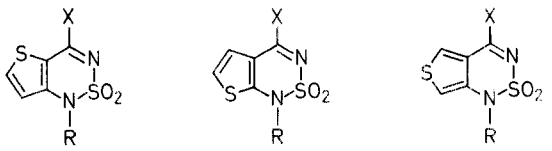
Synthesis of 4-Oxo-3,4-dihydro-1*H*-thieno[3,4-*c*]- and thieno[3,2-*c*][1,2,6]thiadiazine 2,2-Dioxides

Pilar Goya,* Jaime Lissavetzky, Isabel Rozas

Instituto de Química Médica (CSIC), Juan de la Cierva 3, E-28006-Madrid, Spain

4-Oxo-3,4-dihydro-1*H*-thieno[3,4-*c*][1,2,6]thiadiazine 2,2-dioxide (**3**) has been synthesized in a two-step approach involving sulfamoylation of 3-amino-4-methoxycarbonylthiophene (**1**) and subsequent ring closure. A modification of this procedure, which involves isolation of the intermediate thiophenecarboxylic acid derivatives **4** and **9**, has been used to prepare new 4-oxo-3,4-dihydro-1*H*-thieno[3,4-*c*]- and thieno[3,2-*c*][1,2,6]thiadiazine 2,2-dioxides **6** and **10**, respectively.

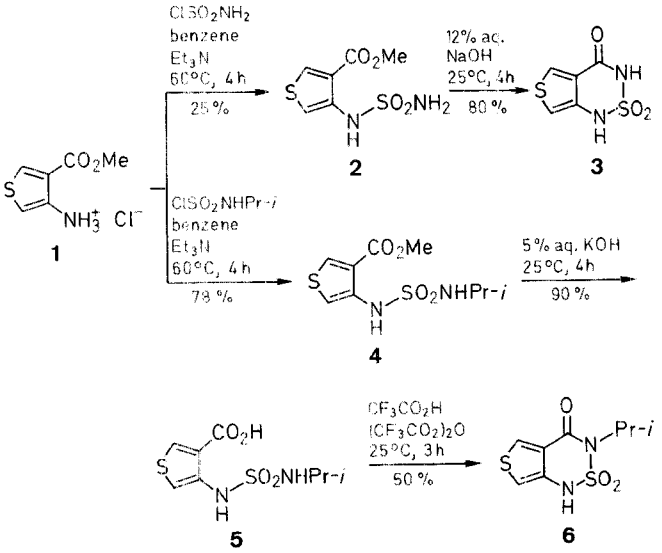
Heterocycles bearing the sulfamido moiety have interested us for some time.[1] Thienothiadiazine 2,2-dioxides belong to fused derivatives of this type, in which the thiophene ring can bind to the thiadiazine moiety in three different positions.



I II III

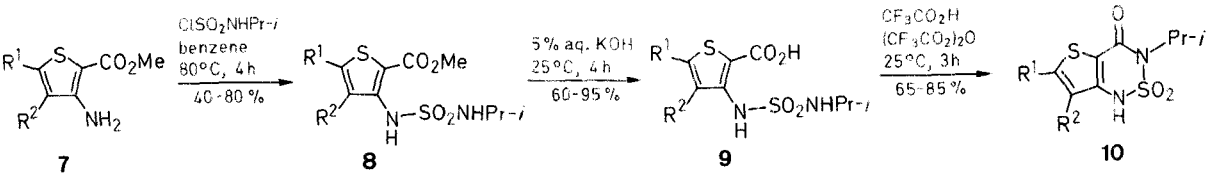
Two patents have dealt with type **I** structures,[2,3] whilst type **II** have been the subject of two previous publications.[4,5] However, to date, type **III** structures have not been reported. The general synthetic approach involves sulfamoylation of an *o*-aminomethoxycarbonyl thiophene derivative followed by ring closure. This is usually achieved in basic medium except when the sulfamoyl rest bears a branched alkyl group. In these cases, treatment with an equimolar mixture of trifluoroacetic acid and trifluoroacetic anhydride, and the use of the *tert*-butyl esters of the corresponding thiophenes has given good results.[2,6] We now wish to report a modification of this procedure, useful for thiophenes resisting direct ring closure, which involves isolation of the intermediate carboxylic acid derivative. Application of this method to the synthesis of 4-oxo-3,4-dihydro-1*H*-thieno[3,4-*c*]- and thieno[3,2-*c*][1,2,6]thiadiazines is described.

