An analysis of substituent effects on ^1H and ^{13}C NMR parameters of substituted furans. Linear free energy relationships and PM3 semiempirical calculations

Carlos Alvarez-Ibarra,* María L. Quiroga-Feijóo and Emilio Toledano

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense,
Ciudad Universitaria, 28040 Madrid, Spain

Forty five furans have been obtained in a synthetic project designed to evaluate monothiosubstituted furans as potential food flavourings. A full NMR (^1H and ^{13}C) study and PM3 molecular orbital semiempirical calculations have been carried out. Substituent-induced chemical shifts (SCS) for six and nine substituents at the 2- and 3-positions have been calculated and a separation of inductive and resonance effects of these substituents has been proposed. Finally, a linear correlation between the net atomic charges localized at ring carbons and their ^{13}C NMR chemical shifts has been established.

Introduction

A large number of substituted furans have been obtained as intermediates or final compounds within a synthetic program designed to obtain and evaluate some monothiosubstituted furans as potential food flavourings;[1] such furans are acquiring increasing importance in the food industry.[2] Although the use of linear free energy relationships to study chemical and biological properties of five-membered ring derivatives has received much attention,[3–5] only a few systematic ^1H and ^{13}C NMR studies of furans have hitherto been carried out.[4,6–12] So far, substituent effects on ^1H and ^{13}C chemical shifts of a wide basis set of polysubstituted furans have not been extensively discussed since only monosubstituted furans have been studied.[4] Carbon shifts and coupling constants have been compared with those in the proton region. Several *ortho*, *meta* and *para* relations have been analyzed and correlations with reactivity parameters have been made.[4] On the other hand, numerous papers have been published to explain on a theoretical basis the properties of furan and some substituted derivatives. Hückel molecular orbitals (HMO),[13] semiempirical calculations such as PPP,[13e,14] CNDO,[15] INDO[13c,16] and MINDO,[16] *ab initio* calculations,[13e,17] and force field methods[18] have been published. So far, an extensive semiempirical PM3 calculation of substituted furans and correlations of electronic parameters thus calculated with ^{13}C NMR chemical shifts and couplings have not been carried out.

In this paper we report: (*a*) a detailed study of ^1H and ^{13}C NMR chemical shifts of 40 furans (Table 1); (*b*) the calculation of contributions of six substituents (Me, CO_2H, SMe, SPh, 2-furylthio, Et) at the 2-position and nine substituents (Me, CO_2H, SMe, SPh, Br, SCOPh, SCOMe, SH, 2,5-dimethyl-3-furyldithio at the 3-position; (*c*) the linear correlations between proton substituent-induced chemical shifts (SCS), carbon SCS values and proton–carbon SCS parameters; (*d*) the tentative correlation of the calculated ^1H and ^{13}C SCS values with the reactivity parameters of Swain and Lupton[19] to separate the inductive and resonance contributions to chemical shifts; (*e*) the relationships between the observed direct coupling $^1J(^{13}C, ^1H)$ and the inductive effects of the substituents which incorporate the furan ring; and (*f*) the linear correlation of the observed ^{13}C NMR chemical shifts with the calculated net charges at ring carbon nuclei by PM3 semiempirical calculation.

Results and discussion

Synthesis

Furans **7**, **8**, **11–13**, **19**, **20–23**, **25**, **26**, **29**, **37**, **39**, **44** and **45** have been previously reported.[20] Furans **30–33** were obtained using the procedures previously described by Evers *et al.*[21] Directed *ortho*-metallation by a heteroatom (oxygen, sulfur or bromine) with lithium diisopropylamide (LDA) and then alkylation of 2(5)-unsubstituted furans has been the synthetic pathway followed for the synthesis of furans **16**, **18**, **34–36**, **40–43** (Scheme 1). On the other hand, furans **24**, **27**, **28** and **38** were obtained by metal–bromine exchange reaction of the corresponding 3-bromofuran **18**, **19** or **36** with $LiBu^t$ and by trapping the metallated intermediate furans with an electrophile (Scheme 1).[22] Furan **17** was obtained by decarboxylation of furan **34** with Cu–quinoline at high temperature.[33] Furans **4–6**, **14** and **15** were synthesized by metallation of furan or 2-methylfuran with $LiBu^n$ and by trapping the metallated intermediates with a sulfenylation reagent.

NMR Spectra

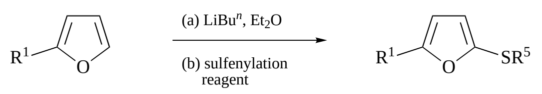
The ^1H and ^{13}C chemical shifts and the $^1J(^{13}C, ^1H)$ coupling constants of substituted furans **1–45** are given in Tables 2–4, respectively.

