A CONVENIENT SYNTHESIS OF 3(2)-TRIFLUOROACETYLAMINOBENZO-[b]THIOPHENES AND THIOPHENES AND SOME OF THEIR IODO DERIVATIVES

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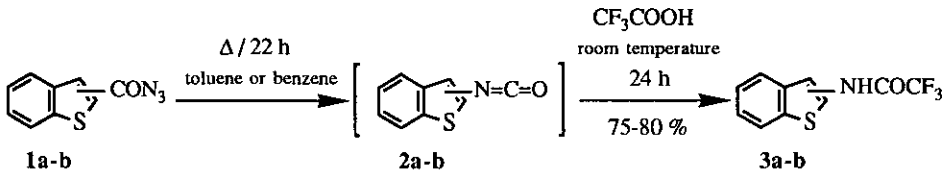
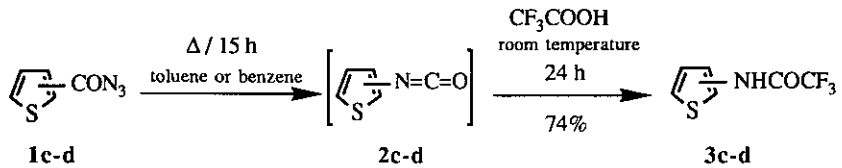
Abstract- Trifluoroacetylamino derivatives of benzo[b]thiophene and thiophene (**3a-d**) have been obtained by Curtius rearrangement of the corresponding acyl azides (**1a-d**) with trifluoroacetic acid. The iodination of these amide derivatives with iodine under mild conditions leads to iodinated products in excellent yield, except in the case of the 3-trifluoroacetylaminobenzo[b]thiophene (**3a**), which only gives a polymeric residue.

As part of our research program[1] directed toward the development of methodologies suitable for the preparation of polycyclic heteroaromatic compounds, we required a method to introduce iodine in the α-position to the amide group of a thiophene ring. Moreover, it is well known that the 3(2)-aminothiophene and 3(2)-aminobenzo[b]thiophene are labile.[2] A solution to this problem requires the direct generation of the amide functionality. We have previously described the preparation of the tert-butyl carbamates of thiophene and benzo[b]thiophene by Curtius rearrangement of the corresponding acyl azides in tert-butyl alcohol under reflux,[3] and studied their halogenation[3] and their reactivity as dianions toward bis-electrophilic reagents.[1] Also we have shown that a Curtius rearrangement reaction can be used for the synthesis of 2-trifluoroacetylaminothiophene (**3d**).[1]

We now report on the extension of this method to the preparation of 3(2)-trifluoroacetylaminobenzo[b]thiophenes (**3a**) and (**3b**), and 3-trifluoroacetylaminothiophene (**3c**). These amide derivatives of thiophene and benzo[b]thiophene and the corresponding iodinated products are potential starting materials to obtain thieno- and benzo[b]thienoindole derivatives either via a $S_{RN}1$ process, as we have previously described for 3-amino-2-chloropyridine,[4] or via their reactivity as organodimetallic reagents as we have previously reported for the tert-butyl carbamate analogs and for the amide (**3d**).[1]

Thus, the amide derivatives (**3a-d**) are synthesized by heating the acyl azides (**1a-d**) in anhydrous benzene or toluene to avoid the formation of urea derivatives in the Curtius rearrangement. Treatment of the isocyanate derivatives (**2a-d**) formed with trifluoroacetic acid at room temperature gives the desired 3(2)-trifluoroacetylamino compounds (**3a-d**) in ca. 75-80 % yield (Table I, Scheme 1). It is interesting to point out that the yield of **3d** increases from a 60%[1] to a 74% only by changing the solvent (toluene to benzene).



