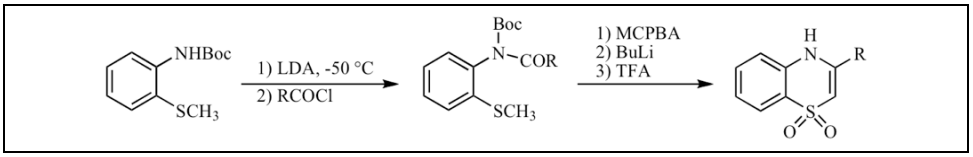
High Yield Synthesis of 4*H*-1,4-Benzothiazine-1,1-dioxide Derivatives

Stefania De Montis, Claudia Fattuoni,* Enzo Cadoni, Maria G. Cabiddu, Michele Usai, Salvatore Cabiddu

Dipartimento di Scienze Chimiche, University of Cagliari, Cittadella Universitaria di Monserrato, SS. 554, Bivio per Sestu. I-09042 Monserrato (CA), Italy
Tel.: +39-070-6754387; fax: +39-070-6754388; E-mail: cfattuon@unica.it

Received March 28, 2008



4*H*-1,4-Benzothiazine-1,1-dioxide derivatives were synthesized through a sequence of almost quantitative reactions. The commercial starting material 2-(methylsulfanyl)aniline was Boc-protected, *N*-acylated and oxidized at the sulfur atom to obtain a sulfonyl derivative. An anionic transposition of the acyl group followed by a simultaneous deprotection-cyclization gave the title products in excellent yields. All products and intermediates were fully characterized.

J. Heterocyclic Chem., **45**, 1445 (2008).

INTRODUCTION

1,4-Benzothiazine derivatives have drawn much interest in the pharmacologic field due to their structural similarity with the phenothiazine system [1]. In particular the synthesis of the *S*-oxidized system, 4*H*-1,4-benzothiazine-1,1-dioxide, has been the object of several studies and patents for industrial and pharmacological applications [2-5]. The synthesis of such systems usually started from 2-aminobenzenethiols which were treated with β-diketones to give the 2,3-disubstituted heterocyclic ring through the formation of an intermediate enaminoketone [4-8]. The further step, *i.e.* the oxidation at the sulfur, was usually performed with 30% hydrogen peroxide in glacial acetic acid [6-8]. An alternative method reported by Schou started from pyridinium sulfonate salts which were converted into 2-cyanomethylsulfonyl acetanilides: base catalyzed ring closure gave the *S*-oxidized benzothiazinic system [3]. Another recent method involved the microwave assisted cyclization of α-phenylsulfonyl enaminoacrylates [9].

In this paper we report a new high yield synthesis of 3-substituted 4*H*-1,4-benzothiazine-1,1-dioxides: this procedure is characterized by few almost quantitative steps allowing the preparation of the target compounds bearing a free, unsubstituted NH suitable for further functionalization. The starting compound 2-(methylsulfanyl)aniline (**1**) is commercial and all reagents are easily available and inexpensive.

RESULTS AND DISCUSSION

The first step of the synthetic pathway consisted in the protection of the amino group in **1** with Boc (*tert*-butoxycarbonyl), an easily removable protecting group, to give **2** (Scheme I). This compound was then lithiated with lithium diisopropylamide (LDA) at -50 °C and treated with an acyl chloride RCOCl where R was an aryl, heteroaryl or alkyl group to give the *N*-acylated products **3a-e** (yield 60-77%, Table 1). Compounds **3a-e** were oxidized at the sulfur atom with *m*-chloroperbenzoic acid (MPCBA) to give the sulfones **4a-e** (yield 80-100%, Table 1), which after treatment with butyllithium (BuLi) at -50 °C underwent an acyl migration from the nitrogen atom to the methylsulfonyl group affording products **5a-e** (yield 71-100%, Table 1). The acyl group transfer is likely to occur by an intramolecular mechanism: in fact, from the reaction mixture no product of type **A** or **B** could be isolated, even performing the reaction with a higher substrate concentration (Figure 1).

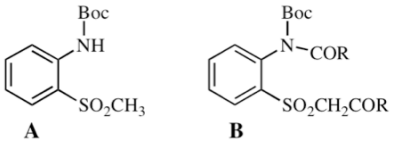
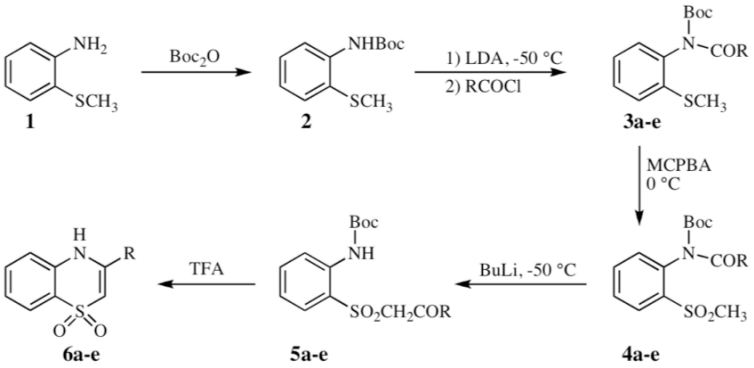


