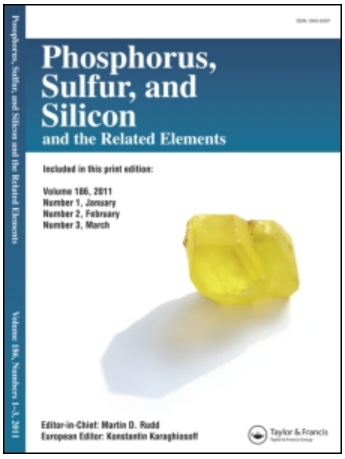

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PREPARATION OF 2-(2-PYRIDYL)-3-MORPHOLINO-2,3-DIHYDROBENZO[b] THIOPHENE 1,1-DIOXIDE-6-SULFONYLMORPHOLIDATE FROM THE REACTION OF 2-STYRYLPYRIDINE WITH CHLOROSULFONIC ACID

Jatinder P. Bassin[a]; Richard J. Cremlyn[b]; Stephen Graham[b]
[a] Department of Chemistry, American University of Beirut, Beirut, Lebanon [b] Division of Chemical Sciences, University of Hertfordshire, Hatfield, Hertfordshire, England

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PREPARATION OF 2-(2-PYRIDYL)-3-MORPHOLINO-2,3-DIHYDROBENZO[b] THIOPHENE 1,1-DIOXIDE-6-SULFONYLMORPHOLIDATE FROM THE REACTION OF 2-STYRYLPYRIDINE WITH CHLOROSULFONIC ACID

JATINDER P. BASSIN[a], RICHARD J. CREMLYN[b] and STEPHEN GRAHAM[b*]

[a]*Department of Chemistry, American University of Beirut, Beirut, Lebanon and* [b]*Division of Chemical Sciences, University of Hertfordshire, Hatfield, Hertfordshire AL10 9AB, England*

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Styrylpyridine (**1**) reacted with chlorosulfonic acid (6 mole equivalents) and excess thionyl chloride to the give the corresponding *para* sulfonyl chloride, which was characterized as the *N,N*-dimethyl sulfonamide. The pyridine ring appeared to deactivate the double bond sufficiently to inhibit the substrate degradation observed previously with analogous hydrocarbon systems. The reaction of styrylpyridine (**1**) with chlorosulfonic acid, (12 mole equivalents, 24 hour reflux) under more forcing conditions, caused a further cyclisation of the substrate which was characterized as 2-(2-Pyridyl-)3-morpholino-2,3-dihydrobenzo[b]thiophene 1,1-dioxide-6-sulfonylmorpholidate (**3**) by reaction with excess morpholine.

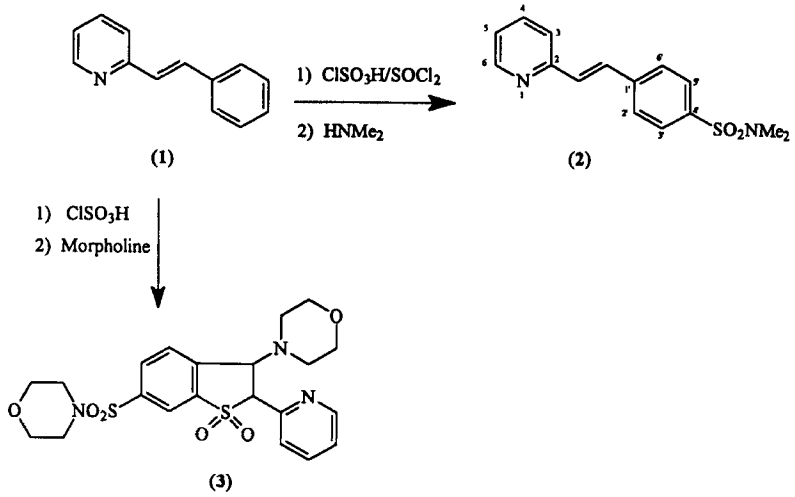
Keywords: 2-Styrylpyridine; chlorosulfonic acid; 2,3-dihydrobenzo[b]thiophene