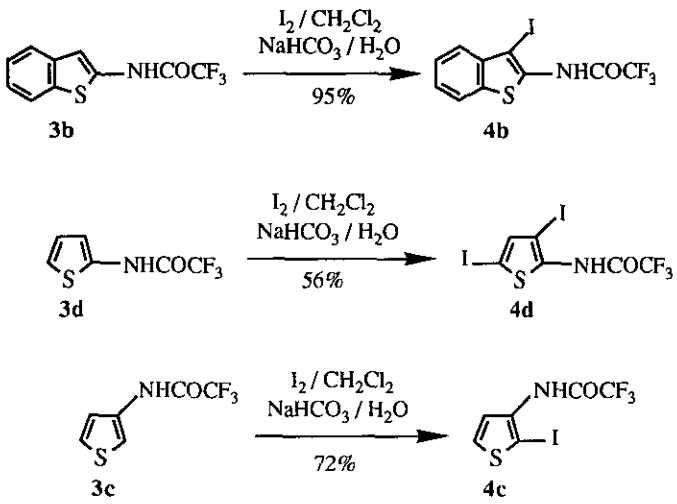


Scheme 1

Thiophene and benzo[b]thiophene derivatives can generally be iodinated by direct methods with iodine in the presence of, most commonly, an oxidizing agent,[5] and by indirect methods that include initial thallation,[6] mercuration,[7] or diazotization.[8] Some of these methods suffer from several disadvantages (potential side reactions such as oxidation of the substrate, the severe toxicity of thallium compounds, etc.). All halogenations of aminothiophenes and their derivatives are routinely carried out on N-protected derivatives.[9] Direct iodinations are relatively rare,[9] and the preferred method is normally mercuration followed by replacement with iodine.[10] Iodine monochloride[11] and N-iodosuccinimide[12] have been used occasionally as reagents with tendency to generate iodonium ions to iodinate some N-protected derivatives of thiophene. Noteworthy, Yang and coworkers have reported the preparation of thiophene iodocarbamates from iodothiophenecarboxylic acids via a modified Curtius reaction.[13]

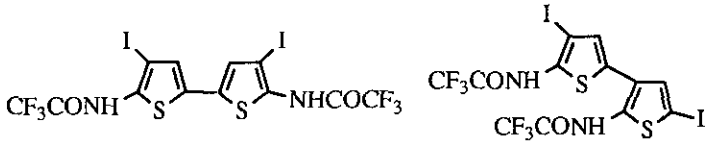
In this work, we have carried out the iodination of compounds (**3b-d**) with good yields by a simple procedure, using a modified method previously described for aniline.[14] This procedure consist on adding a solution of iodine in dichloromethane to a heterogeneous mixture formed by a solution of the amide derivative in dichloromethane and a saturated aqueous solution of sodium bicarbonate. When this treatment was applied to 3-trifluoroacetylaminobenzo[b]thiophene (**3a**) only an unidentified polymeric material was obtained. The results are summarized in Table II. It is interesting to remark that the formation of the iodo compound (**4c**) in 72% yield

was only achieved using a large excess of iodine (molar ratio substrate/iodine, 1:2). On the other hand, when we tried to monoiodinate the compound (**3d**) using a molar ratio substrate/iodine 1:1, the presence of the starting material and the diiodinated product (**4d**) could only be detected (tlc). The reaction was completed when we added a second mole of iodine to give the diiodinated compound (**4d**) in 56% yield (Scheme 2).



Scheme 2

Finally, we have observed that the modification of reaction conditions alters considerably the results of the reaction. Remarkably, when we carried out the same reaction using a concentration of iodine and substrate four times higher at room temperature, only traces of the diiodinated compound (**4d**) was found along with a 30% yield of dimeric compounds (**5**) and (**6**), and a large amount of untractable tarry material.



In conclusion, we have demonstrated that the present method provides a convenient direct route to obtain the amide and iodoamide derivatives of benzo[b]thiophene and thiophene (**3a-d**) and (**4b-d**), taking into account the reactivity of these systems[9,15] and the known lability of their 2- and 3-amino derivatives.[2]

Table 1. Trifluoroacetylaminoderivatives of benzo[b]thiophene and thiophene.

