Direct Conversion of an *ortho*-Allylphenol into a Chlorosulfonyl-3-methyl-1,2-benzoxathiin 2,2-Dioxide

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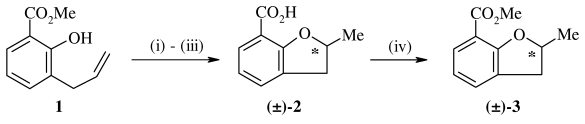
A one-pot synthesis of methyl 6-chlorosulfonyl-3-methyl-1,2-benzoxathiin-8-carboxylate 2,2-dioxide (**9**), characterized as its 6-(4-methylpiperazin-1-yl)sulfonyl derivative **10**, is achieved *via* direct reaction of methyl 3-allylsalicylate (**1**) with chlorosulfonic acid at −7 °C. The latter reagent converts methyl 2-methyl-2,3-dihydrobenzofuran-7-carboxylate (**3**) into the respective 5-chlorosulfonyl derivative **7** (identified as its 5-(4-methylpiperazin-1-yl)sulfonyl derivative **8**), while contrary to literature reports, the aromatic δ-sultones **9**, **10** (anticipated to be produced from **3**) were not detected.

Key words: Methyl 3-Allylsalicylate, Chlorosulfonic Acid, 1,2-Benzoxathiin 2,2-Dioxide

Introduction

The 2,3-dihydrobenzofuran nucleus and the parent benzo[*b*]furan are found to occur in several biologically interesting natural products [1]. 2,3-Dihydrobenzofurans are accessible from the respective *ortho*-allylphenols as exemplified by the one-pot intramolecular cyclization of **1** into **2** (Scheme 1) [2]. In this versatile synthetic route, the requisite *o*-allylphenol precursors are readily available *via* the well-known Claisen rearrangement of the corresponding allyl aryl ethers [3]. Type **2** compounds were utilized for further derivatizations, such as the preparation of the respective biologically active 7-carboxamide derivatives [4]. Complementary to a recent patent [5], we have employed **2** and **3** for the synthesis of 5-(2,3-dihydro-7-benzofuryl)pyrazolo[4,3-*d*]pyrimidone [6], an analogue of Viagra® [7].

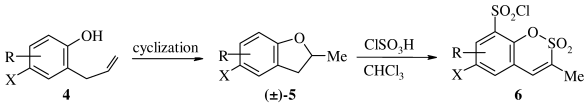


1 **(±)-2** **(±)-3**

(i) $Hg(OAc)_2$, THF, Δ
(ii) $NaBH_4$, aq. NaOH ; then $NaHCO_3$
(iii) aq. KOH, Δ; then aq. HCl / 0 °C
(iv) MeOH, $SOCl_2$, Δ

Scheme 1.

The reaction of chlorosulfonic acid with substituted 2-methyl-2,3-dihydrobenzofurans (**5**, accessible *via* cyclization of the respective *o*-allylphenol precursors **4** [8]) at −7 °C was reported to yield the corresponding 8-chlorosulfonyl-1,2-benzoxathiin 2,2-dioxides **6** (Scheme 2), useful as intermediates for sulfonylurea herbicides and plant growth hormones [8]. This mode of facile ring enlargement, converting **5** into their aromatic δ-sultones (**6**), has spurred our interest in cyclic sulfonates (sultones), a fundamental heterocyclic system that has been the subject of a recent review [9]. In particular, we sought to utilize **3** and adopt it to Foery's method [8] in order to prepare methyl 6-chlorosulfonyl-3-methyl-1,2-benzoxathiin 2,2-dioxide (**9**) (convertible to its sulfonamide **10**, Scheme 3), conceived as a suitable synthon for further manipulation.

