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Acid-Catalysed or Radical-Promoted Allylic Substitution of 2-Methylene-2,3-dihydrobenzofuran-3-ols with Thiol Derivatives: a Novel and Expedient Synthesis of 2-(Thiomethyl)benzofurans

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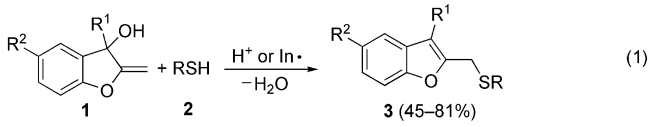
The 2-thiomethylbenzofuran derivatives **3** are conveniently prepared in good yields through the reactions between the readily available 2-methylene-2,3-dihydrobenzofuran-3-ols **1** and the thiol derivatives **2** (including alkyl thiols, thiophenol, and thioacetic acid). The allylic substitution process may be either acid-catalysed or promoted by radical initiators. In the first case, the reactions are carried out at 90 °C in 1,2-dimethoxyethane (DME) as the solvent in the presence of H_2SO_4 as the proton source. The radical-promoted reactions take place in DME at 90 °C in the presence of azobis(isobutyronitrile) (AIBN) or benzoyl peroxide (BP) as the radical initiator.

Introduction

Benzofurans are a very important class of heterocyclic compounds. A variety of molecules containing the benzofuran ring system display a wide range of biological activities, including anti-HIV, anticancer and antimicrobial activities.[1] The preparation of functionalized benzofurans with high efficiency and selectivity from readily available starting materials is therefore of particular interest in current synthesis.[2,3]

We have recently reported a novel method for the synthesis of the 2-methylene-2,3-dihydrobenzofuran-3-ols **1**, based on palladium-catalysed cycloisomerization of readily available 2-(1-hydroxyprop-2-ynyl)phenols, and have shown that these derivatives can be conveniently converted into 2-(hydroxymethyl)benzofurans and 2-(alkoxymethyl)benzofurans by acid-catalysed allylic isomerization or allylic nucleophilic substitution.[3d] We have now found that the dihydrobenzofurans **1** are also excellent starting materials for a novel approach to the 2-thiomethylbenzofurans **3**,[4] through their reactions with the thiol derivatives **2** under either acidic or radical conditions, see Equation (1).



1 **2** **3** (45–81%) (1)

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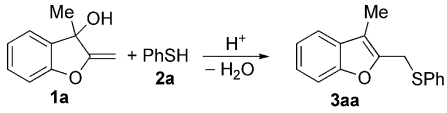
Results and Discussion

The reaction between 3-methyl-2-methylene-2,3-dihydrobenzofuran-3-ol (**1a**, R^1 = Me, R^2 = R^3 = H) and thiophenol (**2a**, R = Ph) was first investigated under acidic conditions, with H_2SO_4 as the proton source, in 1,2-dimethoxyethane (DME) as the solvent, at 70 °C and with a **2a**/**1a** molar ratio of 2. Under these conditions, the degree of conversion of **1a** was 70% after 5 h, with selective formation of 3-methyl-2-[(phenylsulfanyl)methyl]benzofuran (**3aa**) in 61% isolated yield (Table 1, Entry 1). Substrate conversion reached 100% after 15 h, with a yield of **3aa** as high as 81% (Table 1, Entry 2). The yield of **3aa** was lower at lower temperatures (Entries 3–4), whereas at 100 °C it remained practically unchanged (Entry 5). A less satisfactory yield was also obtained at 90 °C with an equimolar amount of **2a** with respect to **1a** (Entry 6), or with use of more concentrated acidic conditions (Entry 7). On the other hand, no formation of **3aa** occurred in the absence of H_2SO_4 (only partial decomposition of **1a** was observed under these conditions; Entry 8).

These results show that thiophenol (**2a**) can be successfully employed as a nucleophile in the acid-catalysed allylic nucleophilic substitution of **1a** to afford **3aa** by the general mechanism shown in Scheme 1. The key intermediate of the process is the allyl cation **I** formed by protonation of the substrate followed by loss of water. Regiospecific nucleophilic attack by the thiol on **I** then leads to the final product with regeneration of the proton.