Figure 1

The treatment of compounds of type **5** with trifluoroacetic acid (TFA) allowed the simultaneous Boc-deprotection and cyclization giving products **6a-e** (yield 70-100%, Table 1). It is noteworthy that products of type **5** did not cyclize in the presence of BuLi, through an attack of the anionic nitrogen to the carbonyl group: this is due to the low reactivity as nucleophile of the Boc-protected N, even as an anion (Figure 2).

Scheme I



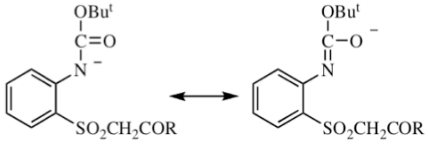


Figure 2

The cyclization took place only when the N was deprotected in an acidic medium: the attack of the free NH_2 to the carbonyl carbon did not lead to the expected imine, but to an enaminic product because of the strong acidity of the SO_2-CH_2 hydrogens.

All products were fully characterized by elemental analysis, IR, ^{1}H-NMR, ^{13}C-NMR and mass spectroscopy (see Experimental).

The ^{13}C NMR spectra of products **3e** and **4e**, bearing two *tert*-butyl groups, showed a remarkable feature: the signals due to the methyl groups of the *tert*-butyl moieties are observed as an unresolved multiplet. This phenomenon clearly depended upon the closeness of such bulky groups, whose free rotation around the C-O or C-C bond was forbidden. When the same spectra were recorded at 55 °C, the signals relative to the CH_3 appeared as two clean singlets.

Table 1. Yields of pure isolated products **3a-e, 4a-e, 5a-e** and **6a-e.**

R		3	4	5	6
Ph	**a**	77	90	96	100
4-$MeOC_6H_4$	**b**	70	92	71	81
4-FC_6H_4	**c**	65	92	78	75
	**d**	65	100	80	81
$C(CH_3)_3$	**e**	60	80	100	70

In conclusion, we have reported an easy method to prepare monosubstituted 4*H*-1,4-benzothiazine-1,1-dioxides, using inexpensive reagents and allowing to introduce in the 3-position different groups (aryl, heteroaryl or alkyl).

EXPERIMENTAL

NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference. IR spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer. The GC-MS analyses were performed at 70 eV with a Hewlett-Packard 5989A GC-MS system with HP 5890 GC fitted with a capillary column (50 m×0.2 mm) packed with DH 50.2 Petrocol (0.50 μm film thickness) using a direct-inlet system for solid products. Chromatography was performed on silica gel 60, 0.04-0.063 mm (Fluka). Melting points were determined with a Kofler hot stage microscope and are uncorrected. Microanalyses were carried out on a Carlo Erba 1106 element analyzer. Reagent-grade commercially available reagents and solvents were used. Solutions of BuLi in hexane were purchased from Aldrich Chemical Company and were analyzed before use [10]. 2-(Methylsulfanyl)aniline (**1**) (Fluka) was protected by literature method to give **2** [11].

General procedure for the synthesis of compounds 3a-e. To a stirred solution of LDA (24.0 mL, 31.6 mmol) in anhydrous THF (60 mL) at -50 °C, a solution of **2** (3.00 g, 12.6 mmol) in anhydrous THF (60 mL) was added under argon, and stirring was continued for 1h. Then the appropriate acyl chloride was added at the same temperature, and after 30 minutes the mixture was poured into a saturated solution of aqueous NH_4Cl. The organic layer was separated, the aqueous layer extracted with CH_2Cl_2, the extracts combined, dried (Na_2SO_4) and concentrated to give products **3a-e**.

***tert*-Butyl benzoyl[2-(methylthio)phenyl]carbamate (3a)**. The crude product was purified by chromatography using diethyl ether/light petroleum (1:2) as eluent to give **3a** as colourless crystals, 3.33 g (77%), mp 122-123 °C (EtOH); ir (Nujol): 1725, 1670 cm^{-1}; ^{1}H nmr ($CDCl_3$): δ 1.21 (s, 9H, CH_3C), 2.44 (s, 3H, SCH_3), 7.23 (m, 2H, ArH), 7.35 (m, 2H, ArH), 7.43 (m, 2H, ArH), 7.49 (m, 1H, ArH), 7.81 (m, 2H, ArH); ^{13}C nmr ($CDCl_3$): δ 15.7, 27.3, 83.4, 125.9, 127.3, 127.9, 128.1, 128.9, 129.3, 131.3, 136.9, 137.1, 137.7, 152.5, 172.0; ms: m/z 343 (M^+, 5), 243 (6), 196 (48), 165 (56), 105 (100), 77 (72), 57 (77), 41 (36). *Anal*. calcd. for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08; S, 9.34. Found: C, 66.42; H, 6.18; N, 4.02; S, 9.30.