Product	Time (h)	Solvent	Yield (%)	mp (°C)	Ir (KBr) ν (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) δ (ppm), *J* (Hz)	^{13}C-Nmr ($CDCl_3$/TMS) δ (ppm), *J* (Hz)	Ms (70 eV) m/z (%)
3a	22	Toluene	80	101-103	3290, 1700	7.34 (m, 2 H_{arom}), 7.51 (m, 1 H_{arom}), 7.77 (m, 1 H_{arom}), 7.86 (s, 1 H_{arom}), 8.32 (br s, 1 H, NH)	115.9 (CF_3, *J* = 288), 116.1, 118.6, 123.4, 124.6, 125.4 (CH_{arom}), 131.8, 138.0 (C_{arom}), 154.9 (CO, *J* = 38)	245 (M^+, 68), 148 (100), 121 (90)
3b	22	Benzene	74	184-186	3250, 1730, 1695	7.22 (m, 1 H_{arom}), 7.36 (m, 2 H_{arom}), 7.70 (m, 1 H_{arom}), 7.79 (m, 1 H_{arom}), 8.80 (br s, 1 H, NH)	111.8 (CH_{arom}), 115.6 (CF_3, *J* = 287), 122.1, 123.1, 124.5, 125.0 (CH_{arom}), 135.6, 135.7 136.9 (C_{arom}), 154.0 (CO, *J* = 38)	245 (M^+, 43), 148 (34), 121 (100)
3c	15	Toluene	73	105-107	3300, 1705	7.11 (dd, $J_{4,5}$ = 5.2, $J_{4,2}$ = 1.4 1 H_{arom}, H_4), 7.33 (dd, $J_{5,4}$ = 5.2, $J_{5,2}$ = 3.3, 1 H_{arom}, H_5) 7.69 (dd, $J_{2,5}$ = 3.2, $J_{2,4}$ = 1.4, 1 H_{arom}, H_2), 8.42 (br s, 1 H, NH)	113.4 (CH_{arom}), 115.9 (CF_3 *J* = 288), 121.1, 125.6 (CH_{arom}), 132.7 (C_{arom}), 154.6 (CO, *J* = 38)	195 (M^+, 78), 98 (100), 69 (98)
3d	15	Benzene	74	115-117	3260, 1690	6.94 (m, 2 H_{arom}), 7.07 (m, 1 H_{arom}), 8.97 (br s, 1 H, NH)	115.7 (CF_3, *J* = 287), 116.0, 120.4, 124.7 (CH_{arom}), 135.6 (C_{arom}), 153.8 (CO, *J* = 38)	195 (M^+, 56), 98 (76), 69 (100)

Table II. Iodotrifluoroacetylaminoderivatives of benzo[b]thiophene and thiophene.

Product	Time (h)	Temp. (°C)	Yield (%)	mp (°C)	Ir (KBr) ν (cm^{-1})	^{1}H-Nmr ($CDCl_3$/TMS) δ (ppm), *J* (Hz)	Ms (70 eV) m/z (%)
4b	3	5	95	119-121	3330, 1725	7.44 (m, 2 H_{arom}), 7.67(m, 1 H_{arom}), 7.77 (m, 1 H_{arom}), 8.73 (br s, 1 H, NH)	371 (M^+, 100), 274 (29), 244 (61), 146 (47), 69 (78)
4c	115	25	72	96-98	3280, 1705	7.57 (d, *J* = 5.9, 1 H_{arom}), 7.65 (d, *J* = 5.8, 1 H_{arom}), 7.97 (br s, 1 H, NH)	321 (M^+, 14), 224 (39), 194 (100), 174 (43), 127 (61), 69 (71)
4d	42	25	56	108-110	3250, 1710	7.10 (s, 1 H_{arom}), 8.50 (br s, 1 H, NH)	447 (M^+, 45), 350 (37), 320 (43), 223 (60), 127 (45), 69 (100)

EXPERIMENTAL SECTION

Melting points were determined on a Büchi apparatus and are uncorrected. Elemental analyses were performed by the C.S.I.C. (Barcelona) Micro-Analysis Laboratory. Ir spectra were recorded on a Perkin-Elmer 681 Infrared spectrophotometer. Nmr spectra were recorded using a Varian XL 200 spectrometer (^{1}H: 200 MHz; ^{13}C: 50.3 MHz). As internal standards, TMS (δ = 0.0) was used for ^{1}H-nmr spectra, and the solvent signal ($CDCl_3$, δ = 77.0) for ^{13}C-nmr spectra. The assignments of ^{13}C chemical shifts were made with the aid of distortionless enhancement by polarization transfer (DEPT) sequence. Ms spectra were obtained on a Hewlett-Packard 5988-A spectrometer.