All ^1H assignments were made from the observed chemical shifts taking into account the relative integration of signals, the relative order and magnitude of vicinal and long range coupling constants described in the literature[8,41–44] as well as the fact that the deshielding of α-protons is much larger than for β-protons.[41]

All ^{13}C chemical shifts were determined from the proton decoupled spectra. The ^{13}C assignments were made from the observed chemical shifts taking into account the greater deshielding of the α-carbons than the β-carbons.[4,10,11] Substituted carbons were identified by their lower intensity as expected for a substituent-bearing carbon as well by the absence of the direct coupling in the coupled spectra. α-Carbons were identified by their largest direct coupling, and the assignment of β-carbons was based on consideration of the relative order and magnitude of the long-range coupling constants.

Substituent-induced chemical shifts

Because of the high number of substituted furans considered in this paper, a calculation of substituent-induced chemical shifts (SCS) in ^1H and ^{13}C NMR spectra has been carried out. The ^1H and ^{13}C chemical shifts of the ring hydrogens and carbons depend on the nature of the substituents R^1–R^4 and on their relative position to the considered atom. The ^1H SCS values of Me, CO_2H, SPh, SMe, 2-furylthio and Et at the 2-position, and of Me, CO_2H, SPh, SMe, Br, SCOPh, SCOMe, SH and 2,5-dimethyl-3-furyldithio at the 3-position were calculated using eqns. (1)–(4), where $\delta_{H\text{-}n}$ is the chemical shift of hydrogen *n*; β_{mn},

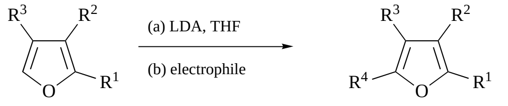


1 $R^1 = H$
2 $R^1 = Me$

4–6, 14, 15

Reagent	R^1	R^5	Furan	Yield	Ref.[a]
MeSSMe	H	Me	**4**	70^b	36–38
PhSSPh	H	Ph	**5**	90^b	33–36
S_8	H	—[d]	**6**	50^c	—
PhSSPh	Me	Ph	**14**	56^b	35
MeSSMe	Me	Me	**15**	60^b	39–40

[a] Literature yields: furan **5**: 90 (ref. 34), 42 (ref. 35), 59 (ref. 36), 50 (ref. 33); furan **4**: 27 (ref. 36), 35 (ref. 37, 38); furan **14**: 85 (ref. 35); furan **15**: 68 (ref. 39), 53 (ref. 40). [b] Spectroscopic yields. [c] Isolated product. [d] 2-Furyl.

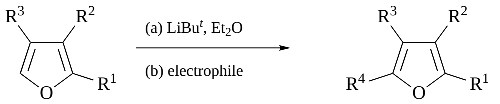


8 $R^1 = R^3 = H, R^2 = Br$
16 $R^1 = CO_2H, R^2 = Br, R^3 = H$
19 $R^1 = H, R^2 = R^3 = Br$
20 $R^1 = H, R^2 = Br, R^3 = Me$
22 $R^1 = Me, R^2 = SPh, R^3 = H$
25 $R^1 = H, R^2 = Me, R^3 = SMe$
29 $R^1 = Me, R^2 = SMe, R^3 = H$

16, 18, 34–36, 40, 41, 42, 43

Electrophile	R^1	R^2	R^3	R^4	Furan	Yield
CO_2(s)	CO_2H	Br	H	H	**16**	70^a
MeSSMe	SMe	Br	H	H	**18**	30^b
PhSSPh	CO_2H	Br	H	SPh	**34**	67^b
MeSSMe	SMe	Br	Br	H	**35**	44^b
MeSSMe	SMe	Br	Me	H	**36**	65^b
Et_2SO_4	Et	SMe	Me	H	**40**	13^b
Me_2SO_4	Me	SPh	H	Me	**41**	$50^{b,c}$
Me_2SO_4	Me	SMe	H	Me	**42**	40^b
MeSSMe	SMe	Br	Br	SMe	**43**	10^b

[a] Isolated product. [b] Spectroscopic yield. [c] Literature yield: 66%.



18 $R^1 = SMe, R^3 = H$
19 $R^1 = H, R^3 = Br$
36 $R^1 = SMe, R^3 = Me$

24, 27, 28, 38

Electrophile	R^1	R^2	R^3	R^4	Furan	Yield
MeSSMe	H	SMe	SMe	H	**24**	—[a]
EtI	Et	H	H	SMe	**27**	16^b
H_2O	SMe	H	Me	H	**28**	$64^{b,c}$
Me_2SO_4	SMe	Me	Me	H	**38**	49

[a] Traces. [b] Spectroscopic yield. [c] Literature yield: 19%.