***tert*-Butyl 4-methoxybenzoyl[2-(methylthio)phenyl]-carbamate (3b)**. The crude product was purified by chromatography using first light petroleum and then diethyl ether/light petroleum (1:2) as eluents to give **3b** as white crystals, 3.29 g (70%), mp 114-115 °C (EtOH/ H_2O); ir (nujol):

1720, 1665 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.27 (s, 9H, CH_3C), 2.43 (s, 3H, SCH_3), 3.84 (s, 3H, OCH_3), 6.92 (d, 2H, J=9.0 Hz, ArH), 7.20 (m, 2H, ArH), 7.31 (m, 2H, ArH), 7.81 (d, 2H, J=9.0 Hz, ArH); ^{13}C nmr ($CDCl_3$): δ 15.6, 27.5, 55.3, 83.0, 113.2, 125.8, 127.1, 128.7, 128.7, 129.3, 130.7, 137.5, 137.7, 152.8, 162.4, 171.3; ms: m/z 373 (M^+, 0.1), 273 (2), 226 (14), 165 (18), 135 (100), 107 (8), 77 (18), 57 (35), 41 (32). *Anal*. calcd. for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75; S, 8.59. Found: C, 64.28; H, 6.25; N, 3.78; S,8.61.

***tert*-Butyl 4-fluorobenzoyl[2-(methylthio)phenyl]-carbamate (3c)**. The crude product was washed with light petroleum first and then with diethyl ether to give **3c** as white crystals, 2.96 g (65%), mp 109-111 °C (EtOH); ir (nujol): 1725, 1670 cm^{-1}; ^1H nmr ($CDCl_3$): 1.35 (s, 9H, CH_3C), 2.51 (s, 3H, SCH_3), 7.20 (m, 2H, ArH), 7.30 (br s, 2H, ArH), 7.42 (br s, 2H, ArH), 7.93 (m, 2H, ArH); ^{13}C nmr ($CDCl_3$): δ 15.4, 27.3, 83.3, 114.9 (J_{CF} = 22.0 Hz), 125.7, 127.0, 128.9, 129.1, 130.6 (J_{CF} = 8.6 Hz), 132.7 (J_{CF} = 3.6 Hz), 136.9, 137.5, 152.3, 164.4 (J_{CF} = 252.8 Hz), 170.6; ms: m/z 361 (M^+, 3), 261 (17), 214 (100), 165 (80), 123 (93), 95 (32), 57 (43), 41 (26). *Anal*. calcd. for $C_{19}H_{20}FNO_3S$: C, 63.14; H, 5.58; N, 3.88; S, 8.87. Found: C, 63.11; H, 5.61; N, 3.92; S, 8.92.

***tert*-Butyl 2-(methylthio)phenyl(2-thienylcarbonyl)-carbamate (3d)**. The crude product was purified by flash-chromatography using diethyl ether/light petroleum (1:2) as eluent to give **3d** as yellow crystals, 2.86 g (65%), mp 123-125 °C (EtOH); ir (nujol): 1720, 1665 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.28 (s, 9H, CH_3C), 2.29 (s, 3H, SCH_3), 6.88 (br s, 1H, ArH), 7.08 (br s, 2H, ArH), 7.19 (br s, 2H, ArH), 7.39 (br s, 1H, ArH), 7.45 (br s, 1H, ArH); ^{13}C nmr ($CDCl_3$): δ 15.3, 27.4, 83.1, 125.6, 126.8, 126.8, 128.9, 129.2, 131.9, 132.6, 137.0, 138.1, 138.4, 152.3, 164.2; ms: m/z 349 (M^+, 15), 294 (52), 250 (44), 249 (38), 232 (29), 202 (100), 165 (66), 111 (68), 57 (79), 41 (42). *Anal*. calcd. for $C_{17}H_{19}NO_3S_2$: C, 58.43; H, 5.48; N, 4.01; S, 18.35. Found: C, 58.39; H, 5.50; N, 4.03; S, 18.37.