3-Azidocarbonylbenzo[b]thiophene (**1a**),[3] 2-azidocarbonylbenzo[b]thiophene (**1b**),[16] 3-azidocarbonylthiophene (**1c**),[17] and 2-azidocarbonylthiophene (**1d**)[18] were prepared by treatment of the corresponding carboxylic acids with ethyl chloroformate and triethylamine followed by reaction of the resulting mixed anhydride with sodium azide, according to a general method devised by Weinstock.[19]

Trifluoroacetylaminoderivatives of benzo[b]thiophene and thiophene (3a-d); General Procedure. In a dried, nitrogen-filled round-bottomed flask fitted with a stirrer, addition funnel and Dimroth reflux condenser, a solution of the appropriate acyl azide (**1a-d**) (0.03 mol) in anhydrous benzene or toluene (225 ml) was heated under reflux for 15-24 h (see Table I). After cooling at room temperature, trifluoroacetic acid (5.70 g, 0.05 mol) was added all at once. The mixture was stirred at room temperature for 24 h, then quenched with a saturated solution of $NaHCO_3$ (100 ml). The organic layer was washed with H_2O (3 × 25 ml) and dried ($MgSO_4$). The solvent was evaporated and the residue was recrystallized from n-hexane/dichloromethane to give the desired product. The results are summarized in Table I.

3-Trifluoroacetylaminobenzo[b]thiophene (**3a**). Anal. Calcd for $C_{10}H_6NOF_3S$: C, 48.98; H, 2.47; N, 5.71; S, 13.08. Found: C, 48.78; H, 2.57; N, 5.81; S, 13.23.

2-Trifluoroacetylaminobenzo[b]thiophene (**3b**). Anal. Calcd for $C_{10}H_6NOF_3S$: C, 48.98; H, 2.47; N, 5.71; S, 13.08. Found: C, 48.80; H, 2.52; N, 5.76; S, 13.18.

3-Trifluoroacetylaminothiophene (**3c**). Anal. Calcd for $C_6H_4NOF_3S$: C, 36.92; H, 2.07; N, 7.18; S, 16.42. Found: C, 37.12; H, 2.02; N, 7.33; S, 16.32.

3-Iodo-2-trifluoroacetylaminobenzo[b]thiophene (4b). To a solution of **3b** (1.00 g, 4.08 mmol) in CH_2Cl_2 (5 ml) was added all at once a solution of $NaHCO_3$ (0.83 g, 9.88 mmol) in H_2O (30 ml). The mixture was then cooled to 5 °C and iodine (1.40 g, 5.52 mmol) in CH_2Cl_2 (25 ml) was added dropwise. The reaction mixture is maintained at 5 °C for 3 h. The organic layer was washed with 10% $NaHSO_3$ (3 × 10 ml) and H_2O (3 × 10 ml), dried ($MgSO_4$), and concentrated at reduced pressure to a solid. This crude product was chromatographed on a silica gel column (20 cm × 4 cm; 230-400 mesh) using CH_2Cl_2 as the eluant to yield the desired product **4b** (1.44 g, 95%) (Table II). Anal. Calcd for $C_{10}H_5NOF_3IS$: C, 32.37; H, 1.36; N, 3.77; S, 8.64.

Found: C, 32.12; H, 1.48; N, 3.89; S, 8.54.

