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Previous works of our group have dealt with the synthesis of 1-(aryl)-3-[4-(aryl)piperazin-1-yl]propane derivatives in the search for new and efficient antidepressants with a dual mode of action: serotonin reuptake inhibition and 5-HT_{1A} receptor afinity [1-4]. From these studies we concluded that the 3-[4-(aryl)piperazin-1-yl]-1-(benzo[*b*]thiophen-3-yl)propane derivatives led to the best results. The continuation of this research project required the preparation of some new 3-acyl-5-substituted benzo[*b*]thiophenes with a wide variety of substituents at the 5 position, ranging from nitro to hydroxyl derivatives. To obtain these derivatives we acylated the corresponding 5-substituted benzo[*b*]thiophenes when it was possible.

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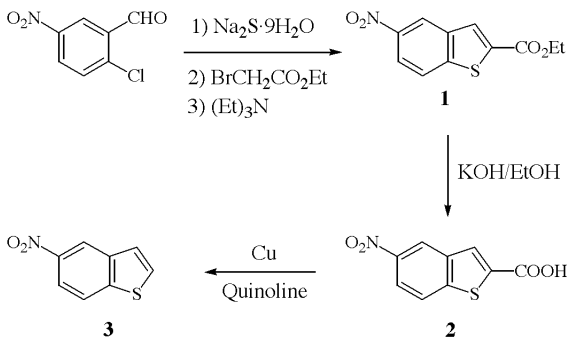
It has been described that Friedel-Crafts acylation of 5-substituted benzo[*b*]thiophene derivatives gives different isomers depending on the susbstituent; benzo[*b*]-thiophene derivatives with weakly activating or deactivating substituents such as chloro or acetoxy, mainly give the 3-acylated product [5]. Acetylation of 5-methyl-benzo[*b*]thiophene gives a mixture of the 2- and 3-ketone derivatives in which the 3-isomer predominates [6]. A very similar mixture of isomers is obtained when the starting material is benzo[*b*]thiophene itself [7]. Finally, although we also needed 3-acylbenzo[*b*]thiophenes with activating substituents at the 5-position, they could not be obtained directly from the acetylation of their corresponding benzo[*b*]thiophenes: the acylation of benzo[*b*]thiophenes containing 5-hydroxy, 5-methoxy or 5-amino groups at the 5 position occurs mainly on the benzene ring [5]. For this reason, these types of derivatives had to be obtained from benzo[*b*]thiophenes already acylated at the 3 position.

In this paper we describe the synthesis of 3-acyl-5-substitutedbenzo[*b*]thiophenes by Friedel-Crafts acylation of 5-substitutedbenzo[*b*]thiophenes. The starting compounds for the acylating reactions were synthesized according to described methods, which in most cases, were modified in order to optimize the yields and to facilitate the isolation of the product.

5-Nitrobenzo[b]thiophene was synthesized according to the literature [8,9], with slight modifications. In the first step, 5-nitro-2-chlorobenzaldehyde was treated with sodium sulfide nonahydrate and ethyl bromoacetate in basic medium, yielding ethyl 5-nitrobenzo[*b*]thiophene-2-carboxylate **1** (Scheme 1). Alkaline hydrolysis of this compound gave the corresponding acid **2**, which was decarboxylated in copper-quinoline to 5-nitrobenzo[*b*]-thiophene **3** following described methods [8].