Scheme 1

$$\delta_{H\text{-}2} = a + \beta_{32} + \gamma_{42} + \delta_{52} \quad (1)$$

$$\delta_{H\text{-}3} = b + \beta_{23} + \beta_{43} + \gamma_{53} \quad (2)$$

$$\delta_{H\text{-}4} = b + \gamma_{24} + \beta_{34} + \beta_{54} \quad (3)$$

$$\delta_{H\text{-}5} = a + \beta_{45} + \gamma_{35} + \delta_{25} \quad (4)$$

γ_{mn} and δ_{mn} are the effects of substituents bound to the carbon *m* in position β, γ and δ, respectively, relative to the hydrogen *n*; *n* and *m* could vary from 2 to 5; *a* and *b* are the chemical shifts of a reference unsubstituted compound which are introduced as two additional variables in the proposed model. From symmetry, the following identities can be considered: $\gamma_{42} \cong \gamma_{35}$, $\beta_{45} \cong \beta_{32}$, $\beta_{43} \cong \beta_{34}$, $\beta_{54} \cong \beta_{23}$, $\gamma_{53} \cong \gamma_{24}$ and $\delta_{52} \cong \delta_{25}$.

The application of eqns. (1)–(4) to furans **2**–**45** generated a data basis set with 79 equations and 45 independent variables. An analysis performed on this data basis[45] led to 141 solutions for each independent variable, and a statistical analysis[46] of these variables yielded the results shown in Table 5.

The ^{13}C SCS values of Me, CO_2H, SPh, SMe, 2-furylthio and Et at the 2-position, and of the Me, CO_2H, SPh, SMe, Br, SCOPh, SCOMe, SH and 2,5-dimethyl-3-furyldithio at the 3-position were calculated using eqns. (5)–(8), where $\delta_{C\text{-}n}$ is the

$$\delta_{C\text{-}2} = c + \alpha_2 + \beta_{32} + \gamma_{42} + \delta_{52} \quad (5)$$

$$\delta_{C\text{-}3} = d + \alpha_3 + \beta_{23} + \beta_{43} + \gamma_{53} \quad (6)$$

$$\delta_{C\text{-}4} = d + \alpha_4 + \gamma_{24} + \beta_{34} + \beta_{54} \quad (7)$$

$$\delta_{C\text{-}5} = c + \alpha_5 + \delta_{25} + \gamma_{35} + \beta_{45} \quad (8)$$

chemical shift of carbon *n*; α_n is the effect of the *ipso*-substituent on carbon *n*, *i.e.* the effect of R^1, R^2, R^3 and R^4 on carbons C-2, C-3, C-4 and C-5, respectively; β_{mn}, γ_{mn} and δ_{mn} are the effects of substituent bound to a carbon *m* in position β, γ and δ, respectively, relative to carbon *n*; *a* and *b* are the chemical shifts of a reference unsubstituted compound which are introduced as two additional variables in the proposed model. The application of this model to the backbone of the furans implies the identity of the following interactions: $\alpha_4 \cong \alpha_3$, $\alpha_5 \cong \alpha_2$, $\beta_{32} \cong \beta_{45}$, $\beta_{34} \cong \beta_{43}$, $\gamma_{35} \cong \gamma_{42}$, $\delta_{52} \cong \delta_{25}$, $\gamma_{53} \cong \gamma_{24}$ and $\beta_{54} \cong \beta_{23}$. The application of eqns. (5)–(8) to furans **2**–**45** generates a data basis with 172 equations and 62 independent variables. An analysis performed on this data basis[45] generated 202 solutions for each independent variable, and a statistical analysis[46] of these solutions yielded the results shown in Table 6.

Eqns. (1)–(8) allow one to estimate with high precision the ^1H and ^{13}C chemical shifts, respectively, of hydrogens and carbons for furans **2**–**45**. The standard deviations of the proposed SCS values can be estimated from the linear regression straight line between the observed and calculated chemical shifts (Table 7).

The goodness of fit between the calculated and observed chemical shifts supports the validity and the additive character of the proposed SCS values.

Linear correlations between proton, carbon and proton–carbon SCS parameters

In order to study the internal comparison of SCS data for polysubstituted furans, it can be considered that the 3-, 4- and 5-positions in relation to a substituent at the 2-position, and the *ortho*, *meta* and *para* positions of a monosubstituted benzene are affected by the substituent in similar ways.[4] Furthermore, the 2- and 5-positions in relation to a substituent at the 3-position correspond to *ortho* and *meta* positions of a monosubstituted benzene, while the 4-positions show many properties that deviate from those of a true benzene *ortho* position.[4,5,48,49] From ^1H and ^{13}C SCS values collected in Tables 5 and 6 together with the SCS parameters described in the literature[4] for the OMe, Cl, I, CH_2OH, CHO, $COCH_3$ and CN groups, certain linear correlations could be established. The results are shown in Table 8.

