

From thiophene *S*-oxides to 7-thiabicyclo[2.2.1]hept-5-enes

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Oligocycles with a 7-thiabicyclo[2.2.1]hept-5-ene unit have been prepared stereoselectively by cycloaddition of thiophene *S*-oxides to alkenes and subsequent deoxygenation of the sulfoxy bridge of the cycloadducts with PBr₃.

Keywords: thiophene *S*-oxides, cycloaddition, phosphorus tribromide, deoxygenation

Thiophene *S*-oxides such as **4a–c**, which can be prepared by oxidation of thiophenes with *m*-CPBA in the presence of BF₃·Et₂O¹ or with H₂O₂ in the presence of a protic acid,² are good dienes in cycloaddition reactions.³ With alkenes as dienophiles, they yield 7-thiabicyclo[2.2.1]hept-5-ene *S*-oxides³ (see also Scheme 2). These cycloadducts are good precursors to multifunctionalised arenes,⁴ to cyclohexadienes⁵ and in certain cases to diaryl disulfides.⁶ Previously, the authors have used this combination of reaction to construct such diverse molecules as crown ethers,⁷ cyclophanes⁸ and amino acids.⁹ We have reported one example of a transformation of a 7-thiabicyclo[2.2.1]heptene *S*-oxide to a 7-thiabicyclo[2.2.1]heptene.⁵ We now report that this deoxygenation of bridged sulfoxides to bridged sulfides is a general reaction.

Thiophene *S*-oxides **4** undergo facile cycloaddition to alkenes **3**, **5**, and **8** (Scheme 2). Thus, a solution in chloroform of 3,4-dibromo-2,5-thiophene *S*-oxide (**4a**), accessible from 3,4-dibromo-2,5-dimethylthiophene in one step, was heated with dibutyl maleate (**5**) to give cycloadduct **6** in good yield. Cycloadduct **6** is formed stereoselectively as the *endo*-product. Cycloadducts **9a/b** are also *endo*-products and are formed as one stereoisomer only, with the lone electron pair on sulfur being on the same side as the newly formed double bond of the cycloadducts. Compounds **9a/b** can also be formed in a one-pot oxidation-cycloaddition reaction of the corresponding thiophenes and *N*-phenylmaleimides **8a/b** by the action of meta chloroperoxybenzoic acid (*m*-CPBA) in the presence of BF₃·Et₂O.^{1,3} The yield of the cycloaddition of the isolated thiophene *S*-oxides **4b/c** and the thiophene *S*-oxides formed *in situ* in the one-pot procedure are comparable. Compound **7** is formed as the *exo-endo* product, with all nine stereocentres controlled over the course of two consecutive cycloaddition reactions. The first of these cycloadditions involves the synthesis of a dienophile 3,4-dibenzoyl-tricyclo[4.2.10^{2,5}]nona-3,7-diene (**3**) itself, which is achieved by reaction of quadricyclane (**1**) with dibenzoylacetylene (**2**) (Scheme 1), reminiscent of the reaction of quadricyclane with alkynes,

published previously.¹⁰ The stereochemical outcome of the reactions can be predicted from extensive work on single crystal X-ray analysis on cycloadducts of thiophene *S*-oxides and alkenes carried out by us and others.^{3,11–13}

Reaction with PBr₃ deoxygenates 7-thiabicyclo[2.2.1]heptene *S*-oxides **6**, **7**, and **9a/b** efficiently to 7-thiabicyclo[2.2.1]heptenes **10**, **11**, and **12a/b**, respectively. A temperature of 0°C must be maintained carefully during the addition of PBr₃. Temperatures higher than 25°C should also be avoided during the reaction itself. Elevated temperatures favour the extrusion of the entire SO-bridge and lead to mixtures of aromatic systems and cyclohexadienes.

