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A facile and efficient one-pot synthesis of thiochromans from bis(2-formylphenyl) disulfide and alkenols via iodine-promoted generation and subsequent intramolecular cycloaddition of *ortho*-thiobenzoquinone methides

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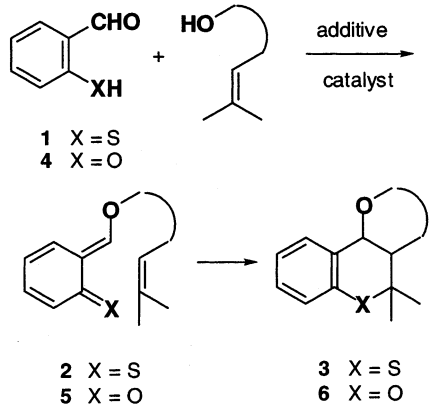
Abstract—Stereoselective synthesis of tetrahydrofuro- and tetrahydropyrano[3,2-*c*]benzothiopyrans was achieved by intramolecular [4+2]cycloaddition of *o*-thiobenzoquinone methides that were generated in situ from bis(2-formylphenyl) disulfide and alkenols in the presence of iodine under mild reaction conditions.

Chemistry of sulfur-containing six-membered heterocycles, thiopyran derivatives,[1] has been less extensively studied than that of oxygen analogs, pyrans.[2] This is probably in part due to the fact that pyran derivatives, e.g. flavonoids, catechins and pterocarpans, are found abundant in nature and have been shown to possess a wide range of physiological and biological activities.[3] However, the interest in sulfur heterocycles of this class such as thiopyrans is growing because of the recent reports of their pharmacological and medicinal importance.[4] Hence, the development of new and facile synthetic methods for such heterocycles is considered to be of great significance.[5]

Keeping this and our continued interest in the hetero Diels–Alder (HDA) reaction of 1-thiabuta-1,3-dienes in view,[6] we have initiated an investigation in search for an effective method for the generation and subsequent stereoselective cycloaddition of *o*-thiobenzoquinone methides as the 4π-heterodiene component to obtain benzothiopyrans. Hitherto reported successful methods for the generation and subsequent cycloaddition of *o*-thiobenzoquinone methides require rather stringent reaction conditions such as thermolysis or photolysis of their precursors,[7] and hence result in less than satisfactory yields, regio- and stereoselectivities and diversity of the cycloadducts.[8] Alternatively, specified stabilizing substituent(s) are required for the isolation and treatment of these *o*-thioquinone methide species.[9]

It has recently been reported that iodine plays an interesting and specific role in various organic transformations.[10] In the present study it has been found to be an effective reagent for the generation of *o*-thiobenzoquinone methide. We report herein for the first time a stereoselective one-pot synthesis of thiochromans from bis(2-formylphenyl) disulfide and alkenols via iodine-promoted generation and subsequent intramolecular cycloadditions of *o*-thiobenzoquinone methides.



Scheme 1.

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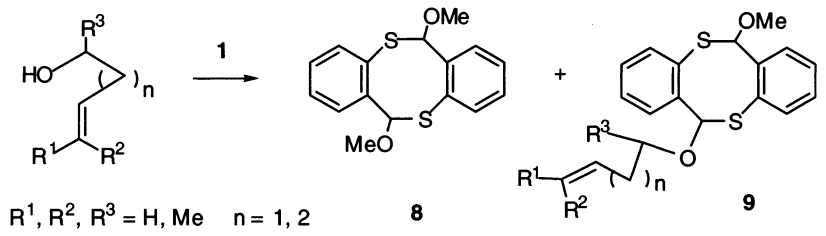


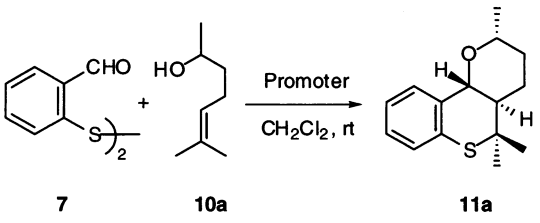
(1)

