
4b	92	192-195	$C_{12}H_8O_4S.H_2O$	53.8	3.1	54.1	3.0
4c	78	243-244	$C_{12}H_7ClO_4S$	51.0	2.5	50.6	2.5
4d	86	242-243	$C_{12}H_7BrO_4S.½H_2O$	43.2	2.3	42.9	2.4
4e	87	209-211	$C_{13}H_{10}O_5S.½H_2O$	54.8	3.5	54.4	3.8
4f	84	263-264	$C_{10}H_6O_5S$	50.4	2.6	50.4	2.5
4g	90	253-255	$C_{10}H_6O_4S_2$	47.6	2.5	47.5	2.5

Table 10

Proton nmr ($CDCl_3$/DMSO-D_6) and ir (KBr) spectra of (**4**)

Cpd	CO_2H	ThH	R	ν_{max} cm^{-1}
4a	11.07	7.30	2.51, Me	1700, 1610
4b	11.82	7.34	7.52-7.67, 3H, m, H3'-5' 7.92-7.95, 2H, m, H2'/6'	1690, 1610
4c	10.99	7.81	7.33-7.48, 4H, m, H3'-6'	1680, 1610
4d		7.31	7.68, 2H, d, H2, J = 8.6Hz 7.85, 2H, d, H3, J = 8.6Hz	1680, 1610
4e	11.54	7.36	7.15-7.49, 4H, m, H2'+4'-6' OMe 3.86	1700, 1620
4f	11.93	7.32	6.74, 1H, dd, H4, J = 1.3, 3.3Hz 7.54, 1H, d, H3, J = 3.3Hz 7.97, 1H, d, H5, J = 1.3Hz	1695, 1600
4g	11.83	7.35	7.29, 1H, m, H4; 7.89, 1H, m, H5 8.11, 1H, d, H3, J = 3.3Hz	1690, 1590

[a] broad singlet [b] singlet

Table 11
Carbon-13 nmr spectra ($CDCl_3$/DMSO-D_6) of (**4**)

Cpd	C2	C3	C4	C5	COR	CO_2H	R
4a	138.1	124.5	162.5	122.5	191.9	159.3	28.6, Me
4b	141.0	123.6	165.9	116.3	191.2	162.6	1', 137.7; 2'/6', 128.2 3'/5', 128.6; 4', 132.8
4c	141.1	124.2	162.5	120.3	188.5	162.5	1' 138.3; 2', 130.1 3', 129.8; 4', 131.4 5', 126.8; 6', 130.1
4d	140.9	123.9	164.6	117.0	189.4	162.5	1', 136.6; 2'/6', 130.0 3'/5', 131.8; 4', 127.4
4e	140.3	124.0	163.4	117.8	189.1	162.3	1', 139.1; 2', 113.2 3', 159.2; 4', 117.8 5', 129.5; 6', 120.6 55.3, OMe
4f	140.1	121.5	164.7	112.9	174.8	161.0	2', 149.2; 3', 117.7 4', 111.7; 5', 146.5
4g	140.3	123.7	165.4	115.5	181.2	162.4	2', 142.0; 3', 132.9 4', 128.6; 5', 135.0

Table 12
Decarboxylation of (**4**) to give (**5**)

Cpd	Acid g	Quinoline ml	Catalyst g	Temp °C	Time h	Work-up or crystallisation solvent
5a	25.5	200	a : 18	230	2	steam distillation
5b	7.15	100	a : 10	200	2	
5c	0.9	15	b : 1	180	2	EtOAc/PE (bp 60-80°C)
5d	3	30	a : 2	180	4	PE (bp 60-80°C)
5e	2	25	b : 2	180	2	bp 200-202°/0.05 mm Hg
5f	2.48	25	b : 2	180	3	PE (bp 60-80°C)
5g	4.6	50	a : 5	200	2	

Catalysts : a, Cu bronze; b, Cu_2O

Table 13
Yields, Mp's/Bp's and analyses of 2-acyl-3-hydroxythiophenes (**5**)

Cpd	Yield	Mp	Molecular	Found %		Required %	
	%	°C	Formula	C	H	C	H
5a	85	51.4-52.7 [a]					
5b	86	65-66 [b]					
5c	83	158-159	$C_{11}H_7ClO_2S$	55.2	2.9	55.3	2.9
5d	84	135-136	$C_{11}H_7BrO_2S$	46.6	2.4	46.6	2.5
5e	80	- [c]	$C_{12}H_{10}O_3S$	61.8	4.3	61.5	4.3
5f	85	84-85	$C_9H_6O_3S$	55.6	3.1	55.7	3.1
5g	70	62-64 [d]					

[a] lit.[2] 51.5-52.5°C [b] lit.[5b] 62°C [c] bp 200-202°C/0.05 mmHg
[d] lit.[1] 63.5-64.5°C

Table 14
Proton nmr ($CDCl_3$) and ir spectra of (**5c-f**)

Cpd	OH	H4*	H5*	R	$\nu_{max}cm^{-1}$
5c		7.81	7.19	7.44-8.38, 4H, m, H3'-6'	1650
5d	12.3	7.55	6.82	7.65, 2H, d, J = 8.6Hz 7.85, 2H, d, J = 8.6Hz	1600
5e	12.39	7.50	6.80	7.06-7.53, 4H, m, H2'+4'-6' 3.82, OMe	1600
5f	12.41	7.58	6.80	6.62-7.71, 3H, m, H3'-5'	1580

ir in KBr discs except for 5c which was as a thin film
* all doublets, J = 5.3Hz

Table 15
Carbon-13 nmr spectra ($CDCl_3$) of (5)

Cpd	C2	C3	C4	C5	CO	R
5a	114.4	166.1	119.7	132.3	194.6	Me, 27.5
5b	112.1	168.8	119.7	132.4	190.9	1', 138.3; 2'/6', 128.6 3'/5', 128.2; 4', 134.7
5c	122.0	159.0	118.0	134.0	172.7	1', 156.2; 2', 121.5 3', 124.7; 4', 133.8 5', 118.2; 6', 126.2
5d	111.8	169.1	119.9	135.0	189.7	1', 137.0; 2'/6', 129.8 3'/5', 132.0; 4', 127.5
5e	112.1	168.9	119.6	135.0	190.6	1', 139.5; 2', 112.4 3', 159.7; 4', 118.8 5', 129.7; 6', 120.6 MeO, 55.4
5f	110.2	169.7	119.2	135.9	176.7	2', 151.4; 3', 118.2 4', 112.8; 5', 146.8
5g	111.0	169.2	119.7	132.1	181.5	2', 143.5; 3', 133.6 4', 128.5; 5', 133.9

washed with 4M HCl (3x), water (3x) and once with brine then dried ($MgSO_4$) and evaporated. The resulting products were then purified as shown in Table 12; analytical results are given in Table 13 and the spectroscopic data are presented in Tables 14 and 15.

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