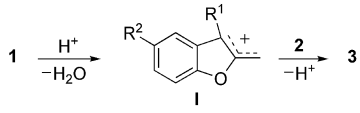
In view of the tendency of thiols and thiophenols to form thiyl radicals,[5] we also tested the reactivity of **1a** with **2a** in the presence of radical initiators, such as azobis(isobutyronitrile) (AIBN) or benzoyl peroxide (BP). The results obtained under different experimental conditions are shown

Table 1. Synthesis of 3-methyl-2-[(phenylsulfanyl)methyl]benzofuran (**3aa**) through acid-catalysed allylic nucleophilic substitution of 3-methyl-2-methylene-2,3-dihydrobenzofuran-3-ol (**1**)**a** with thiophenol (**2a**).[a]



Entry	**2a**/**1a** molar ratio	Temp. [°C]	Time [h]	Conv. of **1a** [%][b]	Yield of **3aa** [%][c]
1	2	90	5	70	61
2	2	90	15	100	81
3	2	80	15	100	72
4	2	70	15	100	53
5	2	100	15	100	82
6	1	90	15	100	45
7[d]	2	90	15	100	52
8[e]	2	90	15	31	0

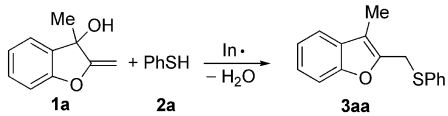
[a] Unless otherwise noted, all reactions were carried out in 9:1 mixtures of DME/H_2SO_4 (3.74×10^{-2} M in DME; substrate concentration: 0.22 mmol of **1a** per mL of solvent, 1.2 mmol scale based on **1a**). Formation of heavy products (chromatographically immobile materials) accounted for the difference between the conversion of **1a** and the yield of **3a** in each case. [b] Based on starting **1a**, by GLC. [c] Isolated yield based on starting **1a**. [d] The reaction was carried out in a 9:1 mixture of DME/H_2SO_4 (0.37 M in DME). [e] The reaction was carried out in pure DME in the absence of H_2SO_4.



Scheme 1. Plausible mechanism for the acid-catalysed conversion of the dihydrobenzofurans **1** into the 2-thiomethylbenzofurans **3** with the thiol derivatives **2** as nucleophiles.

in Table 2. As can be seen, formation of **3aa** was observed with both AIBN and BP. In DME at 70 or 80 °C for 2 h in the presence of AIBN (10 mol-%) and a twofold excess of **2a** with respect to **1a**, substrate conversion was not quantitative, and **3aa** was formed in 31% and 65% yields, respectively (Table 2, Entries 1 and 2). Under similar conditions, but at 90 °C, substrate conversion was 100% and the yield of **3aa** reached 74% (Entry 3). This yield did not improve with a higher **2a**/**1a** molar ratio (Table 2, Entry 4), whereas the use of equimolar amounts of **1a** and **2a** led to a significantly lower yield of the product, due to the formation of a complex mixture of heavy, chromatographically immobile products (Table 2, Entry 5). Lower yields of **3aa** were also observed in dioxane (Table 2, Entry 6) or acetonitrile (Table 2, Entry 7) as solvents. With BP, the best yield of **3aa** (80%) was observed under conditions similar to those of Entry 3, but after a reaction time of 15 h rather than 2 h (Table 2, Entry 13).

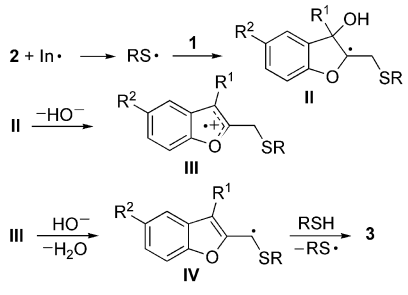
Table 2. Synthesis of 3-methyl-2-[(phenylsulfanyl)methyl]benzofuran (**3aa**) through allylic substitution of 3-methyl-2-methylene-2,3-dihydrobenzofuran-3-ol (**1a**) with thiophenol (**2a**) under radical conditions.[a]



Entry	**2a**/**1a** molar ratio	Radical initiator	Solvent	Temp. [°C]	Time [h]	Conv. of **1a** [%][b]	Yield of **3aa** [%][c]
1	2	AIBN	DME	70	2	60	31
2	2	AIBN	DME	80	2	85	65
3	2	AIBN	DME	90	2	100	74
4	5	AIBN	DME	90	2	100	69
5	1	AIBN	DME	90	15	100	27
6	2	AIBN	dioxane	90	2	83	44
7	2	AIBN	MeCN	90	2	72	32
8	2	BP	DME	70	2	67	33
9	2	BP	DME	80	2	80	53
10	2	BP	DME	90	2	90	59
11	2	BP	dioxane	90	2	72	36
12	2	BP	MeCN	90	2	69	21
13	2	BP	DME	90	15	100	80
14	1	BP	DME	90	15	100	34

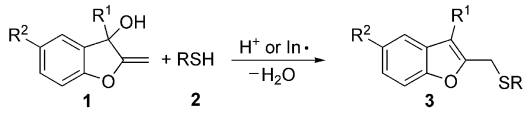
[a] Unless otherwise noted, all reactions were carried out in DME (substrate concentration: 0.22 mmol of **1a** per mL of solvent, 1.2 mmol scale based on **1a**) in the presence of radical initiator (10 mol-% with respect to **1a**). Formation of heavy products (chromatographically immobile materials) accounted for the difference between the conversion of **1a** and the yield of **3a** in each case. [b] Based on starting **1a**, by GLC. [c] Isolated yield based on starting **1a**.