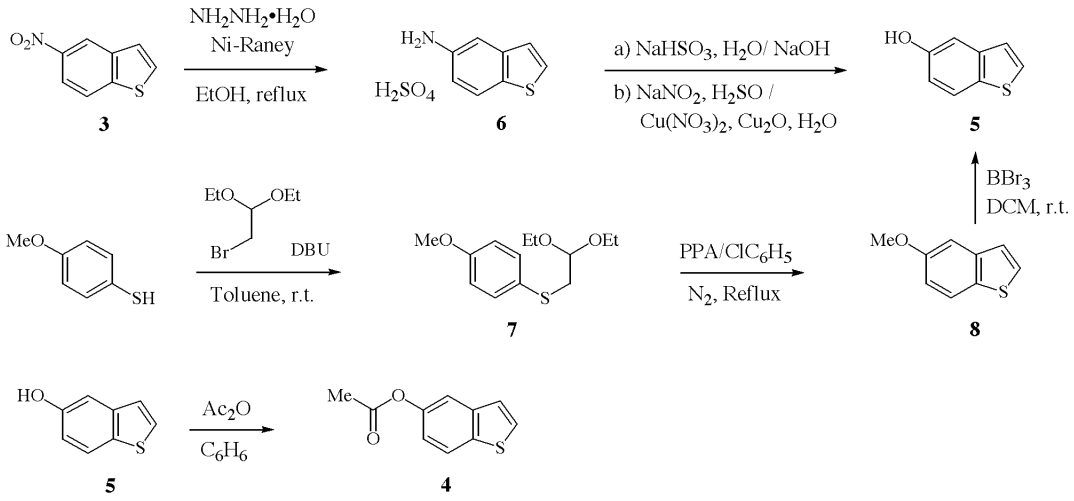
5-Acetoxybenzo[*b*]thiophene **4** was readily available by reaction of 5-hydroxybenzo[*b*]thiophene **5** with acetic anhydride [9]. Four different methods were tried in order to obtain 5-hydroxybenzo[*b*]thiophene (Scheme 2). Decar-boxylation of 5-hydroxybenzo[*b*]thiophene-2-carboxylic acid with copper-quinoline, following the synthetic pathway described in the literature [10], yielded 5-hydroxybenzo-[*b*]thiophene only in moderate yields (32%). In a second attempt, 5-aminobenzo[*b*]thiophene sulfate **6**, obtained by reduction of the nitro compound with hydrazine mono-hydrate and Raney nickel [10], was converted to the hydroxy derivative *via* a Bücherer reaction. This method was aban-doned due to its poor yield (5%). We then tried to convert the amine sulfate to the 5-hydroxy derivative by forming the diazonium salt of the amine, followed by the generation and oxidation of the benzo[*b*]thiophenyl radical (Scheme 2) [11]. This reaction is fundamentally different from the previous thermal method *via* benzo[*b*]thiophenyl cation described in the literature [8]. The product was obtained by this method with a moderate yield (40%) . Finally, 5-hydroxybenzo-[*b*]thiophene was more easily obtained when starting from 4-methoxybenzenethiol according to Scheme 2. Cyclization of (arylthio)acetaldehyde dialkyl acetals has been exten-sively used to synthesize a wide variety of benzo[*b*]thio-phenes, but very poor yields were obtained for 5-methoxy-benzo[*b*]thiophene in neat polyphosphoric acid (PPA) at 180 °C [12]. Although better yields are obtained in a hetero-geneous system of PPA and chlorobenzene, no cyclization

Scheme 1



Synthesis of 5-Nitrobenzo[*b*]thiophene

Scheme 2

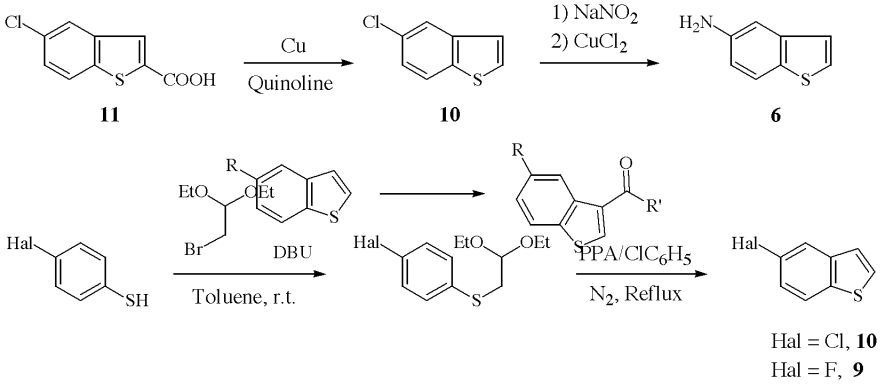


Synthesis of 5-Hydroxybenzo[*b*]thiophene and 5-Acetooxybenzo[*b*]thiophene

was observed for *p*-methoxyphenylacetaldehyde dimethyl acetal, and the starting material was quickly degraded [13]. We describe here conditions that support the synthesis of 5-methoxybenzo[*b*]thiophene **8** by cyclization of *p*-methoxyphenylacetaldehyde diethyl acetal **7** instead of dimethyl acetal. The change of methyl acetal by ethyl acetal could be important in this reaction. A better product yield is sometimes obtained using diethyl acetals as the starting material instead of the corresponding dimethyl acetals [14]. The acetal was synthesized by reaction of *p*-methoxybenzenethiol with bromoactaldehyde diethyl acetal and 1,8-diazabycicle[5.4.0]undec-7-ene (DBU), according to an adaptation of a synthesis of sulfides described in the literature [15]. Reaction of 5-methoxybenzo[*b*]thiophene **8** with boron tribromide afforded **5** in 50% yield