The starting thiophenes **1**,[7,8,9] **7a**,[10] and **7b**[11] and the sulfamoyl chlorides[12,13] were prepared according to the literature. Reaction of 3-amino-4-methoxycarbonylthiophene (**1**) hydrochloride with sulfamoyl and isopropylsulfamoyl chloride afforded the corresponding 2-[(amino and isopropylamino)sulfonyl]amino-3-methoxycarbonylthiophenes **2** and **4**, which were cyclized directly or via the carboxylic acid **5** to the desired 4-oxo-3,4-dihydro-1*H*-thieno[3,4-*c*][1,2,6]thiadiazine 2,2-dioxides **3** and **6**, respectively.



1 2 3 4 5 6

This synthetic route was used for the preparation of new thieno[3,2-*c*][1,2,6]thiadiazine 2,2-dioxides, and thus, the 6-phenyl derivative **10a** and the benzo condensed compound **10b** were obtained through the cyclization of the carboxylic acids **9a** and **9b**.



7-10	R^1	R^2
a	Ph	H
b	—CH=CH—CH=CH—	

Table 1. [(Amino)sulfonyl]amino Derivatives of Thiophenes

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (Nujol)[c] ν(cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[d] δ, J(Hz)
2	25	114–116 ($CHCl_3$)	$C_6H_8N_2O_4S_2$ (236.3)	3400–3100, 1690, 1380, 1160	3.83 (s, 3H, OCH_3); 7.08 (d, 1H$_{thiophene}$, J = 3); 7.33 (m, 2H, NH_2); 8.35 (d, 1H$_{thiophene}$, J = 3); 8.82 (m, 1H, NH)
4	78	95–97 (EtOAc/ *n*-hexane)	$C_9H_{14}N_2O_4S_2$ (278.3)	3300–3200, 1690, 1380, 1160	1.00 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 3.40 (m, 1H, CH); 3.83 (s, 3H, OCH_3); 7.10 (d, 1H$_{thiophene}$, J = 3); 7.72 (d, 1H, J = 6, N$\underline{H}$Pr-*i*); 8.38 (d, 1H$_{thiophene}$, J = 3); 8.88 (m, 1H, NH)
5	90	160–162 ($CHCl_3$/ acetone)	$C_8H_{12}N_2O_4S_2$ (264.3)	3300–3100, 2700–2500, 1660, 1370, 1140	0.98 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 3.37 (m, 1H, CH); 7.03 (d, 1H$_{thiophene}$, J = 3); 7.68 (d, 1H, J = 6, N$\underline{H}$Pr-*i*); 8.32 (d, 1H$_{thiophene}$, J = 3)
8a	78	150–152 (EtOH)	$C_{15}H_{18}N_2O_4S_2$ (354.4)	3300–3260, 1675, 1380, 1150	1.08 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 3.41 (m, 1H, CH); 3.53 (s, 3H, OCH_3); 7.46–7.58 (m, 3H$_{arom}$); 7.72 (s, 1H, NH); 7.73–7.84 (m, 2H$_{arom}$); 8.13 (d, 1H, J = 6, N$\underline{H}$Pr-*i*); 9.31 (s, 1H$_{thiophene}$)
8b	31	94–96 ($CHCl_3$)	$C_{13}H_{16}N_2O_4S_2$ (328.4)	3280–3220, 1695, 1350, 1150	0.97 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 3.43 (m, 1H, CH); 3.88 (s, 3H, OCH_3); 7.80–7.97 (m, 4H$_{arom}$); 9.23 (s, 1H, NH)
9a	98	148–150 (water)	$C_{14}H_{16}N_2O_4S_2$ (340.4)	3300–3260, 2700–2500, 1640, 1370, 1145	1.05 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 3.43 (m, 1H, CH); 7.37–7.53 (m, 3H$_{arom}$); 7.63 (s, 1H, NH); 7.67–7.80 (m, 2H$_{arom}$); 8.07 (d, 1H, J = 6, N$\underline{H}$Pr-*i*); 9.43 (s, 1H$_{thiophene}$)
9b	57	220–222 (water)	$C_{12}H_{14}N_2O_4S_2$ (314.4)	3300–3100, 2740–2500, 1660, 1370, 1170	0.90 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 3.43 (m, 1H, CH); 7.30–8.50 (m, 4H$_{arom}$); 10.42 (s, 1H, NH)