A plausible mechanism for the formation of compounds **3** under free-radical conditions is shown in Scheme 2. Regiospecific addition of RS• (formed by the reaction between **2** and In•) to the exocyclic carbon of the double bond of **1** may afford the radical intermediate **II**. Direct fragmentation of **II** to give **3** and the hydroxyl radical HO• appears unlikely in view of the high instability of the latter species.[6] Alternatively, intermediate **II** can undergo ionic fragmentation with elimination of HO^- and formation of a radical cation species **III**.[7,8] Deprotonation of the latter by HO^- can then afford the stabilized radical species **IV**. Reaction of the latter with RSH leads to the formation of **3** with regeneration of RS•.



Scheme 2. Plausible mechanism for the radical-promoted conversions of the dihydrobenzofurans **1** into the 2-thiomethylbenzofurans **3** by treatment with the thiol derivatives **2**.

Table 3. Synthesis of the 2-thiomethylbenzofurans **3** by allylic substitution of the 2-methylene-2,3-dihydrobenzofuran-3-ols **1** with the thiol derivatives **2** under acidic or radical conditions.[a]



1 **2** **3**

Entry	**1**	R^1	R^2	**2**	R	Conditions[a]	**3**	Yield of **3** [%][b]
1	**1a**	Me	H	**2a**	Ph	A	**3aa**	81
2	**1a**	Me	H	**2a**	Ph	B	**3aa**	74
3	**1a**	Me	H	**2a**	Ph	C	**3aa**	80
4	**1a**	Me	H	**2b**	Bn	A	**3ab**	67
5	**1a**	Me	H	**2b**	Bn	B	**3ab**	60
6	**1a**	Me	H	**2b**	Bn	C	**3ab**	67
7	**1a**	Me	H	**2c**	$Ph(CH_2)_2$	A	**3ac**	51
8	**1a**	Me	H	**2c**	$Ph(CH_2)_2$	B	**3ac**	56
9	**1a**	Me	H	**2c**	$Ph(CH_2)_2$	C	**3ac**	60
10	**1a**	Me	H	**2d**	Ac	A	**3ad**	36
11	**1a**	Me	H	**2d**	Ac	B	**3ad**	78
12	**1a**	Me	H	**2d**	Ac	C	**3ad**	60
13	**1b**	H	H	**2a**	Ph	A	**3ba**	47
14	**1b**	H	H	**2a**	Ph	B	**3ba**	traces[c]
15	**1b**	H	H	**2a**	Ph	B[d]	**3ba**	5[e]
16	**1b**	H	H	**2a**	Ph	C	**3ba**	3[f]
17	**1b**	H	H	**2b**	Bn	A	**3bb**	30
18	**1b**	H	H	**2b**	Bn	B	**3bb**	55
19	**1b**	H	H	**2b**	Bn	C	**3bb**	66
20	**1b**	H	H	**2d**	Ac	A	**3bd**	26
21	**1b**	H	H	**2d**	Ac	B	**3bd**	77
22	**1b**	H	H	**2d**	Ac	C	**3bd**	74
23	**1c**	Me	Cl	**2b**	Bn	A	**3cb**	63
24	**1c**	Me	Cl	**2b**	Bn	B	**3cb**	61
25	**1c**	Me	Cl	**2b**	Bn	C	**3cb**	60
26	**1c**	Me	Cl	**2d**	Ac	A	**3cd**	47
27	**1c**	Me	Cl	**2d**	Ac	B	**3cd**	86
28	**1c**	Me	Cl	**2d**	Ac	C	**3cd**	71
29	**1d**	H	OMe	**2a**	Ph	A	**3da**	45
30	**1d**	H	OMe	**2a**	Ph	B[d]	**3da**	12[g]
31	**1d**	H	OMe	**2a**	Ph	C	**3da**	8[h]
32	**1d**	H	OMe	**2b**	Bn	A	**3db**	23
33	**1d**	H	OMe	**2b**	Bn	B	**3db**	55
34	**1d**	H	OMe	**2b**	Bn	C	**3db**	47
35	**1d**	H	OMe	**2c**	$Ph(CH_2)_2$	A	**3dc**	64
36	**1d**	H	OMe	**2c**	$Ph(CH_2)_2$	B	**3dc**	45
37	**1d**	H	OMe	**2c**	$Ph(CH_2)_2$	C	**3dc**	42
38	**1d**	H	OMe	**2d**	Ac	A	**3dd**	38
39	**1d**	H	OMe	**2d**	Ac	B	**3dd**	71
40	**1d**	H	OMe	**2d**	Ac	C	**3dd**	80