Initially, in view of the reported protocol for synthesis of benzopyrans **6** from salicylaldehydes **4** (Scheme 1),[11] it was envisaged that *o*-thiobenzoquinone methides **2** could be generated in situ by reacting *o*-mercaptobenzaldehydes **1** and alkenols under mild reaction conditions and efficiently trapped to provide tricyclic benzothiopyrans **3**. Unfavorably, the required *o*-mercaptobenzaldehyde **1**[12] is very air-sensitive and readily oxidized to disulfide **7**. In any case, aldehyde **1** was allowed to react with several alkenols according to Inoue's protocol conditions [$CH(OMe)_3$, *p*-TsOH, C_6H_6, rt, 2–24 h] (Eq. (1)). However, these efforts resulted in the formation of dimerized bis-cycloadducts **8** and **9** as major products with a trace amount of the desired thiochroman derivative **11a** only in case of $R^1=R^2=R^3=Me$, $n=2$. This is probably due to the instability and higher nucleophilicity of the mercapto group of **1** as compared to the hydroxyl group of analog **4**. In order to overcome this problem, it was felt that the disulfide **7**, by virtue of its relative stability and the fact that a disulfide bond is readily cleaved reversibly by action of certain reagents under mild conditions, could potentially be a convenient reagent for in situ generation of *o*-thiobenzoquinone methides. Keeping these facts in mind a number of efforts were made in the desired direction (screening of promoters, stoichiometry, solvent, and conditions), and it was finally discovered that molecular iodine (300 mol%) effectively promoted the desired reaction to afford the *trans*-fused pyrano[3,2-*c*]benzothiopyran derivative **11a** as a single stereoisomer in good yield (93%, Table 1, run 1)[13] (Eq. (2)). In the absence of iodine, the reaction did not afford any product even under reflux conditions. Hydrogen iodide (runs 2 and 3), bromine (run 4), and Ph_3P/p-$TosOH/H_2O$ (run 5) also resulted in the formation of compound **11a** albeit in lower yields. The reagents $Ph_3P/DMF–H_2O–MeOH$ (run 6), by which disulfide **7** is converted to *o*-mecaptobenzaldehyde **1** by reduction,[12] failed to form compound **11a**.

Table 1. Screening of promoters for reaction of **7** with **10a** to afford thiochroman **11a**

Run	Promoter	Conditions	Yield (%)[a]
1	I_2	CH_2Cl_2, rt, 30 min	93
2	Aq. 57% HI	CH_2Cl_2, rt, 72 h	22 (81)
3	Aq. 57% HI[b]	CH_2Cl_2, rt, 15 min	73
4	Br_2	CH_2Cl_2, rt, 30 min	36 (67)
5	Ph_3P/p-$TsOH–H_2O$	CH_2Cl_2, rt, 72 h	Trace
6	$Ph_3P/DMF–H_2O$ –MeOH	rt, 24 h	0

[a] Isolated yield. In parentheses, yield based on conversion percentage.
[b] In the presence of anhydrous $MgSO_4$.

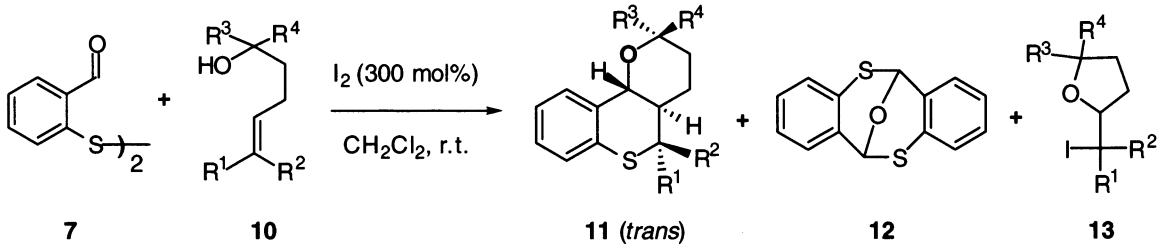


(2)

