Tetrahedron Letters 51 (2010) 3205–3207

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Staudinger and retro-Staudinger reactions. The dichloro-β-lactam moiety as a useful handle for the synthesis of 4-aryl-2*H*-1,3-benzothiazine 1,1-dioxides

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ARTICLE INFO

Article history:
Received 13 January 2010
Revised 22 March 2010
Accepted 12 April 2010
Available online 18 April 2010

Keywords:
1,3-Benzothiazine
Dichloro-β-lactam
Staudinger reaction
Oxidation

ABSTRACT

The dichloro-β-lactam ring, obtained via Staudinger reaction of 4-aryl-2*H*-1,3-benzothiazines, proved to be a useful protecting strategy for the synthesis of 4-aryl-2*H*-1,3-benzothiazine 1,1-dioxides. After oxidation of the 1,1-dichloroazeto[2,1-*c*][1,3]-benzothiazin-2-ones, the thiazine ring could be recovered selectively and in good yield by treatment with base. Thus, novel 4-aryl-2*H*-1,3-benzothiazine 1,1-dioxides were obtained efficiently.

Among condensed sulfur–nitrogen heterocycles, sulfones such as 1,4-benzothiazepine 1,1-dioxides exhibit a broad range of biological activity (antiatherosclerotic,[1] antihyperlipidaemic,[2] muscle relaxation accelerator[3] and antiarrhythmic effects[4]). The six-membered homologues, 1,4-benzothiazine 1,1-dioxides, inhibit peptide deformylase, for example,[5] while 1,2-benzothiazine 1,1-dioxides include 'oxicam' drugs such as meloxicam and piroxicam.[6] In contrast, the 1,3-benzothiazine 1,1-dioxide ring system has been prepared in a few cases through ring-enlargement reactions of substituted saccharin derivatives.[7] (It is noteworthy that this method is only suitable for the synthesis of dihydro- or 4-oxo-1,3-benzothiazine sulfones.) This stems from the synthetic difficulties encountered during conventional procedures; the oxidation of various 1,3-benzothiazines results in a ring-contraction reaction, providing 1,2-benzoisothiazoles as products.[8]

As part of a programme aimed at investigations of different condensed *S,N*-heterocycles, including β-lactam-condensed derivatives,[9a] we wanted to devise a procedure for the preparation of potentially pharmacologically active 2*H*-1,3-benzothiazine sulfones **6a–c** (Scheme 1).

We previously studied the reactions of monochloro-, dichloro- and aryl-substituted β-lactam-condensed benzothiazines. Under basic conditions, several ring-enlargement reactions occurred. Thus, 1,4-[9b,c] and 4,1-benzothiazepines,[9d] isoquinolines[9e] and thiazoles[9e] were obtained. In the course of our present investigations, we prepared angularly-condensed dichloro-β-lactams **3a–c** by Staudinger reaction[10] of 4-aryl-benzothiazines **1a–c**.[11] Surprisingly, on treatment with sodium methoxide in methanol at reflux, the latter β-lactams did not display the expected reactivity (ring enlargement,[9b–e] ester formation[12] or chloro-methoxy exchange[13]). Instead, the starting 1,3-benzothiazines **1a–c** were recovered, almost quantitatively, via retro-Staudinger reaction.[14]

This observation led us to examine the use of the dichloro-β-lactam moiety as a protecting strategy for the synthesis of sulfones **6a–c**, which we could not obtain earlier by the direct oxidation of benzothiazines **1a–c**. As an example, treatment of 6,7-dimethoxy-1,3-benzothiazines **1a–c** with peracetic acid furnished 1,2-benzothiazoles **2a–c** instead of the expected sulfone products **6a–c** (Scheme 1).[8] For the oxidation of β-lactam-condensed 1,3-thiazines **3a–c**, peroxyacetic acid proved to be a mild and efficient reagent, and azetothiazine sulfones **4a–c** were obtained selectively in good yields.[15] In this oxidation reaction the dichloro-β-lactam moiety protected the benzothiazine ring from undergoing ring-contraction. Treatment of **4a–c** with a refluxing solution of sodium methoxide provided the novel target sulfones **6a–c**, most probably via **5a–c** as intermediates.[14] The Staudinger reactions of **6a–c** with dichloroacetyl chloride in refluxing toluene afforded β-lactams **4a–c** (Scheme 1).[11]

The structures of the new compounds were confirmed by IR and NMR spectroscopy.[11,14,15]

