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Benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide—a versatile reagent in the synthesis of spiroheterocycles

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ABSTRACT

New applications of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide have been investigated. The synthesis of a new heterocyclic system 3*H*,2′*H*-spiro[benzo[*b*]thieno[3,2-*b*]pyridine-3,2′-benzo[*b*]thiophene] is described and a mechanism for the cyclisation is proposed.

1. Introduction

Several synthetic methods for obtaining tetrahydropyridines with geminal substituents have been already reported. Thus, under Hantzsch reaction conditions an ester of *p*-nitrobenzoylacetic acid with hexamethylenetetramine and ammonium acetate forms a derivative of 3,3,5-tricarbonyl-1,2,3,4-tetrahydropyridine with geminal substituents at position 3, instead of the corresponding 1,4-dihydropyridine derivative.[1] Alternatively, the condensation of ethyl benzoylacetate with 1,3,5-trimethylhexahydro-1,3,5-triazine gives a tetrahydropyridine with geminal substituents at position 5 of the 1,4,5,6-tetrahydropyridine ring.[2]

Only a few types of spiroderivatives of fused tetrahydropyridines have been previously synthesised. The cyclic β-diketone, 1,3-indandione, with formaldehyde and primary amines readily forms 2-spiroindan-1,3-diones.[3] *N*-Monosubstituted 3-aminoindene-1-ones with formaldehyde and free secondary amines also afford spirocyclic indenopyridine derivatives instead of the expected bicyclic Mannich products.[4] The formation of spirocyclic derivatives from 3-aminocyclohex-2-enones with formaldehyde was investigated in detail and a reaction mechanism was proposed.[5,6] The *gem*-dimethyl groups of the dimedone derivative directed the reaction to give exclusively the spirocyclic compound formed by an internal Mannich reaction. In the case of unsubstituted cyclohexanedione enaminones mixtures of spirocyclic compounds and acridinedione derivatives were formed.

Herein, we describe the synthesis of a novel heterocyclic system 3*H*,2′*H*-spiro[benzo[*b*]thieno[3,2-*b*]pyridine-3,2′-benzo[*b*]-thiophene] from a β-diketone analogue—benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide.

2. Results and discussion

The main task of our studies was to identify reaction conditions directing the cyclisation of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **1** into the new sulfonyl group containing spirocyclic heterocycles.

Benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide[7] **1** is a versatile reagent containing a sulfonyl group for the synthesis of polycyclic pyridines. Previously, we have found that the compound **1**, like 1,3-indandione, undergoes cyclisation to 1,4-dihydrobenzothieno-[3,2-*b*]-pyridine-5,5-dioxides.[8] Compound **1** with aromatic aldehydes easily forms 2-ylidene derivatives **6**.[9]

1,5-Dicarbonyl derivatives **2** were obtained in the reaction of compound **1** with aromatic aldehydes in ethanol/DMF mixture in the presence of catalytic piperidine and acetic acid at reflux temperature in 2 h (Scheme 1). In the case of **2a**, the crystals obtained from the reaction mixture were suitable for X-ray analysis.

We examined the internal Mannich reaction approach to generate 3,2′-spiroderivatives **3** from 1,5-dicarbonyl derivatives **2**. Previously, the formation of spirocyclic derivatives was achieved only from 3-aminocyclohex-2-enones[5] and 1,3-indandiones.[3] This study disclosed the ability of aryl substituted 1,5-dicarbonyl compounds **2a–c** to undergo cyclisation into spirocycles **3a–c**. The condensation of derivatives **2a–c** with hexamethylenetetramine in acidic medium leads to the expected new heterocyclic spirosystems **3a–c**, which might reasonably arise from an internal Mannich reaction of compounds **2a–c** due to the steric hindrance of the aryl substituent. NMR spectroscopic studies have shown the existence of chiral stereomers and *meso* forms of 1,5-dicarbonyl compounds **2a–c** in the approximate ratio 2:1.

Investigation of the reaction course has demonstrated that the reactivity of stereoisomers of 1,5-dicarbonyl derivatives **2a–c** was not affected by its configurational structure, since compounds **2a–c** rapidly disappeared from the reaction mixture. The putative