Table 2. The reaction of **7** with alkenols **10** to afford pyranobenzothiopyrans **11** or **12** and **13** (substituent effect)

Run	Alkenol	R^1	R^2	R^3	R^4	Time (h)	Product (yield %)[a]	*trans*:*cis*[b]
1	**10a**	Me	Me	Me	H	0.5	**11a** (93)	>95:5
2	**10b**	Me	Me	Me	Me	1.5	**11b** (73)	>95:5
3	**10c**	Me	H	H	H	20	**11c** (70)	69:31
4	**10d**	H	Me	H	H	1	**12** (85), **13d** (92)	–
5	**10e**	H	H	H	H	1	**12** (96), **13e** (90)	–

[a] Isolated yield.
[b] Ratio of stereoisomers determined by ^1H NMR spectroscopy. Ratio >95:5 denotes that no *cis* isomer was detected.

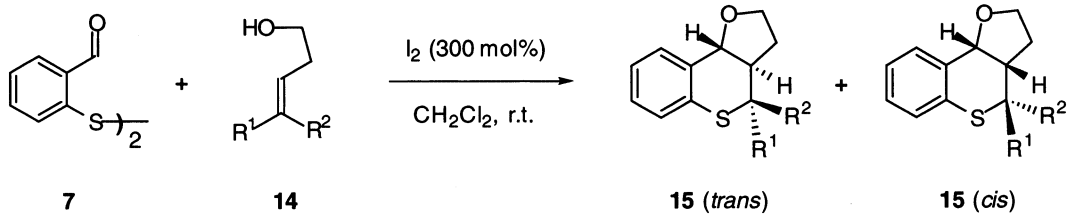


(3)

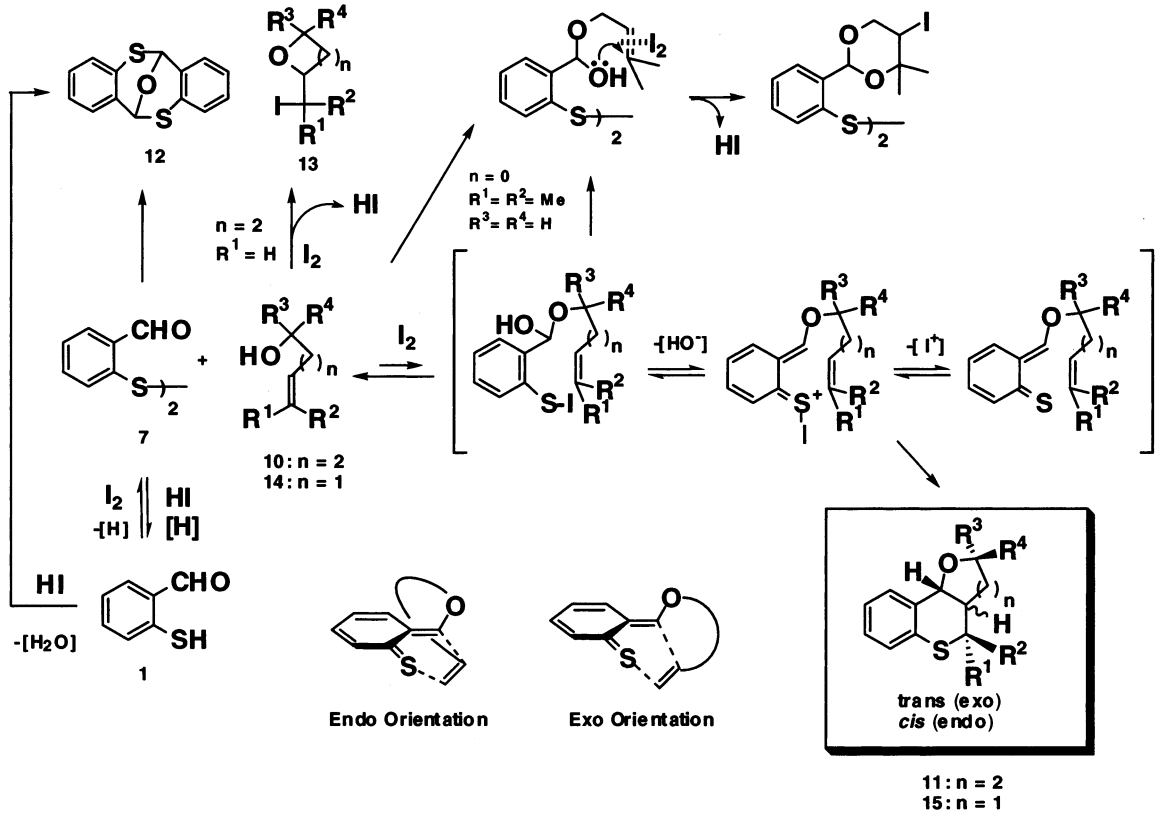
Table 3. The reaction of **7** with alkenols **14** to afford furanobenzothiopyrans **15**