5-Halobenzo[*b*]thiophene derivatives were better prepared by reaction of their corresponding (arylthio)-acetaldehyde diethyl acetals with PPA in chlorobenzene as shown in Scheme 3. 5-Fluorobenzo[*b*]thiophene **9** was obtained according to literature [16]. 5-Chlorobenzo[*b*]-thiophene **10** was prepared in a similar way [2], and was also prepared by two alternative routes (Scheme 3); in the first one, 5-chlorobenzo[*b*]thiophene-2-carboxylic acid **11** was decarboxylated with copper-quinoline, but the yield was not satisfactory (19%). 5-chlorobenzo[*b*]thiophene-2-carboxilic acid was prepared from ethyl 5-nitrobenzo[*b*]-thiophene-2-carboxylate according to a previously described method [17]. In the second one, the sulfate of 5-aminobenzo[*b*]thiophene **6** was diazotizated according to a classic Sandmeyer reaction, but the yield of the

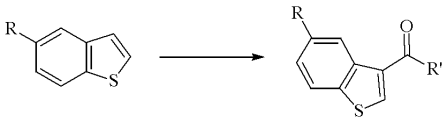
Scheme 3



Synthesis of 5-Chloro and 5-Flourobenzo[*b*]thiophene

Table I

Yields and Reaction Conditions for the Acetylation and/or Acylation of Benzo[*b*]thiophene and 5-Substituted Benzo[*b*]thiophene



Compound	R	Acylating agent	Reaction Time (hours)	Catalyst/solvent	R'	Yield (%)	Ref.
12	NO_2	Ac_2O	24	$FeCl_3$/AcOH	CH_3	50	-
13	NO_2	$Cl(CH_2)_2COCl$	48	$AlCl_3/CHCl_3$	CH_2CH_2Cl	35	-
14	CH_3	Ac_2O	8	$BF_3{\cdot}EtO_2/C_6H_6$	CH_3	60	[5]
15	CH_3	$Cl(CH_2)_2COCl$	48	$AlCl_3/CHCl_3$	CH_2CH_2Cl	37	-
16	H	$Cl(CH_2)_2COCl$	48	$AlCl_3/CHCl_3$	CH_2CH_2Cl	40	-
17	H	$Cl(CH_2)_3COCl$	48	$AlCl_3/CHCl_3$	$CH_2CH_2CH_2Cl$	27	-
18	CH_3COO	AcCl	6	$AlCl_3/CHCl_3$	CH_3	35	[9]
19	CH_3COO	$Cl(CH_2)_2COCl$	48	$AlCl_3/CHCl_3$	CH_2CH_2Cl	43	-
20	F	AcCl	56	$AlCl_3/CHCl_3$	CH_3	58	[2]
21	F	$Cl(CH_2)_2COCl$	48	$AlCl_3/CHCl_3$	CH_2CH_2Cl	43	[2]
22	F	$Cl(CH_2)_3COCl$	39	$AlCl_3/CHCl_3$	$CH_2CH_2CH_2Cl$	39	-
23	Cl	AcCl	24	$AlCl_3/CHCl_3$	CH_3	60	[2,17]

reaction was also slightly higher than that obtained for the decarboxylation, which was low (23%). In conclusion, the cyclization of the acetal seems to be the best synthetic method, presenting a significant higher yield (73%).

3-Acetyl-5-nitrobenzo[*b*]thiophene **12** was obtained by acetylation of **3** with acetic anhydride in refluxing acetic acid in the presence of a catalytic amount of anhydrous iron(III)chloride. Under these conditions, a small amount of the 2-isomer also formed and could be identified in the mixture by ^{1}H-nmr. We could not detect formation of the 2-isomer in the other acylation reactions of benzo[*b*]thiophene derivatives with electron-withdrawing substituents such as acetoxy, chloro or fluoro, under the conditions that were used. The method previously described for the acetylation of 5-chlorobenzo[*b*]thiophene [18] was slightly modified in a previous work in our laboratory in order to obtain both the 5-chloro and the 5-fluoro-3-acetyl derivatives (compounds **20** and **23**, Table I) [2]. Acylation of all benzo[*b*]thiophene derivatives with 3-chloropropionyl chloride (compounds **13**, **15**, **16**, **19** and **21**) and with 4-chlorobutanoyl chloride (compounds **17** and **22**) were carried out using chloroform as solvent and aluminum trichloride as catalyst.