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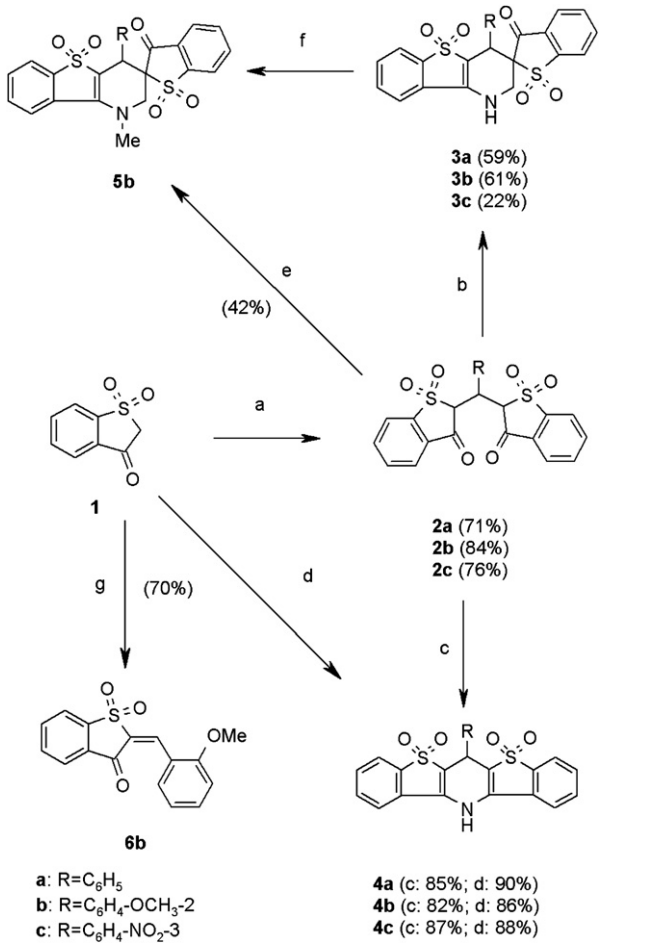
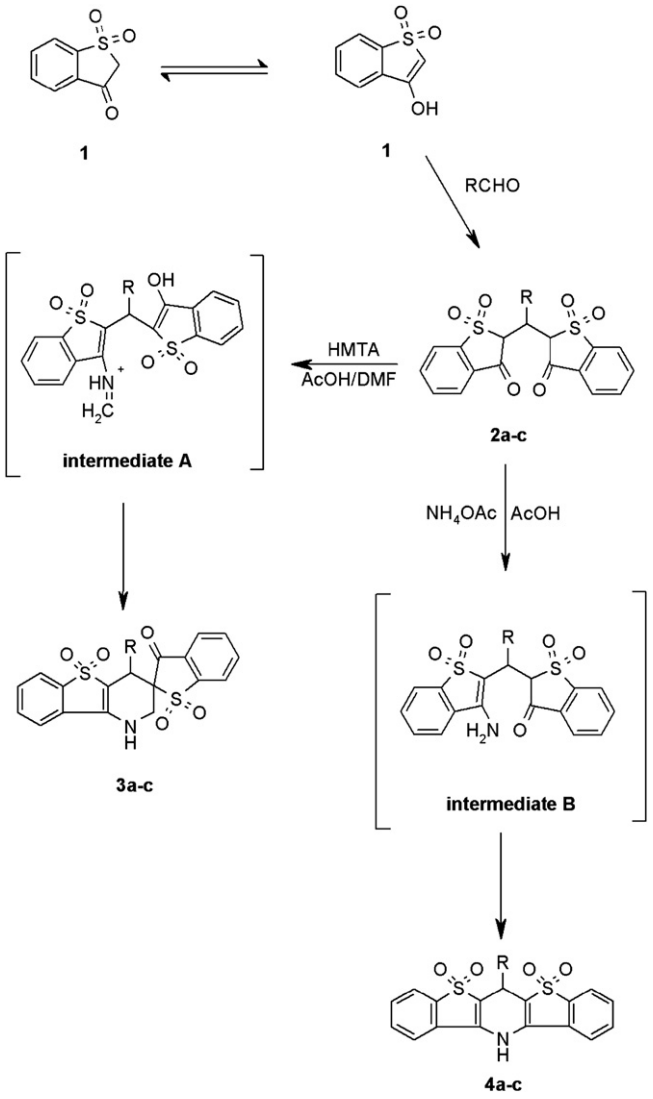


Scheme 1. Formation of 3,2′-spirocycles **3a**–**c** and dihydrodibenzothienopyridines **4a**–**c** from 1,5-dicarbonyl compounds **2a**–**c**. Reagents and conditions: (a) RCHO, EtOH/DMF, rt or reflux; (b) hexamethylenetetramine (HMTA), AcOH/DMF; (c) $AcONH_4$, AcOH, reflux; (d) RCHO, $AcONH_4$, AcOH, reflux; (e) 1,3,5-trimethylhexahydro-1,3,5-triazine, AcOH, reflux; (f) MeI/NaH or Me_2SO_4/NaH; (g) RCHO, $AcONH_4$, EtOH/AcOH, rt.



Scheme 2. Proposed mechanism for the formation of 3,2′-spirocycles **3a**–**c** from 1,5-dicarbonyl compounds **2a**–**c** and hexamethylenetetramine via internal Mannich reaction.

mechanism of formation of spirocyclic derivatives from 3-aminocyclohex-2-enones with formaldehyde was proposed by Greenhill et al.[5,6] According to the authors the 3,2′-spirocyclic compounds might reasonably arise from an internal Mannich reaction. Possible mechanism for the cyclocondensation of 1,5-dicarbonyl compounds **2a**–**c** and hexamethylenetetramine is shown in Scheme 2.

The unstable Mannich intermediate **A** gives the target spirocycles **3a**–**c**. On the other hand, compounds **2a**–**c** in reaction with ammonium acetate form the intermediate **B**. The intramolecular addition of amino group to the carbonyl group (intermediate **B**) furnishes dihydrodibenzothienopyridines **4a**–**c** via Hantzsch type cyclisation. Ring-opening–ring-closure rearrangements were previously described for transformation of 3,3,5-tricarbonyl-1,2,3,4-tetrahydropyridines into pyridine derivatives with loss of formaldehyde.[1] 3,2′-Spirocyclic derivatives were not rearranged to compounds **4a**–**c** in acidic media.

Alkylation of compound **3b** required rather drastic conditions, such as MeI/NaH and Me_2SO_4/NaH. Using this method, only a mixture of alkylated and N–H products was obtained, where the alkylated product **5b** was the minor compound. The approach was found to be inefficient for the preparation of *N*-alkylated derivatives **5** via alkylation of 3,2′-spirocycles **3**. To avoid tedious purification work, a better approach to *N*-alkylated derivative **5b** was developed, which involved condensation of 1,5-dicarbonyl compound **2b** and 1,3,5-trimethylhexahydro-1,3,5-triazine in acetic acid.

