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Synthesis of Polysubstituted 3-Thiofurans by Regiospecific Mono-*ipso*-substitution and *ortho*-Metallation from 3,4-Dibromofuran

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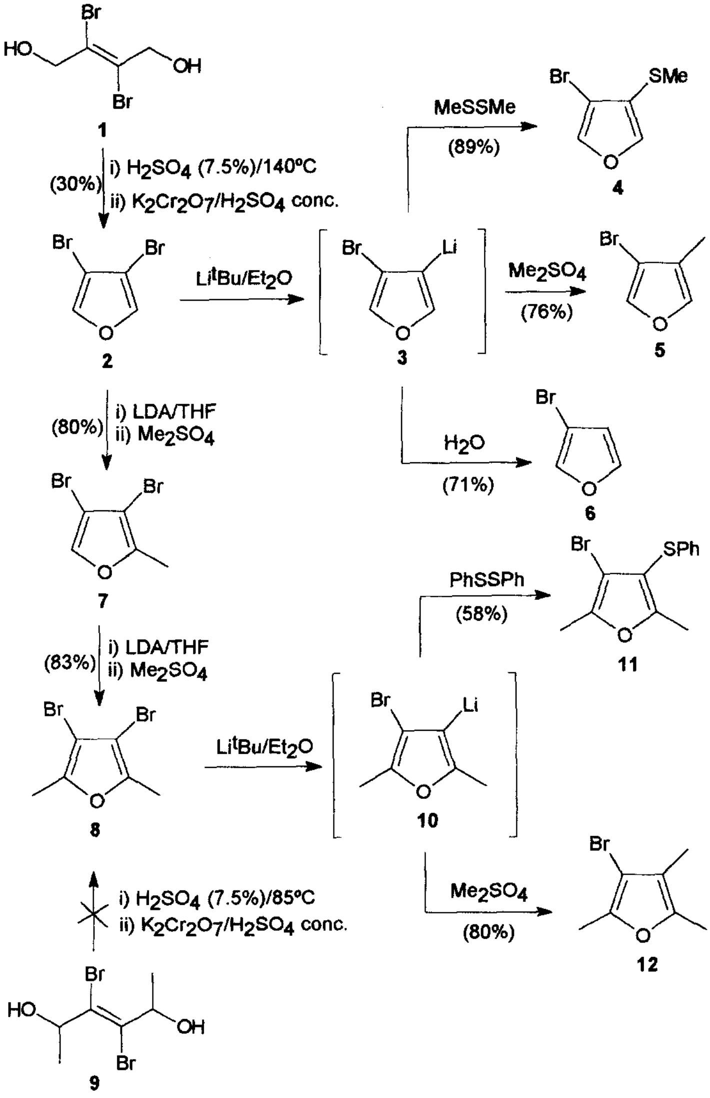
Abstract: The synthetic potential of 3,4-dibromofuran has been assessed by its conversion into 3,4-disubstituted furans via mono-*S*-*ipso*-substitution. The ability of 3-methylthio and 3-phenylthio substituents for directing the metallation at position α-relative to the substituent has allowed the regiospecific alkylation. It provides a straightforward approach to several 3-monothiosubstituted furans which are receiving increasing interest as odour and flavour chemicals.

INTRODUCTION

Furan derivatives substituted in the 3 position with sulfur are very powerful odour and flavour chemicals[1-9] and are quite different in odour and flavour character than the corresponding furans substituted at the 2 position.[10] Some synthetic routes to these compounds have already been reported.[11-13] Recently, a general method for introducing a S-function at the prospective 3-position of the furan ring from an open chain precursor has been described.[14] Further cyclization and transfunctionalization of the 3-thiosubstituted furans afforded derivatives which had been previously identified in foods and in model reaction mixtures of the cooking processes.[1-9]

In this paper, the scarcely used regiospecific mono-*ipso*-substitution of 3,4-dibromofuran **2** with 1 equiv. of *tert*-butyllithium at low temperatures is described as the foremost step to obtain polysubstituted furans.[15] Subsequent workup of 3-bromo-4-lithiofuran **3** by addition of dimethyldisulfide, dimethyl sulfate or hydrochloric acid afforded 3-bromo-4-methylthiofuran **4**, 3-bromo-4-methylfuran **5**, and 3-bromofuran **6**, respectively (Scheme 1). The propensity of these 3-bromofuran derivatives to undergo the *ortho*-metallation and subsequent electrophilic reaction at the carbon C2 as well as a second metal-bromine exchange reaction, discloses the 3,4-dibromofuran **2** as a prominent starting material for synthesising polysubstituted furans bearing a S-function at position 3 (Scheme 2 and 3).