Acylation of both benzo[*b*]thiophene and 5-methylbenzo[*b*]thiophene gives a mixture of the 2- and 3-isomers, in which the 3-isomer predominates (about 80%). The desired 3-isomer could be separated by flash chromatography or by recrystallization of the mixture from dichloromethane/light petroleum (compounds **14**, **15**, **16** and **17**). The 2-isomers were not isolated because this was not of interest in our investigation; nevertheless, as in the case of the acetylation reaction, their presence in the crude reaction product was easily detected by ^{1}H-nmr.

Finally, destruction of the catalyst in the reaction mixture was carried out in most cases by slow addition of dilute sulfuric acid. The rate of the addition seems to be critical for the yield of the reaction, probably because rapid addition causes destruction of the benzo[*b*]thiophene ring.

Reaction conditions for acetylation and acylation of benzo[*b*]thiophene and 5-substituted benzo[*b*]thiophene are summarized in Table I.

In general, better yields were obtained in acetylation than in acylation reactions. On the other hand, no significant differences were found between yields of the different benzo[*b*]thiophenes with 3-chloropropionyl chloride, being the yields moderate in each case. However, acylation with 4-chlorobutanoyl chloride afforded lower yields (compounds **17** and **22**), even though the method followed was similar to that used to synthesize the propanone derivatives (compounds **16** and **21**).

In conclusion, we have synthesized new 3-acyl-5-substitutedbenzo[*b*]thiophene derivatives using Friedel-Crafts acylation of benzo[*b*]thiophene derivatives. A number of different methods were evaluated in order to discover the best synthetic route to each of the 5-substituted benzo[*b*]thiophene derivatives.

EXPERIMENTAL

Melting points were determined using a Mettler FP82+FP80 apparatus and are uncorrected. Elemental analyses were obtained from vacuum-dried samples (over phosphorus pentoxide at 4 mm Hg, 24 hours, at *ca.* 80-100 °C). Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR apparatus, using potassium bromide tablets for solid products and sodium chloride plates for liquid products; the frequencies are expressed in cm^{-1}. The ^{1}H

NMR spectra were obtained on a Brucker AC-200E (200 MHz) instrument, with tetramethylsilane as the internal reference, at a concentration of *ca*. 0.1 g/mL and with dimethyl sulfoxide-d_6 (DMSO-d_6) or chloroform ($CDCl_3$) as the solvent; the chemical shifts are reported in parts per million (PPM) of tetramethylsilane in δ units, and the *J* values are given in hertz (Hz). The mass spectra were recorded on a Hewlett-Packard 5988-A instrument at 70 eV.

Thin-layer chromatography (TLC) was carried out on silica gel (DSF-5, Cammaga 0.3 mm thickness) with the indicated solvents, and the plates were scanned under ultraviolet light at 254 and 366 nm. Column chromatography was carried out with Merck silica gel 60 (70-230 mesh ASTM).

Elemental analyses were performed on a Carlo -Erba 1106 instrumental apparatus and the experimentally determined values are within ± 0.4% of the theoretical values.

Ethyl 5-Nitrobenzo[*b*]thiophene-2-carboxylate (**1**).

A solution of 2-chloro-5-nitrobenzaldehyde (15.0 g, 0.081 mol) in ethanol (50 mL) was added to a solution of sodium sulfide nonahydrate (19.41 g, 0.081 mol) in ethanol (1.0 L) at 40 °C. The reaction mixture was refluxed for two hours, and then ethyl bromoacetate (9.0 mL, 0.081 mol) was added drop by drop. The reaction temperature was kept at 50 °C, triethyl amine (11 mL) was added and the reaction mixture was allowed to stand overnight at room temperature. The precipitate which formed during this time was filtered and recrystallized from light-petroleum/ethyl acetate, 15.24 g (75%), mp 165 °C; ^{1}H-nmr (deuteriochloroform): δ 1,36 (t, 3H, C*H*$_3$CH$_2$O); 4,38 (c, 2H, CH$_3$C*H*$_2$O); 8,28 (s, 2H, H$_6$+H$_7$); 8,36 (s, 1H, H$_3$); 8,92 (s, 1H, H$_4$).

Anal. Calcd. for $C_{11}H_9NO_4S$: C, 52.59; H, 3.59; N, 5.58. Found: C, 52.41; H, 3.68; N, 5.41.

5-Nitrobenzo[*b*]thiophene-2-carboxylic Acid (**2**).