All regressions have acceptable correlation coefficients with a high confidence level. It is clear that similar factors determine the *ortho*/*para* ratio (β_{23}/δ_{25} for ^1H and β_{23}/δ_{25} for ^{13}C) as well as the *ortho*/*ortho* ratios (β_{32}/β_{34} and β_{23}/β_{32} for ^1H and β_{32}/β_{34} and β_{23}/β_{32} for ^{13}C) for both the ^1H and ^{13}C substituent chemical shifts, and almost identical slopes are obtained in the plots. On the other hand, good correlations of ^1H SCS parameters with those of ^{13}C for the *ortho*/*meta* ratio were obtained.[50]

Some reasonable consequences of the previous correlations can be established. The influence of a substituent at the

Table 1 Substituted furans **1**–**45**

Furan	R^1	R^2	R^3	R^4	Furan	R^1	R^2	R^3	R^4
1[a]	H	H	H	H	**24**	H	SMe	SMe	H
2[a]	Me	H	H	H	**25**	H	Me	SMe	H
3[a]	CO_2H	H	H	H	**26**	Et	SMe	H	H
4	SMe	H	H	H	**27**	Et	H	H	SMe
5	SPh	H	H	H	**28**	SMe	H	Me	H
6	2-Furylthio	H	H	H	**29**	Me	SMe	H	H
7	H	SMe	H	H	**30**	Me	SCOMe	H	Me
8	H	Br	H	H	**31**	Me	SH	H	Me
9[a]	H	Me	H	H	**32**	Me	—[b]	H	Me
10[a]	H	CO_2H	H	H	**33**	Me	SCOPh	H	Me
11	H	SPh	H	H	**34**	CO_2H	Br	H	SPh
12	H	SCOPh	H	H	**35**	SMe	Br	Br	H
13	H	SCOMe	H	H	**36**	SMe	Br	Me	H
14	SPh	H	H	Me	**37**	Me	Br	Br	H
15	SMe	H	H	Me	**38**	SMe	Me	Me	H
16	CO_2H	Br	H	H	**39**	Me	SMe	Me	H
17	SPh	H	Br	H	**40**	Et	SMe	Me	H
18	SMe	Br	H	H	**41**	Me	SPh	H	Me
19	H	Br	Br	H	**42**	Me	SMe	H	Me
20	H	Br	Me	H	**43**	SMe	Br	Br	SMe
21	Me	Br	H	H	**44**	Me	Br	Br	Me
22	Me	SPh	H	H	**45**	Me	Br	SPh	Me
23	H	Br	SMe	H					

[a] Ref. 4. [b] 2,5-Dimethyl-3-furyldithio.

Table 2 ^1H NMR chemical shifts (δ, $CDCl_3$) of furans **1**–**42**

Furan	H-2	H-3	H-4	H-5	Furan	H-2	H-3	H-4	H-5
1[a]	7.38	6.30	6.30	7.38	**22**	—	—	6.37	7.23
2[a]	—	5.87	6.16	7.19	**23**	7.47	—	—	7.38
3[a]	—	7.17	6.53	7.68	**24**	7.36	—	—	7.36
4	—	6.42	6.36	7.47	**25**	7.22	—	—	7.32
5	—	6.73	6.45	7.55	**26**	—	—	6.36	7.28
6	—	6.61	6.36	7.46	**27**	—	5.96	6.36	—
7	7.35	—	6.41	7.41	**28**	—	6.29	—	7.24
8	7.43	—	6.45	7.36	**29**	—	—	6.37	7.27
9	7.15	—	6.16	7.27	**30**	—	—	5.90	—
10	8.14	—	6.76	7.57	**31**	—	—	5.87	—
11	7.60	—	6.43	7.49	**32**	—	—	5.96	—
12	7.65	—	6.53	7.58	**33**	—	—	5.99	—
13	7.55	—	6.43	7.51	**34**	—	—	6.58	—
14	—	6.60	6.06	—	**35**	—	—	—	7.54
15	—	5.95	6.35	—	**36**	—	—	—	7.28
16	—	—	6.68	7.60	**37**	—	—	—	7.34
17	—	6.75	—	7.55	**38**	—	—	—	7.22
18	—	—	6.47	7.44	**39**	—	—	—	7.10
19	7.45	—	—	7.45	**40**	—	—	—	7.12
20	7.39	—	—	7.19	**41**	—	—	5.93	—
21	—	—	6.33	7.24	**42**	—	—	5.94	—

[a] In CD_3COCD_3, ref. 4.