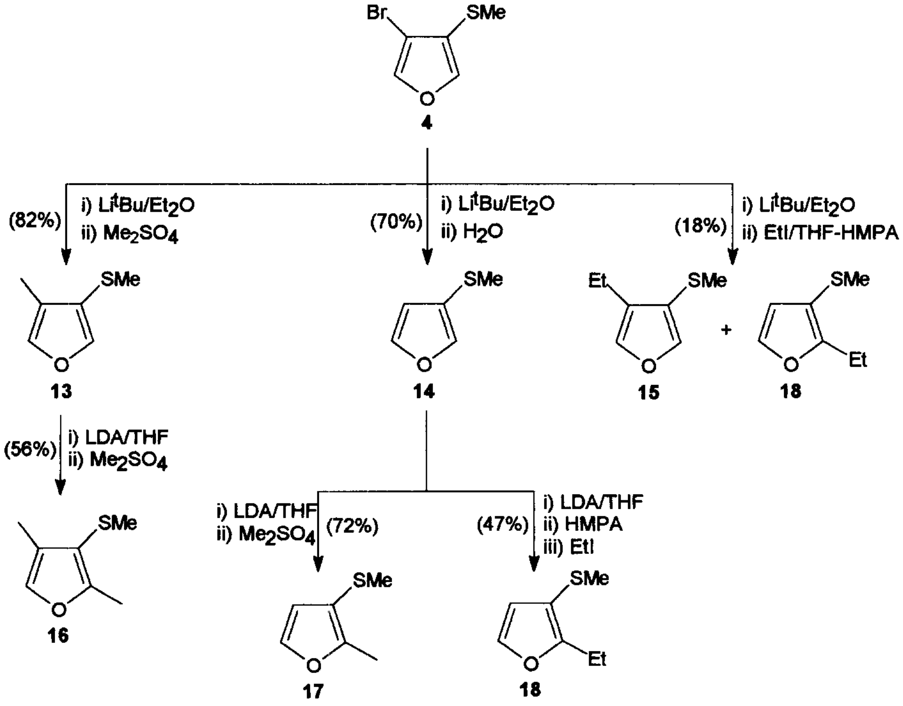
RESULTS AND DISCUSSION



Scheme 1

The synthesis of 3,4-dibromofuran **2** was achieved from 2,3-dibromo-2-buten-1,4-diol **1** by the one-pot method previously described by Riwicki *et al.*[20] However, this method was unsuccessful for obtaining 3,4-dibromo-2,5-dimethylfuran **8** from 3,4-dibromo-3-hexen-2,5-diol **9**. The synthesis of **8** was achieved by mono-*ortho*-metallation of compound **2** and subsequent methylation, yielding 3,4-dibromo-2-methylfuran **7**, which was then subjected to the same reactions as **2**. On the other way, compound **2** was firstly treated with *tert*-butyllithium (1:1) in ether and then with the electrophile reagents -dimethyldisulfide, dimethyl sulfate, and water- to obtain compounds **4**, **5** and **6**, respectively. Unsymmetrically 3,4-disubstituted derivatives as **11** and **12** were similarly obtained by reaction of derivative **8** with *tert*-butyllithium *via* the intermediate **10** (Scheme 1).

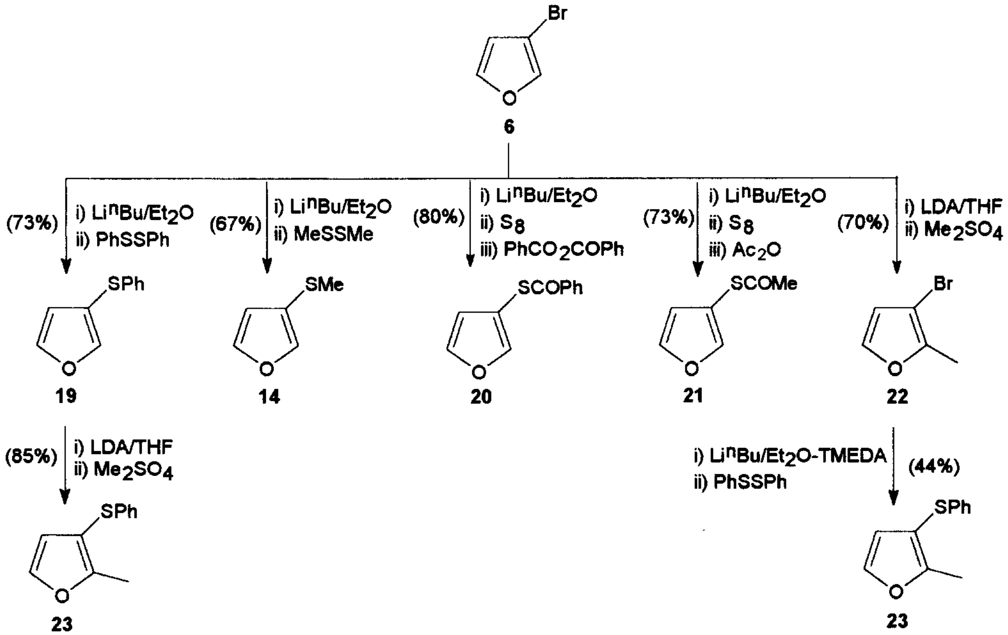
All 3-bromosubstituted furans (**4-6**, **11**, **12**) are versatile intermediates for achieving the synthesis of 3-thiosubstituted furans. Compound **6** is a commercially available but expensive starting material. The synthesis of **6** from compound **2** showed the pivotal role of this compound for obtaining differently substituted furans. Other sophisticated methods to obtain C3 and C4 substituted furans from 3,4-bis(trimethylsilyl)furan and 3,4-bis(tributylstannyl)furan have been recently reported.[26, 27] The strategy described in this paper also represents an easy pathway to obtain unsymmetrical 3,4-disubstituted furans. Another outstanding fact of this synthetic pathway was that both highly substituted derivatives as well as monosusbtituted furans, were readily available from 3,4-dibromofuran **2** as starting material. The substituents were introduced by metal-halogen exchange reaction or *ortho*-metallation and then alkylation of 2(5)-unsubstituted furans. This synthetic potential has been assessed by conversion of compounds **4** and **6** into several 3-monothiosubstituted furans (Schemes 2 and 3).



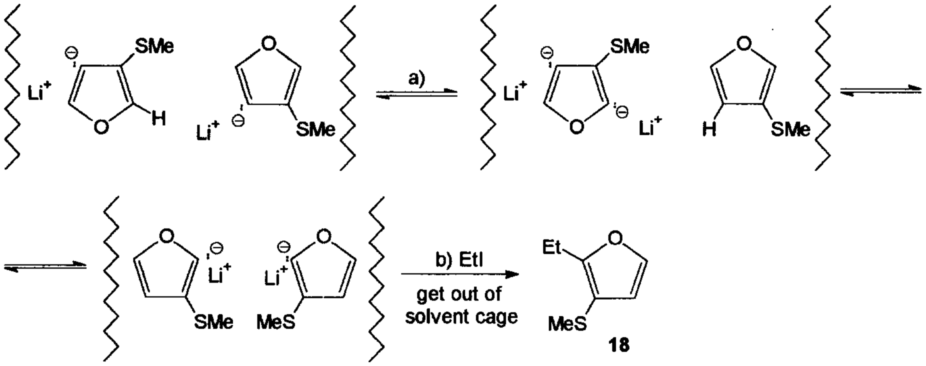
Scheme 2

Thus, when compound **4** was subjected to a new set of metal-halogen exchange reactions, just like compound **2**, the furans **13**, **14**, and **15** were obtained (Scheme 2). The last derivative was obtained with a poor yield although HMPA was used for trying to avoid the competitive elimination reaction on ethyl iodide. In this reaction, the main product was the 3-methylthiofuran **14** whereas the 2-ethyl-3-methylthiofuran **18** was obtained in the same proportion as compound **15**. In fact, the HMPA is a polar solvent which enhances the reactivity of carbanion species as a consequence of the formation of solvent-separated ionic pairs. Thus, fast and consecutive acid-base bimolecular reactions could occur before the nucleophile reagent escapes from the solvent cage so leading to the isomerization of 3-lithio-4-methylthiofuran. The regioselectivity of subsequent alkylation reaction is directed by the greater acidity of the H-atom bound at C2 position (Scheme 4).