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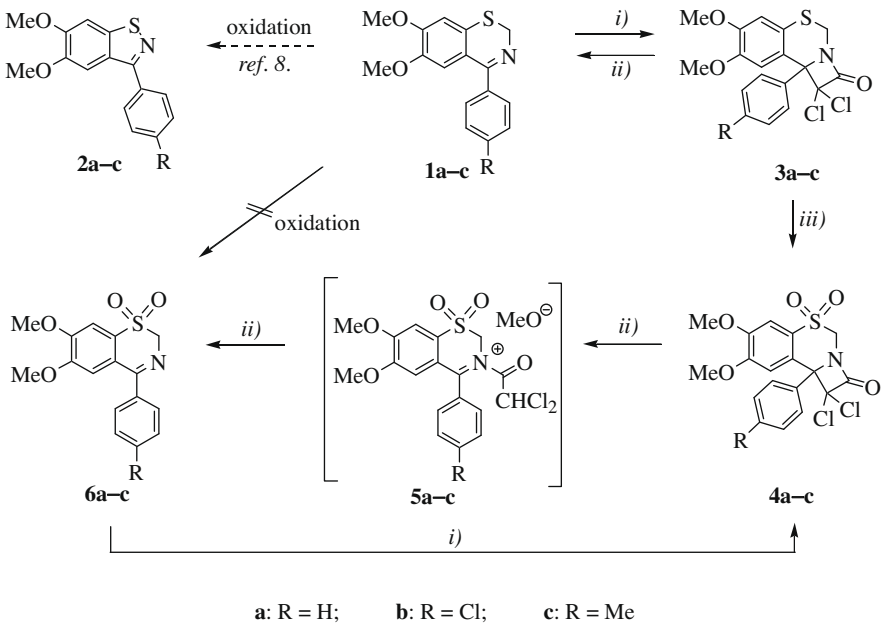
doi:10.1016/j.tetlet.2010.04.051



Scheme 1. Reagents and conditions: (i) $Cl_2CHCOCl$, Et_3N, toluene, reflux, 1 h; (ii) NaOMe, MeOH, reflux, 15 min; (iii) MeC(O)OOH, MeCOOH, rt, 1 d.

The presence of a β-lactam ring was proved by the IR frequency (1785–1808 cm^{-1}) which is higher than expected[16a] for condensed azetidinones, due to the electron-withdrawing effect of the neighbouring CCl_2 group.

The oxidation to sulfones (products **4** and **6**) follows from the appearance of a stretching IR band-pair due to the SO_2 group at frequencies in accord with literature data,[16b] and the significant shifts in the ^1H and ^{13}C NMR spectra of the neighbouring methylene group (by ~20 and 27.5 ppm in the ^{13}C NMR spectra of **4** and **6**), and of the H-6 proton (7.39–7.55 ppm) relative to the values measured for **3a**,**b** (6.69 and 6.67 ppm). A similar shift was observed for the C-5a resonance (from 122.8 ± 0.1 ppm to 131.4 ± 0.1 ppm). As a consequence of the molecular symmetry, the CH_2 resonances occur as singlets in derivatives of type **6**, and as two doublets for the other compounds investigated.

The singlet due to the methylene protons was shifted downfield in **4a–c** relative to **3b**,**c** (by 0.06 ppm) due to the *–I* effect of the sulfone group in the *para* position, while products **6a–c** exhibited opposite shifts (by 0.20 ppm). This phenomenon can be explained by the compensating (electron-releasing) effect of the nitrogen atom (of electron-reservoir character) in the contiguous conjugated bond chain.

In summary, we have developed a new procedure for the preparation of 4-aryl-2*H*-1,3-benzothiazine 1,1-dioxides **6a–c**. Staudinger reaction of the substrate 4-aryl-2*H*-1,3-benzothiazines **1a–c** results in efficient formation of the dichloro-β-lactam subunit which can be removed on treatment with sodium methoxide in methanol following oxidation. This appears to be the first report of a retro-Staudinger reaction. To the best of our knowledge, no protecting group is available for imines from which they can be subsequently recovered.[17] Further investigations are in progress to extend the applicability of the dichloro-β-lactam moiety as a protecting group.

Acknowledgements

The authors express their thanks to the Hungarian Scientific Research Foundation (OTKA) for financial support. We are indebted to Mrs. E. Juhász Dinyáné for technical assistance.