[a] Unless otherwise noted, reaction conditions were the following. *Conditions A*: reactions were carried out at 90 °C for 15 h in a 9:1 mixture of DME/H_2SO_4 (3.74×10^{-2} in DME) (substrate concentration: 0.22 mmol of **1** per mL of solvent, 1.2 mmol scale based on **1**), with a **2**/**1** molar ratio of 2. *Conditions B*: reactions were carried out at 90 °C for 2 h in DME (substrate concentration: 0.22 mmol of **1** per mL of solvent, 1.3 mmol scale based on **1**), with a **2**/**1**/AIBN molar ratio of 20:10:1. *Conditions C*: reactions were carried out at 90 °C for 15 h in DME (substrate concentration: 0.22 mmol of **1** per mL of solvent, 1.3 mmol scale based on **1**), with a **2**/**1**/BP molar ratio of 20:10:1. Unless otherwise noted, substrate conversion was quantitative in all cases, and the formation of heavy products (chromatographically immobile materials) accounted for the difference between the conversion of **1** and the yield of **3** in all cases. [b] Isolated yield based on starting **1**. [c] Substrate conversion was ca. 10%. [d] Reaction time was 15 h. [e] Substrate conversion was ca. 30%. [f] Substrate conversion was ca. 40%. [g] Substrate conversion was ca. 50%. [h] Substrate conversion was ca. 55%.

With the goal of expanding the scope of the reaction, we then tested the reactivity of **1a** and the other differently substituted 2-methylene-2,3-dihydrobenzofuran-3-ols **1b**–**d** (bearing a secondary alcoholic group together with an electron-withdrawing or a π-donating group on the aromatic ring) with several thiol derivatives **2a**–**d** (including thiophenol, alkyl thiols, thioacetic acid) under the conditions (both acidic and radical) already optimized for the reaction between **1a** and thiophenol (**2a**; summarized in Table 3, Entries 1–3). The results obtained are shown in Table 3. As can be seen, fair to high yields of the corresponding 2-thiomethylbenzofurans **3** were obtained in most cases (Table 3, Entries 1–9, 11–13, 18–19, 21–29, 33–37, and 39–40), although some combinations of dihydrobenzofurans **1** and thiol derivatives **2** gave lower yields under particular conditions. More specifically, the radical process did not work well in the case of the reaction of substrates bearing a secondary alcoholic group (R^1 = H) with thiophenol **2a** (R = Ph, Table 3, Entries 14–16 and 30–31), probably due to competitive attack of PhS· on the hydrogen at C-3. On the other hand, the use of thioacetic acid **2d** (R = Ac) led in some cases to less satisfactory results under acidic conditions (Table 3, Entries 10, 20, and 38), whereas the radical process proceeded well (Table 3, Entries 11–12, 21–22, and 39–40).

Conclusions

In conclusion, we have shown that the 2-methylene-2,3-dihydrobenzofuran-3-ols can easily be converted in a one-step fashion and under mild conditions into 2-thiomethylbenzofurans by treatment with thiols (including thiophenol, alkyl thiols, and thioacetic acid) under either acidic or radical conditions. The methodology reported here thus allows an innovative and convenient route to the sulfur-functionalized benzofuran derivatives from readily available starting materials.

Experimental Section

General: The starting 2-methylene-2,3-dihydrobenzofuran-3-ols **1** were prepared as described previously.[3d] The thiol derivatives **2** and DME were commercially available (Aldrich, Fluka) and were used as received. H_2SO_4 (96% w/w) was purchased from Carlo–Erba Reagenti (Milan, Italy) and was used as received. The solution of H_2SO_4 in DME (3.74×10^{-2} M) was prepared as follows: H_2SO_4 (96% w/w, d = 1.835 g mL^{-1}, 1.0 mL) was diluted with DME in a volumetric flask (10 mL) to a total volume of 10 mL, and a portion of this solution (200 μL) was then transferred into another volumetric flask (10 mL) and diluted with DME up to a total volume of 10 mL.

All reaction mixtures were analysed by TLC on silica gel (60 F_{254}, Merck) and by GLC with a Shimadzu GC-2010 gas chromatograph and capillary columns with polymethylsilicone + 5% phenylsilicone as the stationary phase (HP-5). Column chromatography was performed with silica gel 60 (Merck, 70–230 mesh). Evaporation refers to the removal of solvent under reduced pressure. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C with a Bruker DPX

Avance 300 spectrometer in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (J) are given in ppm and in Hz, respectively. IR spectra were taken with a Jasco FT-IR 4200 spectrometer. Mass spectra were obtained with a Shimadzu QP-2010 GC–MS apparatus at 70 eV ionization voltage. Microanalyses were carried out with a Carlo–Erba Elemental Analyzer Mod. 1106.