***tert*-Butyl 2,2-dimethylpropanoyl[2-(methylthio)phenyl]-carbamate (3e)**. The crude product was purified by chromatography using diethyl ether/light petroleum (1:8) as eluent to give **3e** as colourless crystals, 2.44 g (60%), mp 69-71 °C (H_2O); ir (nujol): 1720 and 1665 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.38 (s, 9H, CH_3C), 1.40 (s, 9H, CH_3C), 2.42 (s, 3H, SCH_3), 7.04 (d, 1H, J = 7.6 Hz, ArH), 7.16 (m, 1H, ArH), 7.27 (m, 2H, ArH); ^{13}C nmr ($CDCl_3$): δ 15.5, 27.9, 43.5, 82.4, 125.5, 126.9, 128.3, 128.5, 137.7, 138.3, 153.1, 183.7; ms: m/z 323 (M^+, 6), 224 (13), 223 (17), 232 (29), 176 (47), 165 (98), 57 (100), 41 (60). *Anal*. calcd. for $C_{17}H_{25}NO_3S$: C, 63.13; H, 7.79; N, 4.33; S, 9.91. Found: C, 63.11; H, 7.82; N, 4.30; S, 9.94.

General procedure for the synthesis of compounds 4a-e. A solution of one compound of type **3** (5.6 mmol) in CH_2Cl_2 (150 mL) was treated with MCPBA (3.03 g, 12.3 mmol) at 0 °C. After the addition was complete the temperature was allowed to warm to room temperature and the reaction was monitored by tlc till completion. The mixture was treated with 10% aqueous NaOH, the organic layer was dried (Na_2SO_4) and concentrated to give products **4a-e**.

***tert*-Butyl benzoyl[2-(methylsulfonyl)phenyl]carbamate (4a).** The crude product was washed with diethyl ether to give **4a** as colourless crystals, 1.89 g (90%), mp 178-179 °C (EtOH); ir (nujol): 1715, 1680, 1310, 1155 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.20 (s, 9H, CH_3C), 3.14 (s, 3H, SO_2CH_3), 7.40 (m, 4H, ArH), 7.62 (t, 1H, J = 7.5 Hz, ArH), 7.76 (m, 3H, ArH), 8.15 (d, 1H, J = 7.5 Hz, ArH); ^{13}C nmr ($CDCl_3$): δ 27.3, 44.4, 84.3, 128.0, 128.0, 129.5, 130.8, 131.4, 131.8, 134.7, 136.5, 137.6, 137.6, 152.1, 172.6; ms: m/z 276 (3), 197 (23), 196 (29), 105 (100), 77 (45), 57 (47), 41 (28). *Anal*. calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 60.72; H, 5.66; N, 3.76; S, 8.57.

***tert*-Butyl 4-methoxybenzoyl[2-(methylsulfonyl)phenyl]-carbamate (4b)**. The crude product was washed with diethyl ether to give **4b** as colourless crystals, 2.09 g (92%), mp 166-168 °C (EtOH); ir (nujol): 1715, 1670, 1310, 1150 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.26 (s, 9H, CH_3C), 3.12 (s, 3H, SO_2CH_3), 3.87 (s, 3H, OCH_3), 6.96 (d, 2H, J = 8.8 Hz, ArH), 7.38 (d, 1H, J = 7.8 Hz, ArH), 7.60 (t, 1H, J = 7.8 Hz, ArH), 7.72 (t, 1H, J = 7.8 Hz, ArH), 7.79 (d, 2H, J = 8.8 Hz, ArH), 8.14 (d, 1H, J = 7.8 Hz, ArH); ^{13}C nmr ($CDCl_3$): δ 27.4, 44.3, 55.4, 83.9, 113.2, 128.1, 129.3, 130.7, 130.8, 131.8, 134.6, 137.5, 137.9, 152.4, 162.6, 171.8; ms: m/z 305 (2), 226 (13), 135 (100), 77 (7), 57 (14), 41 (10). *Anal*. calcd. for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45; S, 7.91. Found: C, 59.22; H, 5.74; N, 3.43; S, 7.90.

***tert*-Butyl 4-fluorobenzoyl[2-(methylsulfonyl)phenyl]-carbamate (4c).** The crude product was washed with diethyl ether to give **4c** as white crystals, 2.02 g (92%), mp 178-179 °C (EtOH); ir (nujol): 1710, 1670, 1310, 1150 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.25 (s, 9H, CH_3C), 3.12 (s, 3H, SO_2CH_3), 7.14 (t, 2H, J =8.2 Hz, ArH), 7.38 (d, 1H, J = 7.8 Hz, ArH), 7.62 (t, 1H, J = 7.8 Hz, ArH), 7.74 (t, 1H, J = 7.8 Hz, ArH), 7.81 (m, 2H, ArH), 8.14 (d, 1H, J = 7.8 Hz, ArH); ^{13}C nmr ($CDCl_3$): δ 27.4, 44.4, 83.5, 115.2 (J_{CF} = 22.0 Hz), 129.6, 130.7 (J_{CF} = 8.6 Hz), 130.8, 131.8, 132.4 ($J_{C\ F}$= 3.6 Hz), 134.7, 137.4, 137.5, 152.1, 164.7 (J_{CF} = 252.8 Hz), 171.4; ms: m/z 293 (8), 214 (70), 197 (22), 123 (100), 77 (25), 57 (9), 41 (7). *Anal*. calcd. for $C_{19}H_{20}FNO_5S$: C, 58.00; H, 5.12; N, 3.56; S, 8.15. Found: C, 57.99; H, 5.14; N, 3.57; S, 8.18.