On the other hand, the regiospecific metallation at carbon 2 with LDA/THF has been shown to be an efficient method for achieving the proton-metal exchange even when a reactive halogen substituent was present in the initial furan.[28] The nmr spectra of the crude products obtained by LDA-metallation and alkylation of compounds **13** and **14** show unequivocally the *ortho*-director effect of the methylthio group. In addition, the assignment of signals of carbons C2 and C5 in **13** and **14** was made from the observed $^1J(^{13}C,^1H)$ coupling constants. Thus, the highest values must be related to the nearest carbon atoms of methylthio group because its electron-withdrawing effect increases the acidity[29] of the adjacent hydrogens for allowing the regiospecific metallation.



Scheme 3



Scheme 4

When compound **6** was treated in the usual fashion with LiBu^n at -78°C a 3-lithiofuran intermediate resulted which was quenched with S-electrophilic reagents as diphenyldisulfide, dimethyldisulfide, and sulfur (Scheme 3). In this last case, the thioesters **20** and **21** were obtained with better yields than other previously reported method[30-32] when benzoic anhydride or acetic anhydride were added for trapping the intermediate thiolate.

2-Methyl-3-phenylthiofuran **23** was obtained in good yield by metallation of furan **19** with LDA and reaction with dimethyl sulfate. This result reflects the increase of acidity of the α-hydrogens to the phenylthio group and the *ortho*-director character of this substituent. The synthesis of furan **23** was also tried out from 3-bromo-2-methylfuran **22**. However, the yield was poor because the isolation of furan **23** from the mixture of the remaining diphenyldisulfide and *n*-buthyphenylsulfide originating as by-products in the reaction was very difficult.

CONCLUSIONS

The results described above demonstrate that 3,4-dibromofuran is a pivotal compound in the synthesis of 3-monothio polysubstituted furans. A large variety of substituent arrangements was achieved by combining a suitable choice of metallation reagent together with a fitting selection of the electrophilic reagents. The synthetic capacity of well-established alkylation or coupling reactions has been revealed as the only limiting factor for the results described herein.

EXPERIMENTAL SECTION

THF and Et_2O were distilled after refluxing over Na-benzophenone under argon prior to use. Solutions of LiBu^n in hexane and LiBu^t in pentane were stored under argon and entitled prior to use.[33] Diisopropylamine was dried over NaOH and freshly distilled after refluxing over NaH under argon prior to use.[34] Dimethyl disulfane was filtered over neutral alumina prior to use. Diethyl sulfate was purified by washing with 3% aqueous solution of Na_2CO_3, distillation of water, dried over dry $CaCl_2$, and distilled at reduced pressure.[34] Dimethyl sulfate was dried over K_2CO_3 and distilled at reduced pressure after refluxing over dry CaO.[34] Silica gel 60 F_{254} was used for TLC and the spots were detected with a UV lamp. Flash chromatographies were carried out on silica gel 60 (230-400 mesh). Kugelrohr distillations reflect the oven temperatures and were listed as "Kd °C/torr". IR spectra were recorded as neat film between NaCl windows or as KBr pellets for solid compounds. ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded in $CDCl_3$ solutions with TMS as internal reference and full assignment of ^{13}C NMR spectra was carried out with the aid of coupled spectra or 2D heteronuclear ^1H-^{13}C correlation spectra.

3,4-Dibromofuran 3. The title compound was obtained according to the procedure previously described[20] as a colourless practically pure oil from (*E*)-2,3-dibromo-2-buten-1,4-diol (45.0 g, 183 mmol) (yield: 30%) and used directly without further purification. ^1H NMR: δ(ppm) 7.45 (s, H2 and H5). ^{13}C NMR: δ(ppm) 103.8 (s, C3 and C4), 141.4 (d, ^1J = 212.6 Hz, C2 and C4).

Metallation of 2(5)-Unsubstituted Furans. Typical Procedure. To a solution of diisopropylamine (0.7 mL, 4.87 mmol) in THF (5 mL) at -78°C was added a 1.2 M solution of $LiBu^n$ in hexane (3.7 mL, 4.43 mmol) dropwise, and the solution was stirred for 10 min at -78°C. The LDA solution was then cannulated under argon into a solution of the furan derivative (4.4 3 mmol) in dry THF (15 mL) dropwise, the mixture was stirred for 30 min at -78°C, and the corresponding electrophilic reagent was added. Reaction conditions, work up of reaction mixtures and purification of reaction crudes have been described below.

Metallation of 3(4)-Bromofurans. Typical Procedure. Metallations were carried out under argon atmosphere by using $LiBu^t$ or $LiBu^n$ for achieving the metal-halogen exchange in the bromofuran derivative.

To a solution of 3(4)-bromofuran derivative (11.1 mmol) in dry Et_2O (25 mL) at -78°C was added a solution of organolithium reagent (11.1 mmol; $LiBu^t$/pentane or $LiBu^n$/hexane) dropwise, the solution was then stirred for 30 min at -78°C, and the corresponding electrophilic reagent was added. Reaction conditions, work-up of reaction mixtures, and purifications of reaction crudes have been described below.

3-Bromo-4-methylthiofuran 4. To a solution of 3-bromo-4-lithiofuran which was performed as described above from 3,4-dibromofuran **2** (24.0 g, 106.3 mmol) in Et_2O (240 mL) and 1.1 M solution of $LiBu^t$ (96.6 mL, 106.3 mmol) was added dropwise the dimethyldisulfide (9.5 mL, 106.3 mmol). The mixture was then vigorously stirred at -78°C for 1 h, the temperature was then allowed to rise to rt., and the stirring was maintained for 2 h at rt. After cooling the reaction mixture to 0°C, a saturated aqueous ammonium chloride solution (20 mL) was then added. The mixture was extracted with Et_2O/pentane (1/1; v/v) (2 x 20 mL), the combined organic layers were washed with brine (2 x 30 mL), and dried over $MgSO_4$. After concentration of the solution under reduced pressure, a colourless oil crude product was obtained (over 87% pure by ^1H NMR; yield: 69%) and used without further purification. ^1H NMR: δ(ppm) 2.35 (s, 3H, SMe), 7.38 (d, 1H, ^4J = 1.5

Hz, H5), 7.47 (d, 1H, ^{4}J = 1.5 Hz, H2). ^{13}C NMR: δ(ppm) 18.1 (q, ^{1}J = 140.4 Hz, SMe), 104.8 (dd, ^{2}J = 11.1 Hz, ^{3}J = 8.0 Hz, C3), 120.3 (dq, ^{2}J = 12.1 Hz, $^{3}J_{C4,H2}$ = $^{3}J_{C4,Me}$ = 5.0 Hz, C4), 141.7 (dd, ^{1}J = 210.5 Hz, ^{3}J = 6.0 Hz, C2), 143.0 (dd, ^{1}J = 208.5 Hz, ^{3}J = 6.0 Hz, C5).