General Procedure for the Synthesis of the 2-(Thiomethyl)benzofurans 3 by Reactions between 2-Methylene-2,3-dihydrobenzofuran-3-ols 1 and Thiols 2 under Acidic Conditions (Table 3, Conditions A): In a typical experiment, a mixture of the 2-methylene-2,3-dihydrobenzofuran-3-ol **1** (1.23 mmol), the thiol derivative **2** (2.46 mmol) and H_2SO_4 (3.74×10^{-2} M in DME, 560 μL) in DME (5.0 mL) was stirred under nitrogen at 90 °C for 15 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with hexane/AcOEt 99:1 as eluent to give the pure thiomethylbenzofurans **3**. **3aa** is a pale yellow oil (254 mg, 81%; Table 3, Entry 1); **3ab** is a pale yellow oil (220 mg, 67%; Table 3 Entry 4); **3ac** is a pale yellow oil (178 mg, 51%; Table 3, Entry 7); **3ad** is a pale yellow oil (98 mg, 36%; Table 3, Entry 10); **3ba** is a pale yellow oil (140 mg, 47%; Table 3, Entry 13); **3bb** is a pale yellow oil (94 mg, 30%; Table 3, Entry 17); **3bd** is a pale yellow oil (65 mg, 26%; Table 3, Entry 20); **3cb** is a pale yellow oil (236 mg, 63%; Table 3, Entry 23); **3cd** is a pale yellow oil (148 mg, 47%; Table 3, Entry 26); **3da** is a pale yellow solid, m.p. 69–71 °C (150 mg, 45%, Table 3, Entry 29); **3db** is a pale yellow oil (80 mg, 23%; Table 3, Entry 32); **3dc** is a pale yellow oil (235 mg, 64%; Table 3, Entry 35); **3dd** is a pale yellow oil (111 mg, 38%; Table 3, Entry 38).

General Procedure for the Synthesis of the 2-(Thiomethyl)benzofurans 3 by Reactions between 2-Methylene-2,3-dihydrobenzofuran-3-ols 1 and Thiols 2 under Radical Conditions with AIBN as Initiator (Table 3, Conditions B): In a typical experiment, a mixture of the 2-methylene-2,3-dihydrobenzofuran-3-ol **1** (1.28 mmol), the thiol derivative **2** (2.56 mmol) and AIBN (21 mg, 0.13 mmol) in DME (5.8 mL) was stirred under nitrogen at 90 °C for 2 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with hexane/AcOEt 99:1 as eluent to give the pure thiomethylbenzofurans **3**. **3aa** is a pale yellow oil (240 mg, 74%; Table 3, Entry 2); **3ab** is a pale yellow oil (205 mg, 60%; Table 3 Entry 5); **3ac** is a pale yellow oil (202 mg, 56%; Table 3, Entry 8); **3ad** is a pale yellow oil (221 mg, 78%; Table 3, Entry 11); **3bb** is a pale yellow oil (180 mg, 55%; Table 3, Entry 18); **3bd** is a pale yellow oil (204 mg, 77%; Table 3, Entry 21); **3cb** is a pale yellow oil (235 mg, 61%; Table 3, Entry 24); **3cd** is a pale yellow oil (280 mg, 86%; Table 3, Entry 27); **3db** is a pale yellow oil (200 mg, 55%; Table 3, Entry 33); **3dc** is a pale yellow oil (171 mg, 45%; Table 3, Entry 36); **3dd** is a pale yellow oil (216 mg, 71%; Table 3, Entry 39).

General Procedure for the Synthesis of the 2-(Thiomethyl)benzofurans 3 by Reactions between 2-Methylene-2,3-dihydrobenzofuran-3-ols 1 and Thiols 2 under Radical Conditions with BP as Initiator (Table 3, Conditions C): In a typical experiment, a mixture of the 2-methylene-2,3-dihydrobenzofuran-3-ol **1** (1.32 mmol), the thiol derivative **2** (2.64 mmol) and BP (32 mg, 0.13 mmol) in DME (6.0 mL) was stirred under nitrogen at 90 °C for 15 h. After evaporation of the solvent, the residue was purified by column chromatography on silica gel with hexane/AcOEt 99:1 as eluent to give the pure thiomethylbenzofurans **3**. **3aa** is a pale yellow oil (270 mg, 80%; Table 3, Entry 3); **3ab** is a pale yellow oil (236 mg, 67%; Table 3 Entry 6); **3ac** is a pale yellow oil (225 mg, 60%; Table 3, Entry 9); **3ad** is a pale yellow oil (175 mg, 60%; Table 3, Entry 12); **3bb** is a pale yellow oil (223 mg, 66%; Table 3, Entry 19); **3bd** is a pale yellow oil (201 mg, 74%; Table 3, Entry 22); **3cb** is a pale yellow oil (240 mg, 60%; Table 3, Entry 25); **3cd** is a pale yellow oil (240 mg, 71%; Table 3, Entry 28); **3db** is a pale yellow oil (175 mg, 47%; Table 3, Entry 34); **3dc** is a pale yellow oil (167 mg, 42%; Table 3, Entry 37); **3dd** is a pale yellow oil (250 mg, 80%; Table 3, Entry 40).