[a] Uncorrected, measured with a Kofler melting point apparatus.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.39, N ±0.38, S ±0.40.
[c] Recorded on a Perkin-Elmer 257 spectrophotometer
[d] Obtained on a Varian EM-90 spectrometer (90 MHz).

Table 2. 4-Oxo-3,4-dihydro-1*H*-thieno[3,4-*c*]- and thieno[3,2-*c*][1,2,6]thiadiazine 2,2-Dioxides Prepared

Product	Yield (%)	mp (°C)[a] (solvent)	Molecular Formula[b]	IR (Nujol)[c] ν(cm^{-1})	^{1}H-NMR (DMSO-d_6/TMS)[d] δ, J(Hz)	^{13}C-NMR (DMSO-d_6/TMS)[c] δ, J(Hz)
3	80	173–174 (EtOAc/ *n*-hexane)	$C_5H_4N_2O_3S_2$ (204.2)	3200–3100, 1690, 1380, 1180	7.21 (d, 1H$_{thiophene}$, J = 3); 8.46 (d, 1H$_{thiophene}$, J = 3)	111.6 (C-7); 123.3 (C-4a); 132.9 (C-5); 135.2 (C-7a); 159.3 (C-4)
6	50	136–138 ($CHCl_3$/ CH_3OH)	$C_8H_{10}N_2O_3S_2$ (246.3)	3600–3200, 1630, 1325, 1150	1.45 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 4.85 (m, 1H, CH); 7.35 (d, 1H$_{thiophene}$, J = 3); 8.48 (d, 1H$_{thiophene}$, J = 3)	–[f]
10a	85	182–184 (CH_3OH)	$C_{14}H_{14}N_2O_3S_2$ (322.4)	3100, 1615, 1345, 1180	1.46 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 4.82 (m, 1H, CH); 7.30 (s, 1H$_{thiophene}$); 7.40–7.50 (m, 3H$_{arom}$); 7.67–7.83 (m, 2H$_{arom}$)	20.7 (CH_3); 47.7 (CH); 115.0 (C-7a); 116.5 (C-7); 126.1, 129.3, 129.8 (C$_{arom}$); 132.0 (C-6); 142.8 (C-4a); 151.0 (C$_{arom}$); 158.1 (C-4)
10b	64	190–191 ($CHCl_3$)	$C_{12}H_{12}N_2O_3S_2$ (296.4)	3100, 1625, 1380, 1170	1.48 [d, 6H, J = 6, CH(C$\underline{H}_3$)$_2$]; 4.90 (m, 1H, CH); 7.45–7.68 (m, 2H$_{arom}$); 7.92–8.15 (m, 2H$_{arom}$); 9.81 (m, 1H, NH)	20.7 (CH_3); 47.8 (CH); 114.0 (C-7a); 123.1, 123.9, 125.4, 129.0 (C$_{arom}$); 130.8 (C-7); 138.5 (C-6); 139.3 (C-4a); 159.2 (C-4)

[a,c,d] Refers to footnotes a, c, d in Table 1.
[b] Satisfactory microanalyses obtained: C ±0.40, H ±0.27, N ±0.40, S +0.33.
[c] Recorded on a Bruker WP-SY-80 spectrometer (20 MHz).
[f] Spectrum could not be recorded due to lack of sufficient material.