3-Bromo-4-methylfuran **5**. The synthesis was performed as described above for furan **4** from 3,4-dibromofuran **2** (25.0 g, 110.7 mmol) in Et$_2$O (250 mL), LiBu^t (1.25 M, 88.6 mL, 110.7 mmol) and dimethyl sulfate (21.0 mL, 221.4 mmol). After cooling the reaction mixture to 0°C, a concentrated aqueous ammonium hydroxide (500 mL) was added and the mixture was extracted with Et$_2$O (3 x 100 mL). The combined organic layers were then washed with brine (3 x 100 mL) and dried over MgSO$_4$. After concentration of the solution under reduced pressure, a colourless oil was obtained (11.76 g., yield: 66%). IR (film): ν 3140, 2920, 1590, 1450 cm^{-1}. ^{1}H NMR: δ(ppm) 1.99 (dd, 3H, ^{4}J = 1.2 Hz, ^{5}J = 0.3 Hz, CH$_3$), 7.19 (dq, 1H, ^{4}J = 1.8 Hz, ^{4}J = 1.2 Hz, H5), 7.39 (dq, 1H, ^{4}J = 1.8 Hz, ^{5}J = 0.3 Hz, H2). ^{13}C NMR: δ(ppm) 8.4 (q, ^{1}J = 128.3 Hz, CH$_3$), 103.4 (ddq, $^{2}J_{C3,H2}$ = 9.8 Hz, $^{3}J_{C3,H5}$ = 8.0 Hz, $^{3}J_{C3,Me}$ = 5.0 Hz, C3), 120.7 (dq, $^{2}J_{C4,H5}$ = 12.5 Hz, $^{2}J_{C4,Me}$ = $^{3}J_{C4,H2}$ = 7.0 Hz, C4), 139,5 (dq, ^{1}J = 202.5 Hz, ^{3}J = 6.0 Hz, C5), 140.6 (dd, ^{1}J = 208.0 Hz, ^{3}J = 5.5 Hz, C2). Anal. Calcd. for C$_5$H$_5$OBr: C, 37.30; H, 3.13. Found: C, 37.50; H, 3.00.

3-Bromofuran **6**. This compound was obtained as described above from 3,4-dibromofuran **2** (500 mg, 2.21 mmol), LiBu^t (1.1 M, 2.2 mL, 2.43 mmol) and distilled water as electrophile (6 mL). The reaction mixture was extracted with Et$_2$O (3 x 15 mL) and the combined organic layers were washed with brine (3 x 20 mL) and dried over MgSO$_4$. A careful elimination of the solvent at atmospheric pressure through a Vigreux column allowed the isolation of a crude product (260 mg, over 87% pure by ^{1}H NMR, yield:70%) which was purified by distillation at reduced pressure in a Kugelrohr oven Bp: 55°C/20 torr. Lit:[22b,35] 103°C. ^{1}H NMR: δ(ppm) 6.45 (dd, 1H, ^{3}J = 2.1 Hz, ^{4}J = 0.8 Hz, H4), 7.36 (dd, 1H, ^{3}J = 2.1 Hz, ^{4}J = 1.6 Hz, H5), 7.43 (dd, 1H, ^{4}J = 1.6 Hz, ^{4}J = 0.8 Hz, H2). ^{13}C NMR: δ(ppm) 99.5 (dd, ^{2}J = 11.1 Hz, ^{2}J = 9.1 Hz, C3), 113.2 (ddd, ^{1}J = 180.8 Hz, ^{2}J = 13.6 Hz, ^{3}J = 5.1 Hz, C4), 140.9 (dt, ^{1}J = 209.5 Hz, ^{3}J = 5.5 Hz, C2), 143.4 (ddd, ^{1}J = 205.5 Hz, ^{2}J = 10.1 Hz, ^{3}J = 7.1 Hz, C5).

3,4-Dibromo-2-methylfuran **7**. This compound was obtained as described above from 3,4-dibromofuran **2** (2.0 g, 8.91 mmol), LDA solution (8.9 mmol) and dimethyl sulfate (1.7 mL, 17.8 mmol) as electrophile. The reaction was accomplished as described before in the typical procedure. After addition of Me$_2$SO$_4$, the reaction mixture was allowed to rise slowly to rt. and stirred for 30 min. at rt. The solvent was then eliminated at reduced pressure and the reaction crude was dissolved in Et$_2$O (200 mL), cooled to 0°C and a cool concentrated aqueous ammonium hydroxide solution (150 mL) was then added. The organic layer was decanted, washed with brine (3 x 50 mL) and dried over MgSO$_4$. After concentration of the solution under reduced pressure, a colourless oil was obtained (over 80% pure by ^{1}H NMR; yield: 63%) and used without further purification because all attempts at separation by flash chromatography or TLC were unsuccessful. ^{1}H

NMR: δ(ppm) 2.232 (d, 3H, ^5J = 0.3 Hz, CH_3), 7.34 (q, 1H, ^5J = 0.3 Hz, H5). ^{13}C NMR: δ(ppm) 12.3 (CH_3), 100.1 (C3), 103.6 (C4), 138.9 (C5), 150.3 (C2).

3,4-Dibromo-2,5-dimethylfuran 8. This compound was synthesised as described above from the crude 3,4-dibromo-2-methylfuran 7 (1.0 g, 3.35 mL) previously obtained, LDA solution (9.3 mmol) and dimethyl sulfate (1.8 mL, 18.61 mmol) as electrophile. Work-up of reaction mixture was identical to the procedure previously described for 3,4-dibromo-2-methylfuran 7. A colourless oil was obtained (1.34 g.; over 83% pure by ^1H NMR; yield: 64%) which was used without further purification. ^1H NMR: δ(ppm) 2.27 (s 2x Me). ^{13}C NMR: δ(ppm) 12.6 (2 x Me), 99.7 (C3 and C4), 147.5 (C2 and C5).