2-Iodo-3-trifluoroacetylaminothiophene (4c). To a mixture of **3c** (0.20 g, 1.02 mmol) and $NaHCO_3$ (0.19 g, 2.30 mmol) in H_2O (10 ml) at 5 °C, was added dropwise a solution of iodine (0.32 g, 1.26 mmol) in CH_2Cl_2 (20 ml). After stirring the mixture for 15 h at room temperature, the reaction was not still complete (tlc on silica gel using CH_2Cl_2 as the eluant). Then, $NaHCO_3$ (0.12 g, 1.43 mmol) in H_2O (20 ml) and iodine (0.20 g, 0.79 mmol) in CH_2Cl_2 (20 ml) were added at room temperature. After stirring the mixture for 100 h, the usual workup afforded a crude material which was recrystallized from n-hexane to give the product **4c** (0.23 g, 72%) (Table II). Anal. Calcd for $C_6H_3NOF_3IS$: C, 22.44; H, 0.94; N, 4.36; S, 9.98. Found: C, 22.19; H, 1.04; N, 4.41; S, 10.08.

2,4-Diiodo-5-trifluoroacetylaminothiophene (4d). Procedure A. To a solution of **3d** (0.10 g, 0.52 mmol) in CH_2Cl_2 (3 ml) was added all at once a solution of $NaHCO_3$ (0.09 g, 1.02 mmol) in H_2O (20 ml). The mixture was cooled to 5 °C and a solution of iodine (0.13 g, 0.52 mmol) in CH_2Cl_2 (20 ml) was added dropwise. After stirring the mixture for 15 h at room temperature, the reaction was not complete (tlc on silica gel using CH_2Cl_2 as the eluant). Then, $NaHCO_3$ (0.09 g, 1.05 mmol) in H_2O (15 ml) and iodine (0.13 g, 0.52 mmol) in CH_2Cl_2 (15 ml) were added. After stirring the mixture for 27 h at room temperature, the usual workup afforded a crude material which was recrystallized from n-hexane to give the product **4d** (0.13 g, 56%) (Table II). Anal. Calcd for $C_6H_2NOF_3I_2S$: C, 16.12; H, 0.45; N, 3.13; S, 7.17. Found: C, 15.92; H, 0.55; N, 3.33; S, 7.07.

Procedure B. To a solution of **3d** (0.50 g, 2.56 mmol) in CH_2Cl_2 (4 ml) was added all at once a solution of $NaHCO_3$ (0.55 g, 6.52 mmol) in water (12 ml). Then, a solution of iodine (0.78 g, 3.08 mmol) in CH_2Cl_2 (30 ml) was added dropwise at room temperature. After stirring the resulting mixture for 6 h, $NaHCO_3$ (0.55g, 6.55 mmol) in water (12 ml) and iodine (0.79 g, 3.09 mmol) in CH_2Cl_2 (35 ml) were added. After stirring the mixture for 17 h the usual workup gave 400 mg of a crude material that was purified by flash chromatography (silica gel, CH_2Cl_2) to yield trace amounts of diiodinated compound **4d**, 75 mg (9%) of **5**, and 174 mg (21%) of **6**.

(2,2'-Bithienyl)-4,4'-diiodo-5,5'-ditrifluoroacetamide (**5**). mp 223-225 °C; ^{1}H-nmr (Acetone-d_6) δ: 10.30 (1 H, br s, NH), 7.35 (1 H, s, H_{arom}); ir (KBr) ν: 3370, 3070, 1710 cm^{-1}; ms, m/z (relative intensity): 640 (M^+, 23), 639 (40), 69 (100). Anal. Calcd for $C_{12}H_4N_2O_2F_6I_2S_2$: C, 22.52; H, 0.63; N, 4.38; S, 10.02. Found: C, 22.30; H, 0.70; N, 4.48; S, 10.17.

(2,3'-Bithienyl)-4,5'-diiodo-5,2'-ditrifluoroacetamide (**6**). mp 189-191 °C; ^{1}H-nmr (Acetone-d_6) δ: 10.85 (1 H, br s, NH), 10.35 (1 H, br s, NH), 7.56 (1 H, s, H_{arom}), 7.40 (1 H, s, H_{arom}); ir (KBr) ν: 3250, 3100, 1725, 1710 cm^{-1}; ms, m/z (relative intensity): 640 (M^+, 84), 69 (100). Anal. Calcd for $C_{12}H_4N_2O_2F_6I_2S_2$: C, 22.52; H, 0.63; N, 4.38; S, 10.02. Found: C, 22.27; H, 0.55; N, 4.30; S, 10.17.

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