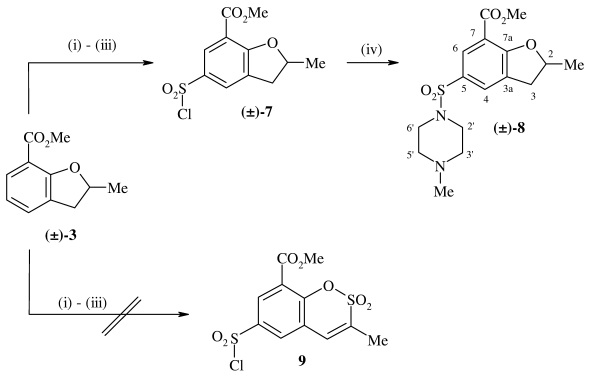


4 **(±)-5** **6**

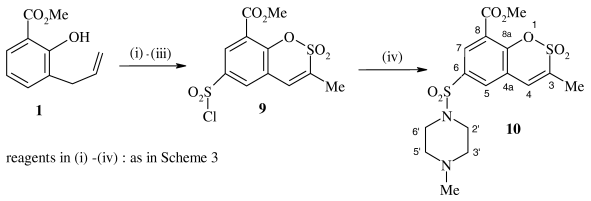
X = Cl, Br, I
R = H, halogen, NO_2, CN, acyl, alkyl, OR', SR' (R' = alkyl, alkenyl, alkynyl)

Scheme 2.

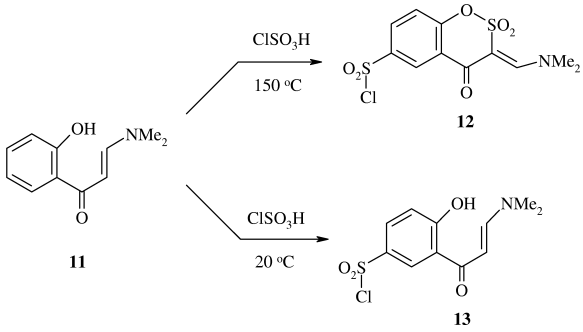
Having (±)-**3** in hand [6], we have investigated its reaction with chlorosulfonic acid as a plausible synthetic route towards the δ-sultone **9**. However, this reaction failed to deliver the desired 6-chlorosulfonylsultone **9**; instead, the major crude product was **7**, identified as its 5-(4-methylpiperazin-1-yl)sulfonyl derivative **8** (Scheme 3, *vide infra*). Herein we wish



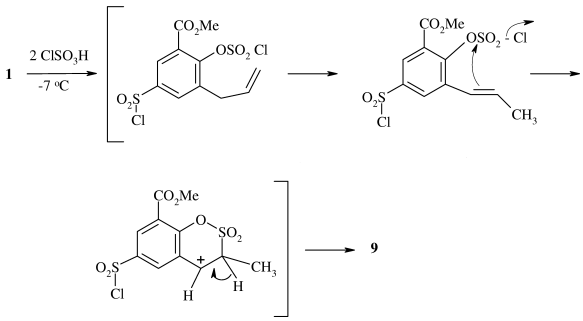
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

to report on the synthesis of **10**, obtainable by piperazinylation of **9** which is now made accessible from the reaction of chlorosulfonic acid with methyl 3-allylsalicylate (**1**) (Scheme 4).

Results and Discussion

Direct interaction between methyl 2-methyl-2,3-dihydrobenzofuran-7-carboxylate (±)-**3** and chlorosulfonic acid was conducted in the cold (−5 to −7 °C) for 10 – 12 h. Work-up of the reaction mixture in the conventional manner gave methyl 5-chlorosulfonyl-3-methyl-2,3-dihydrobenzofuran-7-carboxylate (**7**) that was directly converted into the corresponding 5-(4-methylpiperazin-1-yl)sulfonyl derivative **8** in 72% overall yield (Scheme 3). Comparable results were also obtained when the reaction was conducted at room temperature for 5 – 6 h, and at 65 – 70 °C for 1 – 2 h, followed by piperazinylation. Under these reaction conditions the putative 6-(4-methylpiperazin-1-yl)sulfonyl derivative **10** could not be detected (Scheme 3). Apparently, the 2,3-dihydrofuran moiety in **3** has survived the reaction conditions and is retained unchanged in the products **7** and **8**. Though not unexpected , these results *per se* are in contrast with literature reports [8] describing the conversion of related 2,3-dihydrobenzofurans into the respective sultones (**5** → **6**, Scheme 2).