2-position on SCS values is higher than at the 3-position which in turn is higher than at the 5-position ($\beta_{23} > \delta_{25}$) or at the 3-position than at the 4-position ($\beta_{23} > \gamma_{24}$), or at the 5-position than at the 4-position ($\delta_{25} > \gamma_{24}$). On the other hand, the SCS values at the 4-position are higher than at the 2-position when the substituent is positioned at the 3-position ($\beta_{34} > \beta_{32}$). The *ortho*- and *para*-influences of a substituent positioned at the 2-position are higher than the *ortho*- and *meta*-influences of a substituent positioned at the 3-position. Finally, the *ortho*-influence of a substituent at the 2-position on ^{13}C SCS values is higher than the *ortho*-influence at the 2-position of a substituent localized at the 3-position ($\beta_{23} > \beta_{32}$). All ^1H–^{13}C relationships are higher for ^{13}C SCS values than for ^1H SCS parameters.

Correlations with reactivity parameters

The calculated ^1H and ^{13}C SCS parameters were tentatively correlated by a generalized DSP equation[51] to separate polar and resonance effects [eqn. (9)], where S_I and S_R are substituent parameters which measure the effect of field or inductive and resonance contributions, respectively,[19,52,53] and *a* and *b* are weighting factors for the field and resonance effects, respectively. Unlike the mathematical models used in the literature[53] with empirical equations based on three-parameters linear correlations to study the effect of substituents on the short range interactions (positions *ipso*, *ortho* and *meta*), the model based upon an empirical equation with two parameters has given good results. Another problem has arisen during the past two decades when many substituent parameters were proposed in the literature.[54] The validity of all these substituent parameters has been extensively tested by Fahdil.[53a] The results give a conclusive indication that two factors are sufficient to reproduce the SCS data and that the best substituent parameters are the Reynolds[60] and Swain–Lupton[19] models.[65] For all these reasons, an empirical equation with two parameters including the substituent parameters (*F* and *R*) proposed by Swain and Lupton[19] has been used to separate polar and resonance effects [eqn. (10)].[66]

$$(^1H \text{ or } ^{13}C)\ \mathrm{SCS} = aS_I + bS_R + c \qquad (9)$$

$$\mathrm{SCS} = fF + rR + c \qquad (10)$$

Table 3 ^{13}C NMR chemical shifts (δ, $CDCl_3$) of furans **1**–**45**

Furan	C-2	C-3	C-4	C-5	Furan	C-2	C-3	C-4	C-5
1[a]	143.6	110.4	110.4	143.6	**24**	142.6	128.7	128.7	142.6
2[a]	152.7	106.3	111.1	141.7	**25**	140.0	119.7	121.8	142.4
3[a]	145.9	119.1	112.9	147.9	**26**	158.0	111.2	113.8	140.4
4	147.2	114.1	111.3	144.7	**27**	160.6	105.7	115.9	144.6
5	142.9	119.4	111.7	146.4	**28**	146.9	116.7	121.6	141.4
6	142.7	116.7	111.5	145.6	**29**	153.1	112.1	113.8	140.4
7	140.9	118.7	112.2	143.3	**30**	154.1	104.3	110.0	150.4
8	140.9	99.5	113.2	143.4	**31**	151.7	102.2	111.2	149.7
9	140.2	120.5	112.9	143.5	**32**	155.0	112.9	110.0	150.2
10	149.6	120.5	110.9	145.4	**33**	154.7	103.2	110.4	150.6
11	146.0	113.8	114.5	144.1	**34**	142.0	111.4	120.6	152.8
12	146.0	108.6	114.3	143.7	**35**	146.7	109.5	104.6	142.9
13	145.7	109.5	114.1	143.8	**36**	144.9	110.0	122.6	141.1
14	140.1	121.1	108.0	156.7	**37**	150.3	100.1	103.6	138.9
15	144.5	116.2	107.5	154.9	**38**	142.5	125.8	121.7	140.6
16	140.2	111.0	117.3	146.8	**39**	155.0	113.2	123.1	136.9
17	142.3	121.3	100.5	144.5	**40**	160.0	112.3	123.1	137.0
18	145.6	106.2	115.0	144.9	**41**	154.9	107.6	110.8	150.6
19	141.4	103.8	103.8	141.4	**42**	149.9	112.3	109.4	151.2
20	140.6	103.4	120.7	139.5	**43**	148.0	109.7	109.7	148.0
21	149.3	96.0	113.5	140.8	**44**	147.5	99.7	99.7	147.5
22	156.7	107.6	115.3	141.1	**45**	147.9	103.0	110.8	155.7
23	141.7	104.8	120.3	143.0					

[a] In CD_3COCD_3, ref. 4.

