Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 2261–2265

A facile tandem protocol for the regioselective synthesis of novel thienobenzothiazepines

Subramanian Vedhanarayanan Karthikeyan and Subbu Perumal*

Department of Organic Chemistry, School of Chemistry, Madurai Kamaraj University, Madurai 625 021, India

Received 29 December 2006; revised 23 January 2007; accepted 31 January 2007
Available online 4 February 2007

Abstract—A series of new 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepines has been synthesised regioselectively from the reaction of 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones with *o*-aminothiophenol in the presence of acetic acid. This transformation presumably occurs via a tandem Michael addition–condensation–isomerisation sequence.

The reaction of *o*-aminothiophenol with an α,β-unsaturated carbonyl functionality leads to benzothiazepines via [4+3]-annulation.[1–4] Benzothiazepines exhibit antifungal,[5] antibacterial,[5] antifeedant,[6] anti-inflammatory,[7] analgesic[7] and anticonvulsant[8] properties. Compounds possessing a thiophene sub-structure also find applications as pharmaceuticals,[9,10] as precursors for natural products,[11] conjugated polymers[12] and other materials.[13] This has prompted us to synthesise 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepines **1** comprising both thiophene and benzothiazepine substructures in a one pot multi-step tandem process from the reaction of 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones **4** with *o*-aminothiophenol **3**. The aromatic stability of the thiophene ring of **1** is envisaged to trigger the isomerisation of **2** in the presence of acetic acid (Scheme 1). Tandem reactions involve one-pot, multi-step transformations which avoid the isolation and purification of intermediates thereby minimising cost, time, labour and waste.[14,15] Hence, they are convergent, elegant, and eco-friendly procedures for the rapid construction of complex molecules and attractive from the viewpoint of green chemistry.[16]

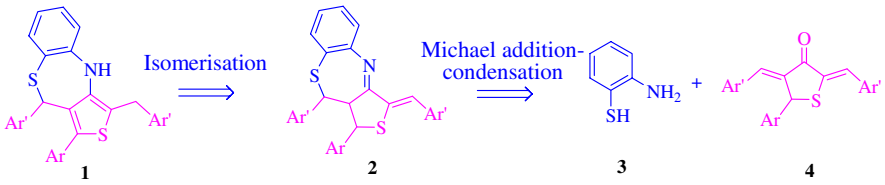
In a typical reaction, the synthesis of 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepines **1**[17] was effected by refluxing a mixture of 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones **4**[18] and *o*-aminothiophenol **3** (Scheme 2) in a 1:1.5 molar ratio in acetic acid for 45–60 min. After completion of the reaction (TLC), products **1** were obtained in a pure state by crystallisation in 55–91% yields.

This reaction was also performed under solvent-free microwave irradiation as described below with a view to exploring whether, (i) the reaction could be expedited and, (ii) the yield of **1** could be enhanced. 5-Aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenone **4** and *o*-aminothiophenol **3**, in the molar ratio 1:1.5, along with a catalytic amount of acetic acid (0.05 mL) were thoroughly mixed and the mixture placed in an open glass tube over a silica bath in a microwave oven and irradiated at maximum power level (600 W) for 2–3 min. The reaction progress was monitored after every 30 s of irradiation by TLC. The temperature of the silica bath after irradiation was complete was found to reach a maximum of 84 °C as measured by stirring the silica bath with a thermometer. After completion of the reaction, the product was purified by flash chromatography on silica gel with petroleum ether-ethyl acetate as eluent to afford a yellow solid, which upon recrystallisation from ethyl acetate afforded pure **1** in moderate yields (42–62%). The reaction under microwave irradiation proceeded rapidly but led to a lower yield of product compared with the thermal reaction (Table 1).