Run	Alkenol	R^1	R^2	Time (h)	Product (yield %)[a]	*trans*:*cis*[b]
1	**14a**	Me	Me	4	**15a** (85)	78:22
2	**14b**	Et	H	24	**15b** (22)	23:77
3	**14c**	H	Et	24	**15c** (20)	5:95<

[a] Isolated yield.
[b] Ratio of stereoisomers determined by ^{1}H NMR spectroscopy. Ratio 5:95< denotes that no *trans* isomer was detected.



(4)



Scheme 2. Possible pathways.

In order to gain deeper insight into the scope, generality, and the mechanism of this process, the reactions were investigated with several other unsaturated alcohols **10b–e** and **14a–c** under the optimized conditions and the results of these investigations are summarized in Tables 2 and 3. The reactions with alkenols **10a–c** bearing a methyl substituent at the R^1 position gave the thiopyran cycloadducts **11a–c** (Table 2, runs 1–3). Whereas, the reactions with (*Z*)-hex-4-en-1-ol (**10d**) and 4-penten-1-ol (**10e**) afforded only condensed dimer **12**[14] and iodocyclization products **13d** and **13e**, respectively (Table 2, runs 4 and 5). On the basis of the data above, it is suggested that the terminal dimethyl or (*E*)-methyl substituent(s) of alkenols **10a–c** are absolutely essential for the cycloaddition to proceed smoothly. These studies were extended to the reactions of **7** with some unsaturated alcohols **14** having one-carbon shorter chain length than **10**. The reaction with 4-methyl-3-penten-1-ol (**14a**) proceeded cleanly in the presence of iodine (300 mol%) at room temperature (4 h) to afford tetrahydrofuro[3,2-*c*]benzothiopyran **15a** in 85% yield with a *trans*:*cis* ratio of 78:22 (Table 3, run 1). The reaction with (*E*)-3-hexen-1-ol (**14b**) also afforded [5]-ring-fused benzothiopyran **15b** in 22% yield with a *trans*:*cis* ratio of 23:77 (run 2). Interestingly, the formation of *cis*-**15b** as a major isomer in reaction of **7** with

alkenol **14b** is in sharp contrast with the formation of *trans*-**11c** in reaction of **7** with alkenol **10c** (Table 2, run 3) (Eq. (3)). Similar treatment with (*Z*)-3-hexen-1-ol (**14c**) gave exclusively the *cis* stereomer of the cycloadduct **15c** in 20% yield (Table 3, run 3). It is also noteworthy that the cycloaddition proceeds with the retention of the *E*- or *Z*-stereochemistry of alkenes (**10c**, **14c** and **14b**). Further, the reaction of **7** with 3-methyl-2-buten-1-ol ($n=0$) resulted only in the iodocyclization product, formed via the hemiacetal of **7**, instead of the anticipated [4]-ring-fused benzothiopyran.