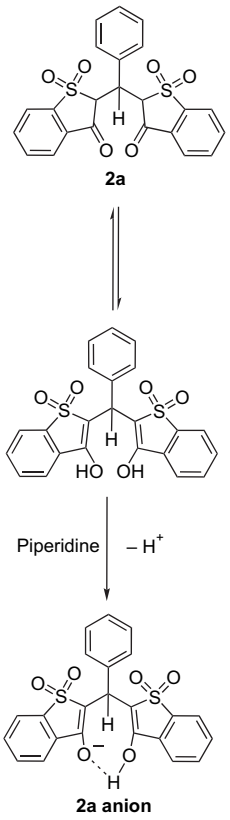
The reaction of the compound **1** with aromatic aldehydes and ammonium acetate in acetic acid under reflux led to dihydrodibenzothienopyridines **4a**–**c**, alternatively, compounds **4a**–**c** can be obtained from 1,5-dicarbonyl derivatives **2a**–**c** under similar reaction conditions.

When reaction of compound **1** with 2-methoxybenzaldehyde and ammonium acetate was performed in a mixture of ethanol and acetic acid at rt only 2-arylidenebenzothiophene derivative **6b** was obtained instead of the expected product **4b**.

Compound **2a** consists of 2 diastereomers of *meso* type—symmetrical (achiral) one with C2 and C2′ configurations equal (*RR* and *SS*) and chiral one with C2 and C2′ configurations different (*RS* and *SR*). Both diastereomers give distinctly different ^1H spectra (see Section 4.2.1). Averaged coupling constant $^3J_{H2-PhCH} \approx 7$ Hz value in achiral diastereomer probably indicates free rotation around C2–PhCH bond. On contrary very distinct values of both $^3J_{H2-PhCH}$ and $^3J_{PhCH-H2'}$ couplings points to serious sterical problems in the chiral diastereomer **2a** and rotations around C2–PhCH as well as around PhCH–C2′ are hindered.

The compound **2a** gives salts due to moveable enol hydrogens (Scheme 3). For the piperidinium salt of **2a**, monocrystals were obtained. X-ray structure analysis of the crystals shows the formation of **2a anion** and hindered rotation occurs in this case.

The X-ray structure of **2a** is given in Supplementary data, as the dimethylformamide solvate of **2a** piperidinium salt.



Scheme 3. Formation of **2a anion**.

The structural elucidation of the new heterocyclic system, 3*H*,2′*H*-spirocyclic compound **3**, was mainly based on NMR spectra and for compound **5b** also on X-ray analysis data.

The determination of structure **3b** was accomplished on the basis of 2D-NMR ^{1}H–^{1}H and ^{1}H–^{13}C spectra recorded in DMSO-d_6 solution. The comparison of ^{1}H–^{1}H TOCSY, ^{1}H–^{1}H DQF-COSY, ^{1}H–^{13}C HSQC and ^{1}H–^{13}C HMBC spectra led to the conclusion that the structure of compound **3b** corresponds to the one depicted in Figure 1. The ^{1}H and ^{13}C chemical shifts given in Section 4 are in full agreement with the proposed structure. 2D ^{1}H–^{1}H ROESY experiment with mixing time 100 ms showed two important

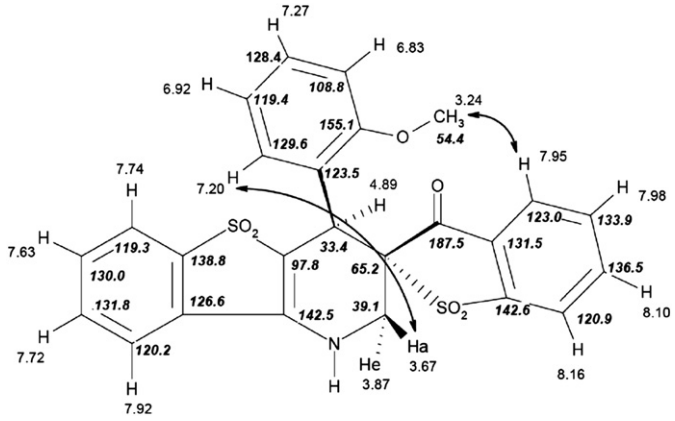


Figure 1. Drawing of structure **3b**. The ^{1}H chemical shifts are given by the numbers with regular type, and ^{13}C ones with the numbers in bold and italics. Arrows indicate the NOEs observed.

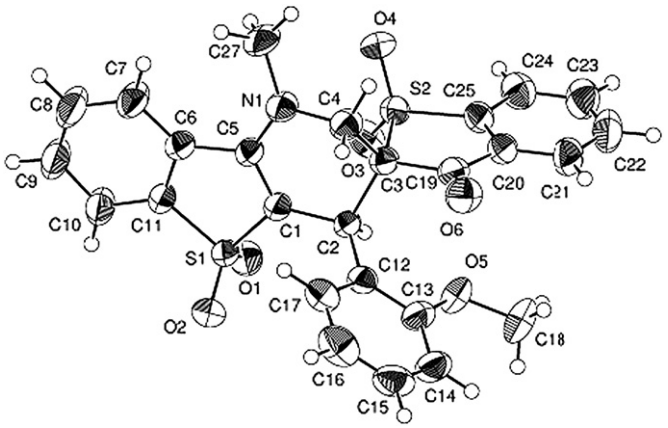


Figure 2. The molecular structure of **5b**.