3-Methyl-2-[(phenylsulfanyl)methyl]benzofuran (3aa): Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.32 (m, 4 H, aromatic), 7.28–7.15 (m, 5 H, aromatic), 4.16 (s, 2 H, CH_2), 1.91 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.3, 149.0, 135.3, 132.2, 129.1, 128.9, 127.4, 124.1, 122.3, 119.1, 112.9, 111.0, 31.3, 7.6 ppm. IR (film): $\tilde{\nu}$ = 1582 (m), 1477 (m), 1439 (s), 1262 (m), 1198 (w), 1079 (m), 743 (s), 690 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 254 (35) $[M]^+$, 147 (8), 146 (50), 145 (100), 127 (30), 117 (12), 116 (24), 115 (51), 109 (31), 102 (8), 91 (32), 89 (11), 77 (25), 75 (10). $C_{16}H_{14}OS$ (254.35): calcd. C 75.55, H 5.55, S 12.61; found C 75.63, H 5.54, S 12.59.

2-[(Benzylsulfanyl)methyl]-3-methylbenzofuran (3ab): Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.40 (m, 2 H, aromatic), 7.38–7.17 (m, 7 H, aromatic), 3.74 (s, 2 H, CH_2), 3.72 (s, 2 H, CH_2), 2.10 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1, 149.7, 137.8, 129.9, 129.0, 128.5, 127.1, 124.0, 122.3, 119.1, 112.2, 111.0, 36.1, 26.0, 8.1 ppm. IR (film): $\tilde{\nu}$ = 1494 (m), 1453 (s), 1262 (w), 1198 (w), 1079 (s), 849 (w), 747 (m), 699 (s) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 268 (20) $[M]^+$, 146 (12), 145 (100), 115 (13), 91 (14). $C_{17}H_{16}OS$ (268.37): calcd. C 76.08, H 6.01, S 11.95; found C 76.15, H 6.04, S 12.01.

3-Methyl-2-[(phenethylsulfanyl)methyl]benzofuran (3ac): Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48–7.39 (m, 2 H, aromatic), 7.33–7.12 (m, 7 H, aromatic), 3.84 (s, 2 H, CH_2SCH_2CH_2), 2.92–2.72 (m, 4 H, CH$_2$SCH_2CH_2), 2.21 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.1, 154.0, 149.8, 140.3, 129.9, 128.5, 126.4, 124.0, 122.3, 119.1, 112.1, 111.0, 36.1, 33.3, 26.8, 8.1 ppm. IR (film): $\tilde{\nu}$ = 1497 (w), 1475 (w), 1454 (s), 1263 (m), 1199 (w), 1080 (w), 1055 (w), 698 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 282 (16) $[M]^+$, 146 (11), 145 (100), 115 (19), 91 (17), 77 (9). $C_{18}H_{18}OS$ (282.40): calcd. C 76.56, H 6.42, S 11.35; found C 76.27, H 6.44, S 11.32.

***S*-(3-Methylbenzofuran-2-yl)methyl Thioacetate (3ad):** Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46–7.34 (m, 2 H, aromatic), 7.28–7.15 (m, 2 H, aromatic), 4.26 (s, 2 H, CH_2), 2.34 [s, 3 H, Me(CO)], 2.24 (s, 3 H, Me at C-3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.4, 154.1, 148.3, 129.8, 124.2, 122.3, 119.2, 112.7, 110.9, 30.3, 24.5, 7.9 ppm. IR (film): $\tilde{\nu}$ = 1496 (w), 1475 (w), 1455 (s), 1263 (m), 1199 (m), 1080 (m), 1055 (w), 747 (s), 698 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 220 (13) $[M]^+$, 146 (11), 145 (100), 115 (19). $C_{12}H_{12}O_2S$ (220.29): calcd. C 65.43, H 5.49, S 14.56; found C 65.51, H 5.51, S 14.51.

2-[(Phenylsulfanyl)methyl]benzofuran (3ba): Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.50–7.41 (m, 2 H, aromatic), 7.41–7.34 (m, 2 H, aromatic), 7.31–7.15 (m, 5 H, aromatic), 6.47 (s, 1 H, 3-H), 4.21 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 154.3, 135.5, 130.9, 129.0, 128.6, 127.1, 124.1, 122.8, 120.8, 111.2, 104.7, 32.4 ppm. IR (film): $\tilde{\nu}$ = 1584 (w), 1479 (m), 1454 (s), 1439 (m), 1253 (s), 1087 (w), 1024 (w), 952 (w), 739 (s), 689 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 240 (15) $[M]^+$, 132 (11), 131 (100), 77 (22). $C_{15}H_{12}OS$ (240.32): calcd. C 74.97, H 5.03, S 13.34; found C 75.15, H 5.95, S 13.31.