***tert*-Butyl 2-(methylsulfonyl)phenyl(2-thienylcarbonyl)-carbamate (4d)**. The crude product was washed with diethyl ether to give **4d** as colourless crystals, 2.13 g (100%), mp 138-139 °C (EtOH); ir (nujol): 1720, 1680, 1320, 1165 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.24 (s, 9H, CH_3C), 3.04 (s, 3H, SO_2CH_3), 7.00 (t, 1H, J = 4.3 Hz, ArH), 7.27 (d, 1H, J = 7.7 Hz, ArH) 7.48 (m, 2H, ArH), 7.60 (m, 2H, ArH), 8.01 (d, 1H, J = 7.7 Hz, ArH); ^{13}C nmr ($CDCl_3$): δ 27.3, 44.1, 84.1, 127.0, 129.4, 130.5, 131.6, 132.0, 132.9, 134.5, 137.3, 137.4, 137.9, 152.1, 165.1; ms: m/z 282 (19), 281 (12), 264 (20), 202 (46), 197 (16), 111 (100), 57 (47), 41 (31). *Anal*. calcd. for $C_{17}H_{19}NO_5S_2$: C, 53.53; H, 5.02; N, 3.67; S, 16.81. Found: C, 53.50; H, 5.05; N, 3.65; S, 16.84.

***tert*-Butyl 2,2-dimethylpropanoyl[2-(methylsulfonyl)-phenyl]carbamate (4e)**. The crude product was purified by flash-chromatography using diethyl ether/light petroleum (1:1) as eluent to give **4e** as colourless crystals, 1.59 g (80%), mp 119-120 °C (EtOH); ir (nujol): 1725, 1700, 1310, 1150 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.37 (s, 9H, CH_3C), 1.45 (s, 9H, CH_3C), 3.10 (s, 3H, SO_2CH_3), 7.17 (d, 1H, J = 7.6 Hz, ArH), 7.53 (t, 1H, J = 7.6 Hz, ArH), 7.66 (t, 1H, J = 7.6 Hz, ArH), 8.07 (d, 1H, J = 7.6 Hz, ArH); ^{13}C nmr ($CDCl_3$): δ 27.6, 43.2, 69.0, 83.5, 128.7, 130.3, 130.9, 134.4, 136.9, 139.4, 152.1, 183.6; ms: m/z 197 (15), 176 (14), 171 (29), 149 (18), 85 (18), 57 (100), 41 (47). *Anal*. calcd. for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94; S, 9.02. Found: C, 57.41; H, 7.11; N, 3.92; S, 9.03.

General procedure for the synthesis of compounds 5a-e. A solution of one compound of type **4** (1.3 mmol) in anhydrous THF (50 mL) was treated dropwise with a 1.6 *M* solution of BuLi in hexane (2.0 mL, 3.2 mmol) at -50 °C under argon, and stirring was continued for 10 minutes. The mixture was poured

into a saturated solution of aqueous NH_4Cl, the organic layer was separated, the aqueous layer extracted with CH_2Cl_2, the extracts combined, dried (Na_2SO_4) and concentrated to give products **5a-e**.

***tert*-Butyl 2-[(2-oxo-2-phenylethyl)sulfonyl]phenyl-carbamate (5a).** The crude product was washed with diethyl ether to give **5a** as colourless crystals, 0.47 g (96%),; mp 118-120°C (EtOH); ir (nujol): 3350, 1730, 1675, 1315, 1155 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.51 (s, 9H, CH_3C), 4.76 (s, 2H, SO_2CH_2), 7.07 (t, 1H, J = 8.2 Hz, ArH), 7.41 (t, 2H, J = 7.5 Hz, ArH), 7.56 (m, 2H, ArH), 7.78 (d, 1H, J = 8.2 Hz, ArH), 7.85 (d, 2H, J = 8.2 Hz, ArH), 8.30 (d, 1H, J = 8.2 Hz, ArH), 8.75 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 27.9, 62.4, 81.1, 120.5, 122.2, 124.2, 128.6, 128.8, 130.1, 134.0, 135.4, 135.4, 138.4, 151.8, 187.1; ms: m/z 375 (M^+, 7), 319 (12), 275 (40), 152 (15), 106 (45), 105 (100), 77 (19), 57 (90), 41 (37). *Anal*. calcd. for $C_{19}H_{21}NO_5S$: C, 60.78; H, 5.64; N, 3.73; S, 8.54. Found: C, 60.75; H, 5.66; N, 3.75; S, 8.57.