The work described in this paper forms part of our on going program concerned with the chemistry of sulfonyl derivatives[1–3]. In particular the chorosulfonation of 2-styrylbenzothiazole and related compounds[4]. Preparation of 2,3-dihydrobenzo[b]thiophene has been well documented in the literature[5,6]. The introduction of a pyridyl group into thiophene or benzothiophene by lithiation, using thienyllithium[7] and 2-benzo[b]thienyllithium[8] with 2-halopyridines to give the respective 2-pyridyl derivatives has been reported. Synthesis of 2 (4-pyridyl) benzo[b]thiophene by the

* Correspondence Author.

classical Hantzsch method using benzo[b]thiophene-2-carboxaldehyde has also been described[9]. We now report a simple, convenient synthesis of 2-(2-pyridyl) substitution in the 2,3-dihydroben[b]thiophene moiety.

Previous studies[10] have shown 1,1-diarylpropenes stirred at room temperature with concentrated sulfuric acid to yield substituted benzo[b]thiophene 1,1-dioxides. However, in the current work, reaction of 1,1-diphenylpropene and stilbene with chlorosulfonic acid gave unidentifiable products, probably due to polymerization. We then decided to investigate the reaction of styrylpyridine **1** with chlorosulfonic acid in the hope that the pyridine ring, under these highly acidic conditions, would deactivate the double bond sufficiently to inhibit polymerization. The reaction of **1** with chlorosulfonic acid under relatively mild conditions (chlorosulfonic acid 6 mole equivalents) in the presence of thionyl chloride afforded the predicted para-sulfonated product **2**, after treatment of the initial sulfonyl chloride with dimethylamine. ^{1}H and ^{13}C NMR spectra of **2** showed the alkenic protons (resonances at δ 7.25 and δ7.43), the methyl protons appeared at δ 2.73. The aliphatic/aromatic ratio of (6:10) was observed. The mass spectrum showed the M^{+}ion (288) and there was no indication of polymeric material (no higher mass ion).



SCHEME 1

Under more forcing conditions (24 hour reflux) we expected to isolate the 2,4-disulfonated product. However, under these conditions a gum was

obtained which was directly treated with morpholine to yield 2-(2-pyridyl)-3-morpholino-2,3-dihydrobenzo[b]thiophene 1, 1-dioxide-6-sulphonylmorpholidate **3** (Scheme 1). It was surprising that even under these forcing conditions polymerization of the styryl pyridine **1** was not observed, indicative of the stabilizing effect of the 2-pyridyl moiety on the double bond. The ^{1}H NMR spectrum of **3** indicated an absence of the signals corresponding to the alkenic protons, however, doublets were observed at δ 5.7 and δ 5.0 (J, 7.0 Hz) due to the protons in the 2 and 3 positions of the benzo[b]thiophene moiety. The structure of compound **3**was fully confirmed by an X-ray analysis. Figure 1 shows a prospective view and atom labeling of the crystal structure. Table I shows the refinement data, Table II gives the atomic coordinates and Table III summarizes the bond lengths and angles for compound **3**.