3-Bromo-2,5-dimethyl-4-phenylthiofuran 11. From 3,4-dibromo-2,5-dimethylfuran **8** (100 mg, over 83% pure, 0.40 mmol) in Et_2O (1 mL), $LiBu^t$ solution (1.7 M, 0.25 mL, 0.40 mmol) and diphenyldisulfide (89 mg, 0.41 mmol) in Et_2O (2 mL) following the procedure previously described for derivative **4**, a colourless oil was obtained (72 mg, over 74% pure by ^1H NMR; yield: 58%). The purification of crude product was carried out by a preparative TLC (pentane-ethyl acetate: 95/5, v/v). ^1H NMR: δ(ppm) 2.30 (s, 3H, Me), 2.37 (s, 3H, Me), 7.24 (m, 5H, SPh). ^{13}C NMR: δ(ppm) 12.3 (q, ^1J = 129.3 Hz, Me), 12.5 (q, ^1J = 129.6 Hz, Me), 103.0 (s, C3), 110.8 (s, C4), 125.3 (dt, ^1J = 162.2 Hz, ^2J = 7.1 Hz, C_{para}), 126.2 (dt, ^1J = 161.9 Hz, ^2J = 6.6 Hz, C_{meta}), 128.7 (dd, ^1J = 160.6 Hz, ^2J = 7.6 Hz, C_{ortho}), 136.8 (s, C_{ipso}), 147.9 (s, C2), 155.7 (s, C5).

3-Bromo-2,4,5-trimethylfuran 12. From 3,4-dibromo-2,5-dimethylfuran **8** (528 mg, over 83% pure, 1.71 mmol) in Et_2O (5 mL), $LiBu^t$ solution (1.3 M, 1.6 mL, 2.1 mmol) and dimethyl sulfate (0.4 mL, 4.2 mmol) following the procedure previously described for derivative **5**, a colourless oil crude was obtained (277 mg, over 85% pure by ^1H NMR; yield: 79%). The purification of crude product was carried out by a flash chromatography (cyclohexane). ^1H NMR: δ(ppm) 1.87 (q, 3H, ^5J = 0.6 Hz, CH_3), 2.18 (septet, 3H, $^5J_{Me,Me} = {}^6J_{Me,Me}$ = 0.6 Hz, CH_3), 2.21 (q, 3H, ^6J = 0.6 Hz, CH_3). ^{13}C NMR: δ(ppm) 9.0 (CH_3), 11.7 (CH_3), 11.9 (CH_3), 99.6 (C3), 14.7 (C4), 145.0 (C5), 145.7 (C2). Anal. Calcd. for C_7H_9OBr: C, 44.47; H, 4.80. Found: C, 44.70; H, 4.65.

3-Methyl-4-methylthiofuran 13. From 3-bromo-4-methylthiofuran **4** (8.0 g, over 87% pure, 35.7 mmol) in Et_2O (80 mL), $LiBu^t$ (1.15 M, 7.5 mL, 79.2 mmol) and dimethyl sulfate (7.5 mL, 70.2 mmol) following the procedure previously described for derivative **5**, a colourless oil crude was obtained (4.65 g, over 76% pure by ^1H NMR; yield: 82%). The purification of crude product was carried out by distillation at reduced pressure in a Kugelrohr oven yielding a fraction of the title compound (2.43 g, over 90% pure by ^1H NMR). Bp.: 75°C/20 torr. ^1H NMR: δ(ppm) 2.03 (dd, 3H, ^4J = 1.2 Hz, ^5J = 0.4 Hz, Me), 2.29 (s, 3H, SMe), 7.22 (dq, 1H, ^4J = 1.6 Hz, ^4J = 1.2 Hz, H2), 7.32 (dq, 1H, ^4J = 1.6 Hz, ^5J = 0.4 Hz, H5). ^{13}C NMR: δ(ppm) 7.9 (q, ^1J = 127.6 Hz, Me), 18.4 (q, ^1J = 139.7 Hz, SMe), 119.7 (tq, $^2J = {}^3J$ 11.6 Hz, ^2J = 4.2 Hz, C3), 121.8 (nonaplet,

${}^2J_{C4,H5} = {}^3J_{C4,H2} = {}^3J_{C4,Me} = {}^3J_{C4,SMe} = 6.3$ Hz, C4), 140.0 (dq, ${}^1J = 199.6$ Hz, ${}^3J_{C2,H5} = {}^3J_{C2,Me} = 6.0$ Hz, C2), 142.4 (dd, ${}^1J = 204.4$ Hz, ${}^3J = 6.0$ Hz, C5).

3-Methylthiofuran 14. From 3-bromo-4-methylthiofuran **4** (500 mg, over 87% pure, 2.25 mmol) in Et_2O, LiBu^t (1.2 M, 2.0 mL, 2.45 mmol) and cold distilled water (6 mL) following the procedure previously described for derivative **6**, a colourless oil crude was obtained (234 mg, over 81% pure by ^{1}H NMR, yield: 76%). The purification of the crude product was carried out by distillation at reduced pressure in a Kugelrohr oven yielding a pure fraction of the title compound (200 mg). Bp.: 71-73°C/80 torr. Lit.:[36] 75-76°C/80 torr. IR (film): ν 3130, 2920, 1710, 1490 cm^{-1}. ^{1}H NMR: δ(ppm) 2.35 (s, 3H, SMe), 6.41 (dd, 1H, ${}^3J = 1.8$ Hz, ${}^4J = 0.9$ Hz, H4), 7.35 (dd, 1H. ${}^4J = 1{,}8$ Hz, ${}^4J = 0.9$ Hz, H2), 7.41 (t, 1H, ${}^3J = {}^4J = 1.8$ Hz, H5). ^{13}C NMR: δ(ppm) 18.2 (q, ${}^1J = 134.0$ Hz, SMe), 112.2 (ddd, ${}^1J = 177.3$ Hz, ${}^2J = 13.1$ Hz, ${}^3J = 5.1$ Hz, C4), 118.7 (br s, C3), 140.9 (dt, ${}^1J = 204.5$ Hz, ${}^3J_{C2,H4} = {}^3J_{C2,H5} = 6.0$ Hz, C2), 143.3 (ddd, ${}^1J = 203.4$ Hz, ${}^2J = 10.1$ Hz, ${}^3J = 7.1$ Hz, C5). Anal. Cald. for C_5H_6OS: C, 52.61; H, 5.30. Found: C, 52.83; H, 5.13.

Additional amounts of 3-methylthiofuran **14** were obtained following the experimental procedure described below for achieving the derivative **19**.