unconventional NOEs between (a) OCH_3 and H4′, and (b) H6″ and H2a (Fig. 1) that together with the long range coupling $^{4}J_{H4-H2e}$=1.5 Hz allowed to define the pseudoaxial stereo orientation of aromatic ring in position 4 of tetrahydropyridine ring. The relative orientation of 3′-CO and 1′-SO_2 substituents in position 3 were tentatively assigned on the basis that there were no strong HMBC cross peaks between H2e and H2a and carbonyl C3′ as well as H4 and carbonyl C3′. This indicates that the dihedral angles ^{1}H4–C4–C3–^{13}C3′, ^{1}H2a–C2–C3–^{13}C3′ and ^{1}H2e–C2–C3–^{13}C3′ all are close to 60° that defines the 'up' orientation of carbonyl C3′ close to 4-(2-methoxyphenyl) ring. This conclusion was confirmed by X-ray analysis of the analogous compound **5b**.

For the confirmation of structure **5b**, X-ray diffraction studies were carried out on monocrystals of **5b**. Figure 2 illustrates a diagram of the molecule **5b** giving the atomic numbering scheme followed in the text. There are only a few examples of crystal structure of benzothiophene dioxides in the literature. A search of the Cambridge Structural Database[10] (Version 5.28, November 2006) indicated that there are only 24 entries of these compounds. The conformation of the six-membered cycle of N1–C5–C1–C2–C3–C4 is near to the envelope. The deviation of atom C3 from the mean least-squares plane of C4–N1–C5–C1–C2 equals to 0.641(4) Å. The intermolecular contacts correspond to the sums of the van der Waals radii.

3. Conclusions

The present study demonstrates the usefulness of sulfonyl group containing 1,3-indandione analogue, benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide, which with aromatic aldehydes easily forms 2,2′-(arylmethylene)bis(benzo[*b*]thiophen-3(2*H*)-one) 1,1,1′,1′-tetraoxides and with aromatic aldehydes and ammonium acetate forms 11-aryl-5,11-dihydrodi(benzo[*b*]thieno)[3,2-*b*:2′,3′-*e*]pyridine 10,10,12,12-tetraoxides. We have performed the synthesis of a novel heterocyclic system, 4-aryl-1,4-dihydro-3*H*,2′*H*-spiro[benzo[*b*]thieno[3,2-*b*]pyridine-3,2′-benzo[*b*]thiophen]-3′-one 1′,1′,5,5-tetraoxides, from 2,2′-(arylmethylene)bis(benzo[*b*]thiophen-3(2*H*)-one) 1,1,1′,1′-tetraoxides and hexamethylenetetramine in the internal Mannich reaction.

4. Experimental

4.1. General

All reagents were purchased from Aldrich, Acros, Fluka or Merck and used without further purification. TLC was performed on 20×20 cm Silica gel TLC-PET F_{254} foils (Fluka). NMR spectra were recorded with a Varian Mercury 200BB (200 MHz) or Bruker DMX-

600 (600 MHz) spectrometer equipped with a cryoprobe in deuterated dimethylsulfoxide (DMSO-d_6) solution at 25 °C. Chemical shifts are reported in parts per million relative to residual solvent signal (δ(^{1}H) 2.50 ppm, δ(^{13}C) 39.5 ppm). Two-dimensional spectra recorded included DQF-COSY, ROESY, TOCSY, sensitivity-enhanced ^{13}C HSQC and ^{13}C–^{1}H HMBC. Pulsed-field gradients were used for all ^{13}C correlation spectra. ^{13}C HMBC spectra were recorded with coupling evolution delay for the generation of multiple-bond correlations set to 62.5 ms. All 2D spectra were run with 4096×1024 points data matrix, giving τ_{2max}=250 ms for ^{1}H nucleus in acquisition dimension and τ_{1max}=200 ms for ^{1}H or τ_{1max}=50 ms for ^{13}C for indirect dimension. Prior to Fourier transform, the data matrix was zero-filled twice and multiplication by shifted sine-bell window function applied. For ^{1}H–^{13}C HMBC the magnitude spectra were calculated. Mass spectral data were determined on an Acquity UPLC system (Waters) connected to a Q-TOF micro hybrid quadrupole time of flight mass spectrometer (Micromass) operating in the ESI positive or negative ion mode on a Aquity UPLC BEH C18 column (1.7 μm, 2.1 mm×50 mm) using a gradient elution with acetonitrile/formic acid (0.1%) in water or Alliance HPLC system (Waters) connected to a Micromass Quatro micro API mass spectrometer (Micromass) operating in the ESI positive ion mode on a Symmetry HPLC C18 column (3.5 μm, 3.0 mm×150 mm) with a mobile phase of acetonitrile/DMF/heptafluorobutyric acid (0.5%) in water (55:5:40 by volume). Melting points were determined on a Boetius apparatus. Elemental analyses were determined on a Carlo-Erba elemental analyser.

4.2. 2,2′-(Arylmethylene)bis(benzo[*b*]thiophen-3(2*H*)-one) 1,1,1′,1′-tetraoxides (2a–c)

General procedure. Benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **1** (1.82 g, 10 mmol) and the corresponding aldehyde (5.0 mmol) were dissolved in the mixture of ethanol (50 mL) and DMF (5 mL) in the presence of the catalytic amount of piperidine and acetic acid. The mixture was heated under reflux with stirring for 2 h. After cooling the white precipitate was filtered off and crystallised from ethanol/DMF (**2a**,**b**) and acetic acid/DMF (**2c**).