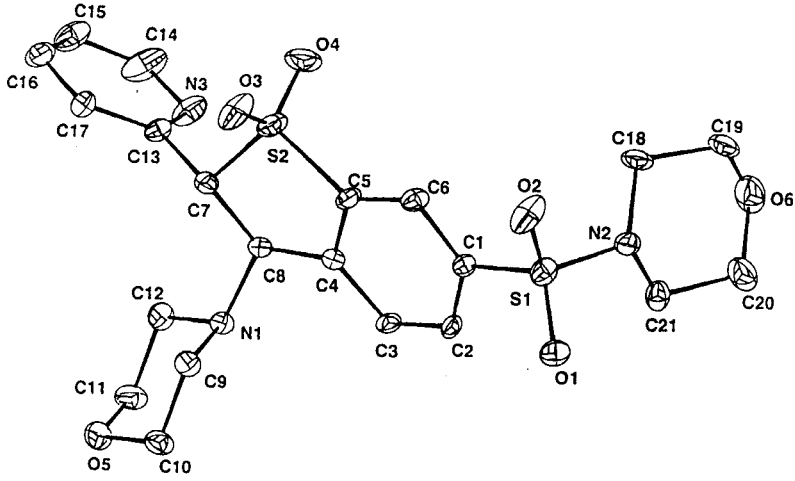


FIGURE 1

The postulated mechanism of the conversion of **1** to **3** is shown in scheme 2. The initial step is considered to involve both N-sulfonation of pyridyl nitrogen atom and para-sulfonation of the phenyl ring (step 1). This is followed by rearrangement of the N-sulfonyl moiety initiated by chlorine anion attack on the alkenic double bond (step 2) and chlorination to the bis-sulfonyl chloride. The latter suffers cyclisation to eventually yield compound **3** after treatment with morpholine.

TABLE I Crystal and Structure Refinement Data for compound **3**

Empirical formula	$C_{21}H_{25}N_3O_6S_2$
Formula weight	479.56
Temperature	150(2) K
Wavelength	0.71069 Å
Crystal system	monoclinic
Space group	P2(l)/n
Unit cell dimension	a = 8.7843(6) Å
	b = 10.8813(7) Å
	c = 24.008(6) Å
Volume	β = 95.933(7) deg. 2282.5(6) $Å^3$
Z	4
Density (calculated)	1.396 g/cm^3
μ	0.276 mm^{-1}
F(000)	1008
Crystal size	0.24 × 0.22 × 0.22 mm
θ range	2.06 to 25.09 deg
Index ranges	-10<=h<=8, −12<=k<=12, −26<=1<=26,
Reflections collected	9010
Independent reflections	3481 [R(int) =0.0795]
Refinement method	Full-matrix least-square on F^2
Data/ restraints/ parameters	3481 / 0 / 289
Goodness-of-fit on F^2	0.689
Final R indices [I>2sigma (I)]	R1 = 0.0455, wR2 = 0.0927
R indices (all data)	R1 = 0,1286, wR = 0,1038
Largest diff. peak and hole	0.466 and −0.239 e.$Å^{-3}$

Experimental

Melting points were determined using a Gallenkamp electric apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer as potassium bromide pellets and frequencies expressed in cm^{-1}. The NMR spectra were recorded with a Brucker AC250 spectrometer using tetramethylsilane as internal standard and deuterochloroform as solvent. El mass spectra were obtained with a VG micromass V15 spectrometer operating at 70 ev.

2-Styrylpyridine was prepared by the reported literature method[11]