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11. *General procedure for azetobenzothiazines (**3a–c** and **4a–c**).* To a stirred solution of the 4*H*-1,3-benzothiazine derivative **(1a–c** or **6a–c)** (2.0 mmol) in anhydrous toluene (10 ml), dichloroacetyl chloride (3.0 mmol) was added. The solution was heated at reflux and Et_3N (0.4 mL, 3.0 mmol) in anhydrous toluene (20 mL) was added dropwise over 1 h. The reaction mixture was then cooled and filtered and the residual triethylammonium chloride was washed with toluene. The organic layer was washed with brine (20 mL) and dried over Na_2SO_4. After evaporation, the oily residue crystallized on trituration with EtOH. Analytical data for **3a** were identical to those reported earlier.[9a] Compound **3b**: white crystalline powder, mp 217–219 °C (from EtOH), yield 95%. ν_{max} (KBr disc) 1788 (νC=O), 1262 (νC–O), 866 ($\gamma C_{Ar}H$, condensed benzene ring), 780 ($\gamma C_{Ar}H$, *para*-disubstituted ring), 677 (CCl_2) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.45 (2H, m, H-2',6'), 7.39 (2H, m, H-3',5'), 7.15 (1H, s, H-9), 6.69 (1H, s, H-6), 5.00 (1H, d, J = 12.1 Hz, SCH_2), 4.44 (1H, d, J = 12.1 Hz, SCH_2), 3.98 (3H, s, 8-OCH_3), 3.88 (3H, s, 7-OCH_3) ppm; ^{13}C NMR δ (125 MHz, $CDCl_3$): 160.4 (C=O), 150.2 (C-7), 146.9 (C-8), 135.9 (C-4'), 135.1 (C-1'), 130.1 (C-2'), 129.1 (C-3'), 122.9 (C-5a), 122.0 (C-9a), 114.7 (C-9), 111.1 (C-6), 90.4 (C-1), 73.7 (C-9b), 38.1 (CH_2) ppm. Anal. Calcd for $C_{18}H_{14}Cl_3NO_3S$ (430.73): C, 50.19; H, 3.28; N, 3.25; S, 7.44. Found: C, 50.35; H, 3.52; N, 3.01; S, 7.68. Compound **3c**: white crystalline powder, mp 186–188 °C (from EtOH), yield 96%. ν_{max} (KBr disc) 1785 (νC=O),

1253 (νC–O), 867 ($\gamma C_{Ar}H$, condensed benzene ring), 778 ($\gamma C_{Ar}H$, *para*-disubstituted ring), 679 (CCl_2) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.40 (2H, m, H-2',6'), 7.23 (2H, m, H-3',5'), 7.17 (1H, s, H-9), 6.67 (1H, s, H-6), 5.00 (1H, d, J = 12.1 Hz, SCH_2), 4.46 (1H, d, J = 12.1 Hz, SCH_2), 3.98 (3H, s, 8-OCH_3), 3.88 (3H, s, 7-OCH_3), 2.38 (3H, s, CH_3) ppm; ^{13}C NMR δ (125 MHz, $CDCl_3$): 160.5 (C=O), 150.0 (C-7), 146.7 (C-8), 139.7 (C-4'), 133.3 (C-1'), 129.6 (C-3'), 128.7 (C-2'), 122.7 (C-5a), 122.2 (C-9a), 115.0 (C-9), 110.8 (C-6), 90.6 (C-1), 74.0 (C-9b), 37.9 (CH_2) ppm. Anal. Calcd for $C_{19}H_{17}Cl_2NO_3S$ (410.31): C, 55.62; H, 4.18; N, 3.41; S, 7.82. Found: C, 55.78; H, 4.01; N, 3.63; S, 8.08. Compounds **4a–c**: the analytical data were identical to those reported.[14] Yields, **4a**: 97%, **4b**: 95%, **4c**: 88%.