*4.2.1. 2,2′-(Phenylmethylene)bis(benzo[b]thiophen-3(2H)-one) 1,1,1′,1′-tetraoxide (**2a**)*

Yield: 1.6 g (71%); white powder, mp 184–186 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ *meso*-**2a**: 4.31 (t, 1H, *J*=7.2 Hz, PhCH), 5.23 (d, 2H, *J*=7.2 Hz, H2, H2′), 7.24 (t, 1H, *J*=8.0 Hz, H4″), 7.32 (t, 2H, *J*=8.0 Hz, H3″, H5″), 7.52 (d, 2H, *J*=8.0 Hz, H2″, H6″), 7.80–8.20 (m, 8H, H4–H7 and H4′–H7′) and diastereomeric mixture of *RS*-**2a** and *SR*-**2a**: 4.46 (dd, 1H, *J*=11.2 and 2.2 Hz, PhCH), 5.17 (d, 1H, *J*=2.2 Hz, H2 or H2′), 5,64 (d, 1H, *J*=11.2 Hz, H2 or H2′), 7.31 (t, 1H, *J*=8.0 Hz, H4″), 7.39 (t, 2H, *J*=8.0 Hz, H3″, H5″), 7.54 (d, 2H, *J*=8.0 Hz, H2″, H6″), 7.80–8.20 (m, 8H, H4–H7 and H4′–H7′); IR (Nujol): 1587 (C═C), 1715 (C═O), 1731 (C═O) cm^{-1}; MS (+ESI) *m*/*z* (relative intensity): 453 ([M+H]$^+$, 15). Anal. Calcd for $C_{23}H_{16}O_6S_2$: C, 61.05; H, 3.56; S, 14.17. Found: C, 60.89; H, 3.50; S, 14.52.

*4.2.2. 2,2′-[(2-Methoxyphenyl)methylene]bis(benzo[b]thiophen-3(2H)-one) 1,1,1′,1′-tetraoxide (**2b**)*

Yield: 2.04 g (84%); white powder, mp 204 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ *meso*-**2b**: 3.83 (s, 3H, overlap), 4.63 (t, 1H, *J*=5.9 Hz), 5.24 (d, 2H, *J*=5.9 Hz, overlap), 7.03 (t, 1H, *J*=8.1 Hz, overlap), 7.34 (t, 1H, *J*=8.1 Hz, overlap), 7.54–7.74 (m, 2H), 7.87–8.25 (m, 8H) and diastereomeric mixture of *RS*-**2b** and *SR*-**2b**: 3.78 (s, 3H, overlap), 4.82 (dd, 1H, *J*=2.2 and 11.7 Hz), 5.13 (d, 1H, *J*=2.2 Hz, overlap), 5.77 (d, 1H, *J*=11.7 Hz), 7.07 (t, 1H, *J*=8.1 Hz, overlap), 7.38 (t, 1H, *J*=8.1 Hz, overlap), 7.54–7.74 (m, 2H), 7.87–8.25 (m, 8H); IR (Nujol): 1580 (C═C), 1720 (C═O), 1730 (C═O) cm^{-1}; MS (+ESI) *m*/*z* (relative intensity): 483 ([M+H]$^+$, 17). Anal. Calcd for $C_{24}H_{18}O_7S_2$: C, 59.74; H, 3.76; S, 13.29. Found: C, 59.73; H, 3.71; S, 13.37.

*4.2.3. 2,2′-[(3-Nitrophenyl)methylene]bis(benzo[b]thiophen-3(2H)-one) 1,1,1′,1′-tetraoxide (**2c**)*

Yield: 1.88 g (76%); white powder, mp 193–194 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ *meso*-**2c**: 4.50 (t, 1H, *J*=6.6 Hz), 5.40 (d, 2H, *J*=6.2 Hz), 7.65–7.81 (m, 5H), 7.90–8.47 (m, 8H) and diastereomeric mixture of *RS*-**2c** and *SR*-**2c**: 4.67 (dd, 1H, *J*=11.0 and 2.9 Hz), 5.39 (d, 1H, *J*=2.9 Hz), 5.78 (d, 1H, *J*=11.0 Hz), 7.65–7.81 (m, 5H), 7.90–8.47 (m, 8H); IR (Nujol): 1580 (C═C), 1730 (C═O) cm^{-1}. Anal. Calcd for $C_{23}H_{15}NO_8S_2$: C, 55.53; H, 3.04; N, 2.82; S, 12.89. Found: C, 55.26; H, 2.97; N, 2.63; S, 13.23.

4.3. 4-Aryl-1,4-dihydro-3*H*,2′*H*-spiro[benzo[*b*]thieno[3,2-*b*]pyridine-3,2′-benzo[*b*]thiophen]-3′-one 1′,1′,5,5-tetraoxides (3a–c)

General procedure. To a mixture of the appropriate 2,2′-(arylmethylene)bis(benzo[*b*]thiophen-3(2*H*)-one) 1,1,1′,1′-tetraoxides **2a**–**c** (1 mmol) in acetic acid (10 mL) and DMF (6 mL) hexamethylenetetramine (0.42 g, 3 mmol) was added, and the reaction mixture was heated under reflux with stirring for 24 h. After cooling the mixture, the precipitated product was filtered off and crystallised from a mixture of acetic acid and DMF.