2-[(Benzylsulfanyl)methyl]benzofuran (3bb): Pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54–7.42 (m, 2 H, aromatic), 7.38–

7.16 (m, 7 H, aromatic), 6.53 (s, 1 H, 3-H), 3.74 (s, 2 H, CH_2), 3.69 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.2, 154.9, 137.8, 129.4, 129.1, 128.6, 127.2, 124.0, 122.8, 120.7, 111.2, 104.4, 36.3, 28.1 ppm. IR (film): $\tilde{\nu}$ = 1494 (w), 1454 (s), 1253 (m), 1192 (w), 1071 (w), 952 (w), 743 (m), 700 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 254 (18) $[M]^+$, 132 (27), 131 (100), 91 (18), 77 (20). $C_{16}H_{14}OS$ (254.35): calcd. C 75.55, H 5.55, S 12.61; found C 75.63, H 5.51, S 12.63.

***S*-(Benzofuran-2-yl)methyl Thioacetate (3bd):** Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.52–7.46 (m, 1 H, aromatic), 7.45–7.39 (m, 1 H, aromatic), 7.28–7.15 (m, 2 H, aromatic), 6.61 (s, 1 H, 3-H), 4.26 (s, 2 H, CH_2), 2.37 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.2, 154.9, 153.4, 128.4, 124.1, 122.8, 120.8, 111.1, 104.8, 30.3, 26.3 ppm. IR (film): $\tilde{\nu}$ = 1695 (s), 1600 (w), 1586 (w), 1454 (m), 1354 (w), 1253 (m), 1131 (m), 954 (m), 743 (m), 697 (w) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 206 (14) $[M]^+$, 132 (9), 131 (100), 91 (5), 77 (19). $C_{11}H_{10}O_2S$ (206.26): calcd. C 64.05, H 4.89, S 15.55; found C 64.15, H 4.87, S 15.59.

2-[(Benzylsulfanyl)methyl]-5-chloro-3-methylbenzofuran (3cb): Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.42–7.17 (m, 8 H, aromatic), 3.74 (s, 2 H, CH_2), 3.70 (s, 2 H, CH_2), 2.07 (s, 3 H, Me) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.4, 151.5, 137.6, 131.3, 128.9, 128.5, 127.9, 127.1, 124.1, 118.8, 111.9, 36.2, 26.0, 8.0 ppm. IR (film): $\tilde{\nu}$ = 1494 (w), 1453 (s), 1267 (m), 1199 (w), 1090 (m), 1058 (w), 803 (w), 758 (w), 701 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 304 (6) $[M + 2]^+$, 302 (16) $[M]^+$, 181 (32), 180 (14), 179 (100), 144 (10), 116 (8), 115 (17), 91 (17). $C_{17}H_{15}ClOS$ (302.82): calcd. C 67.43, H 4.99, Cl 11.71, S 10.59; found C 67.32, H 5.01, Cl 11.75, S 10.57.

***S*-(5-Chloro-3-methylbenzofuran-2-yl)methyl Thioacetate (3cd):** Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 2.1 Hz, 1 H, 4-H), 7.28 (distorted d, *J* = 8.8 Hz, 1 H, 7-H), 7.18 (distorted dd, *J* = 8.8, 2.1 Hz, 1 H, 6-H), 4.24 (s, 2 H, CH_2), 2.36 [s, 3 H, Me(CO)], 2.21 (s, 3 H, Me at C-3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.0, 152.7, 150.2, 131.4, 128.2, 124.4, 119.1, 112.5, 111.9, 30.2, 24.6, 7.8 ppm. IR (film): $\tilde{\nu}$ = 1695 (s), 1452 (s), 1354 (w), 1267 (m), 1199 (w), 1130 (m), 1092 (m), 1061 (w), 957 (w), 905 (w), 863 (m), 803 (m), 701 (m), 623 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 256 (6) $[M + 2]^+$, 254 (17) $[M]^+$, 181 (32), 180 (13), 179 (100), 144 (13), 115 (20). $C_{12}H_{11}ClO_2S$ (254.73): calcd. C 56.58, H 4.35, Cl 13.92, S 12.59; found C 56.65, H 4.33, Cl 14.01, S 12.52.

5-Methoxy-2-[(phenylsulfanyl)methyl]benzofuran (3da): Pale yellow solid, m.p. 69–71 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.40–7.16 (m, 6 H, aromatic), 6.92 (d, *J* = 2.6 Hz, 1 H, 4-H), 6.84 (distorted dd, *J* = 8.8, 2.6 Hz, 1 H, 6-H), 6.40 (s, 1 H, 3-H), 4.17 (s, 2 H, CH_2), 3.80 (s, 3 H, OMe) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 155.1, 150.3, 135.6, 130.9, 129.2, 129.0, 127.1, 112.7, 111.5, 104.8, 103.8, 56.0, 32.4 ppm. IR (film): $\tilde{\nu}$ = 1599 (w), 1476 (s), 1440 (m), 1233 (m), 1210 (s), 1165 (m), 1113 (w), 1031 (m), 954 (m), 843 (m), 735 (s), 710 (w), 689 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 270 (10) $[M]^+$, 162 (11), 161 (100), 146 (7), 118 (19). $C_{16}H_{14}O_2S$ (270.35): calcd. C 71.08, H 5.22, S 11.86; found C 71.16, H 5.21, S 11.91.