3-Ethyl-4-methylthiofuran 15. From 3-bromo-4-methylthiofuran **4** (400 mg, over 87% pure, 1.84 mmol) in Et_2O (4 mL), LiBu^t (1.05 M, 1.9 mL, 2.02 mmol) and ethyl iodide (1.5 mL, 18.4 mmol) dissolved in THF (10 mL) and dry HMPA (0.18 mL) following the procedure previously described for derivative **6**, a crude product (166 mg) which gave, over a mixture of furan **15** (28%), furan **14** (47%) and 2-ethyl-3-methylthiofuran **18** (25%; ^{1}H NMR) was obtained. Yield: 18%. The chromatographic partition was untried because of the similar R_f values of its components in all conditions which were tried. The compounds of crude reaction were characterised by ^{1}H NMR and GC-MS. 3-Ethyl-4-methylthiofuran **15**: ^{1}H NMR: δ(ppm) 1.22 (t, 3H, ${}^3J = 7.5$ Hz, $C\mathit{H}_3CH_2$), 2.31 (s, 3H, SMe), 2.45 (qd, 2H, ${}^3J = 7.5$ Hz, ${}^4J = 1.2$ Hz, $C\mathit{H}_2CH_3$), 7.21 (dt, 1H, ${}^4J = 1.8$ Hz, ${}^4J = 1.2$ Hz, H2), 7.31 (d, 1H, ${}^4J = 1.8$ Hz, H5); GC-MS: m/z(%) 142 (M,100), 127 (39.5), 113 (11.5), 99 (35.9), 65 (72.2), 45 (43.0). 2-Ethyl-3-methylthiofuran **18**: ^{1}H NMR: δ(ppm) 1.21 (t, 3H, ${}^3J = 7.5$ Hz, $C\mathit{H}_3CH_2$), 2.27 (s, 3H, SMe), 2.73 (qd, 2H, ${}^3J = 7.5$ Hz, ${}^5J = 0.3$ Hz, $C\mathit{H}_2CH_3$), 6.36 (dt, 1H, ${}^3J = 1.8$ Hz, ${}^5J = 0.3$ Hz, H4), 7.28 (d, 1H, ${}^3J = 1.8$ Hz, H5); GC-MS: m/z (%) 144 (M+2, 4), 142 (M, 80), 127 (100), 83 (36), 65 (53), 59 (26), 45 (60).

2,4-Dimethyl-3-methylthiofuran 16. From 3-methyl-4-methylthiofuran **13** (2.2 g, over 76% pure, 13.06 mmol) in THF (40 mL), LDA (17.38 mmol) in THF (18 mL)-hexane (15 mL), and dimethyl sulfate (3.3 mL, 34.76 mmol) at -78°C following the procedure previously described for derivative **7**, a colourless oil crude (1.73 g, over 61% pure by ^{1}H NMR, yield: 56%) was obtained. The purification of the crude was carried out by flash chromatography (pentane) for achieving a fraction of the pure title compound. IR (film): ν 3100, 2930, 1600, 1550, 1430 cm^{-1}. ^{1}H NMR: δ(ppm) 2.03 (d, 3H, ${}^4J = 1.2$ Hz, Me at C4), 2.17 (s, 3H, SMe), 2.34 (br s, 3H, Me at C2), 7.10 (qq, 1H, ${}^4J = 1.2$ Hz, ${}^5J = 0.5$ Hz, H5). ^{13}C NMR: δ(ppm) 8.5 (q, ${}^1J = 127.6$ Hz, Me at

C4), 12.0 (q, ^1J = 128.6 Hz, Me at C2), 19.1 (q, ^1J = 139.3 Hz, SMe), 113.2 (m, C3), 123.1 (dq, $^2J_{C4,H5}$ =13.4 Hz, $^2J_{C4,Me}$ at C4 = 6.8 Hz, C4), 136.9 (dq, ^1J = 200.4 Hz, ^3J = 6.0 Hz, C5), 155.0 (quint., ^2J = ^3J = 7.1 Hz, C2). Anal. Calcd. for $C_7H_{10}OS$: C, 59.12; H, 7.09. Found: C, 59.55; H, 7.23.

2-Methyl-3-methylthiofuran 17. From 3-methylthiofuran **14** (1.55 g, 13.60 mmol) in THF (20 mL), LDA (14.77 mmol) in THF (22 mL)-hexane (12 mL), and dimethyl sulfate (3.3 mL, 37.74 mmol) at -78°C following the procedure previously described for derivative **7**, a colourless oil crude (2.15 g, over 84% pure by ^1H NMR; yield: 72%) was obtained. The purification of the reaction crude was carried out by distillation at reduced pressure in a Kugelrohr oven yielding a pure fraction of the title compound (1.5 g). Bp.: 90°C/20 torr. Lit.:[14] 42°C/7 torr. IR (film) ν 3130, 2910, 1590, 1430 cm^{-1}. ^1H NMR: δ(ppm) 2.27 (s, 3H, SMe), 2.33 (t, 3H, $^5J_{Me,H4}$ = $^5J_{Me,H5}$ = 0.4 Hz, Me), 6.37 (dq, 1H, ^3J = 2.0 Hz, ^5J = 0.4 Hz, H4), 7.27 (dq, 1H, ^3J = 2.0 Hz, ^5J = 0.4 Hz, H5). ^{13}C NMR: δ(ppm) 11.6 (q, ^1J = 176.3 Hz, Me), 19.2 (q, ^1J = 139.7 Hz, SMe), 112.1 (m, C3), 113.8 (dd, ^1J = 176.3 Hz, ^2J = 13.1 Hz, C4), 140.4 (dd, ^1J = 203.5 Hz, ^2J = 10.1 Hz, C5), 153.1 (sext., $^2J_{C2,Me}$ = $^3J_{C2,H4}$= $^3J_{C2,H5}$ = 6.7 Hz, C2). Anal. Calcd. for C_6H_8OS: C, 56.22; H, 6.29. Found: C, 56.31; H, 6.34.