A solution of ethyl 5-nitrobenzo[*b*]thiophene-2-carboxylate (**1**) (10 g, 0.040 mol) in ethanol (250 mL) and water (60 mL) was treated with 85% potassium hydroxide (3.8 g, 0.068 mol) and the reaction mixture refluxed for two hours. The reaction was cooled and the salt of the acid filtered and washed with isopropanol. The salt was dissolved in water, and concentrated hydrochloric acid was added drop by drop until pH became acidic. The solid was filtered, washed with water and recrystallized from water/ethanol 7.56 g (85%), mp 238 °C; ^{1}H-nmr (dimethylsulfoxide-d$_6$): δ 8,30 (s, 2H, H$_6$+H$_7$); 8,32 (s, 1H, H$_3$); 8,96 (s, 1H, H$_4$)

Anal. Calcd. for $C_9H_5NO_4S$: C, 48.43; H, 2.23; N, 6.28. Found: C, 48.21; H, 2.36; N, 6.54.

4-Methoxythiophenoxylacetaldehyde Diethyl Acetal (**7**).

1,8 Diazabicyclo[5.4.0]undec-7-ene (DBU) (5.4 mL, 0.036 mol) was added dropwise to a stirred solution of 4-methoxybenzenethiol (5.00g, 0.036 mol) and bromoacetaldehyde diethyl acetal (7.04 g, 5.03 mL, 0.036 mol) in toluene (80 mL) in an ice bath. The reaction mixture was allowed to stand for 24 hours at room temperature and then filtered. The filtrate was washed with water, dried with anhydrous sodium sulfate and evaporated to dryness under reduced pressure. The product was purified by column chromatography (light petroleum to light petroleum/toluene 1:1), obtaining a liquid. Yield: 65%. ^{1}H-nmr (deuteriochloroform): δ 1.16 (t, 6H, CH$_2$C*H*$_3$); 3.04 (d, 2H, SCH$_2$); 3.48-3.73 (m, 4H, O(CH$_2$)$_2$); 3.84 (s, 3H, OCH$_3$); 3.58 (t, 1H, SCH$_2$C*H*); 6.74 (d, 2H, H$_2$+H$_6$); 7.29 (d, 2H, H$_3$+H$_5$).

5-Methoxybenzo[*b*]thiophene (**8**).

All the equipment necessary for this reaction must be dried in an oven. Chlorobenzene was dried with calcium hydride and distilled before use.

A mixture of polyphosphoric acid (PPA) (3.64 mL) and chlorobenzene was refluxed with vigorous stirring under an atmosphere of dry nitrogen. 4-Methoxyphenylthioacetaldehyde diethyl acetal (**7**) was added drop by drop to this mixture. The reaction mixture was refluxed for 24 hours and then allowed to cool. Chlorobenzene was decanted and water (50 mL) was added to the PPA and stirred for 3 hours. The organic layers were collected, washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product purified by flash chromatography using light petroleum as eluent. The product was obtained as a liquid that was pure enough for the next reaction, yield 55%. ^{1}H-nmr (deuteriochloroform): δ 3.87 (s, 3H, OCH$_3$); 6.99 (dd, 1H, H$_6$, J_{46} = 2.3, J_{67} = 8.8); 7.23-7.27 (m, 2H, H$_3$+H$_4$); 7.43 (d, 1H, H$_2$); 7.72 (d, 1H, H$_7$).

5-Hydroxybenzo[*b*]thiophene (**5**).

a) With Copper(II)nitrate and Copper(I)oxide.

5-Aminobenzo[*b*]thiophene sulfate (**6**) (0.50 g, 0.002 mol) was added to a 30 mL of 40% solution of sodium hydrogen sulfite in water. The reaction was refluxed for 48 hours and then cooled. Sodium hydroxide was added until basic pH was obtained, and the reaction mixture was refluxed again for one hour. After cooling the reaction, the reaction was extracted with diethyl ether (15 mL) to remove unreacted amine. The reaction was acidified by adding slowly concentrated hydrochloric acid and then extracted with diethyl ether (2x15 mL). The collected organic layers were dried over anhydrous sodium sulfate and the solvent evaporated under reduced pressure. Further purification was not needed, yield 5%.

b) By Bücherer Reaction.

5-Aminobenzo[*b*]thiophene sulfate (**6**) (1.8 g, 0.0012 mol) was dissolved in sulfuric acid (35%). The temperature was cooled to 15 °C and ice (12.5 g) was added to bring the temperature to 0-5 °C. A solution of sodium nitrite (1.06 g, 0.016 mol) in water (12 mL) was then added slowly under the surface at such a rate that the temperature did not exceed 5 °C. The reaction was stirred for 5 minutes, and then urea (200 mg) was added to destroy the remaining nitrite. Copper nitrate (150 g) in water (200 mL) and copper(I)oxide (1.6 g) was added successively, and the reaction mixture was shaken vigorously for 10 minutes. The product was extracted with diethyl ether (3x50 mL) and the collected organic layers washed with water and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product purified by flash chromatography (toluene). (40%). M.p.: 104 °C;

c) By Removal of Methoxy from 5-methoxybenzo[*b*]thiophene.