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14. *General procedure for the retro-Staudinger reaction of **3a–c** and **4a–c**. Preparation of **1a–c** and **6a–c***. Azeto-1,3-thiazine **3a–c** or **4a–c** (0.66 mmol) was dissolved in dry MeOH (40 mL). To this stirred solution, NaOMe (71 mg, 1.32 mmol) was added. The reaction mixture was stirred at reflux for 15 min. After evaporation, the residue was dissolved in CH_2Cl_2 (20 mL). The organic phase was extracted with H_2O (10 mL), dried (Na_2SO_4) and evaporated. Compounds **1a–c** are known.[18] The atom numbering of compounds **3** and **4** was also used for products **6**. Compound **6a**: white crystalline powder, mp 197–198 °C (from EtOH), yield 94%. ν_{max} (KBr disc) 1300 ($\nu_{as}SO_2$), 1264 (νC–O), 1126 (ν_sSO_2), 851 ($\gamma C_{Ar}H$, condensed benzene ring), 778 ($\gamma C_{Ar}H$, monosubstituted ring), 688 ($\gamma C_{Ar}C_{Ar}$, monosubstituted ring) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.64 (2H, m, H-2',6'), 7.55 (1H, s, H-6), 7.54 (1H, m, H-4'), 7.49 (2H, m, H-3',5'), 6.86 (1H, s, H-9), 5.10 (2H, s, SCH_2), 4.05 (3H, s, 7-OCH_3), 3.78 (3H, s, 8-OCH_3) ppm; ^{13}C NMR δ (125 MHz, $CDCl_3$): 166.9 (C-9b), 152.5 (C-8),* 152.4 (C-7),* 138.3 (C-1'), 131.4 (C-5a), 131.1 (C-4'), 129.4 (C-2'), 128.9 (C-3'), 123.8 (C-9a), 113.5 (C-10), 105.2 (C-6), 66.6 (CH_2) ppm, * reversed assignments are also possible. Anal. Calcd for $C_{16}H_{15}NO_4S$ (317.36): C, 60.55; H, 4.76; N, 4.41; S, 10.10. Found: C, 60.39; H, 5.01; N, 4.23; S, 10.31. Compound **6b**: white crystalline powder, mp 232–233 °C (from EtOH), yield 93%. ν_{max} (KBr disc) 1304 ($\nu_{as}SO_2$), 1277 (νC–O), 1124 (ν_sSO_2), 877 ($\gamma C_{Ar}H$, condensed benzene ring), 849 ($\gamma C_{Ar}H$, *para*-disubstituted ring) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.59 (2H, m, H-2',6'), 7.53 (1H, s, H-6), 7.46 (2H, m, H-3',5'), 6.81 (1H, s, H-9), 5.07 (2H, s, SCH_2), 4.03 (3H, s, 7-OCH_3), 3.79 (3H, s, 8-OCH_3) ppm; ^{13}C NMR δ (125 MHz, $CDCl_3$): 165.8 (C-9b), 152.6 (C-7), 152.5 (C-8), 137.4 (C-4'), 136.6 (C-1'), 131.5 (C-5a), 130.8 (C-2'), 129.2 (C-3'), 123.4 (C-9a), 113.1 (C-9), 105.3 (C-6), 66.6 (CH_2) ppm. Anal. Calcd for $C_{16}H_{14}ClNO_4S$ (351.81): C, 54.62; H, 4.01; N, 3.98; S, 9.11. Found: C, 54.81; H, 3.78; N, 4.13; S, 9.37. Compound **6c**: white crystalline powder, mp 214–215 °C (from EtOH), yield 92%. ν_{max} (KBr disc) 1302 ($\nu_{as}SO_2$), 1277 (νC–O), 1124 (ν_sSO_2), 875 ($\gamma C_{Ar}H$, condensed benzene ring), 829 ($\gamma C_{Ar}H$, *para*-disubstituted ring) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.52 (1H, s, H-6),* 7.51 (2H, m, H-2',6'),* 7.27 (2H, m, H-3',5'), 6.89 (1H, s, H-9), 5.06 (2H, s, SCH_2), 4.02 (3H, s, 7-OCH_3), 3.77 (3H, s, 8-OCH_3), 2.43 (3H, s, CH_3) ppm, * reversed assignments are also possible; ^{13}C NMR δ (125 MHz, $CDCl_3$): 166.8 (C-9b), 152.36 (C-8),** 152.32 (C-7),** 141.4 (C-4'), 135.4 (C-1'), 131.4 (C-5a), 129.6 (C-3'), 129.4 (C-2'), 123.9 (C-9a), 113.6 (C-9), 105.2 (C-6), 66.6 (CH_2), 21.8 (CH_3) ppm, ** reversed assignments are also possible. Anal. Calcd for $C_{17}H_{17}NO_4S$ (331.39): C, 61.61; H, 5.17; N, 4.23; S, 9.68. Found: C, 61.46; H, 5.33; N, 4.01; S, 9.87.