***tert*-Butyl 2-{[2-(4-methoxyphenyl)-2-oxoethyl]sulfonyl}-phenylcarbamate (5b)**. The crude product was washed with light petroleum to give **5b** as colourless crystals, 0.37 g (71%), mp 114-117°C (EtOH/H_2O); ir (nujol): 3340, 1720, 1665, 1310, 1155 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.49 (s, 9H, CH_3C), 3.83 (s, 3H, OCH_3), 4.67 (s, 2H, SO_2CH_2), 6.87 (d, 2H, J = 8.1 Hz, ArH), 7.07 (t, 1H, J = 7.9 Hz, ArH), 7.54 (t, 1H, J = 7.9 Hz, ArH), 7.76 (d, 1H, J = 7.9 Hz, ArH), 7.83 (d, 2H, J = 8.1 Hz, ArH), 8.30 (d, 1H, J = 7.9 Hz, ArH), 8.72 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 28.1, 55.5, 62.5, 81.2, 114.0, 120.7, 122.4, 124.4, 128.6, 130.2, 131.5, 135.5, 138.5, 152.0, 164.4, 185.3;. ms: m/z 405 [M^+] (4), 305 (32), 135 (100), 77 (13), 57 (47), 41 (78). *Anal*. calcd. for $C_{20}H_{23}NO_6S$: C, 59.24; H, 5.72; N, 3.45; S, 7.91. Found: C, 59.22; H, 5.75; N, 3.48; S, 7.90.

***tert*-Butyl 2-{[2-(4-fluorophenyl)-2-oxoethyl]sulfonyl}-phenylcarbamate (5c)**. The crude product was purified by chromatography using diethyl ether/light petroleum (1:1) as eluent to give **5c** as colourless crystals, 0.40 g (78%), mp 137-139 °C (EtOH); ir (nujol): 3350, 1730, 1670, 1320, 1155 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.44 (s, 9H, CH_3C), 4.63 (s, 2H, SO_2CH_2), 7.06 (m, 3H, ArH), 7.51 (t, 1H, J = 8.0 Hz, ArH), 7.70 (d, 1H, J = 8.0 Hz, ArH), 7.85 (m, 2H, ArH), 8.25 (d, 1H, J = 8.0 Hz, ArH), 8.60 (s, 1H, NH);. ^{13}C nmr ($CDCl_3$): 28.2, 62.8, 81.5, 116.1 (J_{CF} = 22.0 Hz), 120.9, 122.6, 124.3, 130.3, 132.0 (J_{CF} = 9.7 Hz), 135.8, 138.6, 138.6, 152.0, 166.4 (J_{CF} = 257.6 Hz), 185.6; ms: m/z 393 (M^+, 2), 293 (32), 211 (10), 171 (17), 152 (15), 123 (65), 106 (20), 95 (12), 57 (100), 41 (48). *Anal*. calcd. for $C_{19}H_{20}FNO_5S$: C, 58.00; H, 5.12; N, 3.56; S, 8.15. Found: C, 57.99; H, 5.14; N, 3.58; S, 8.18.

***tert*-Butyl 2-{[2-oxo-2-(2-thienyl)ethyl]sulfonyl}phenyl-carbamate (5d)**. The crude product was purified by chromatography using diethyl ether/light petroleum (1:1) as eluent to give **5d** as colourless crystals, 0.40 g (80%), mp 104-106 °C (EtOH/H_2O); ir (nujol): 3360, 1740, 1670, 1330, 1170 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.53 (s, 9H, CH_3C), 4.64 (s, 2H, SO_2CH_2), 7.09-7.14 (m, 2H, ArH), 7.58 (t, 1H, J = 8.0 Hz, ArH), 7.68 (d, 1H, J = 4.5 Hz, ArH), 7.74 (d, 1H, J = 4.5 Hz, ArH), 7.81 (d, 1H, J = 8.0 Hz, ArH), 8.32 (d, 1H, J = 8.0 Hz, ArH), 8.71 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 28.2, 63.7, 81.4, 120.8, 122.5, 124.1, 128.6, 130.3, 134.8, 135.8, 136.5, 138.6, 143.0, 152.0, 179.1; ms: m/z 381 (M^+, 5), 282 (21), 281 (37), 152 (14), 111 (35), 106 (20), 57 (100), 41 (48). *Anal*. calcd. for $C_{17}H_{19}NO_5S_2$: C, 53.53; H, 5.02; N, 3.67; S, 16.81. Found: C, 53.50; H, 5.05; N, 3.65; S, 16.82.