*4.3.1. 4-Phenyl-1,4-dihydro-3H,2′H-spiro[benzo[b]thieno[3,2-b]pyridine-3,2′-benzo[b]thiophen]-3′-one 1′,1′,5,5-tetraoxide (**3a**)*

Yield: 0.25 g (59%); grey powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.86 (d, 1H, *J*=13.9 Hz, overlap), 3.98 (dd, 1H, *J*=2.9 and 13.9 Hz, overlap), 4.55 (s, 1H), 7.00–7.08 (m, 2H), 7.09–7.21 (m, 3H), 7.65 (dd, 1H, *J*=7.3 and 8.1 Hz, overlap), 7.68 (dd, 1H, *J*=7.3 and 8.1 Hz, overlap), 7.78 (d, 1H, *J*=6.6 Hz, overlap), 7.87 (d, 1H, *J*=8.1 Hz, overlap), 7.93 (d, 1H, *J*=6.6 Hz, overlap), 8.00 (dd, 1H, *J*=7.3 and 8.1 Hz, overlap), 8.14 (dd, 1H, *J*=7.3 and 8.1 Hz, overlap), 8.28 (d, 1H, *J*=8.1 Hz, overlap), 8.63 (br d, 1H, *J*=3.7 Hz); IR (Nujol): 1705 (C═O), 3300 (N–H) cm^{-1}; MS (+ESI) *m*/*z* (relative intensity): 464 ([M+H]$^+$, 100), 486 ([M+Na]$^+$, 5). Anal. Calcd for $C_{24}H_{17}NO_5S_2$: C, 62.19; H, 3.70; N, 3.02; S, 13.83. Found: C, 61.72; H, 3.59; N, 3.06; S, 14.08.

*4.3.2. 4-(2-Methoxyphenyl)-1,4-dihydro-3H,2′H-spiro-[benzo[b]thieno[3,2-b]pyridine-3,2′-benzo[b]thiophen]-3′-one 1′,1′,5,5-tetraoxide (**3b**)*

Yield: 0.30 g (61%); white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 600 MHz): δ 3.24 (s, 3H, OCH_3), 3.67 (d, 1H, *J*=14.4 Hz, H2a), 3.87 (ddd, 1H, *J*=1.5, 5.5 and 14.4 Hz, H2e), 4.89 (d, 1H, *J*=1.5 Hz, H4), 6.83 (d, 1H, *J*=8.0 Hz, H3″), 6.92 (t, 1H, *J*=8.0 Hz, H5″), 7.20 (dd, 1H, *J*=2.0 and 8.0 Hz, H6″), 7.27 (dt, 1H, *J*=2.0 and 8.0 Hz, H4″), 7.63 (t, 1H, *J*=8.0 Hz, H7), 7.72 (t, 1H, *J*=8.0 Hz, H8), 7.74 (d, 1H, *J*=8.0 Hz, H6), 7.92 (d, 1H, *J*=8.0 Hz, H9), 7.95 (d, 1H, *J*=8.0 Hz, H4′), 7.98 (t, 1H, *J*=8.0 Hz, H5′), 8.10 (dt, 1H, *J*=2.0 and 8.0 Hz, H6′), 8.16 (dd, 1H, *J*=8.0 and 2.0 Hz, H7′), 8.50 (br d, 1H, *J*=5.5 Hz, NH); ^{13}C NMR (DMSO-d_6, 150 MHz): δ 33.4 (C4), 39.1 (C2), 54.4 (OCH_3), 65.2 (C3), 97.8 (C4a), 108.8 (C3″), 119.3 (C6), 119.4 (C5″), 120.2 (C9), 120.9 (C7′), 123.0 (C4′), 123.5 (C1″), 126.6 (C9a), 128.4 (C4″), 129.6 (C6″), 130.0 (C7), 131.5 (C3′a), 131.8 (C8), 133.9 (C5′), 136.5 (C6′), 138.8 (C5a), 142.5 (C9b), 142.6 (C7′a), 155.1 (C2″), 187.5 (C3′); IR (Nujol): 1627, 1705 (C═O), 3300 (N–H) cm^{-1}; MS (+ESI) *m*/*z* (relative intensity) 494 ([M+H]$^+$, 92), 516 ([M+Na]$^+$, 77). Anal. Calcd for $C_{25}H_{19}NO_6S_2$: C, 60.84; H, 3.88; N, 2.84; S, 12.99. Found: C, 60.67; H, 3.73; N, 2.81; S, 12.95.

*4.3.3. 4-(3-Nitrophenyl)-1,4-dihydro-3H,2′H-spiro[benzo-[b]thieno[3,2-b]pyridine-3,2′-benzo[b]thiophen]-3′-one 1′,1′,5,5-tetraoxide (**3c**)*

Yield: 0.11 g (22%); pale yellow powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.81 (d, 1H, *J*=14.7 Hz), 4.05 (dd, 1H, *J*=2.9

and 14.7 Hz), 4.94 (s, 1H), 7.59 (dd, 1H, *J*=7.3 and 7.3 Hz, overlap), 7.62–7.76 (m, 2H overlap), 7.80 (d, 2H, *J*=7.3 Hz, overlap), 7.87–8.02 (m, 4H, overlap), 8.18–8.21 (m, 2H), 8.27 (d, 1H, *J*=7.3 Hz), 8.78 (br d, 1H, *J*=4.4 Hz); IR (Nujol): 1720, 1735 (C=O), 3280 (N–H) cm^{-1}; MS (−ESI) *m*/*z* (relative intensity): 507 ($[M-H]^+$, 100), 508 ($[M+]^+$, 35). Anal. Calcd for $C_{24}H_{16}N_2O_7S_2$: C, 56.69; H, 3.17; N, 5.51; S, 12.61. Found: C, 56.59; H, 2.77; N, 5.27; S, 12.49.