2-[(Benzylsulfanyl)methyl]-5-methoxybenzofuran (3db): Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.41–7.19 (m, 6 H, aromatic), 6.92 (d, *J* = 2.6 Hz, 1 H, 4-H), 6.86 (distorted dd, *J* = 8.8, 2.6 Hz, 1 H, 6-H), 6.47 (s, 1 H, 3-H), 3.83 (s, 3 H, OMe), 3.74 (s, 2 H, CH_2), 3.67 (s, 2 H, CH_2) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.3, 155.8, 150.3, 137.8, 130.4, 129.1, 128.6, 127.2, 112.6, 111.5, 104.6, 103.8, 56.1, 36.3, 28.2 ppm. IR (film): $\tilde{\nu}$ = 1616 (w), 1601 (w), 1476 (s), 1452 (m), 1206 (s), 1167 (m), 1030 (m), 955 (w), 842 (w), 798 (w), 764 (w), 701 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 284 (23) $[M]^+$, 162 (17), 161 (100), 146 (5), 118 (12), 91 (15). $C_{17}H_{16}O_2S$ (284.37): calcd. C 71.80, H 5.67, S 11.28; found C 71.67, H 5.69, S 11.31.

5-Methoxy-2-[(phenethylsulfanyl)methyl]benzofuran (3dc): Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.14 (m, 6 H, aromatic), 6.97 (d, *J* = 2.6 Hz, 1 H, 4-H), 6.85 (dd, *J* = 8.8, 2.6 Hz, 1 H, 6-H), 6.48 (s, 1 H, 3-H), 3.82 (s, 3 H, OMe), 3.79 (s, 2 H, $CH_2SCH_2CH_2$), 2.93–2.76 (m, 4 H, $CH_2SCH_2CH_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.2, 155.9, 150.2, 145.4, 140.4, 129.2, 128.6, 126.6, 112.7, 111.6, 104.4, 103.7, 56.1, 36.1, 33.6, 29.2 ppm. IR (film): $\tilde{\nu}$ = 1616 (w), 1602 (w), 1496 (w), 1476 (s), 1453 (m), 1206 (s), 1167 (m), 1031 (m), 954 (w), 839 (m), 699 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 298 (14) $[M]^+$, 162 (12), 161 (100), 146 (7), 118 (20), 91 (14), 77 (10). $C_{18}H_{18}O_2S$ (298.40): calcd. C 72.45, H 6.08, S 10.75; found C 72.54, H 6.06, S 10.78.

***S*-(5-Methoxybenzofuran-2-yl)methyl Thioacetate (3dd):** Pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 (distorted d, *J* = 8.8 Hz, 1 H, 7-H), 6.95 (distorted d, *J* = 2.6 Hz, 1 H, 4-H), 6.85 (distorted dd, *J* = 8.8, 2.6 Hz, 1 H, 6-H), 6.55 (s, 1 H, 3-H), 4.24 (s, 2 H, CH_2), 3.82 (s, 3 H, OMe), 2.37 [s, 3 H, Me(CO)] ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.4, 156.0, 154.3, 150.0, 129.0, 112.9, 111.6, 105.0, 103.4, 56.0, 30.4, 26.4 ppm. IR (film): $\tilde{\nu}$ = 1694 (s), 1617 (w), 1477 (s), 1448 (m), 1354 (w), 1206 (s), 1168 (m), 1133 (m), 1031 (m), 957 (m), 800 (m), 725 (w), 624 (m) cm^{-1}. GC–MS (EI, 70 eV): *m*/*z* (%) = 236 (22) $[M]^+$, 162 (13), 161 (100), 146 (6), 118 (12), 89 (6). $C_{12}H_{12}O_3S$ (236.29): calcd. C 61.00, H 5.12, S 13.57; found C 61.12, H 5.10, S 13.61.

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[6] A few examples of radical fragmentation to give rather high-energy radicals are known in the literature, but they involve the simultaneous formation of stabilized aromatic compounds; see, for example: a) J. C. Walton, A. Studer, *Acc. Chem. Res.* **2005**, *38*, 794–802; b) J. Guin, C. Mück-Lichtenfeld, S. Grimme, A. Studer, *J. Am. Chem. Soc.* **2007**, *129*, 4498–4503; c) J. Kemper, A. Studer, *Angew. Chem. Int. Ed.* **2005**, *44*, 4914–4917; d) J. Guin, R. Fröhlich, A. Studer, *Angew. Chem. Int. Ed.* **2008**, *47*, 779–782.

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