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Enantioselective synthesis of spirocyclic tetrahydrothiophene derivatives bearing a benzofuran-3(2*H*)-one scaffold. Unusual supramolecular crystal structure with high Z′

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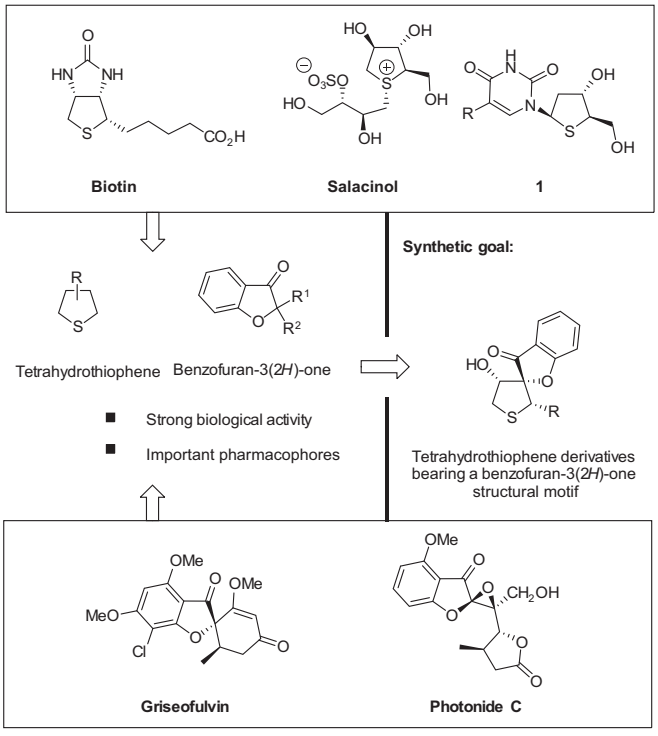
ABSTRACT

Herein, we report our studies on the enantioselective synthesis of spirocyclic tetrahydrothiophene derivatives bearing a benzofuran-3(2*H*)-one scaffold. The developed method utilizes 2-arylidenebenzofuran-3(2*H*)-ones and 2-thioacetaldehyde, generated in situ from 1,4-dithiane-2,5-diol, as starting materials and proceeds in a cascade manner involving a thio-Michael-aldol reaction sequence. The absolute configuration of the obtained tetrahydrothiophenes was assigned by single crystal X-ray analysis. Unusually high Z′ crystal packing was found in the crystal.

Introduction

The stereocontrolled synthesis of specific structural motifs relevant for life-science is of high importance in contemporary organic and medicinal chemistry.[1] Among various biologically important scaffolds, tetrahydrothiophene derivatives occupy a prominent position.[2] Co-enzyme Biotin[3] and Salacinol[4] constitute examples of naturally occurring tetrahydrothiophenes (Scheme 1, top). Furthermore, compound **1** exhibits inhibitory activity against HSV-1 and VZV.[5] The tetrahydrothiophene ring is also present in many synthetically useful compounds which are used as building blocks for the synthesis of chiral ligands and catalysts for asymmetric synthesis and are also widely employed in natural product synthesis.[6]

The benzofuran-3(2*H*)-one scaffold is another structural motif that is widely distributed in Nature (Scheme 1, bottom).[7] For instance, Griseofulvin is a natural product exhibiting strong antifungal activity that has found application in the treatment of skin, nail and hair fungus.[8] The importance of benzofuran-3(2*H*)-one can be further exemplified by the group of natural products called Photonides which have been isolated from the endophytic fungi *Pestalotiopsis Photinia*.[9] Photonide C, containing an additional γ-lactone framework in its structure, is one of the constituents of this family of natural products.



Scheme 1. Relevance of tetrahydrothiophene and benzofuran-3(2*H*)-one scaffolds.

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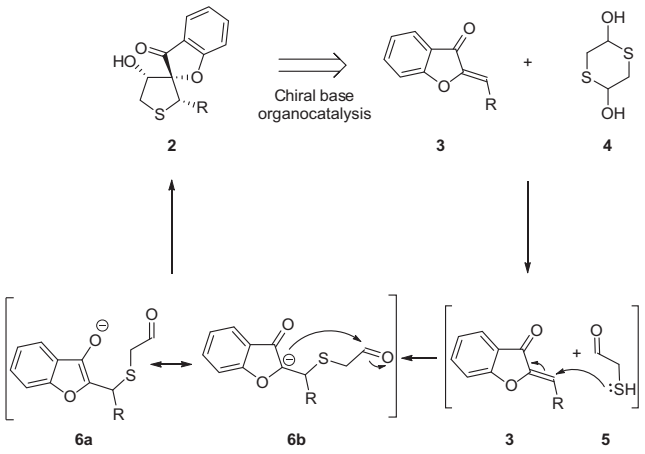


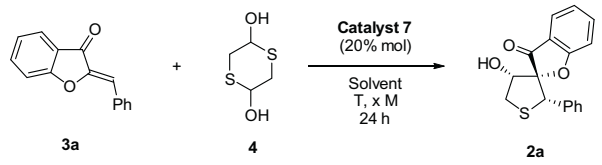
Scheme 2. Stereocontrolled synthesis of tetrahydrothiophenes **2** bearing a benzofuran-3(2*H*)-one scaffold.