Accordingly, we were prompted to puzzle this contrast out. In one lead experiment we have investigated the reaction of chlorosulfonic acid with methyl 3-allylsalicylate **1** (precursor of **3)**, conducted at −5 to −7 °C for 5 – 6 h. Work-up of the reaction mixture gave moderate yield of a crude solid product of the δ-sultone **9** which was characterized by direct conversion into the respective 6-(4-methylpiperazin-1-yl)sulfonyl sultone **10**.

Based on the experimental results noted above (Schemes 3 and 4), we believe that Foery's dihydrobenzofurans (**5**) [8] were fortuitously admixed with their *o*-allylphenol precursors **4**, possibly due to incompletion of the cyclization step (**4** → **5**, Scheme 2). Consequently, compounds **4** seem to be the actual substrates that interact with chlorosulfonic acid to deliver the δ-sultones **6**, convertible into the respective sulfonylurea derivatives. This hypothesis might explain the apparent discrepancy between Foery's results and our findings. Meanwhile, the reported ring-expansion process, converting **5** into **6** under the action of chlorosulfonic acid, is questionable, and for which an amendment has now been advanced.

In this context, it is worth mentioning that the reaction of chlorosulfonic acid with an *o*-phenolic enaminoketone (**11)** at 150 °C was reported [10] to yield the corresponding 1,2-benzoxathiane **12**, whereas at 20 °C, the reaction did not proceed beyond ring – chlorosulfonylation to form compound **13** (Scheme 5) [11].

The formation of **9** probably involves a cascade of plausible substitution – addition – elimination steps tentatively depicted in Scheme 6.

Experimental Section

Melting points (uncorrected) were determined on a Gallenkamp electrothermal melting temperature apparatus. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX-300 instrument with TMS as internal reference. Mass spectra (EI) and high resolution data (HRMS) were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200 °C. Microanalysis was performed at the Microanalytical Laboratory-Inorganic Chemistry Department, Tübingen University, Germany.

*Methyl 5-chlorosulfonyl-2-methyl-2,3-dihydrobenzofuran-7-carboxylate (**7**)*

To a stirred and cooled (−5 to −7 °C) chlorosulfonic acid (10 g, 150 mmol) was added methyl 2-methyl-2,3-dihydrobenzofuran-7-carboxylate (**3**) [6] (1.92 g, 10 mmol) for 20 min, and the reaction mixture was stirred at that temperature for 10 – 12 h. The resulting mixture was poured cautiously onto crushed ice (100 ml) and extracted with diethyl ether (2 × 50 ml). The combined organic extracts were washed with water (30 ml), dried ($MgSO_4$) and the solvent was evaporated. The residual crude product **7** was used as such for the preparation of **8**.

*Methyl 2-methyl-5-(4-methylpiperazin-1-yl)sulfonyl-2,3-dihydrobenzofuran-7-carboxylate (**8**)*

A solution of 1-methylpiperazine (2.0 g, 20 mmol) in THF (15 ml, 150 mmol) was added to a stirred solution of the crude 5-chlorosulfonyl derivative **7** (obtained above from 10 mmol of **3**) in THF (40 ml) at 20 °C, and the mixture was stirred for 1 – 2 h. The solvent was then evaporated, the residue treated with cold water (50 ml) and extracted with dichloromethane (2 × 40 ml). The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated and the residual solid product recrystallized from dichloromethane/*n*-hexane to give 2.55 g (72%) [11] of **8** ; m.p. 55 – 56 °C. – MS: *m/z* (% rel. int.) = 354 (3) [M^+], 323 (2), 205 (2), 159 (1), 149 (4), 131 (4), 99 (100). – HRMS: calcd. for $C_{16}H_{22}N_2O_5S$: 354.12494, found 354.13049. – ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.57$ (d, $J = 6.3$ Hz, 3H, C2-C*H*$_3$), 2.28 (s, 3H, N-C*H*$_3$), 2.50 (t, $J = 7.4$ Hz, 4H, C3'-*H*$_2$/C5'-*H*$_2$), 2.88 (dd, $J_{AB} = 16.0$ Hz, $J_{AX} = 7.4$ Hz, 1H, C3-*H*$_A$ part of ABX system), 3.41 (dd, $J_{BA} = 16.0$ Hz, $J_{BX} = 9.0$ Hz, 1H, C3-*H*$_B$), 3.04 (br t, $J = 4.7$ Hz, 4H, C2'-*H*$_2$/C6'-*H*$_2$), 3.92 (s, 3H, CO_2CH_3), 5.22 (m, 1H, C2-*H*), 7.65 (d, $J = 1.5$ Hz, 1H, C4-*H*), 8.16 (d, $J = 1.5$ Hz, 1H, C6-*H*). – ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 21.9$ (C2-*C*H$_3$), 35.7 (C-3), 45.7 (N-*C*H$_3$), 46.0 (C-2'/C-6'), 52.3 (O*C*H$_3$), 53.9 (C-3'/C-5'), 82.7 (C-2), 112.8 (C-7), 126.6 (C-3a), 128.1 (C-4), 131.1 (C-6), 131.2 (C-5), 163.5 (C-7a), 164.3 (-C=O). – $C_{16}H_{22}N_2O_5S$ (354.43): calcd. C 54.22, H 6.26, N 7.90, S 9.05; found C 54.06, H 6.18, N 7.82, S 8.93.