***tert*-Butyl 2-[(3,3-dimethyl-2-oxobutyl)sulfonyl]phenyl-carbamate (5e).** The crude product was washed with diethyl ether to give **5e** as colourless crystals, 0.46 g (100%), mp 56-58 °C (EtOH/H_2O); ir (nujol): 3350, 1730, 1710, 1320, 1150 cm^{-1}; ^1H nmr ($CDCl_3$): δ 1.04 (s, 9H, CH_3C), 1.46 (s, 9H, CH_3C), 4.24 (s, 2H, SO_2CH_2), 7.10 (t, 1H, J = 7.9 Hz, ArH), 7.52 (t, 1H, J = 7.9 Hz, ArH), 7.78 (d, 1H, J = 7.9 Hz, ArH), 8.23 (d, 1H, J = 7.9 Hz, ArH), 8.64 (s, 1H, NH); ^{13}C nmr ($CDCl_3$): δ 25.4, 28.2, 45.3, 59.9, 81.4, 121.9, 122.6, 125.3, 130.4, 135.4, 138.3, 152.2, 202.3; ms: m/z 355 (M^+, 14), 299 (17), 256 (18), 198 (67), 171 (15), 156 (19), 57 (100), 41 (66). *Anal*. calcd. for $C_{17}H_{25}NO_5S$: C, 57.44; H, 7.09; N, 3.94; S, 9.02. Found: C, 57.42; H, 7.10; N, 3.97; S, 9.05.

General procedure for the synthesis of compounds 6a-e. A solution of one compound of type **5** (1.3 mmol), CH_2Cl_2 (4.5 mL) and trifluoroacetic acid (1.9 mL, 24.3 mmol) was stirred at room temperature for 10 minutes, then cooled at 0 °C and treated with 20% aqueous NaOH. The solid thus separated was filtered and ir lamp dried.

3-Phenyl-4*H*-1,4-benzothiazine 1,1-dioxide (6a). White crystals, 0.33 g (100%), mp 250-252 °C (EtOH) (lit. [12] 271-274 °C); ir (nujol): 3300, 1310, 1110 cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.39 (s, 1H), 7.45 (t, 1H, J = 7.5 Hz), 7.66-7.77 (m, 5H), 7.83-7.86 (m, 2H), 8.00 (d, 1H, J = 7.5 Hz), 11.02 (s, 1H, D_2O exchangeable, NH); ^{13}C nmr ($CDCl_3$): δ 96.4, 118.5, 122.1, 123.6, 123.7, 127.7, 129.1, 130.9, 132.4, 133.9, 137.2, 145.3; ms: m/z 257 (M^+, 30), 193 (100), 165 (17). *Anal*. calcd. for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.32; H, 4.34; N, 5.47; S, 12.49.

3-(4-Methoxyphenyl)-4*H*-1,4-benzothiazine 1,1-dioxide (6b). White crystals, 0.30 g (81%), mp 278-280 °C (EtOH) (lit. [12] 256-260 °C); ir (nujol): 3280, 1260, 1115 cm^{-1}; ^1H nmr (DMSO): δ 3.95 (s, 3H, OCH_3), 6.22 (s, 1H), 7.20 (d, 2H, J = 8.6 Hz), 7.39 (t, 1H, J = 7.4 Hz), 7.63 (d, 1H, J = 7.4 Hz), 7.70 (t, 1H, J = 7.4 Hz), 7.82 (d, 2H, J = 8.6 Hz), 7.93 (d, 1H, J = 7.4 Hz); ^{13}C nmr (DMSO): δ 55.53, 95.17, 114.30, 118.46, 121.90, 123.35, 123.58, 125.96, 129.15, 132.11, 137.24, 144.96, 161.29; ms: m/z 287 (M^+, 40), 223 (86), 208 (100), 180 (38), 152 (14). *Anal*. calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.87; S, 11.16. Found: C, 62.67; H, 4.58; N, 4.85; S, 11.19.

3-(4-Fluorophenyl)-4*H*-1,4-benzothiazine 1,1-dioxide (6c). Colourless crystals, 0.27 g (75%), mp 315-317 °C (EtOH); ir (nujol): 3300, 1310, 1115 cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.37 (s, 1H), 7.43-7.98 (m, 9H); ^{13}C nmr ($CDCl_3$): δ 96.3, 116.1 (J_{CF} = 22.0 Hz), 118.8, 122.1, 123.7, 123.7, 130.3 (J_{CF} = 8.6 Hz), 130.7, 132.4, 137.5, 144.6, 163.7 (J_{CF} = 247.8 Hz); ms: m/z 275 (M^+, 40), 211 (100), 165 (19). *Anal*. calcd. for $C_{14}H_{10}FNO_2S$: C, 61.08; H, 3.66; N, 5.09; S, 11.65. Found: C, 61.05; H, 3.68; N, 5.11; S, 11.67.