2-Ethyl-3-methylthiofuran 18. From 3-methylthiofuran **14** (200 mg, 1.75 mmol) in THF (4 mL), LDA (2.28 mmol) in THF (3 mL)-hexane (1.5 mL) and ethyl iodide (1.4 mL, 17.5 mmol) in dry HMPA (0.4 mL) at -78°C for 21 h following the procedure previously described for derivative **6**, a yellow pale oil crude (176 mg, over 66% pure by ^1H NMR; yield: 47%) was obtained. The crude was purified by distillation at reduced pressure in a Kugelrohr oven yielding a fraction of the entitled compound (87 mg, over 87% pure by ^1H NMR) which was characterised from its ^1H NMR, ^{13}C NMR, and GC-MS spectra. Bp.: 100°C/20 torr. ^1H NMR: δ(ppm) 1.21 (t, 3H, ^3J = 7.5 Hz, CH_3CH_2), 2.27 (s, 3H, SMe), 2.73 (qd, ^3J = 7.5 Hz, ^5J = 0.3 Hz, CH_2CH_3), 6.36 (dt, 1H, ^3J = 1.8 Hz, ^5J = 0.3 Hz, H4), 7.28 (d, 1H, ^3J = 1.8 Hz, H5). ^{13}C NMR: δ(ppm) 12.7 (qt, ^1J = 127.9 Hz, ^2J = 5.1 Hz, CH_3CH_2), 19.4 (tq, ^1J = 128.2 Hz, ^2J = 4.6 Hz, CH_2), 19.5 (q, ^1J = 139.7 Hz, SMe), 111.2 (dd, ^2J = 4.5 Hz, ^3J = 2.5 Hz, C3), 113.8 (dd, ^1J = 176.3 Hz, ^2J = 13.1 Hz, C4), 140.4 (dd, ^1J = 202.5 Hz, ^2J = 10.0 Hz, C5), 158.0 (dq, $^3J_{C2,H4 \text{ or } H5}$ = 11.1 Hz, $^2J_{C2,H5 \text{ or } H4}$ = $^2J_{C2,CH2}$ = 6.0 Hz, C2). GC-MS: m/z (%): 144 (M+2, 4), 142 (M, 80), 127 (100), 83 (36), 65 (53), 59 (26), 45 (60).

3-Phenylthiofuran 19. The intermediate 3-lithiofuran was obtained from 3-bromofuran **6** (2.8 mL, 30.62 mmol) in Et_2O (50 mL) and LiBu^n (1.15 M, 26.6 mL, 30.62 mmol) following the procedure previously described for metallation of 3(4)-bromofurans. Diphenyldisulfide (6.67 g, 30.62 mmol) in Et_2O (50 mL) was then added at -78°C and the reaction mixture was stirred at -78°C for 1 h and at rt. for 2 h. Distilled water (25 mL) and Et_2O were then added. The organic layer was decanted and the aqueous phase was extracted with pentane-Et_2O (1/1; v/v) (3 x 50 mL). The combined organic layers were washed with 2N aqueous NaOH (3 x 50 mL), brine (3 x 50 mL), and dried over $MgSO_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (pentane/ethyl acetate: 95/5, v/v) yielding 3.0 g. of pure title compound. Yield: 71%. IR (film) ν 3140, 3050, 1940, 1860, 1770, 1490 cm^{-1}. ^1H NMR: δ(ppm) 6.43 (dd, 1H, 3J = 2.0 Hz,

^4J = 0.8 Hz, H4), 7.19 (m, 5H, SPh), 7.49 (dd, 1H, ^3J = 2.0 Hz, ^4J = 1.7 Hz, H5), 7.60 (dd, 1H, ^4J = 1.7 Hz, ^4J = 0.8 Hz, H2). ^{13}C NMR: δ(ppm) 113.8 (ddd, ^2J = 12.1 Hz, ^2J = 7.1 Hz, ^3J = 2.5 Hz, C3), 114.5 (ddd, ^1J = 178.3 Hz, ^2J = 13.1 Hz, C4), 125.6 (dt, ^1J = 161.5 Hz, ^2J = 7.1 Hz, C_{para}), 127.1 (dt, ^1J =162.5 Hz, ^2J = 6.3 Hz, C_{meta}), 128.8 (dd, ^1J = 161.2 Hz, ^2J = 6.1 Hz, C_{ortho}), 137.2 (t, ^2J = 8.1 Hz, C_{ipso}), 144.1 (ddd, ^1J = 204.5 Hz, ^2J = 10.1 Hz, ^3J = 7.0 Hz, C5), 146.0 (dt, ^1J = 206.1 Hz, ^3J = 6.0 Hz, C2). Anal. Calcd. for $C_{10}H_8OS$: C, 68.15; H, 4.58. Found: C, 68.30; H, 4.39.

***S*-3-Furyl thiobenzoate 20**. From 3-bromofuran **6** (2.7 mL, 30.0 mmol) in Et_2O (20 mL) and LiBu^n (1.6 M, 18.7 mL, 30.0 mmol) following the procedure previously described for metallation of 3(4)-bromofurans, a reaction mixture was obtained. Then, sulfur (1.06 g, 33.0 mmol) was added portionwise at -78°C under flash argon flow and the reaction mixture was stirred at -78°C for 1.5 h. After the temperature was raised to -15°C, a solution of benzoic anhydride (7.46 g, 33.0 mmol) in Et_2O (20 mL) was added and the stirring of the reaction mixture was continued overnight at rt. Distilled water (20 mL) at 0°C and Et_2O (25 mL) were then added. The organic layer was decanted and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic layers were washed with brine (3 x 25 mL) and dried over Na_2SO_4. After concentration of the solution, the pale yellow reaction crude (5.61 g, over 97% pure by ^1H NMR) was purified by flash chromatography (hexane/ethyl acetate: 95/5, v/v) and by recrystallization (pentane) giving a white solid (4.9 g) which was identified as *S*-3-furyl thiobenzoate **20**. Yield: 80%. Mp.: 49-50°C. IR (KBr) ν 3150, 1690, 1460 cm^{-1}. ^1H NMR: δ(ppm) 6.53 (dd, 1H, ^3J = 2.0 Hz, ^4J = 0.9 Hz, H4), 7.48 (m, 2H, H_{meta}), 7.58 (dd, 1H, ^3J = 2.0 Hz, ^4J = 1.5 Hz, H5), 7.61 (m, 1H, H_{para}), 7.65 (dd, 1H, ^4J = 1.5 Hz, ^4J = 0.9 Hz, H2), 8.02 (m, 2H, H_{ortho}). ^{13}C NMR: δ(ppm) 108.6 (C3), 114.3 (C4), 127.3 (C_{ortho}), 128.6 (C_{meta}), 133.6 (C_{para}), 136.1 (C_{ipso}), 143.7 (C5), 146.0 (C2), 189.4 (CO). Anal. Calcd. for $C_{11}H_8O_2S$: C, 64.7; H, 3.9. Found: C, 64.3; H, 4.0.