Table 4 $^{1}J(^{13}C, ^{1}H)$ coupling constants (in Hz) of ring carbons observed in the substituted furans **6**–**8**, **11**, **13**, **15**, **16**, **18**, **20**–**23**, **25**–**29**, **35**, **36** and **38**–**42**

Furan	C-2	C-3	C-4	C-5	Furan	C-2	C-3	C-4	C-5	Furan	C-2	C-3	C-4	C-5
6	—	179.3	176.2	203.5	**20**	208.0	—	—	202.5	**29**	—	—	176.3	203.5
7	204.5	—	177.3	203.4	**21**	—	—	179.3	205.0	**35**	—	—	—	212.6
8	209.5	—	180.6	205.5	**22**	—	—	177.3	203.5	**36**	—	—	—	203.7
11	206.1	—	178.3	204.5	**23**	210.5	—	—	208.5	**38**	—	—	—	199.4
13	207.5	—	180.3	204.5	**25**	199.6	—	—	204.4	**39**	—	—	—	200.4
15	—	173.9	175.8	—	**26**	—	—	176.3	202.5	**40**	—	—	—	200.5
16	—	—	184.3	207.5	**27**	—	173.2	176.2	—	**41**	—	—	176.3	—
18	—	—	181.3	207.5	**28**	—	174.9	—	200.2	**42**	—	—	174.4	—

Table 5 ^{1}H empirical SCS parameters (ppm) for eqns. (1)–(4) and standard errors (SE)[a,b]

Substituent at C-2	β_{23}	γ_{24}	δ_{25}	Substituent at C-3	β_{32}	β_{34}	γ_{35}
Me	−0.425[c]	−0.135[c]	−0.171[c]	Me	−0.211[d]	−0.135[c]	−0.091[d]
CO_2H	0.875[c]	0.235[c]	0.319[d]	CO_2H	0.779[d]	0.465[c]	0.209[d]
SMe	0.125[c]	0.065[c]	0.109[d]	SMe	−0.011[c]	0.115[c]	0.049[d]
SPh	0.435[c]	0.155[c]	0.189[d]	SPh	0.239[d]	0.135[c]	0.129[d]
2-Furylthio	0.315[c]	0.065[c]	0.099[d]	Br	0.069[d]	0.155[c]	−0.001[d]
Et	−0.40[e]	−0.06[e]	−0.13[f]	SCOPh	0.289[d]	0.235[c]	0.219[d]
				SCOMe	0.189[d]	0.135[c]	0.149[d]
				SH		0.14[g]	—
				2,5-Dimethyl-3-furyldithio	—	0.23[g]	—

[a] Calculated values for *a* and *b*: $a = 7.361 \pm 0.003$ ppm and $b = 6.295 \pm 0.009$ ppm. These values are in excellent concordance with the experimental chemical shifts for H-2 and H-3 of furan: $\delta_{H\text{-}2} = 7.38$ ppm and $\delta_{H\text{-}3} = 6.30$ ppm (ref. 47). [b] Empirical SCS parameters described in the literature for monosubstituted furans:[4] SMe at 2-position: $\beta_{23} = 0.07$, $\gamma_{24} = 0.03$, $\delta_{25} = 0.09$; Me at 2-position: $\beta_{23} = -0.43$; $\gamma_{24} = -0.14$, $\delta_{25} = -0.19$; SMe at 3-position: $\beta_{32} = 0.00$, $\beta_{34} = 0.11$, $\gamma_{35} = 0.07$; Br at 3-position: $\beta_{32} = 0.18$, $\beta_{34} = 0.17$, $\gamma_{35} = 0.08$; Me at 3-position: $\beta_{32} = -0.23$, $\beta_{34} = -0.14$, $\gamma_{35} = -0.11$; CO_2H at 2-position: $\beta_{23} = 0.87$, $\gamma_{24} = 0.23$, $\delta_{25} = 0.30$. [c] SE: ±0.009 ppm. [d] SE: ±0.003 ppm. [e] SE: ±0.02 ppm. [f] SE: ±0.05 ppm. [g] SE: ±0.03 ppm.

The values of the *f* and *r* weighting factors have been optimised by a bilinear regression.[67] The treatment includes the SCS values calculated in this work for Br, SMe, Me, CO_2H, Et and SH substituents together with the SCS values reported in the literature[4] for the OMe, Cl, I, $COCH_3$ and CN groups. The regression equations for all SCS values are given in Table 9.

Very good correlations were obtained but γ_{24}, β_{32} and γ_{35} ^{1}H SCS values are of somewhat poorer quality. The following considerations apply. It may be noted that the four SCS values of the *meta* positions give acceptable correlations in the Swain–Lupton treatment (^{1}H: γ_{24}, γ_{35}; ^{13}C: γ_{24}, γ_{35}). This finding is a significant improvement on the results of Gronowitz *et al.*[4] The above-mentioned good correlations provide information about the systematic variation of the transmittance of the inductive and resonance effects to different positions in the furan ring.