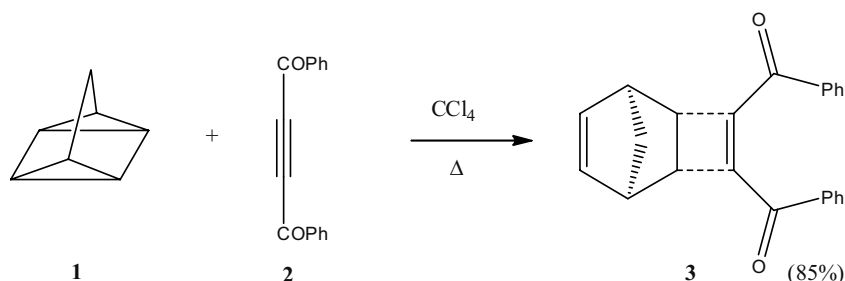
In conclusion, we have shown that oligocycles with a 7-thiabicyclo[2.2.1]hept-5-ene unit can be prepared with total stereochemical control in very few steps.

Experimental

General

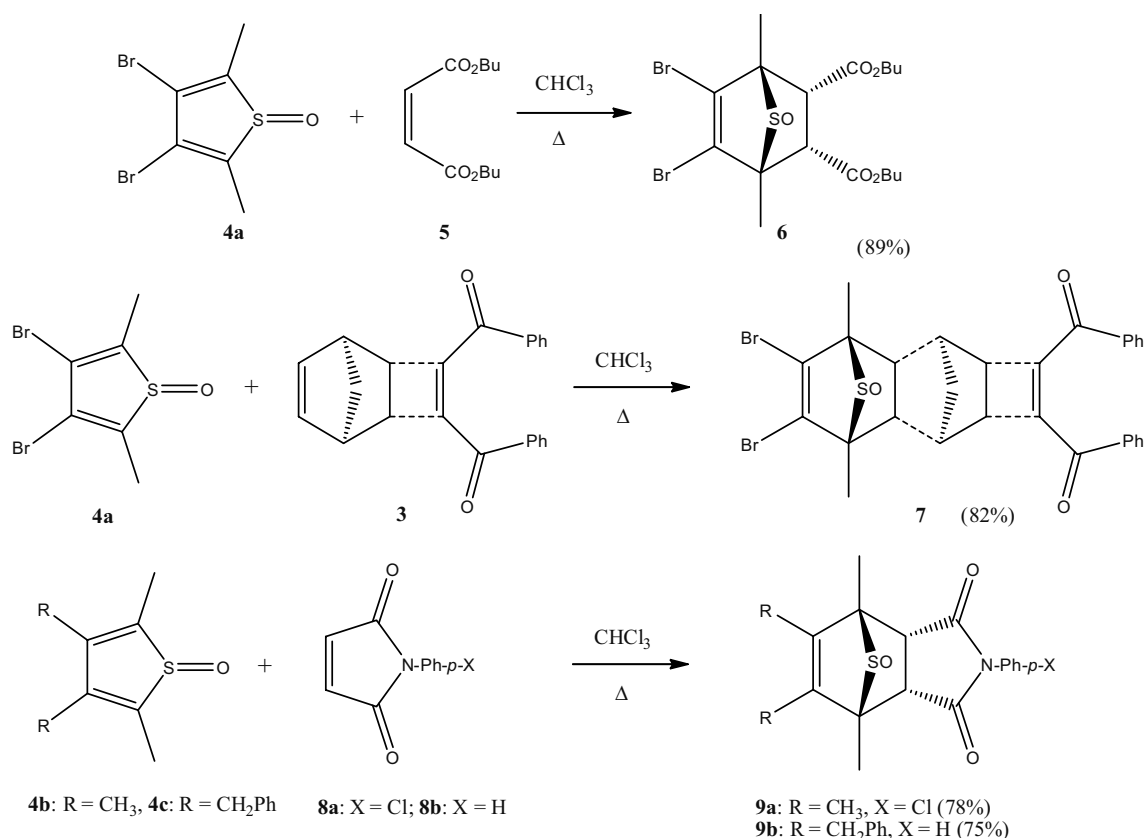
Melting points were determined on a Mitamuraiken MELT THERMO and are uncorrected. IR spectra were recorded on a JASCO-102 spectrometer. NMR spectra were recorded at 270 MHz (proton) and at 67.8 MHz (carbon-13) with a JEOL EX-270 spectrometer. The chemical shifts are relative to TMS (solvent CDCl₃, unless noted otherwise). DEPT (Distortionless Enhancement by Polarisation Transfer) was used to help assign the carbon signals, where (+) denotes primary and tertiary, (–) secondary and C_{quat} quaternary carbons. Mass spectra were measured with a JMS-01-SG-2 spectrometer (EI, 70 eV). Column chromatography was carried out Wako gel C300. Thiophene *S*-oxides **4** were prepared by oxidation of the corresponding thiophenes with meta-chloroperoxybenzoic acid (*m*-CPBA) in the presence of BF₃·Et₂O, as reported previously.¹⁴ **9a**¹ was prepared analogous to **9b** (see below). DMF was dried over CaH₂ and distilled. PBr₃ was distilled before use.