TABLE II Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for compound **3**. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	X	*Y*	*Z*	*U(eq)*
S(1)	1435(1)	2969(1)	5884(1)	32(1)
S(2)	5931(1)	2915(1)	4439(1)	38(1)
N(1)	3100(4)	4671(3)	3297(2)	23(1)
N(2)	577(4)	1650(3)	5906(2)	29(1)
N(3)	6006(4)	2222(4)	3052(2)	46(1)
O(1)	310(3)	3893(3)	5941(1)	37(1)
0(2)	2772(3)	2910(3)	6279(1)	51(1)
0(3)	7011(3)	3622(3)	4816(2)	54(1)
0(4)	6230(4)	1648(3)	4365(2)	59(1)
O(5)	2924(3)	6873(3)	2648(1)	40(1)
0(6)	-827(5)	-665(3)	5729(2)	66(1)
C(1)	2058(5)	3134(4)	5214(2)	24(1)
C(2)	1057(5)	3539(4)	4768(2)	26(1)
C(3)	1559(5)	3703(4)	4251(2)	26(1)
C(4)	3072(5)	3485(4)	4161(2)	23(1)
C(5)	4053(5)	3079(4)	4618(2)	27(1)
C(6)	3568(5)	2895(4)	5148(2)	29(1)
C(7)	5544(5)	3690(4)	3772(2)	25(1)
C(8)	3786(5)	3634(4)	3622(2)	24(1)
C(9)	3351(5)	5887(4)	3552(2)	30(1)
C(10)	2459(5)	6828(4)	3206(2)	37(1)
C(11)	2666(5)	5706(4)	2393(2)	38(1)
C(12)	3548(5)	4709(4)	2721(2)	34(1)
C(13)	6535(5)	3191(4)	3350(2)	27(1)
C(14)	6901(6)	1786(5)	2666(2)	58(2)
C(15)	8299(6)	2244(5)	2588(2)	48(2)
C(16)	8850(5)	3227(5)	2904(2)	42(2)
C(17)	7930(5)	3727(4)	3289(2)	30(1)
C(18)	1495(6)	534(4)	5915(2)	47(2)
C(19)	524(6)	-531(5)	6085(3)	58(2)
C(20)	-1700(6)	398(4)	5737(2)	50(2)
C(21)	-859(5)	1511(4)	5550(2)	33(1)

TABLE III Bond lengths (Å) and angles (deg) for compound **3**

S(1)-O(1)	1.426(3)		S(1)-O(2)	1.434(3)	
S(1)-N(2)	1.625(4)		S(1)-C(1)	1.760(4)	
S(2)-O(4)	1.419(3)		S(2)-O(3)	1.460(3)	
S(2)-C(5)	1.756(4)		S(2)-C(7)	1.812(4)	
N(1)-C(8)	1.465(5)		N(1)-C(9)	1.465(5)	
N(1)-C(12)	1.475(5)		N(2)-C(21)	1.456(5)	
N(2)-C(18)	1.457(5)		N(3)-C(13)	1.330(5)	
N(3)-C(14)	1.363(6)		O(5)-C(11)	1.417(5)	
O(5)-C(10)	1.441(5)		O(6)-C(20)	1.389(5)	
O(6)-C(19)	1.395(6)		C(1)-C(6)	1.377(5)	
C(1)-C(2)	1.386(6)		C(2)-C(3)	1.370(6)	
C(3)-C(4)	1.389(5)		C(4)-C(5)	1.395(6)	
C(4)-C(8)	1.506(6)		C(5)-C(6)	1.398(6)	
C(7)-C(13)	1.503(6)		C(7)-C(8)	1.550(5)	
C(9)-C(10)	1.489(6)		C(11)-C(12)	1.508(6)	
C(13)-C(17)	1.379(5)		C(14)-C(15)	1.355(6)	
C(15)-C(16)	1.370(6)		C(16) C(17)	1.399(6)	
C(18)-C(19)	1.520(6)		C(20)-C(21)	1.511(6)	
O(1)-S(1)-O(2)		119.7(2)	O(1)-S(1)-N(2)		106.9(2)
O(2)-S(1)-N(2)		106.8(2)	O(1)-S(1)-C(1)		107.5(2)
O(2)-S(1)-C(1)		107.4(2)	N(2)-S(1)-C(1)		108.0(2)
0(4)-S(2) –0(3)		118.2(2)	0(4)-S(2) -C(5)		108.7(2)
0(3)-S(2)-C(5)		111.2(2)	0(4)-S(2)-C(7)		111.2(2)
0(3)-S(2) -C(7)		110.7(2)	C(5)-S(2)-C(7)		94.2(2)
C(8)-N(1)-C(9)		115.9(4)	C(8)-N(1)-C(12)		112.6(3)
C(9)-N(1)-C(12)		108.9(3)	C(21)-N(2)-C(18)		111.5(4)
C(21)-N(2)-S(1)		116.7(3)	C(18)-N(2)-S(1)		118.6(3)
C(13)-N(3)-C(14)		116.6(4)	C(11)-O(5)-C(10)		108.8(3)
C(20)-0(6)-C(19)		109.9(4)	C(6)-C(1)-C(2)		120.9(4)
C(6)-C(1)-S(1)		118.7(4)	C(2)-C(1)-S(1)		120.4(3)
C(3)-C(2) -C(1)		120.2(4)	C(2)-C(3)-C(4)		121.4(5)
C(3)-C(4)-C(5)		117.1(4)	C(3)-C(4)-C(8)		127.3(4)
C(5)-C(4)-C(8)		115.6(4)	C(4)-C(5)-C(6)		122.7(4)
C(4)-C(5)-S(2)		111.1(3)	C(6)-C(5)-S(2)		126.2(4)