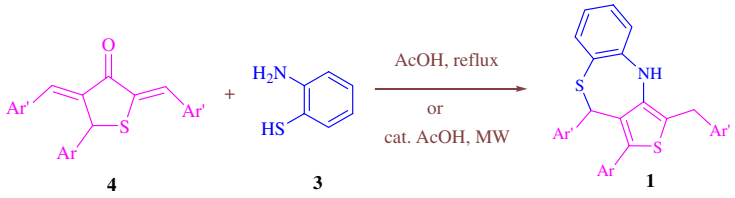
The structures of the 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepines **1** were established from ^{1}H, ^{13}C and 2D NMR spectroscopic data as illustrated for a representative example **1g**. In the ^{1}H NMR

Keywords: Benzothiazepines; Tandem sequence; 3-Thiophenones; *o*-Aminothiophenol.
* Corresponding author. Tel./fax: +91 452 2459845; e-mail: subbu.perum@gmail.com

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.01.168



Scheme 1. Retrosynthesis of thienobenzothiazepines, **1**.



Scheme 2.

Table 1. Synthesis of 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepines **1**

Entry	Product	Ar	Ar′	Reaction time (min)		Yield (%)		
				MW[a]	AcOH reflux	MW[b]	AcOH reflux[c]	Mp (°C)
1	**1a**	C_6H_5	C_6H_5	2	50	53	65	155–157
2	**1b**	C_6H_5	*p*-MeC_6H_4	2	50	48	55	152–153
3	**1c**	C_6H_5	*p*-ClC_6H_4	2	45	54	88	176–177
4	**1d**	C_6H_5	*p*-$MeOC_6H_4$	3	60	42	91	168–170
5	**1e**	C_6H_5	*p*-FC_6H_4	2	60	54	56	152–153
6	**1f**	C_6H_5	*o*-MeC_6H_4	3	60	47	58	167–168
7	**1g**	C_6H_5	*o*-$MeOC_6H_4$	2	50	50	62	183–184
8	**1h**	*p*-MeC_6H_4	*p*-MeC_6H_4	3	60	62	73	96–97
9	**1i**	*p*-ClC_6H_4	*p*-MeC_6H_4	2	45	60	72	99–100
10	**1j**	*o*,*p*-$Cl_2C_6H_3$	*p*-ClC_6H_4	2	45	59	74	109–110

[a] Irradiated with a catalytic amount of acetic acid.
[b] Yield after column chromatographic purification.
[c] Yield after crystallisation.

spectrum of **1g**, H-10 appears as a 1H singlet at 5.74 ppm which shows HMBC correlations (Fig. 1) with the *ipso* carbon (C-2″) at 155.4 ppm bearing the methoxy group, C-1″ at 120.6 ppm, C-6″ at 128.1 ppm and C-3a at 138.1 ppm. The diastereotopic 11-CH_2 protons appeared as doublets at 4.03 ppm and 4.21 ppm with *J* values of 15 Hz corresponding to geminal coupling. These protons showed HMBC correlations with C-2′, C-3, C-3a, and C-6′ appearing, respectively, at 156.5 ppm, 115.6 ppm, 138.1 ppm and 128.9 ppm. From C,H–COSY correlations, the carbon signals at 43.5 ppm and 26.9 ppm were assigned to C-10 and C-11, respectively. The NH proton gave a broad singlet at 6.93 ppm and had a HMBC correlation with C-3. The aromatic protons appeared as a multiplet in the range 6.48–7.36 ppm. The methoxy groups gave proton signals at 3.83 ppm and 4.00 ppm and carbon signals at 55.8 ppm and 55.9 ppm.

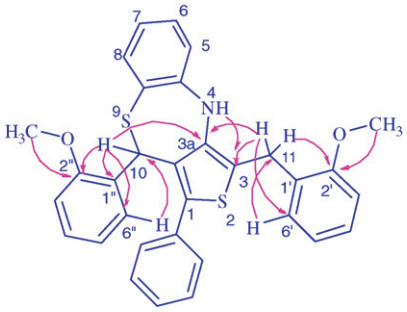


Figure 1. HMBC correlations in **1g**.