A solution of (**8**) (2.80 g, 0.017 mol) in dichloromethane (48 mL, previously dried over calcium chloride and freshly distilled) was placed in a dried 100 mL three-necked found-bottomed flask fitted with two rubber septums and a calcium chloride drying tube. The reaction was purged with N_2 and cooled at 0 °C in an ice-bath for half an hour. A solution of 1 *M* boron tribromide in dichloromethane (22.0 mL, 0.017 mol) was

added drop by drop. The reaction was stirred for 3 hours at room temperature and monitored by TLC (toluene). When the reaction finished, water (20 mL) was slowly added. The organic layer was washed with water, dried with anhydrous sodium sulfate, and evaporated under reduced pressure. The product was purified by flash chromatography (toluene). Yield: 50%. mp 102-104 °C; ^{1}H-nmr (deuteriochloroform): δ 4.83 (s, 1H, OH); 6.91 (dd, 1H, H_6); 7.23 (d, 1H, H_2); 7.24 (d, 1H, H_4); 7.44 (d, 1H, H_3); 7.71 (d, 1H, H_7).

Anal. Calcd. for C_8H_6OS: C, 55.67; H, 3.09. Found: C, 55.28; H, 3.11.

5-Chlorobenzo[*b*]thiophene (**10**).

a) By Decarboxylation of 5-Chlorobenzo[*b*]thiophene-2-carboxylic Acid.

To a solution of 5-chlorobenzo[*b*]thiophene-2-carboxylic acid [17] (1.00 g, 0.005 mol) in quinoline (50 mL) copper (0.40 g) was added. The reaction mixture was heated with magnetic stirring at 180-190 °C for half an hour and allowed to cool. It was then extracted with diethyl ether (3 x 50 mL) and the collected organic layers washed thoroughly with 6 *N* hydrochloric acid until the aqueous layer became nearly colorless. The organic phase was dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. No further purification was needed (18%).

b) By diazotization of 5-Aminobenzo[*b*]thiophene.

5-Aminobenzo[*b*]thiophene sulfate (**6**) (0.50 g, 3.30 x 10^{-3} mol) was dissolved in sulfuric acid (0.6 mL) and water (1.0 mL). The solution was cooled at 15 °C. Ice (1.60 g) was added and the solution cooled at 0-5 °C. A solution of sodium nitrite (0.14 g) in water (1.50 mL) at 0 °C was added slowly keeping the reaction temperature below 5 °C. After finishing the addition, a solution of copper(II)chloride (0.27 g) in water (2.7 mL) was added and the reaction stirred at room temperature for half an hour. The reaction was then refluxed for one hour. After cooling, it was poured over water and extracted with diethyl ether. The organic phase was washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product purified by chromatography using light petroleum as eluent (23%).

Cyclization of the Acetal with PPA.

A better yield of **10** was obtained by reaction of 4-chlorophenylthiooxyacetaldehyde diethyl acetal with a refluxing mixture of PPA and chlorobenzene as it has been described [2]. mp liquid. Yield: 80% [12] and 73% [2]; ^{1}H-nmr (deuteriochloroform): δ 7,26-7,32 (m, 2H, H_2+H_6); 7,50 (d, 1H, H_3, J = 5,4); 7,76-7,80 (m, 2H, H_4+H_7).

Anal. Calcd. for C_8H_5ClS: C, 56.97; H, 2.97. Found: C, 56.64; H, 3.06.

3-Acetyl-5-nitrobenzo[*b*]thiophene (**12**).

A solution of 5-nitrobenzo[*b*]thiophene (**3**) (1.00 g, 5.59 x 10^{-3} mol), acetic anhydride (5.0 mL) and iron trichloride (0.50 g) was refluxed for 24 hours. The same quantity of iron trichloride and acetic anhydride were then added and the reaction was refluxed for another 24 hours. The reaction was diluted with water (250 mL), filtered to remove inorganic salts, and extracted with ethyl acetate (2 x 40 mL). The organic layer was washed with diluted sodium hydrogen carbonate and water. The organic phase was dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The product was purified by chromatography using toluene as eluent (50%). mp 147 °C; ^{1}H-nmr (deuteriochloroform): δ 2,67 (s, 3H, CH_3); 7,95 (d, 1H, H_7); 8,26 (d, 1H, H_6); 8,42 (s, 1H, H_2); 9,62 (s, 1H, H_4)

Anal. Calcd. for $C_{10}H_7NO_3S$: C, 54.30; H, 3.18; N, 6.33. Found: C, 53.99; H, 3.43; N, 5.96.