3,4-Dibenzoyltricyclo[4.2.10^{2,5}]nona-3,7-diene (3): A solution of tetracyclo[3.2.0.0^{2,7}.0^{4,6}]heptane (**1**, 100 mg, 1.09 mmol) and dibenzoylacetylene (**2**, 234 mg, 1.00 mmol) in CCl₄ (2 mL) was held at reflux for 48 h. Thereafter, CCl₄ was removed *in vacuo* and the residue was subjected to column chromatography on silica gel (hexane/ether 1:2) to give **3** (270 mg, 85%) as a pale yellow solid, m.p. 104°C. (Found: M⁺, 326.1309. C₂₃H₁₈O₂ requires M⁺,



Scheme 1 Synthesis of dienophile 3,4-dibenzoyl-tricyclo[4.2.10^{2,5}]nona-3,7-diene (**3**).

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Scheme 2 Cycloaddition of thiophene S-oxides to alkenes.

326.1307). ν_{max} (neat/cm⁻¹) 2994, 2974, 2948, 1648, 1598, 1449, 1317, 1290, 1279, 947, 865, 703, 660; δ_{H} (270 MHz, CDCl₃) 1.55 (1H, d, 2J = 9.6 Hz), 1.74 (1H, d, 2J = 9.6 Hz), 2.89 (2H, d, J = 1.7 Hz), 2.91 (2H, brs), 6.52 (2H, s), 7.22–7.72 (10H, m); δ_{C} (67.8 MHz, CDCl₃) 39.4, 40.1, 45.4, 128.5, 128.8, 133.2, 136.0, 136.7, 149.9, 190.8; MS (EI, 70 eV) m/z (%) = 326 (M⁺) (30).