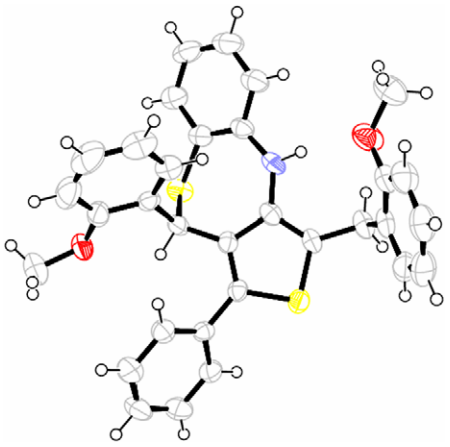
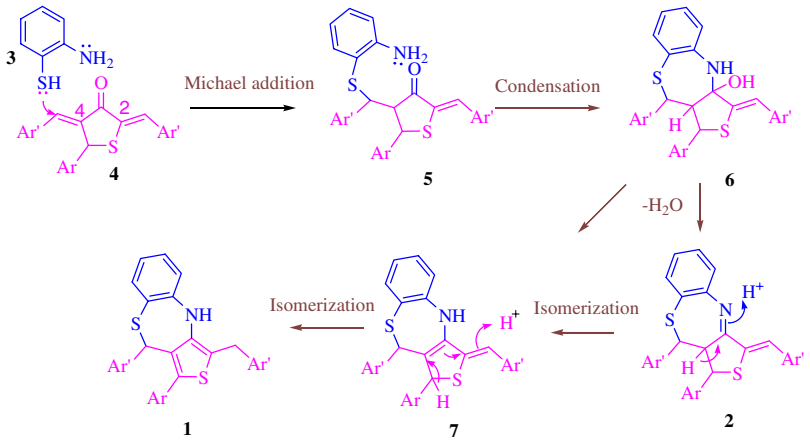
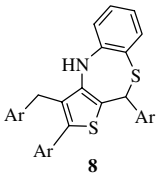


Figure 2. X-ray crystal structure of **1g**.



Scheme 3. Mechanism for the formation of thienobenzothiazepines **1**.



(not formed)

Figure 3.

The structure deduced for **1g** from the NMR studies was in accord with that determined from a single crystal X-ray crystallographic study (Fig. 2).[19]

The tandem reaction leading to **1** presumably proceeds through an initial Michael addition of *o*-aminothiophenol **3** to 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones **4** affording **5** with concomitant condensation to afford **7** either directly from **6** or through **2** (Scheme 3). Presumably, the aromatic stability of the thiophene ring provides the impetus for the isomerisation of **7** to furnish **1** as envisaged in Scheme 1. It is pertinent to note that thienobenzothiazepine **8**, a regioisomer of **1** (Fig. 3) arising from initial Michael addition of **4** to the other benzylidene C=C bond at the 2-position of **4** was not formed, even in traces, in this reaction. This selectivity could probably be ascribed to the conjugation of the sulfur in the five-membered ring with the proximate C=C bond diminishing the electrophilicity and the reactivity of the C=C bond towards the initial Michael addition, which, in turn, determines the regioisomer formed in this tandem sequence.

The present work describes a tandem protocol for the regioselective synthesis of new 3-benzyl-1,10-diaryl-4*H*,10*H*-thieno[3,4-*c*][1,5]benzothiazepines via a Michael addition–condensation–isomerisation sequence. A library of thienobenzothiazepines bearing different substituents on the aryl rings and the electron-rich benzene ring of the benzothiazepine sub-structure can be rapidly accessed using this methodology. The thienobenzothiazepines having two sulfur and one secondary amine functional groups can serve as useful synthons in further synthetic endeavours.

Acknowledgements

S.P. thanks the Council of Scientific and Industrial Research, New Delhi, for a major research project [No. 01(1926/04/EMR II)] and the Department of Science and Technology, New Delhi, for funds under, (i) IRHPA programme for the purchase of a high resolution NMR spectrometer and, (ii) FIST programme and the University Grants Commission, New Delhi for funds under the DRS and ASIST programmes.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.168.