On the basis of the experimental results and semi-empirical calculations,[15] a tentative pathway leading to the benzothiopyrans (**11** and **15**) together with some of the by-products is proposed in Scheme 2. In this scheme it is assumed that the disulfide **7** reacts with iodine in the presence of an alkenol to form the transient hemiacetalized sulfenyl iodide,[16] and elimination of hypoiodous acid from the sulfenyl iodide generates the *o*-thiobenzoquinone methide, via its iodosulfonium ion species. The latter ionic intermediate then preferentially undergoes inverse electron-demanding intramolecular *exo* or *endo* [4+2]cycloaddition to afford the *trans* or *cis* ring-fused benzothiopyran, respectively (Eq. (4)).

In summary, we have developed a novel stereoselective synthesis of ring-fused thiochromans via iodine-promoted generation of *o*-thiobenzoquinone methides and their subsequent intramolecular cycloaddition under mild reaction conditions.

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12. *o*-Mercaptobenzaldehyde **1** was readily prepared from commercially available thiosalicylic acid by (i) LAH-reduction (95%),[17] followed by (ii) PCC-oxidation of the formed *o*-mercaptobenzyl alcohol (60%),[18] and then (iii) Ph_3P/DMF–MeOH/H_2O treatment of bis(2-formylphenyl) disulfide **7**[19] (90%).[18]
13. Compound **11a**: colorless crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.29 (3H, d, $J=6.1$, 2-Me), 1.31–1.48 (2H, m, H-3-ax, H-4-ax), 1.32 (3H, s, Me), 1.35 (3H, s, Me), 1.77 (1H, dddd, $J=9.8$, 4.1, 2.9, 2.0, H-3-eq), 1.98 (1H, ddd, $J=12.6$, 11.2, 3.6, H-4a-ax), 2.04 (1H, dddd, $J=12.7$, 4.1, 3.6, 2.9, H-4-eq), 3.67 (1H, dqd, $J=11.0$, 6.1, 2.0, H-2-ax), 4.31 (1H, d, $J=11.2$, H-10b-ax), 7.01 (1H, dd, $J=$ 7.0, 2.1), 7.07 (1H, ddd, $J=7.0$, 7.0, 2.1), 7.09 (1H, ddd, $J=7.0$, 7.0, 2.1), 7.62 (1H, dd, $J=7.0$, 2.1); ^{13}C NMR (125.65 MHz, $CDCl_3$, DEPT): δ 21.78 (q), 24.00 (q), 24.47 (t), 27.89 (q), 33.33 (t), 44.56 (s), 46.29 (d), 74.09 (d), 76.61 (d), 124.19 (d), 125.85 (d), 127.42 (d), 127.79 (d), 132.78 (s), 132.98 (s); MS m/z 248 (M^+, 100%). Anal. calcd for $C_{15}H_{20}OS$: C, 72.53: H, 8.12. Found: C, 72.34; H, 8.15%.
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15. For example, a mixture of diphenyl disulfide and disulfide **7** in a 1:1 molar ratio undergoes disproportionation readily at rt in the presence of iodine to give a mixture of diphenyl disulfide: mixed disulfide: **7** in a ratio of ca. 1:2:1, which suggests that a sulfenyl iodide species[16] can be a key transient intermediate in this process. The semi-empirical MO calculations of (*o*-formylphenyl)sulfenyl iodides, *o*-thiobenzoquinone methide and disulfide **7** (Keyword: AM1, EF, PRECISE) and the transition state of intramolecular [4+2]cycloaddition of *o*-thiobenzoquinone methide (Keyword: AM1, TS, PRECISE) were performed using a WinMOPAC version 3.0 program. Details as well as further investigation of this process including its intermolecular cycloaddition variant will be reported in due course.
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