*Methyl 6-chlorosulfonyl-3-methyl-1,2-benzoxathiin 2,2-dioxide (**9**)*

Methyl 3-allylsalicylate (**1**) [2] (1.92 g, 10 mmol) was added dropwise during 30 min to a stirred and cooled (−5 to −7 °C) chlorosulfonic acid (10 ml, 150 mmol). The reaction mixture was stirred at that temperature for additional 5 h, then poured cautiously onto crushed ice (100 ml) and extracted with diethyl ether (2 × 50 ml). The combined ether extracts were washed with water (40 ml), dried ($MgSO_4$) and the solvent was evaporated. The residual crude product **9** (thick oil) was employed as such for the preparation of **10**.

*Methyl 3-methyl-6-(4-methylpiperazin-1-yl)sulfonyl-1,2-benzoxathiin-8-carboxylate 2,2-dioxide (**10**)*

To a solution of the crude 6-chlorosulfonyl derivative **9** (obtained above from 10 mmol of **1**) in THF (20 ml) was added 1-methylpiperazine (2.0 g, 20 mmol) in THF (20 ml), and the resulting mixture stirred at 20 °C for 1 h. The solvents were evaporated *in vacuo*, and the residue was treated with cold water (20 ml). The resulting solid product was collected and recrystallized form CH_2Cl_2/*n*-hexane to give 1.54 g (37%) of compound **10**; m.p. 161 – 162 °C. – MS: *m/z* (% rel. int.) = 416 (2) [M^+], 385 (3), 354 (4), 352 (1), 307 (3), 279 (4), 221 (2), 99 (100). – FD-MS: $m/z = 416$ [M^+]. – HRMS: calcd. for $C_{16}H_{20}N_2O_7S_2$: 416.071119, found 416.07265. – ^{1}H NMR (300 MHz, DMSO-d$_6$): $\delta = 2.16$ (s, 3H, C3-C*H*$_3$), 2.37 (s, 3H, N-C*H*$_3$), 2.41 (br t, 4H, C3'-*H*$_2$/C5'-*H*$_2$), 2.97 (br t, 4H, C2'-*H*$_2$/C6'-*H*$_2$), 3.93 (s, 3H, CO_2CH_3), 7.65 (d, $J = 1.4$ Hz, 1H, C4-*H*), 8.16 (d, $J = 2.2$ Hz, 1H, C7-*H*), 8.29 (d, $J = 2.2$ Hz, 1H, C5-*H*). – ^{13}C NMR (75 MHz, DMSO-d$_6$): $\delta = 15.4$ (C3-*C*H$_3$), 45.7 (N-*C*H$_3$), 46.1 (C-2'/C-6'), 53.6 (O*C*H$_3$), 53.9 (C-3'/C-5'), 121.9 (C-3), 125.2 (C-8), 131.3 (C-7), 131.4 (C-5), 132.6 (C-4), 133.2 (C-6), 134.6 (C-4a), 151.0 (C-8a), 162.3 (-C=O). – $C_{16}H_{20}N_2O_7S_2$ (416.47): calcd. C 46.14, H 4.84, N 6.73, S 15.40; found C 45.92, H 4.76, N 6.68, S 15.27.

Acknowledgements

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