15. *General procedure for the oxidation of **3a–c**. Preparation of **4a–c***. Compounds **3a–c** (1.0 g) were suspended in AcOH (10 mL), followed by the addition of freshly prepared peroxyacetic acid[18] (15 mL). After complete dissolution, the reaction mixture was allowed to stand at room temperature for 1 d and then poured onto ice (30 g). The crystals that separated were removed by filtration, and washed with cold H_2O (5 mL) and MeOH (5 mL). Compound **4a**: white crystalline powder, mp 160–161 °C (from EtOH), yield 98%. ν_{max} (KBr disc) 1808 (νC=O), 1316 ($\nu_{as}SO_2$), 1268 (νC–O), 1138 (ν_sSO_2), 841 ($\gamma C_{Ar}H$, condensed benzene ring), 750 ($\gamma C_{Ar}H$, monosubstituted ring), 691 ($\gamma C_{Ar}C_{Ar}$, monosubstituted ring), 679 (CCl_2) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.52 (2H, m, H-2',6'), 7.47 (2H, m, H-3',5')*, 7.47 (1H, m, H-4')*, 7.41 (1H, s, H-6), 7.07 (1H, s, H-9), 5.30 (1H, d, J = 13.8 Hz, SCH_2), 4.55 (1H, d, J = 13.8 Hz, SCH_2), 4.04 (3H, s, 8-OCH_3), 3.99 (3H, s, 7-OCH_3) ppm, * two overlapping signals; ^{13}C NMR δ (125 MHz, $CDCl_3$): 159.6 (C=O), 151.8 (C-8), 151.0 (C-7), 134.1 (C-1'), 131.4 (C-5a), 130.5 (C-4'), 129.3 (C-3'), 128.8 (C-2'), 126.8 (C-9a), 112.9 (C-9), 106.3 (C-6), 91.5 (C-1), 74.6 (C-9b), 59.2 (CH_2) ppm. Anal. Calcd for $C_{18}H_{15}Cl_2NO_5S$ (428.29): C, 50.48; H, 3.53; N, 3.27; S, 7.49. Found: C, 50.36; H, 3.77; N, 3.42; S, 7.62. Compound **4b**: white crystalline powder, mp 118–120 °C (from EtOH), yield 94%. ν_{max} (KBr disc) 1803 (νC=O), 1320 ($\nu_{as}SO_2$), 1262 (νC–O), 1140 (ν_sSO_2), 838 ($\gamma C_{Ar}H$, condensed benzene ring), 818 ($\gamma C_{Ar}H$, *para*-disubstituted ring), 669 (CCl_2) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.44 (2H, m, H-2',6')*, 7.44 (2H, m, H-3',5')*, 7.40 (1H, s, H-6), 6.98 (1H, s, H-9), 5.27 (1H, d, J = 13.8 Hz, SCH_2), 4.49 (1H, d, J = 13.8 Hz, SCH_2), 4.04 (3H, s, 8-OCH_3), 3.98 (3H, s, 7-OCH_3) ppm, * two overlapping signals; ^{13}C NMR δ (125 MHz, $CDCl_3$): 159.4 (C=O), 151.9 (C-8), 151.1 (C-7), 136.9 (C-4'), 132.6 (C-1'), 131.3 (C-5a), 130.2 (C-2'), 129.5 (C-3'), 126.2 (C-9a), 112.6 (C-9), 106.4 (C-6), 91.4 (C-1), 74.1 (C-9b), 59.0 (CH_2) ppm. Anal. Calcd for $C_{18}H_{14}Cl_3NO_5S$ (462.73): C, 46.72; H, 3.05; N, 3.03; S, 6.93. Found: C, 46.97; H, 3.28; N, 3.19; S, 7.16; Compound **4c**: white crystalline powder, mp 220–221 °C (from EtOH), yield 97%. ν_{max} (KBr disc) 1802 (νC=O), 1317 ($\nu_{as}SO_2$), 1264 (νC–O), 1137 (ν_sSO_2), 841 ($\gamma C_{Ar}H$, condensed benzene ring), 814 ($\gamma C_{Ar}H$, *para*-disubstituted ring), 670 (CCl_2) cm^{-1}. ^1H NMR δ (500 MHz, $CDCl_3$): 7.39 (1H, s, H-6), 7.37 (2H, m, H-2',6'), 7.25 (2H, m, H-3',5'), 7.03 (1H, s, H-9), 5.26 (1H, d, J = 13.8 Hz, SCH_2), 4.50 (1H, d, J = 13.8 Hz, SCH_2), 4.04 (3H, s, 8-OCH_3), 3.98 (3H, s, 7-OCH_3), 2.39 (3H, s, CH_3) ppm; ^{13}C NMR δ (125 MHz, $CDCl_3$): 159.6 (C=O), 151.7 (C-8), 150.9 (C-7), 140.8 (C-4'), 131.4 (C-5a), 130.9 (C-1'), 130.0 (C-3'), 128.8 (C-2'), 127.0 (C-9a), 112.9 (C-9), 106.3 (C-6), 91.6 (C-1), 74.5 (C-9b), 59.1 (CH_2), 21.5 (CH_3) ppm. Anal. Calcd for $C_{19}H_{17}Cl_2NO_5S$ (442.31): C, 51.59; H, 3.87; N, 3.17; S, 7.25. Found: C, 51.45; H, 4.10; N, 3.41; S, 7.08.
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