3-(2-Thienyl)-4*H*-1,4-benzothiazine 1,1-dioxide (6d). White crystals, 0.30 g (81%), mp 276-278 °C (EtOH); ir (nujol): 3300, 1290, 1100 cm^{-1}; ^1H nmr ($CDCl_3$): δ 6.44 (s, 1H), 7.38 (t, 1H, J = 4.2 Hz), 7.46 (t, 1H, J = 7.2 Hz), 7.69-7.78 (m, 2H), 7.89 (d, 1H, J = 4.2 Hz), 7.88-7.99 (m, 2H), 10.94 (s, 1H, D_2O exchangeable, NH); ^{13}C nmr ($CDCl_3$): δ 95.5, 118.4, 121.9, 123.8, 123.8, 128.4, 129.0, 129.8, 132.4, 135.4, 136.8, 139.0; ms: m/z 263 (M^+, 62), 199 (100), 171 (17), 167 (15). *Anal*. calcd. for $C_{12}H_9NO_2S_2$: C, 54.73; H, 3.44; N, 5.32; S, 24.35. Found: C, 54.70; H, 3.48; N, 5.30; S, 24.30.

3-*tert*-Butyl-4*H*-1,4-benzothiazine 1,1-dioxide (6e). Colourless crystals, 0.22 g (70%), mp 260-262 °C (EtOH); ir (nujol): 3310, 1240, 1100 cm^{-1}; ^1H nmr (DMSO): δ 1.39 (s, 9H, CH_3C), 5.91 (s, 1H), 7.37 (t, 1H, *J* = 7.2 Hz), 7.70 (m, 2H), 7.90 (d, 1H, *J* =

7.2 Hz); ^{13}C nmr (DMSO): δ 28.1, 35.9, 94.3, 118.0, 121.9, 122.8, 123.0, 132.1, 137.4, 154.3; ms: m/z 237 (M^+, 37), 222 (30), 173 (14), 158 (100). *Anal*. calcd. for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.70; H, 6.39; N, 5.92; S, 13.54.

Acknowledgement. Financial support from the Ministero dell'Università e della Ricerca Scientifica e Tecnologica, (Rome) and from the University of Cagliari is gratefully acknowledged. One of us (Michele Usai) acknowledges financial support from Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi (C.I.N.M.P.I.S.) Bari.

REFERENCES

[1] Thomas, L.; Gupta, A.; Gupta, V. *J. Fluor. Chem.* **2003**, *122*, 207-213, and references cited therein.

[2] Armenise, D.; Trapani, G.; Arrivo, V.; Laraspata, E.; Morlacchi, F. *J. Heterocyclic Chem.* **2000**, *37*, 1611-1616, and references cited therein.

[3] Schou, S. C.; Hansen, H. C.; Tagmose, T. M.; Boonen, H. C. M.; Worsaae, A.; Drabowski, M.; Wahl, P.; Arkhammar, P. O. G.; Bodvarsdottir, T.; Antoine, M. H.; Lebrun, P.; Hansen, J. B. *Bioorg. Med. Chem.* **2005**, *13*, 141-155.

[4] Armenise, D.; Trapani, G.; Stasi, F.; Morlacchi, F. *Arch. Pharm. Pharm. Med. Chem.* **1998**, *331*, 54-58.

[5] Rathore, B. S.; Kumar, M. *Bioorg. Med. Chem.* **2006**, *14*, 5678-5682.

[6] Hamadi, M. Y.; Gupta, R.; Gupta, R. R. *J. Fluor. Chem.* **1999**, *94*, 169-174.

[7] Sharma, P. R.; Gupta, V.; Gautam, D. C.; Gupta, R. R. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2003**, *178*, 1483-1488.

[8] Kumar, G.; Gupta, V.; Gautam, D. C.; Gupta, R. R. *Phosphorus, Sulfur, Silicon Relat. Elem.* **2004**, *179*, 1941-1948.

[9] Lopez, S.E.; Salazar, J.; Rebollo, O.; Restrepo, J. *J. Heterocyclic Chem.* **2005**, *42*, 1007-1010.

[10] Duhamel, L.; Plaquevent, J. C. *J. Org. Chem.* **1979**, *44*, 3404-3405.

[11] Cabiddu, M.G.; Cabiddu, S.; Cadoni, E.; De Montis, S.; Fattuoni, C.; Melis, S. *Tetrahedron* **2003**, *59*, 2893-2897.

[12] MacKenzie, N.E.; Thomson, R.H.; Greenhalgh, C.W. *J. Chem. Soc. Perkin I* **1980**, 2923-2932.