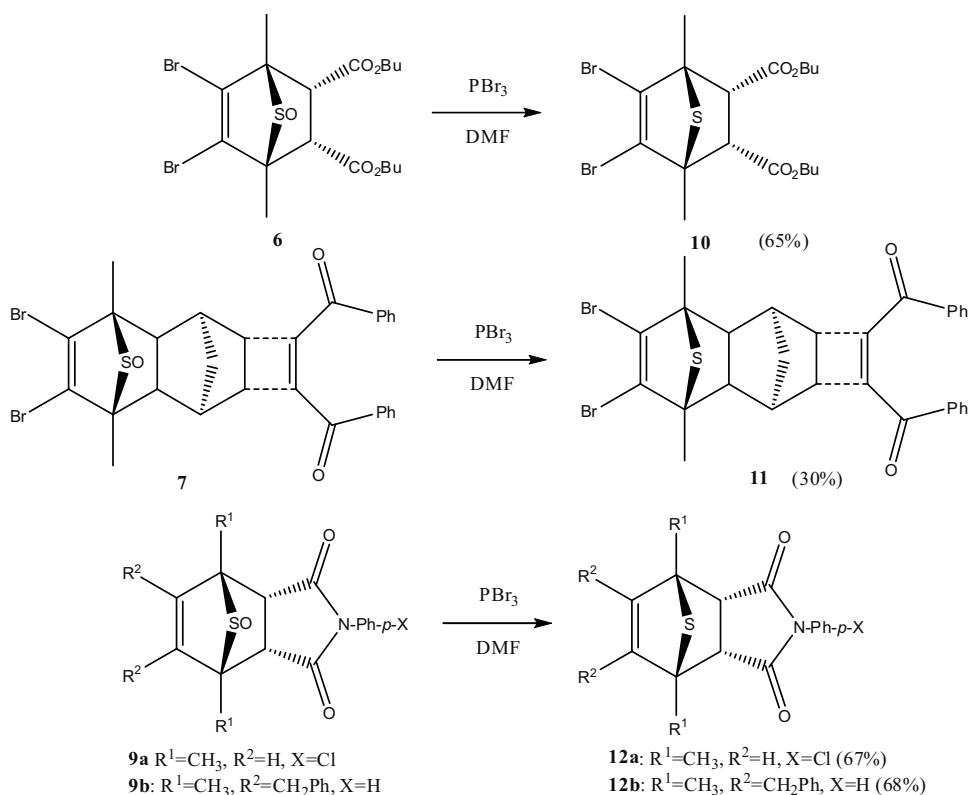
Dibutyl 2,3-dibromo-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate 7-oxide (6): A mixture of 3,4-dibromo-2,5-dimethylthiophene S-oxide (**4a**) (150 mg, 0.52 mmol) and dibutyl maleate (**5**) (237 mg, 1.04 mmol) in chloroform (2 mL) was heated under reflux for 24 h. Thereafter, the solution was cooled and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether 2:1) to give **6** (240 mg, 89%) as a colourless solid; m.p. 69–70°C. (Found: M⁺, 513.9848. C₁₈H₂₆O₅⁷⁹Br⁸¹BrS requires M⁺, 513.9847). ν_{max} (neat/cm⁻¹) 2960, 2870, 1737, 1566, 1450, 1383, 1328, 1282, 1246, 1171, 1146, 1110, 1084, 1063, 1025, 950. δ_{H} (270 MHz, CDCl₃) 0.93 (6H, t, 3J = 7.2 Hz, 2 CH₃), 1.36 (4H, m), 1.59 (4H, m), 1.68 (6H, s, 2 CH₃), 3.89 (2H, s), 4.04 (4H, m); δ_{C} (67.8 MHz, CDCl₃, DEPT 90, DEPT 135) 13.7 (+, 2C, CH₃), 15.5 (+, 2C, CH₃), 19.1 (–, 2C), 30.4 (–, 2C), 52.7 (+, 2C, CH), 65.6 (–, 2C), 75.2 (C_{quat}, 2C), 125.4 (C_{quat}, 2C), 169.1 (C_{quat}, 2C). MS (70 eV) m/z (%) = 516 ([⁸¹Br₂]M⁺, 4), 514 ([⁸¹Br⁷⁹Br]M⁺, 8), 512 ([⁷⁹Br₂]M⁺, 4), 468 ([⁸¹Br₂]M⁺–SO, 38), 264 (100).

5,6-Dibenzoyl-11,12-dibromo-1,10-dimethyl-14-thiapentacyclo[8.2.1.1.3⁸⁰.2⁹⁰.4⁷]penta-deca-5,11-diene 14-oxide (7): A solution of **3** (100 mg, 0.31 mmol) and **4a** (44 mg, 0.15 mmol) in chloroform (1.5 mL) was held at reflux for 21 h. Then, the cooled solution was concentrated *in vacuo* and subjected to column chromatography on silica gel (ether/hexane 1:1) to give **7** (75 mg, 82%) as a colourless solid; m.p. 184°C. (Found: MH⁺, 612.9870. C₂₉H₂₅O₃⁷⁹Br⁸¹BrS requires MH⁺, 612.9873 [FAB]). ν_{max} (KBr/cm⁻¹) 3054, 3026, 2960, 2920, 1653, 1597, 1444, 1315, 1286, 1110, 712, 687, 656; δ_{H} (270 MHz, CDCl₃) 1.48 (2H, m), 1.65 (6H, s, 2 CH₃), 2.51 (2H, bs), 2.52 (2H, bs), 3.07 (2H, bs), 7.18–7.24 (4H, m), 7.33–7.39 (2H, m), 7.60–7.63 (4H, m); δ_{C} (67.8 MHz, CDCl₃, DEPT, DEPT 135) 16.2 (+, 2C, CH₃), 27.8 (–, 2C), 35.0 (+, 2C, CH), 42.3 (+, 2C, CH), 53.3 (+, 2C, CH), 77.2 (C_{quat}, 2C), 125.8 (C_{quat}, 2C), 128.5 (+, 4C, CH), 128.8 (+, 4C, CH), 133.4 (+, 2C, CH), 136.4 (C_{quat}, 2C), 145.9 (C_{quat}, 2C), 190.5 (C_{quat}, 2C, C=O); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) = 613 (MH⁺, 35), 564 (15).