3-Cloro-1-(5-nitrobenzo[*b*]thiophen-3-yl)-1-propanona (**13**).

To a solution of aluminium trichloride (0.65 g) in dry chloroform (20 mL) at room temperature a solution of 5-nitrobenzo[*b*]thiophene (**3**) (1.00 g, 5.59 x 10-3 mol) and 3-chloropropionyl chloride (0.65 mL, 6.64 x 10-3 mol) in chloroform (40 mL) was added drop by drop. After 24 hours of reaction at room temperature, the same quantities of aluminium trichloride and 3-chloropropionyl chloride were added. The reaction was allowed to react for another 48 hours, and after that cooled with an ice-salt bath. Then, 1.5 *N* hydrochloric acid (100 mL) was added drop by drop with efficient stirring. The organic layer was decanted and washed with diluted sodium hydrogen carbonate and water. The organic phase was dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The product was purified by chromatography using light petroleum/toluene (1:3) as eluent (30%). mp 128 °C; ^{1}H-nmr (deuteriochloroform): δ 3,51 (t, 2H, CH_2CO); 3,98 (t, 2H, CH_2Cl); 7,99 (d, 1H, H_7), 8.29 (dd, 1H, H_6); 8,49 (s, 1H, H_2); 9,64 (d, 1H, H_4).

Anal. Calcd. for $C_{11}H_8ClNO_3S$: C, 48.98; H, 2.97; N, 5.19. Found: C, 48.63; H, 2.81; N, 5.35.

3-Chloro-1-(5-methylbenzo[*b*]thiophen-3-yl)-1-propanone (**15**).

To a solution of aluminum trichloride (1.35 g) in dry chloroform (20 mL) cooled at 0 °C, a solution of 5-methylbenzo[*b*]thiophene (1.50 g, 0.010 mol) and 3-chloropropionyl chloride (0.9 mL, 0.010 mol) in dry chloroform (20 mL) was slowly added. The reaction mixture was allowed to react for 48 hours, and cooled. After cooling the reaction with an acetone-carbon dioxide bath, a solution of 96% sulfuric acid (0.8 mL) and water (12 mL) was slowly added. The organic layer was decanted and the aqueous layer extracted with dichlomethane. The collected organic phases were washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product purified by chromatography (light petroleum to light petroleum/toluene 9:1). Yield: 37%. mp 100-102 °C; ^{1}H-nmr (deuteriochloroform): δ 2.45 (s, 3H, CH_3); 3.41 (t, 2H, $COCH_2$); 3.90 (t, 2H, CH_2Cl); 7.21 (d, 1H, H_6, J = 8.2); 7.68 (d, 1H, H_7); 8.22 (s, 1H, H_2); 8.53 (s, 1H, H_4).

Anal. Calcd. for $C_{12}H_{11}ClOS$: C, 62.27; H, 4.39. Found: C, 62.11; H, 4.65.

1-(3-Benzo[*b*]thiophenyl)-3-chloro-1-propanone (**16**).

To a solution of aluminum trichloride (20.50 g, 0.14 mol) in dry chloroform (75 mL) cooled at 0 °C and in N_2 atmosphere, a solution of benzo[*b*]thiophene (18.78 g, 0.14 mol) and 3-chloropropionyl chloride (15.9 mL, 0.14 mol) in dry chloroform (75 mL) was added as such rate that the addition was completed after 2 hours. The reaction mixture was allowed to react for 24 hours, and then refluxed for one hour. The reaction was cooled with an acetone-carbon dioxide bath and a solution of 96% sulphuric acid (9.5 mL) and water (150 mL) was slowly added. The organic layer was decanted, washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated

under reduced pressure and the product purified by flash chromatography (light petroleum to light petroleum/ethyl acetate 95:5). Yield: 40%. mp 55-57 °C ^{1}H-nmr (deuteriochloroform): δ 3,43 (t, 2H, CH_2CO); 3,87 (t, 2H, CH_2Cl); 7,32-7,48 (m, 2H, H_5+H_6), 7,80 (d, 1H, H_4, *J*= 7,6); 8,24 (s, 1H, H_2); 8,47 (d, 1H, H_7).