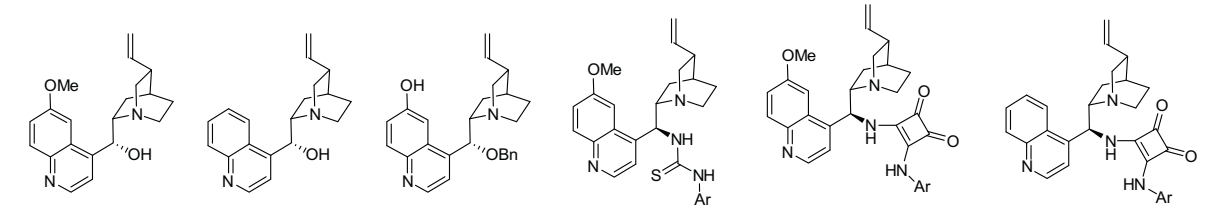
Given the importance of both the tetrahydrothiophene and benzofuran-3(2*H*)-one structural motifs, herein, we report our studies on the organocatalytic synthesis of spirocyclic tetrahydrothiophenes **2** bearing a benzofuran-3(2*H*)-one scaffold. It was anticipated that the synthesis of **2** could be realized based on a cascade reaction between 2-arylidenebenzofuran-3(2*H*)-ones **3** and 2-thioacetaldehyde **5**, generated in situ from 1,4-dithiane-2,5-diol **4** (Scheme 2). Our synthetic strategy is initiated by a thio-Michael reaction to give an anion that possesses an aromatic character and can be described by mesomeric structures **6a** and **6b**. Subsequent intramolecular aldol reaction furnishes the tetrahydrothiophene scaffold in **2**.[10] It was anticipated that the reaction should be possible to realize under basic conditions and that the use of a chiral Brønsted base as a catalyst[11] should enable stereochemical control of the reaction outcome, thus leading to the formation of optically active products **2**.

Results and discussion

Studies were initiated with the goal of finding optimal conditions for the studied reaction (for detailed screening results, see the ESI). 2-Benzylidenebenzofuran-3(2*H*)-one **3a** was selected as a model carbonyl compound. Catalyst screening was initially performed and gratifyingly it was found that simple cinchona alkaloids such as quinine **7a** or cinchonidine **7b** promoted the reaction which could thus be performed under basic conditions (Table 1, entries 1, 2). The reaction was terminated within 24 h and tetrahydrothiophene **2a** was obtained in high yields of 90% and 99%, respectively. However, both the enantio- and diastereoselectivities of the process were not satisfactory (Table 1, entries 1, 2). Therefore, various bifunctional catalysts **7c–f**, derived from cinchona alkaloids, were tested (Table 1, entries 3–6). It was found that the presence of a strong H-bonding unit in the catalyst structure was beneficial for the stereochemical outcome. In particular the application of catalysts **7d–f**, bearing either a thiourea or squaramide moiety, led to a significant increase in the reaction enantioselectivity, however its diastereoselectivity remained low (Table 1, entries 4–6).

Table 1
Stereocontrolled synthesis of tetrahydrothiophenes **2** bearing a benzofuran-3(2*H*)-one scaffold—optimization studies[a]





Entry	Catalyst **7**	Solvent	*T* [°C]	Reaction time [h]	Concentration [M]	Yield [%]	dr[b]	er (major/minor)[c]
1	**7a**	CH_2Cl_2	RT	24	0.25	90	1.5:1	74:26/52:48
2	**7b**	CH_2Cl_2	RT	24	0.25	99	5:1	52:48/67:33
3	**7c**	CH_2Cl_2	RT	24	0.25	99	2:1	69.5:30.5/55.5:44.5
4	**7d**	CH_2Cl_2	RT	24	0.25	95	4:1	81:19/95:5
5	**7e**	CH_2Cl_2	RT	24	0.25	90	1:1.2	97.5:2.5/99.5:0.5
6	**7f**	CH_2Cl_2	RT	24	0.25	94	2.5:1	93.5:6.5/96:4
7	**7f**	$CHCl_3$	RT	24	0.25	98	1:1.5	88:12/94:6
8	**7f**	Toluene	RT	24	0.25	95	1:1	93:7/98.5:1.5
9	**7f**	CH_3CN	RT	24	0.25	95	1:1	81.5:18.5/94:6
10	**7f**	1,4-Dioxane	RT	24	0.25	95	7:1	91:9/99.5:0.5
11	**7f**	THF	RT	24	0.25	73	3:1	95:5/99:1
12	**7f**	1,4-Dioxane	10	72	0.25	99	20:1	98:2/99.5:0.5
13	**7f**	1,4-Dioxane	10	72	0.125	90	10:1	95:5/99.5:0.5
14	**7f**	1,4-Dioxane	10	72	0.5	99	10:1	89.5:10.5/98:2

[a] Reactions performed on 0.1 mmol scale using **3a** (1 equiv), **4** (1 equiv), solvent (0.4 mL) (see ESI for detailed reaction conditions).
[b] Determined by ^{1}H NMR of the crude reaction mixture.
[c] Determined by chiral phase HPLC.