N-Phenyl-5,6-benzyl-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-5-ene-2,3-carboxamide 7-oxide (9b): A solution of 3,4-dibenzyl-2,5-dimethylthiophene S-oxide (**4c**, 406 mg, 1.32 mmol) and N-phenylmaleimide (**8b**, 250 mg, 1.45 mmol) in CHCl₃ (4 mL) was stirred at 60°C for 18 h under an inert atmosphere. Thereafter, the solvent was evaporated *in vacuo* and the residue was subjected to a short column chromatography on silica gel (ether/CHCl₃/hexane 2:1:1) to give **9b** (475 mg, 75%) as a colourless solid, m.p. 73°C. (Found: M⁺, 481.1718. C₃₀H₂₇NO₃S requires M⁺, 481.1712). ν_{max} (KBr/cm⁻¹) 1700, 1060; δ_{H} (270 MHz, CDCl₃) 1.67 (6H, s, 2 CH₃), 3.56 (2H, d, 2J = 16.0 Hz), 3.76 (2H, s), 3.82 (2H, d, 2J = 16.0 Hz), 7.04–7.52 (15H, m); δ_{C} (67.8 MHz, CDCl₃) 13.5, 32.7, 51.2, 73.9, 126.1, 126.8, 128.4, 128.7, 128.8, 129.0, 129.1, 131.6, 137.0, 137.1, 174.1; MS (EI, 70 eV) m/z (%) = 433 (M⁺–SO, 47), 342 (6.9), 193 (100). Anal Calcd for C₃₀H₂₇NO₃S (481.60): C, 74.82; H, 5.65; N, 2.91. Found: C, 74.82; H, 5.84; N, 2.83%.

Dibutyl 2,3-dibromo-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate (10): A solution of **7** (114 mg, 0.22 mmol) and PBr₃ (110 μ L, 313 mg, 1.16 mmol) in dry DMF (2.0 mL) was set at 0°C and stirred at r.t. for 25 min. Thereafter, the mixture was cooled again to 0°C and ether (10 mL) was added. Then, water (300 μ L) was added dropwise. The mixture was extracted with water (15 mL) and ether (2 \times 15 mL). The combined organic phase was dried over anhydrous MgSO₄ and concentrated *in vacuo*. Column chromatography on silica gel (hexane/ether 2.5:1) gave **10** (71 mg, 65%) as a colourless oil. (Found: M⁺, 497.9896. C₁₈H₂₆O₄⁷⁹Br⁸¹BrS requires M⁺, 497.9899). ν_{max} (neat/cm⁻¹) 2956, 2854, 1748, 1587, 1459, 1382, 1195; δ_{H} (270 MHz, CDCl₃) 0.92 (6H, t, 3J = 7.5 Hz, 2 CH₃), 1.20–1.34 (4H, m), 1.56 (4H, m), 1.78 (6H, s, 2 CH₃), 3.94 (2H, s), 3.92–4.10 (4H, m); δ_{C} (67.8 MHz, CDCl₃) 13.7 (+, 2C, CH₃), 19.2 (+, 2C, CH₃ and 2C, CH₂), 30.5 (–, 2C), 60.7 (+, 2C, CH), 65.1 (–, 2C), 65.9 (C_{quat}, 2C), 132.3 (C_{quat}, 2C), 169.3 (C_{quat}, 2C, C=O); MS (70 eV) m/z (%) = 500 ([⁸¹Br₂]M⁺, 10), 498 ([⁷⁹Br⁸¹Br]M⁺, 19), 496 ([⁷⁹Br₂]M⁺, 10), 419 (M⁺–Br, 31), 417 (M⁺–Br, 30), 308 (94), 271 (52), 269 (100), 267 (50).