Anal. Calcd. for $C_{11}H_9ClOS$: C, 58.80; H, 4.01. Found: C, 59.01; H, 3.93.

1-(3-Benzo[*b*]thiophenyl)-4-chloro-1-butanone (**17**).

To a solution of aluminium trichloride (10.00 g, 0.075 mol) in dry chloroform (40 mL) cooled at 0 °C and in N_2 atmosphere, a solution of benzo[*b*]thiophene (10.00 g, 0.075 mol) and 4-chlorobutanoyl chloride (10.5 mL, 0.075 mol) in dry chloroform (40 mL) was slowly added. The reaction mixture was allowed to react for 24 hours, and then refluxed for one hour. The reaction was cooled with an acetone-carbon dioxide bath and a solution of 96% sulphuric acid (4.75 mL) and water (80 mL) was slowly added. The organic layer was decanted, washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product purified by recrystallisation from light petroleum (27%). The product was characterized as an oil. ^{1}H-nmr (deuteriochloroform): δ 2.22 (q, 2H, CH_2CH_2Cl); 3.13 (t, 2H, $COCH_2$); 3.66 (t, 2H, CH_2Cl); 7.34-7.51 (m, 2H, H_5+H_6); 7.83 (d, 1H, H_7, *J* = 8.0); 8.25 (s, 1H, H_2); 8.74 (d, 1H, H_4).

1-(5-Acetoxybenzo[*b*]thiophen-3-yl)-3-chloro-1-propanone (**19**).

To a solution of aluminium trichloride (1.20 g) in chloroform (35 mL) cooled at 0 °C a solution of 5-actoxybenzo[*b*]thiophene (**4**) (1.70 g, 8.85 x 10^{-3} mol)and 3-chloropropionyl chloride (1.12 g, 8.85 x 10^{-3} mol) in chloroform (60 mL) was added drop by drop. The reaction was stirred at room temperature for 24 hours. Monitoring the reaction with TLC (toluene) showed unreacted benzo[*b*]thiophene, so the reaction mixture was refluxed for one hour and then allowed to cool. After cooling the reaction with an ice-salt bath, a solution of 96% sulphuric acid (0.5 mL) and water (7.5 mL) was slowly added drop by drop. The organic layer was decanted, and the aqueous layer extracted with dichloromethane. The collected organic phases were washed with diluted sodium hydrogen carbonate and water. The organic phase was dried with anhydrous sodium sulfate and the solvent evaporated under reduced pressure. The product was purified by chromatography using toluene as eluent (38%). mp 84 °C; ^{1}H-nmr (deuteriochloroform): δ 2.35 (s, 3H, CH_3); 3.47 (t, 2H, CH_2CO); 3.96 (t, 2H, CH_2Cl); 7.18 (dd, 1H, J_{67} = 8.6 and J_{46} = 1.8); 7.84 (d, 1H, H_6); 8.35 (s, 1H, H_2); 8.48 (d, 1H, H_4)

Anal. Calcd. for $C_{13}H_{11}ClO_3S$: C, 55.22; H, 3.89. Found: C, 55.49; H, 3.81.

4-Chloro-1-(5-fluorobenzo[*b*]thiophen-3-yl)-1-butanone (**22**).

To a solution of aluminium trichloride (2.05 g, 0.015 mol) in dry chloroform (7.5 mL) cooled at 0 °C and in N_2 atmosphere, a solution of 5-fluorobenzo[*b*]thiophene (2.30 g, 0.015 mol) and 4-chlorobutanoyl chloride (1.7 mL, 0.015 mol) in dry chloroform (7.5 mL) was slowly added. The reaction mixture was allowed to react for 24 hours. The reaction was cooled with an acetone-carbon dioxide bath and a solution of 96% sulphuric acid (1 mL) and water (15 mL) was slowly added. The organic layer was decanted, washed with water and dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product purified by recrystallisation from light petroleum (39%). ^{1}H-nmr (deuteriochloroform): δ 2.23 (q, 2H, $COCH_2CH_2$); 3.16 (t, 2H, $COCH_2$); 3.67 (t, 2H, CH_2Cl); 7.10-7.20 (m, 1H, H_6); 7.74 (dd, 1H, H_7, J_{67} = 9.0, J_{F7} = 4.8); 8.37 (s, 1H, H_2); 8.43 (dd, 1H, H_4, J_{F4} = 10.4, J_{46} = 2.6).

Anal. Calcd. for $C_{12}H_{10}ClFOS$: C, 56.14; H, 3.90. Found: C, 56.49; H, 4.19.

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REFERENCES AND NOTES

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