References and notes

1. Katritzky, A. R.; Odens, H. H.; Zhang, S. *J. Org. Chem.* **2001**, *66*, 6792.
2. Prakash, O.; Kumar, A.; Sadana, A.; Prakash, R.; Singh, S. P.; Claramunt, R. M.; Sanz, D.; Alkorta, I.; Elguero, J. *Tetrahedron* **2005**, *61*, 6642.
3. Braun, R. U.; Muller, T. J. J. *Tetrahedron* **2004**, *60*, 9463.
4. Levai, A. *J. Heterocycl. Chem.* **2004**, *41*, 399.
5. (a) Mane, R. A.; Ingle, D. B. *Indian J. Chem., Sect. B* **1982**, *21B*, 973; (b) Jadhav, K. P.; Ingle, D. B. *Indian J. Chem. Sect. B* **1983**, *22B*, 180; (c) Attia, A.; Abdel-salam, O. I.; Abo-Ghalia, M. H.; Amr, A. E. *Egypt. J. Chem.* **1995**, *38*, 543.
6. Reddy, R. J.; Ashok, D.; Sarma, P. N. *Indian J. Chem., Sect. B* **1993**, *32*, 404.
7. Satyanarayana, K.; Rao, M. N. A. *Indian J. Pharm. Sci.* **1993**, *55*, 230.
8. DeSarro, G.; Chimirri, A.; DeSarro, A.; Gitto, R.; Grasso, S.; Zappala, M. *Eur. J. Med. Chem.* **1995**, *30*, 925.
9. *The Chemistry of Heterocyclic Compounds: Thiophene and its Derivatives*; Gronowitz, S., Ed.; Wiley: New York, 1991; Vol. 44.
10. (a) Pinto, I. L.; Jarvest, R. L.; Serafinowska, H. T. *Tetrahedron Lett.* **2000**, *41*, 1597; (b) Luker, T. J.; Beaton, H. G.; Whiting, M.; Mete, A.; Cheshire, D. R. *Tetrahedron Lett.* **2000**, *41*, 7731.