5,6-Dibenzoyl-11,12-dibromo-1,10-dimethyl-14-thiapentacyclo[8.2.1.1.3⁸⁰.2⁹⁰.4⁷]penta-deca-5,11-diene (11): A solution of **7** (67 mg, 0.11 mmol) and PBr₃ (110 μ L, 313 mg, 1.16 mmol) in dry DMF (1.5 mL) was set at 0°C and stirred at r.t. for 25 min. Thereafter, the mixture was cooled again to 0°C and ether (10 mL) was added. Then, water (300 μ L) was added dropwise. The mixture was extracted with water (15 mL) and ether (2 \times 15 mL). The combined



Scheme 3 Deoxygenation of compounds with a 7-thiabicyclo[2.2.1]heptene S-oxide subunit.

organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether 3 : 1) to give **11** (19 mg, 30%) as a colourless solid, m.p. 176–179 °C. (Found: MH^+ , 596.9922. $C_{29}H_{25}O_2^{79}Br^81BrS$ requires MH^+ , 596.9923 [FAB]). ν_{max} (KBr/ cm^{-1}) 3058, 2960, 2922, 2856, 1651, 1598, 1446, 1314, 1284, 1262, 866, 741, 713, 689; δ_H (270 MHz, $CDCl_3$) 1.56 (2H, bs), 1.72 (6H, s, 2 CH_3), 2.38 (2H, s), 2.62 (2H, s), 2.99 (2H, s), 7.17–7.23 (4H, m), 7.32–7.38 (2H, m), 7.60–7.63 (4H, m); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 20.5 (+, 2C, CH_3), 35.4 (+, 2C, CH), 50.0 (+, 2C, CH), 62.3 (+, 2C, CH), 68.2 (+, 2C, CH), 128.9 (+, 4C, CH), 129.3 (+, 4C, CH), 132.5 (C_{quat} , 2C), 133.8 (+, 2C, CH), 137.0 (C_{quat} , 2C), 146.4 (C_{quat} , 2C), 191.1 (C_{quat} , 2C, CO); MS (FAB, 3-nitrobenzyl alcohol) m/z (%) = 599 ($[^81Br_2]MH^+$, 0.9), 597 ($[^{79}Br^81Br]MH^+$, 1.5), 595 ($[^{79}Br_2]MH^+$, 0.85).

N-(*p*-Chlorophenyl)-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-5-ene-2,3-dicarboxamide (**12a**): PBr_3 (300 μL , 855 mg, 3.16 mmol) at 0 °C and within 25 min was added to a solution of **9a** (100 mg, 0.30 mmol) in dry DMF (2.5 mL). The resulting slurry was stirred at r.t. for 25 min, then cooled to 0 °C and ether (15 mL) was added. Then, water (300 μL) was added dropwise. Thereafter, the mixture was extracted with water (15 mL) and ether (2 \times 15 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane/ether 2 : 1) to give **12a** (64 mg, 67%) as colourless needles, m.p. 153–154 °C. (Found: M^+ , 320.0518. $C_{16}H_{15}O_2N^{35}ClS$ requires M^+ , 320.0512). ν_{max} (KBr/ cm^{-1}) 3098, 2966, 2928, 2870, 1703, 1492, 1453, 1378, 1181, 1167, 1087, 836, 804, 741; δ_H (270 MHz, $CDCl_3$) 1.95 (6H, s, 2 CH_3), 3.83 (2H, s), 6.31 (2H, s), 7.09 (2H, d, $^3J=8.6$ Hz), 7.40 (2H, d, $^3J=8.6$ Hz); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 18.3 (+, 2C, CH_3), 57.8 (+, 2C, CH), 64.6 (C_{quat} , 2C), 127.6 (+, 2C, CH), 129.3 (+, 2C, CH), 129.9 (C_{quat}), 134.5 (C_{quat}), 141.2 (+, 2C, CH), 173.4 (C_{quat} , 2C, C=O); MS (70 eV) m/z (%) = 321 ($[^{37}Cl]M^+$, 3), 319 ($[^{35}Cl]M^+$, 8), 207 (13), 112 (100). Anal. Calcd for $C_{16}H_{14}NO_2ClS$ (319.81): C, 60.09; H, 4.41; N, 4.38. Found: C, 60.17; H, 4.45; N, 4.43%.