C(1)-C(6)-C(5)	117.7(4)	C(13)-C(7)-C(8)	117.5(4)
C(13)-C(7)-S(2)	111.0(3)	C(8)-C(7)-S(2)	106.2(3)
N(1)-C(8)-C(4)	110.8(3)	N(1)-C(8)-C(7)	116.0(3)
C(4)-C(8)-C(7)	107.3(4)	N(1)-C(9)-C(10)	109.9(4)
O(5)-C(10)-C(9)	111.0(4)	0(5)-C(11)-C(12)	111.6(4)
N(1)-C(12)-C(11)	109.7(4)	N(3)-C(13)-C(17)	122.9(4)
N(3)-C(13)-C(7)	117.0(4)	C(17)-C(13)-C(7)	120.1(4)
C(15)-C(14)-N(3)	124.0(5)	C(14)-C(15)-C(16)	119.0(5)
C(15)-C(16)-C(17)	118.3(5)	C(13)-C(17) -C(16)	119,1(5)
N(2)-C(18)-C(19)	108.3(4)	O(6)-C(19)-C(18)	112.4(5)
O(6)-C(20)-C(21)	112.1(4)	N(2)-C(21)-C(20)	109.3(4)

2-Styrylpyfidine-4'-N,N-dimethylsulfonamide 2

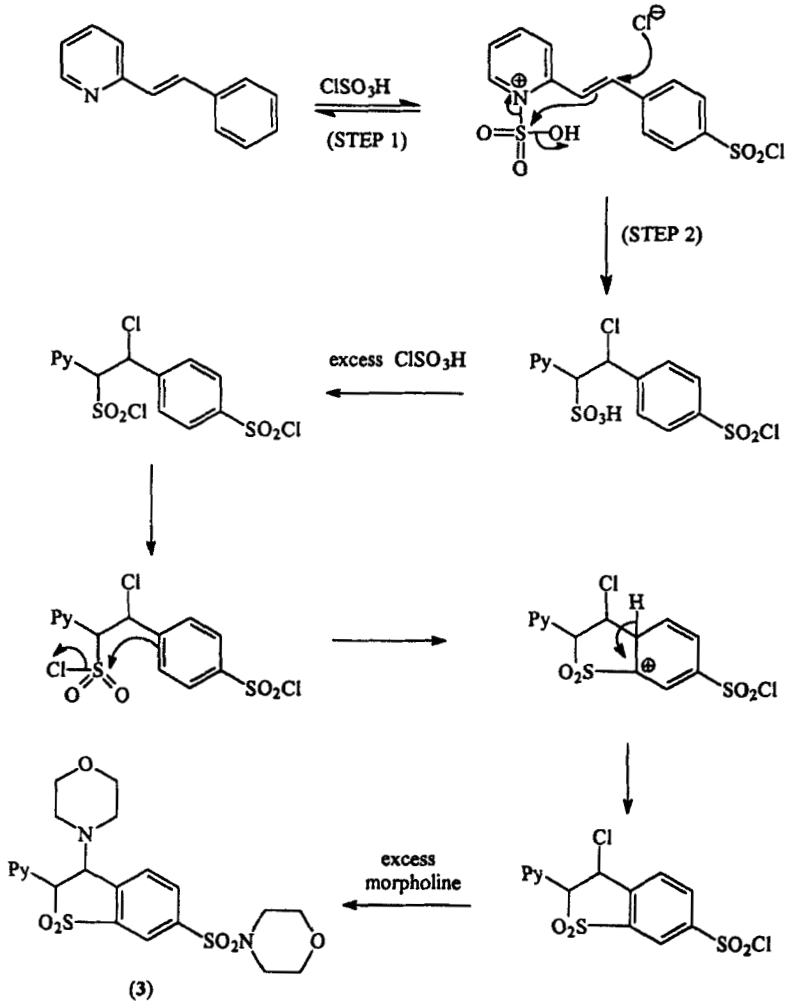
2-Styrylpyridine (3g, 0.017 mole) was added portionwise to a mixture of chlorosulfonic acid (9.8g, 0.084 mole) and thionyl chloride (20 ml). The mixture was refluxed for 2 hours, and left at room temperature for 2 weeks. The solution was poured onto crushed ice producing a yellowish gum, which was reacted with 40% aqueous dimethylamine in ethanol. The resultant crude product was recrystallised from methanol to give pure **2.** (3.7g, 46%), mp 134°C; IR: υ_{max} 1660 (ArC=C), 1360 and 1170 (SO_2) ; ^{1}H NMR: δ 8.7–7.2 (m, 10H Py**H**, Ar**H** and C**H**=C**H**), δ 2.7 (s, 6H, N(C**H**$_3$)$_2$; MS: m/z 288 (M+)(35%), 287 (M^+-H)(100%), 180 (M-$SO_2N(CH_3)_2$)(30%). ^{13}C NMR: δ154.7(PyC-2), 149.9(PyC-6), 141.1, 134.7 (C-1′, C-4′), 136.8, 131.1, 130.7(PyC-4, C-α, C-β), 128.2(C-2′ & C-6′), 127.4(C-3′, 5′), 122.8 & 122.8(PyC-3 & PyC-5), 38.0(NMe_2).

Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.50; H, 5.55; N, 9.72

Found: C, 62.45 H, 5.23 N, 9.69

2-(2-Pyridyl)-3-morpholino-2,3-dihydrobenzo[b]thiophene1,1-dioxide-6-sulphonylmorpholidate 3

2-Styrylpyridine (3g, 0.017 mole) was added portionwise to chlorosulfonic acid(23.2g, 0.020 mole) at room temperature. The mixture was refluxed for 24 hours, cooled to room temperature, and poured onto crushed ice, producing a gum. This was reacted with excess morpholine in



SCHEME 2

acetone at room temperature for 24 hours. The resultant product was recrystallised from ethanol to give pure **3**(0.67g, 32%) mp 192–193°C; IR: υ_{max} 1700 (C=N), 1590 (ArC=C), 1350, 1160 (SO_2); ^{1}H NMR: δ 8.7–7.4 (m, 7H, Ar**H** and Py**H**), δ 5.7 (1H, d, 7Hz), δ 5.0 (1H, d, 7Hz) and δ 3.8–1.8 (m, 16H, morpholino**H**) FAB (+) MS: 480 (M^+ +1), FAB (-) MS: 478

(M^+ -H). ^{13}C NMR: δ 150.4 (PyC-2), 149.6 (PyC-2), 142.9, 139.9, 138.3 (C-6, C-4a, C-7a), 137.4 (C-5), 132.6 (PyC-4), 127.9 (C-4), 125.6, 124.3, 121.6 (C-7, PyC-3, PyC-5), 67.0, 66.0 (C-2, C-3), 66.7, 66.3 (CO*morpholino*), 49.5, 45.9 (CN*morpholino*).

Anal. Calcd, for $C_{21}H_{25}N_3O_6S_2$: C, 52.60 H, 5.25 N, 8.76, S, 13.36
Found: C, 52.49 H, 5.29 N, 8.55 S, 13.32

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