11. (a) *Thiophene and its Derivatives*; Bohlmann, F., Zdero, C., Gronowitz, S., Eds.; John Wiley & Sons: New York, 1985; Part 1, p 261; (b) Koike, K.; Jia, Z.; Nikaido, T.; Liu, Y.; Zhao, Y.; Guo, D. *Org. Lett.* **1999**, *1*, 197.
12. (a) *Conjugated Conducting Polymers*; Kiess, H., Ed. Springer Series in Solid State Sciences; Springer: New York, 1992; Vol. 102; (b) Roncali, J. *Chem. Rev.* **1992**, *92*, 711; (c) Schopf, G.; Kossmehl, G. *Adv. Polym. Sci.* **1997**, *129*, 1.
13. Watanabe, M.; Yamamoto, T.; Nishiyama, M. *Chem. Commun.* **2000**, 133.
14. (a) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831; (b) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131; (c) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103; (d) Ho, T.-L. *Tandem Organic Reactions*; Wiley Interscience: New York, 1992; (e) Tietze, L. F.; Brasche, C.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiely-VCH, 2006.
15. (a) Alex Raja, V. P.; Perumal, S. *Tetrahedron* **2006**, *62*, 4892; (b) Savitha Devi, N.; Perumal, S. *Tetrahedron* **2006**, *62*, 5931; (c) Srinivasan, M.; Perumal, S. *Tetrahedron* **2006**, *62*, 7726; (d) Indumathi, S.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron* **2007**, *63*, 1411; (e) Srinivasan, M.; Perumal, S. *Tetrahedron*, in press; (f) Kamal Nasar, M.; Ranjith Kumar, R.; Perumal, S. *Tetrahedron Lett.* **2007**, *48*, 2155.
16. Anastas, P. T.; Warner, J. C. *Green Chemistry: Theory and Practice*; Oxford University Press: New York, 2000.
17. *General procedure for the synthesis of 3-benzyl-1,10-diaryl-4H,10H-thieno[3,4-c][1,5]benzothiazepines* **1**: conventional method: *o*-aminothiophenol (0.11 g; 0.9 mmol) and 2,4-bis(arylmethylidene)-5-aryldihydro-3(2*H*)-thiophenone (0.6 mmol) were refluxed in acetic acid (2 mL) for 45–60 min. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was poured on to crushed ice, the resulting solid filtered and crystallized from ethyl acetate to afford **1**.
Under microwave irradiation: *o*-aminothiophenol (0.11 g; 0.9 mmol), 2,4-bis(arylmethylidene)-5-aryldihydro-3(2*H*)-thiophenone (0.6 mmol) and a catalytic amount of acetic acid (0.05 mL) were thoroughly mixed in an open glass tube. The tube was placed in a silica bath in a domestic IFB Microwave oven (Model: Electron, operating at 230 V and 50 Hz with a consumption of 1000 W and microwave power maximum level of 600 W and microwave frequency of 2450 MHz) and irradiated for the appropriate time (2–3 min) at maximum power level (600 W) with intermittent cooling after each 30 s of irradiation. The progress of the reaction was monitored by thin layer chromatography and the product was purified by column chromatography on silica gel employing petroleum ether–ethyl acetate [50:1 (v/v)] as eluent to afford a yellow solid, which upon recrystallisation from ethyl acetate gave pure **1**. Spectroscopic data for representative thienobenzothiazepines are given below.
3-(2-Methoxybenzyl)-10-(2-methoxyphenyl)-1-phenyl-4H,10H-thieno[3,4-c][1,5]benzothiazepine, **1g** (Table 1, entry 7): pale yellow solid; mp = 183–184 °C; IR KBr: 3461 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 3.83 (s, 3H), 4.00 (s, 3H), 4.03 (d, 1H, $J = 15.0$ Hz), 4.21 (d, 1H, $J = 15.0$ Hz), 5.74 (s, 1H), 6.50 (t, 1H, $J = 7.5$ Hz), 6.67 (dd, 1H, $J = 8.1$, 0.9 Hz), 6.72 (dd, 1H, $J = 7.5$, 1.8 Hz), 6.80 (dd, 1H, $J = 7.8$, 1.8 Hz), 6.93 (br s, 1H), 7.29 (dd, 1H, $J = 7.8$, 1.8 Hz), 7.35 (dd, 1H, $J = 7.2$, 1.2 Hz), 6.83–7.26 (m, 11H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 26.9, 43.5, 55.8, 55.9, 110.7, 110.8, 115.6, 117.9, 119.6, 119.9, 120.6, 121.4, 127.5, 127.6, 127.8, 128.1, 128.3, 128.8, 128.9, 129.1, 129.8, 130.4, 130.6, 134.2, 134.3, 135.5, 138.1, 145.6, 155.4, 156.5. Anal. Calcd for $C_{32}H_{27}NO_2S_2$: C, 73.67; H, 5.22; N, 2.68. Found: C, 73.56; H, 5.29; N, 2.61.