***S*-3-Furyl thioacetate 21**. From 3-bromofuran **6** (1.4 mL, 15 mmol) in Et_2O, LiBu^n (1.6 M, 9.4 mL, 15 mmol), sulfur (0.53 g, 16.5 mmol), and acetic anhydride (1.68 g, 16.5 mmol) in Et_2O (10 mL) following the procedure previously described for derivative **20**, a practically pure colourless oil was obtained. The purification by a flash chromatography (hexane/ethyl acetate: 95/5, v/v) yielded a colourless oil (1.56 g, yield: 73%) which was identified as S-3-furyl thioacetate **21**.[30e] IR (film) ν 3140, 2920, 1695, 1485, 1350 cm^{-1}. ^1H NMR: δ(ppm) 2.39 (s, 3H, SCOMe), 6.43 (dd, 1H, ^3J = 1.7 Hz, ^4J = 0.8 Hz, H4), 7.51 (t, 1H, $^3J_{H5,H4}$ = $^4J_{H5,H2}$ = 1.7 Hz, H5), 7.55 (dd, 1H, ^4J = 1.7 Hz, ^4J = 0.8 Hz, H2). ^{13}C NMR: δ(ppm) 29.8 (q, ^1J = 129.7 Hz, Me), 109.5 (ddd, ^2J = 12.6 Hz, ^2J = 7.1 Hz, ^3J = 3.0 Hz, C3), 114.1 (ddd, ^1J = 180.3 Hz, ^2J = 13.1 Hz, ^3J = 5.0 Hz, C4), 143.8 (ddd, ^1J = 204.5 Hz, ^2J = 11.1 Hz, ^3J = 7.0 Hz, C5), 145.7 (dt, ^1J = 207.5 Hz, $^3J_{C2,H4}$ = $^3J_{C2,H5}$ = 6.0 Hz, C2), 163.7 (q, ^2J = 6.5 Hz, CO). Anal. Calcd. for $C_6H_6O_2S$: C, 50.69; H, 4.25. Found: C, 50.49; H, 4.38.

3-Bromo-2-methyfuran 22. From 3-bromofuran **6** (4.9 mL, 54.43 mmol) in Et_2O (50 mL), LDA (59.87 mmol) in THF (65 mL) and dimethyl sulfate (11.3 mL, 0.12 mmol) following the procedure previously described for derivative 7, a pale yellow oil (9.39 g, over 66% pure by ^1H NMR) was obtained. The purification of crude by distillation yielded a pure fraction of the entitled compound (5.1 g). Yield: 70%. Bp.: 103-5°C.[37, 38] IR (film) ν 3150, 3120, 2960, 1510 cm^{-1}. ^1H NMR: δ(ppm) 2.27 (t, 3H, $^5J_{Me,H4} = {}^5J_{Me,H5} = 0.5$ Hz, Me), 6.33 (dq, 1H, $^3J = 2.1$ Hz, $^5J = 0.5$ Hz, H4), 7.24 (dq, 1H, $^3J = 2.1$ Hz, $^5J = 0.5$ Hz, H5). ^{13}C NMR:δ(ppm) 11.6 (q, $^1J =$ 128.9 Hz, Me), 96.0 (dd, $^2J = 7.6$ Hz, $^3J = 3.5$ Hz, C3), 113.5 (dd, $^1J = 179.3$ Hz, $^2J = 13.1$ Hz, C4), 140.8 (dd, $^1J = 205.0$ Hz, $^2J = 9.6$ Hz, C5), 149.3 (m, C2). Anal. Calcd. for C_5H_5OBr: C, 37.30; H, 3.13. Found: C, 37.05; H, 3.43.

2-Methyl-3-phenylthiofuran 23. From 3-bromo-2-methylfuran **22** (118 mg, 0.62 mmol) in Et_2O (1 mL), $LiBu^n$ (1.0 M, 0.56 mL, 0.56 mmol), TMEDA (84 μL, 0.56 mmol) in Et_2O (1 mL), and diphenyl disulfane (122 mg, 0.56 mmol) in Et_2O (2 mL) following the procedure previously described for derivative **19**, a pale yellow reaction crude (122 mg) which was made up of a mixture of 2-methyl-3-phenylthiofuran **23** (39%), *n*-buthyphenylsulfide (15%), and diphenyldisulfide (46%) was obtained. The separation of the compounds of this reaction crude was untried because of R_f values in different solvents or mixtures were practically identical.

However, the furan **23** was obtained from 3-phenylthiofuran **19** (2.7 g, 15.34 mmol) in THF (31 mL), LDA (16.87 mmol) in THF (20 mL) and dimethyl sulfate (3.2 mL, 35.75 mmol) at -78°C for 3 h following the procedure previously described for furan **17**. A pale yellow oil (2.61 g, over 95% pure by ^1H NMR, yield: 85%) was obtained. The purification was accomplished by flash chromatography (pentane/Et_2O: 99/1, v/v) yielding 1.85 g of a colourless oil which was identified as 2-methyl-3-phenylthiofuran **23**.[39] Yield: 61%. IR (film): ν 3050, 2950, 2920 cm^{-1}. ^1H NMR: δ(ppm) 2.34 (t, 3H, $^5J_{Me,H4} = {}^5J_{Me,H5} = 0.4$ Hz, Me), 6.37 (dq, 1H, $^3J = 2.0$ Hz, $^5J = 0.4$ Hz, H4), 7.17 (m, 5H, SPh), 7.37 (dq, 1H, $^3J = 2.0$ Hz, $^5J = 0.4$ Hz, H5). ^{13}C NMR: δ(ppm) 11.7 (q, ^1J = 128.9 Hz, Me), 107.6 (sextet, $^2J_{C3,H4} = {}^3J_{C3,H5} = {}^3J_{C3,Me} = 3.4$ Hz, C3), 115.3 (dd, $^1J = 177.3$ Hz, ^2J 13.1 Hz, C4), 125.0 (dt, $^1J = 162.1$ Hz, $^2J = 7.1$ Hz, C_{para}), 126.0 (dt, $^1J = 161.8$ Hz, $^2J = 6.5$ Hz, C_{meta}), 128.7 (dd, $^1J =$ 161.1 Hz, $^2J = 8.1$ Hz, C_{ortho}), 137.9 (t, $^2J = 8.6$ Hz, C_{ipso}), 141.1 (dd, $^1J = 203.5$ Hz, $^2J = 10.1$ Hz, C5), 156.7 (sextet, $^2J_{C2,Me} = {}^3J_{C2,H4} = {}^3J_{C2,H5} = 6.0$ Hz, C2). Anal. Calcd. for $C_{11}H_{10}OS$: C, 69.44; H, 5.30. Found: C, 69.76; H, 5.18.

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