The structures of all the newly synthesized compounds were established according to analytical and spectroscopic data and are gathered in Tables 1 and 2.

[(Amino- and Isopropylamino)sulfonyl]aminomethoxycarbonylthiophenes 2, 4, 8a, and 8b; General Procedure:

To a solution of the appropriate thiophene **1** or **7** (10 mmol) in anhydrous benzene (30 mL), the corresponding sulfamoyl chloride (10 mmol) dissolved in anhydrous benzene (20 mL) is added dropwise at room temperature. The mixture is refluxed until the total conversion of the starting thiophene, observed by TLC (eluent: $CH_3OH/CHCl_3$, 1:10), and is then concentrated under vacuum. The precipitated solid is filtered and purified by crystallization (Table 1).

[(Isopropylamino)sulfonyl]aminothiophenecarboxylic Acids 5, 9a, and 9b; General Procedure:

The corresponding methyl [(isopropylamino)sulfonyl]aminothiophenecarboxylate (2 mmol) is dissolved in 5% aq. KOH (20 mL). The mixture is stirred at room temperature for 4 h and then treated with conc. HCl to pH = 1. The precipitated product is filtered and purified by crystallization (Table 1).

4-Oxo-3,4-dihydro-1*H*-thieno[3,4-*c*] [1,2,6]thiadiazine 2,2-Dioxide (3):

The 3-(aminosulfonyl)amino-4-methoxycarbonylthiophene (**2**; 1 mmol) is dissolved in 12% aq. NaOH (25 mL). The mixture is stirred at room temperature for 4 h, then treated with conc. HCl to pH = 1 and extracted with EtOAc (3 × 25 mL). The organic layers are separated, and the solvent is removed under vacuum. The resulting solid is purified by crystallization from a mixture of EtOAc/*n*-hexane.

3-Isopropyl-4-oxo-3,4-dihydro-1*H*-thieno[3,2-*c*][1,2,6]thiadiazine 2,2-Dioxides 6, 10a, and 10b; General Procedure:

The corresponding thiophenecarboxylic acid **4** or **9** (2 mmol) is treated with CF_3CO_2H (5 mL) and $(CF_3CO)_2O$ (5 mL). The mixture is stirred at room temperature for 3 h, and the solvent evaporated at reduced pressure. The resulting solid is purified by crystallization except in the case of compound **6**, which is purified by chromatography on silica gel plates eluting with $CH_3OH/CHCl_3$ (1:10).

Received: 8 August 1988; revised: 27 October 1988

(1) Arán, V., Goya, P., Ochoa, C. *Adv. Heterocycl. Chem.*, in press.
(2) Kloek, J.A. *US Patent* 4139700 (1979), Monsanto Co.; *C.A.* **1979**, *90*, 187006.
(3) Kloek, J.A. *US Patent* 4182623 (1980), Monsanto Co.; *C.A.* **1980**, *92*, 198431.
(4) Goya, P., Lissavetzky, J., Rozas, I., Stud, M. *Arch. Pharm. (Weinheim, Ger.)* **1984**, *317*, 777.
(5) Wamhoff, H., Ertas, M. *Synthesis* **1985**, 190.
(6) Kloek, J.A., Leschinsky, K.L. *J. Org. Chem.* **1978**, *43*, 3824.
(7) Hromatka, O., Binder, D., Eichinger, K. *Monatsh. Chem.* **1973**, *104*, 1520.
(8) Rossy, P.A., Hoffman, W., Muller, N. *J. Org. Chem.* **1980**, *45*, 617.
(9) Baker, B.R., Joseph, J.P., Schaub, R.E., McEvoy, F.J., Williams, J.H. *J. Org. Chem.* **1953**, *18*, 138.
(10) Hartmann, H., Liebscher, J. *Synthesis* **1984**, 275.
(11) Beck, J.R. *J. Org. Chem.* **1972**, *37*, 3224.
(12) Graf, R. *Chem. Ber.* **1959**, *92*, 509.
(13) Kloek, J.A., Leschinsky, K.L. *J. Org. Chem.* **1976**, *41*, 4028.