3-(4-Methylbenzyl)-1,10-bis(4-methylphenyl)-4H,10H-thieno[3,4-c][1,5]benzothiazepine, **1h** (Table 1, entry 8): pale yellow solid; mp = 96–97 °C; IR KBr: 3486 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.20 (s, 3H), 2.32 (s, 3H), 2.39 (s, 3H), 4.04 (d, 1H, $J = 16.8$ Hz), 4.12 (d, 1H, $J = 16.8$ Hz), 5.43 (s, 1H), 5.88 (br s, 1H), 6.20 (d, 1H, $J = 8.1$ Hz), 6.48 (t, 1H, $J = 7.5$ Hz), 6.86 (d, 2H, $J = 7.8$ Hz), 7.02 (d, 2H, $J = 7.8$ Hz), 7.21 (d, 2H, $J = 7.8$ Hz), 7.29 (d, 2H, $J = 7.8$ Hz), 6.90–7.09 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.0, 21.2, 22.6, 32.6, 48.7, 115.3, 117.8, 119.3, 119.6, 127.8, 128.4, 128.5, 128.6, 129.0, 129.3, 129.7, 130.0, 131.0, 134.3, 135.1, 135.3, 135.8, 136.7, 137.6, 137.7, 138.5, 144.5. Anal. Calcd for $C_{33}H_{29}NS_2$: C, 78.69; H, 5.80; N, 2.78. Found: C, 78.78; H, 5.70; N, 2.73.
1-(4-Chlorophenyl)-3-(4-methylbenzyl)-10-(4-methylphenyl)-4H,10H-thieno[3,4-c][1,5]benzothiazepine, **1i** (Table 1, entry 9): pale yellow solid; mp = 99–100 °C; IR KBr: 3369 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 2.21 (s, 3H), 2.39 (s, 3H), 4.04 (d, 1H, $J = 16.8$ Hz), 4.13 (d, 1H, $J = 16.8$ Hz), 5.37 (s, 1H), 5.91 (s, 1H), 6.22 (d, 1H, $J = 8.1$ Hz), 6.50 (t, 1H, $J = 7.5$ Hz), 6.90 (d, 2H, $J = 7.8$ Hz), 6.99 (d, 2H, $J = 7.8$ Hz), 7.12 (d, 2H, $J = 8.4$ Hz), 7.24 (d, 2H, $J = 8.1$ Hz), 7.29 (d, 2H, $J = 7.8$ Hz), 6.21–7.30 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.1, 21.2, 32.7, 48.7, 116.0, 118.0, 119.5, 120.0, 127.8, 128.5, 128.7, 128.8, 129.8, 130.4, 130.5, 132.5, 132.8, 133.8, 135.1, 135.2, 136.0, 136.9, 137.9, 138.4, 144.6. Anal. Calcd for $C_{32}H_{26}ClNS_2$: C, 73.33; H, 5.00; N, 2.67. Found: C, 73.24; H, 4.92; N, 2.69.
18. All the 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones **4** described in this work are new. They were obtained from 5-aryldihydro-3(2*H*)-thiophenones by condensation with aromatic aldehydes in ethanolic sodium hydroxide (Supplementary data, Table S1). Except for one, all the 5-aryldihydro-3(2*H*)-thiophenones used for the preparation of **4** are also new and were prepared following a literature method.[20]
General procedure for the preparation of 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenones **4**: a mixture of 5-aryldihydro-3(2*H*)-thiophenone (5.6 mmol) and aromatic aldehyde (11.2 mmol) in ethanol (25 ml) was treated with aqueous sodium hydroxide (25 ml, 10%) and stirred in an ice bath for 2 h and then at room temperature for 3 h. The reaction mixture was poured on to crushed ice, the precipitated solid filtered, washed with water and crystallized from ethanol to afford **4**. Spectroscopic data for a representative 5-aryl-2,4-bis(arylmethylidene)dihydro-3-thiophenone is given below.
2,4-Bis[(2-methoxyphenyl)methylidene]-5-phenyldihydro-3(2H)-thiophenone, **4g**: (see Supplementary data, Table S1, entry 7). Yellow solid; mp = 127–128 °C; IR KBr: 1589, 1157 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ_H 3.83 (s, 3H), 3.88 (s, 3H), 5.63 (d, 1H, $J = 1.5$ Hz), 6.74 (t, 1H, $J = 7.5$ Hz), 6.81 (d, 1H, $J = 8.4$ Hz), 6.88 (d, 1H, $J = 8.4$ Hz), 6.95 (t, 1H, $J = 7.8$ Hz), 7.60 (d, 1H, $J = 7.8$ Hz), 8.14 (s, 1H), 8.22 (d, 1H, $J = 1.5$ Hz), 7.11–7.30 (m, 8H). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 47.9, 55.4, 110.4, 110.6, 120.0, 120.2, 122.2, 123.2, 124.4, 126.8, 127.4, 128.9, 129.3, 130.2, 130.3, 130.9, 131.5, 133.6, 134.3, 142.4, 158.3, 158.6, 191.5. Anal. Calcd for $C_{26}H_{22}O_3S$: C, 75.34; H, 5.35. Found: C, 75.45; H, 5.43.
19. Crystallographic data (excluding structure factors) for thienobenzothiazepine **1g** in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 631499. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK

[fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

20. Reinhoudt, D. N.; Trompenaars, W. P.; Geevers, J. *Synthesis*, **1978**, 368.
5-(4-Methylphenyl)tetrahydro-3-thiophenone: yellow solid; mp = 55–56 °C; IR KBr: 1730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.37 (s, 3H), 2.81 (dd, 1H, $J = 9.3$, 17.7 Hz), 3.00 (dd, 1H, $J = 6.6$, 17.7 Hz), 3.46 (d, 1H, $J = 17.7$ Hz), 3.53 (d, 1H, $J = 17.7$ Hz), 4.62 (dd, 1H, $J = 6.6$, 9.3 Hz), 7.19 (d, 2H, $J = 7.8$ Hz), 7.29 (d, 2H, $J = 7.8$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.0, 39.7, 45.5, 47.6, 126.9, 129.5, 136.8, 137.7, 212.0. Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.29. Found: C, 68.79; H, 6.20.