4.4. 11-Aryl-5,11-dihydrodi(benzo[*b*]thieno)[3,2-*b*:2′,3′-*e*]pyridine 10,10,12,12-tetraoxides (4a–c)

General procedure. Method A: a solution of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **1** (0.46 g, 2.5 mmol), the corresponding aldehyde (2.5 mmol) and ammonium acetate (0.77 g, 10 mmol) in glacial acetic acid was stirred under reflux for 6 h. After cooling the mixture, the pale yellow precipitate was filtered off and crystallised from acetic acid/DMF or washed with hot AcOH/DMF (for **4c**) to give the compounds **4a**–**c**.

*4.4.1. 11-Phenyl-5,11-dihydrodi(benzo[b]thieno)[3,2-b:2′,3′-e]pyridine 10,10,12,12-tetraoxide (**4a**)*

Yield: 0.46 g (85%); white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.21 (s, 1H), 7.29–7.33 (m, 3H), 7.45 (dd, 2H, *J*=1.5 and 7.4 Hz), 7.71 (dd, 2H, *J*=7.5 and 7.5 Hz), 7.89 (dd, 2H, *J*=7.5 and 7.5 Hz, overlap), 7.89 (d, 2H, *J*=7.5 Hz, overlap), 8.33 (d, 2H, *J*=7.5 Hz), 10.55 (br s, 1H); IR (Nujol): 1654 (C=C), 3399 (N–H) cm^{-1}; MS (+ESI) *m*/*z* (relative intensity) 434 ($[M+H]^+$, 10). Anal. Calcd for $C_{23}H_{15}NO_4S_2$: C, 63.72; H, 3.49; N, 3.23; S, 14.79. Found: C, 63.59; H, 3.51; N, 3.21; S, 14.61.

*4.4.2. 11-(2-Methoxyphenyl)-5,11-dihydrodi(benzo[b]thieno)[3,2-b:2′,3′-e]pyridine 10,10,12,12-tetraoxide (**4b**)*

Yield: 0.48 g (82%); white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.81 (s, 3H), 5.60 (s, 1H), 6.86 (dd, 1H, *J*=7.3 and 7.3 Hz), 6.98 (d, 1H, *J*=7.3 Hz), 7.22 (ddd, 1H, *J*=1.5, 7.3 and 7.3 Hz), 7.33 (dd, 1H, *J*=1.5 and 7.3 Hz), 7.68 (dd, 2H, *J*=7.3 and 7.3 Hz, overlap), 7.84 (dd, 2H, *J*=7.3 and 7.3 Hz, overlap), 7.87 (d, 2H, *J*=7.3 Hz, overlap), 8.28 (d, 2H, *J*=7.3 Hz), 10.41 (br s, 1H); IR (Nujol): 1665 (C=C), 3360 (N–H) cm^{-1}. Anal. Calcd for $C_{24}H_{17}NO_5S_2$: C, 62.19; H, 3.70; N, 3.03; S, 13.84. Found: C, 61.91; H, 3.67; N, 2.99; S, 13.72.

*4.4.3. 11-(3-Nitrophenyl)-5,11-dihydrodi(benzo[b]thieno)[3,2-b:2′,3′-e]pyridine 10,10,12,12-tetraoxide (**4c**)*

Yield: 0.52 g (87%); white powder, mp >300 °C; ^{1}H NMR (DMSO-d_6, 200 MHz): δ 5.55 (s, 1H), 7.71 (dd, 2H, *J*=7.3 and 7.3 Hz), 7.88 (dd, 2H, *J*=7.3 and 7.3 Hz, overlap), 7.87 (dd, 1H, *J*=7.3 and 7.3 Hz, overlap), 7.90 (d, 2H, *J*=7.3 Hz, overlap), 8.02 (d, 1H, *J*=7.3 Hz), 8.16 (dd, 1H, *J*=2.2 and 7.3 Hz), 8.34 (d, 2H, *J*=7.3 Hz, overlap), 8.36 (s, 1H, overlap), 10.68 (br s, 1H); IR (Nujol): 1663 (C=C), 3281 (N–H) cm^{-1}. Anal. Calcd for $C_{23}H_{14}N_2O_6S_2$: C, 57.74; H, 2.95; N, 5.86; S, 13.41. Found: C, 54.45; H, 2.85; N, 5.72; S, 12.98.

Method B: to a mixture of the appropriate 2,2′-(arylmethylene)bis(benzo[*b*]thiophen-3(2*H*)-one) 1,1,1′,1′-tetraoxide **2a**–**c** (1 mmol) in glacial acetic acid (20 mL), ammonium acetate (0.77 g, 10 mmol) was added and the reaction mixture was stirred under reflux for 6 h. After cooling the mixture, the precipitated product was filtered off and crystallised from acetic acid/DMF (for **4a**,**b**) or washed with hot AcOH/DMF (for **4c**) to give the compounds **4a**–**c**.

*4.4.4. 11-Phenyl-5,11-dihydrodi(benzo[b]thieno)[3,2-b:2′,3′-e]pyridine 10,10,12,12-tetraoxide (**4a**)*

Yield: 0.39 g (90%). The ^{1}H NMR spectrum is in accordance with the one described in Section 4.4.1 for compound **4a** obtained by method A.

*4.4.5. 11-(2-Methoxyphenyl)-5,11-dihydrodi(benzo[b]thieno)[3,2-b:2′,3′-e]pyridine 10,10,12,12-tetraoxide (**4b**)*

Yield: 0.40 g (86%). The ^{1}H NMR spectrum is in accordance with the one described in Section 4.4.2 for compound **4b** obtained by method A.