The inductive or field effects of the substituents are significantly smaller than the resonance effect for all SCS values with the sole exception of the ^{13}C SCS γ_{24} value. The variations observed for the field effects (^{1}H and ^{13}C: $\beta_{23} > \gamma_{24}$, $\beta_{32} > \gamma_{35}$, $\beta_{34} > \gamma_{35}$) are in accordance with a decay of the inductive effect with increasing distance between the substituent and the nucleus being considered. With the sole exception of the ^{13}C γ_{24} SCS value, the resonance effects for ^{1}H and ^{13}C are always higher than the field effects, and the resonance effects are always higher for ^{13}C SCS values than ^{1}H SCS parameters. These results can be easily justified because the implied orbitals

Table 6 Empirical SCS parameters (ppm) for eqns. (5)–(8) and standard errors (SE)[a,b]

Substituent at C-2	α_2	β_{23}	γ_{24}	δ_{25}	Substituent at C-3	α_3	β_{32}	β_{34}	γ_{35}
Me	9.10[c]	−3.9[d]	0.9[d]	−1.90[c]	Me	10.3[d]	−3.40[c]	2.7[d]	−0.10[c]
CO_2H	2.30[c]	8.9[d]	2.7[d]	4.30[c]	CO_2H	10.3[d]	6.00[c]	0.7[d]	1.80[c]
SPh	−0.70[c]	9.2[d]	1.5[d]	2.80[c]	SPh	3.6[d]	2.40[c]	4.3[d]	0.50[c]
SMe	3.60[c]	3.9[d]	1.1[d]	1.10[c]	SMe	8.5[d]	−2.70[c]	2.0[d]	−0.30[c]
2-Furylthio	−0.88[c]	6.5[d]	1.3[d]	2.00[c]	Br	−10.6[d]	−2.70[c]	3.0[d]	−0.20[c]
Et	16.5[e]	−6.5[f]	1.7[d]	−2.7[d]	SCOPh	−1.6[d]	2.40[c]	4.1[d]	0.10[c]
					SCOMe	−0.6[d]	2.10[c]	3.9[d]	0.20[c]
					SH	−5.0[g]	0.9[g]	4.0[h]	−1.1[g]
					2,5-Dimethyl-3-furyldithio	5.7[g]	4.2[g]	2.8[g]	−0.6[g]

[a] Calculated values for c and d: $c = 143.60 \pm 0.08$ ppm and $d = 110.2 \pm 0.1$ ppm. These values are in excellent concordance with the experimental chemical shifts for carbons C-2 and C-3 of the furan: $\delta_{C\text{-}2} = 143.6$ ppm and $\delta_{C\text{-}3} = 110.4$ ppm (ref. 4). [b] Empirical SCS parameters described in the literature for monosubstituted furans:[4] SMe at 2-position: $\alpha_2 = 4.7$, $\beta_{23} = 4.1$, $\gamma_{24} = 1.8$, $\delta_{25} = 2.1$; Me at 2-position: $\alpha_2 = 9.1$, $\beta_{23} = -4.1$, $\gamma_{24} = 0.7$, $\delta_{25} = -1.9$; CO_2H at 2-position: $\alpha_2 = 2.3$, $\beta_{23} = 8.8$, $\gamma_{24} = 2.5$, $\delta_{25} = 4.2$; SMe at 3-position: $\alpha_3 = 9.9$, $\beta_{32} = -1.7$, $\beta_{34} = 2.8$, $\gamma_{35} = 1.2$; Br at 3-position: $\alpha_3 = -10.1$, $\beta_{32} = -1.4$, $\beta_{34} = 3.7$, $\gamma_{35} = 1.4$; Me at 3-position: $\alpha_3 = 10.1$, $\beta_{32} = -3.4$, $\beta_{34} = 2.5$, $\gamma_{35} = -0.10$. [c] SE: ±0.08 ppm. [d] SE: ±0.1 ppm. [e] SE: ±0.6 ppm. [f] SE: ±0.9 ppm. [g] SE: ±0.4 ppm. [h] SE: ±0.3 ppm.

Table 7 Linear regressions between calculated and observed chemical shifts (^1H and ^{13}C) for furans **2**–**45**

NMR	N[a]	r[b]	Equation[c]
^1H	80	0.993	$\delta_{calc} = 1.00\delta_{obs} - 0.02$
^{13}C	176	0.991	$\delta_{calc} = 1.00\delta_{obs} + 0.2$

[a] Number of points included in the regression analysis. [b] Correlation coefficient. [c] Standard deviations of slopes (s) and independent terms (t): ^1H NMR: $\Delta s = \pm 0.01$, $\Delta_t = \pm 0.09$; ^{13}C NMR: $\Delta s = \pm 0.01$, $\Delta t = \pm 1.3$.

in the resonance effects belong to the carbon instead of the hydrogen atom. The observed variations in resonance effects at each position reveal that the strongest influences are observed at the conjugate positions in relation to the substituent position (2-position: ^1H: $\beta_{23} > \delta_{25} > \gamma_{24}$; ^{13}C: $\beta_{23} \gg \delta_{25} \gg \gamma_{24}$; 3-position: ^1H: $\beta_{32} > \beta_{34} > \delta_{25} > \gamma_{24}$; ^{13}C: $\beta_{32} \gg \beta_{34} \gg \delta_{25}$).