N-Phenyl-5,6-benzyl-1,4-dimethyl-7-thiabicyclo[2.2.1]hept-5-ene-2,3-carboxamide (**12b**): A solution of **9b** (50 mg, 0.10 mmol) and PBr_3 (150 μL , 427 mg, 1.58 mmol) in dry DMF (2.0 mL) was reacted (addition time 20 min, at 0 °C, reaction time 20 min, at r.t.) and worked-up analogous to the preparation of **12a**. Column chromatography on silica gel (hexane/ether 3 : 1) gave **12b** (33 mg, 68%) as colourless needles, m.p. 152–153 °C (hexane). (Found: M^+ , 465.1766; $C_{30}H_{27}O_2NS$ requires M^+ , 465.1763). ν_{max} (KBr/ cm^{-1})

3060, 3024, 2980, 2930, 2870, 1775, 1706, 1600, 1494, 1453, 1382, 1184, 1029, 750, 728, 714, 692; δ_H (270 MHz, $CDCl_3$) 1.77 (6H, s, 2 CH_3), 3.30 (2H, d, $^2J=15.9$ Hz), 3.76 (2H, d, $^2J=15.9$ Hz), 3.85 (2H, s), 7.15–7.32 (12H, m), 7.42–7.53 (3H, m); δ_C (67.8 MHz, $CDCl_3$, DEPT 90, DEPT 135) 18.0 (+, 2C, CH_3), 33.2 (–, 2C, CH_2Ph), 59.0 (+, 2C, CH), 66.5 (C_{quat} , 2C), 126.2 (4C, +, CH), 126.4 (2C, +, CH), 128.4 (4C, +, CH), 128.6 (2C, +, CH), 128.8 (2C, +, CH), 129.3 (+, CH), 131.5 (2C, C_{quat}), 138.6 (2C, C_{quat}), 144.8 (C_{quat}), 173.6 (2C, C_{quat} , C=O); MS (70 eV) m/z (%) = 465 (M^+ , 3), 433 (M^+-S , 38), 292 (100), 173 (44). Anal. Calcd for $C_{30}H_{27}NO_2S$ (465.61): C, 77.39; H, 5.85; N, 3.01. Found: C, 77.21; H, 5.86; N, 2.99%.

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References

- Y.Q. Li, M. Matsuda, T. Thiemann, T. Sawada, S. Mataka and M. Tashiro, *M., Synlett*, 1996, 461.
- P. Pouzet, I. Erdelmeier, P. Ginderow, J.P. Mornon, P.M. Dansette and D. Mansuy, *J. Chem. Soc., Chem. Commun.*, 1995, 473.
- Y.Q. Li, T. Thiemann, T. Sawada, S. Mataka and M. Tashiro, *J. Org. Chem.*, 1997, **62**, 7926.
- T. Thiemann, M.L. S   Melo, A.S. Campos Neves, Y.Q. Li, S. Mataka, M. Tashiro, U. Geissler and D.J. Walton, *J. Chem. Res.*, 1998 (S), 346.
- C. Thiemann, T. Thiemann, Y.Q. Li, T. Sawada, Y. Nagano and M. Tashiro, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 1886.
- T. Thiemann and K. Gopal Dongol, *J. Chem. Res.* (S), 2002, 303; (M) 2002, 701.
- Y.Q. Li, T. Thiemann, T. Sawada and M. Tashiro, *J. Chem. Soc., Perkin Trans. 1*, 1994, 2323.
- Y.Q. Li, T. Thiemann, K. Mimura, T. Sawada, S. Mataka and M. Tashiro, *Eur. J. Org. Chem.*, 1998, 1841.
- K. Gopal Dongol, S. Mataka and T. Thiemann, *J. Chem. Res.*, **2003**, (S) 527; **2003**, (M) 901.
- C.D. Smith, *J. Am. Chem. Soc.*, 1966, **88**, 4273.
- T. Thiemann, Y.Q. Li, C. Thiemann, T. Sawada, D. Ohira, M. Tashiro and S. Mataka, *Heterocycles*, 2000, **52**, 1215.
- N. Furukawa, S. Zhang, E. Horn, O. Takahashi, S. Sato, M. Yokoyama and K. Yamaguchi, *Heterocycles*, 1998, **47**, 793.
- N. Naperstkov, J.B. Macaulay, M.J. Newlands and A.G. Fallis, *Tetrahedron Lett.*, 1989, **30**, 5077.
- T. Thiemann, D. Ohira, K. Arima, T. Sawada, S. Mataka, F. Marken, R.G. Compton, S.D. Bull and S.G. Davies, *J. Phys. Org. Chem.*, 2000, **13**, 648.