*4.4.6. 11-(3-Nitrophenyl)-5,11-dihydrodi(benzo[b]thieno)[3,2-b:2′,3′-e]pyridine 10,10,12,12-tetraoxide (**4c**)*

Yield: 0.42 g (88%). The ^{1}H NMR spectrum is in accordance with the one described in Section 4.4.3 for compound **4c** obtained by method A.

4.5. 4-(2-Methoxyphenyl)-1-methyl-1,4-dihydro-2*H*,3′*H*-spiro[benzo[*b*]thieno[3,2-*b*]pyridine-3,2′-benzo[*b*]thiophen]-3′-one 1′,1′,5,5-tetraoxide (5b)

Method A: to a solution of **3b** (0.25 g, 0.5 mmol) in DMF (2 mL) was added NaH (0.06 g, 1 mmol). The reaction mixture was stirred for 30 min at rt, after which MeI (0.13 mL, 2 mmol) was added and the mixture was stirred for another 1.5 h at 50 °C. The reaction mixture was diluted with water and the precipitated product was filtered off to give a mixture of **5b** and **3b** (0.11 g). ^{1}H NMR (DMSO-d_6, 200 MHz): δ (major peaks) 3.25 (s, 3H, N–CH_3) and 8.62 (br d, 1H, *J*=5.5 Hz, NH).

Method B: to a solution of **3b** (0.25 g, 0.5 mmol) in HMPA (2 mL) was added NaH (0.06 g, 1 mmol). The reaction mixture was stirred for 30 min at rt, after which Me_2SO_4 (0.15 mL, 2 mmol) was added and the mixture was stirred for another 30 min at 50 °C. The reaction mixture was diluted with water and the precipitated product was filtered off to give a mixture of **5b** and **3b** (0.12 g).

Method C: methylamine solution in water (40 wt %, 4 mL, 46.2 mmol) and formaldehyde solution in water (37 wt %, 4 mL, 55.2 mmol) were mixed at −18 °C and kept in a refrigerator for 3 h. The resulting water solution containing 1,3,5-trimethylhexahydro-1,3,5-triazine (8 mL, ca. 15.4 mmol) was added to a suspension of **2b** (0.48 g, 1 mmol) in glacial acetic acid (20 mL) at rt. After being stirred at reflux for 2 h, the resulting mixture was diluted with water and extracted with $CHCl_3$. The extract was washed successively with water and brine, and then dried over $MgSO_4$. After removal of solvents in vacuum the residue was crystallised from methanol giving **5b** as a yellow powder (0.21 g, 42%), mp >300 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.20 (s, 3H), 3.58 (s, 3H), 3.83 (dd, 2H, *J*=3.7 and 1.5 Hz), 4.85 (s, 1H), 6.85 (d, 1H, *J*=8.1 Hz), 6.92 (dd, 1H, *J*=8.1 and 7.4 Hz), 7.26 (d, 1H, *J*=7.3 Hz, overlap), 7.29 (ddd, 1H, *J*=1.5, 6.6 and 7.3 Hz, overlap), 7.70 (dd, 1H, *J*=6.6 and 7.3 Hz, overlap), 7.72 (d, 1H, *J*=6.6 Hz, overlap), 7.83 (d, 1H, *J*=5.9 Hz), 7.99 (ddd, 1H, *J*=1.5, 5.9 and 8.1 Hz, overlap), 8.00 (d, 1H, *J*=5.9 Hz, overlap), 8.17–8.09 (m, 2H), 8.23 (d, 1H, *J*=7.3 Hz); IR (Nujol): 1630, 1710 (C=O) cm^{-1}; MS (+ESI) *m*/*z* (relative intensity): 508 ($[M+H]^+$, 100), 530 ($[M+Na]^+$, 18). Anal. Calcd for $C_{26}H_{21}NO_6S_2$: C, 61.52; H, 4.17; N, 2.76; S, 12.63. Found: C, 61.53; H, 3.93; N, 2.47; S, 12.49.

4.6. Crystal data for compounds 5b and 2a

Calculations were carried out with the complexes of programs.[11,12] For crystallographic data, see Cambridge Crystallographic Data Centre as Supplementary Publication Numbers CCDC 602189 and 684658.

4.7. 2-[1-(2-Methoxyphenyl)-methylidene]-benzo[*b*]thiophen-3(2*H*)-one-1,1-dioxide (6b)

A solution of benzo[*b*]thiophen-3(2*H*)-one 1,1-dioxide **1** (0.46 g, 2.5 mmol), 2-methoxybenzaldehyde (0.38 g, 2.5 mmol) and ammonium acetate (0.39 g, 5 mmol) in ethanol (30 mL) and glacial acetic acid (10 mL) was stirred for 48 h. The yellow precipitate was filtered off and crystallised from acetic acid to give **6b** as bright yellow

crystals (0.53 g, 70%), mp 174 °C. ^{1}H NMR (DMSO-d_6, 200 MHz): δ 3.90 (s, 3H), 8.00 (dd, 1H, J=6.8 and 8.8 Hz, overlap), 8.12 (d, 2H, J=8.8 Hz, overlap), 8.14 (s, 1H, overlap), 8.18–8.26 (m, 5H); IR (Nujol): 1610, 1660, 1690 (C═O) cm^{-1}; MS: 300 [M]$^+$. Anal. Calcd for $C_{16}H_{12}O_4S$: C, 63.99; H, 4.03; S, 10.68. Found: C, 63.57; H, 3.91; S, 10.50.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.07.112.

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