$^1J(^{13}C, ^1H)$ Direct couplings

Some linear correlations of $^1J(^{13}C, ^1H)$ direct coupling of monosubstituted five-membered heterocycles with different parameters related to the electronegativity or inductive effects of the substituents have been studied.[4,68] The best supported and studied relationship of this type is the correlation of the change induced by the substituent on direct couplings of monosubstituted furans, thiophenes and selenophenes with the F values of substituents. So far, the generalization of this type of relationship for polysubstituted furans has never been discussed in the literature. For this reason, we attempted the linear regression of $\Delta^1J(^{13}C, ^1H)$[69] with the algebraic sum of the F parameters of substituents attached to the furan ring (ΣF). The values of these two parameters are given in Table 10, and the linear correlations between the substituent-caused changes in direct coupling constants [$\Delta^1J(^{13}C, ^1H)$] and ΣF values are shown in Table 11.

The above-mentioned good correlations provide information about the systematic influences of substituents on the different direct coupling constants of the ring carbons. The influence of the inductive effects of the substituents on the increase in $^1J(^{13}C, ^1H)$ constants has the same order of magnitude for the three $\Delta^1J(^{13}C, ^1H)$ considered. On the other hand, the σ-withdrawing substituents promote an increase and the σ-donor substituents a decrease in the direct coupling constants of the ring furan carbons.

Semiempirical calculation

An optimization[70] of the electronic structure and geometry of 40 substituted furans by PM3 semiempirical molecular orbital calculations[71] has been carried out. Molecular characteristics of the furans described below correspond to the energy minima obtained by a geometry optimization and a full all degrees of freedom analysis was carried out using the gradient optimization routine in the programs. The semiquantitative agreement of the calculations with our experimental NMR data is the proof of their reasonableness. The most significant molecular parameter to be related with NMR chemical shifts is the net atomic charge on ring carbons. The calculated parameters are shown in Table 12.

The correlation between the net atomic charges and the ^{13}C NMR chemical shifts is well established in the literature.[72] To achieve an acceptable linear correlation between the two parameters mentioned above it was necessary to make use of a previous study of each furan. A careful examination of these earlier results showed that the PM3 semiempirical molecular orbital calculation incorrectly evaluates the net atomic charges of ring carbons attached to an S-substituent. When these carbons were not considered in the mathematical treatment, very good correlations were obtained for all types of furans. The results are shown in Table 13.

From the results collected in Table 13, it is clear that the PM3 method incorrectly evaluates the electronic interaction of the sulfur on the ring *ipso*-carbon. These exceptions are reasonable enough because the parametrization of the d orbitals of sulfur is unoptimized by this semiempirical method and the possible electronic effects which have an effect on *ipso*-carbons are badly evaluated. In all cases, the negative net atomic charges on *ipso*-carbons are overestimated and became significantly higher for carbons C-2 and C-5 *ipso*-*S*-substituted than for carbons C-3 and C-4 *ipso*-*S*-substituted. These results reveal that the PM3 semiempirical molecular orbital calculation overestimates the conjugative effect ($+K$) of the sulfur atom on *ipso*-carbons.

Conclusions

A detailed study of ^1H and ^{13}C NMR spectra of 45 substituted furans has been carried out and substituent-induced chemical shifts (SCS) for six substituents at the 2-position and nine substituents at the 3-position in ^1H and ^{13}C NMR have been calculated. The linear regressions between ^1H–^1H, ^{13}C–^{13}C and ^1H–^{13}C SCS values and the reactivity parameters have allowed the separation of inductive and resonance contributions to chemical shifts. The inductive effects of the substituents are significantly smaller than the resonance effects for all SCS values, and the resonance effects are higher for ^{13}C SCS values than for ^1H SCS parameters. A linear correlation of the change induced by substituents on $^1J(^{13}C, ^1H)$ direct couplings of polysubstituted furans with the inductive effects of substituents bonded to the furan ring has been proposed. The optimization of the electronic structures of 40 furans by PM3 molecular orbital calculation has made possible the study of linear correlations between the net atomic charges localized at ring carbons with the ^{13}C NMR chemical shifts. From these linear correlations it can be concluded that the evaluation of electronic

Table 8 Linear correlations relating ^1H–^1H, ^{13}C–^{13}C and ^1H–^{13}C SCS parameters

Type of regression ^1H–^1H	N^a	r^b	Equation	Type of regression ^1H–^{13}C	N^a	r^b	Equation
β_{23}/δ_{25}	14	0.992	$\delta_{25} = 0.42\beta_{23} - 0.01$	β_{23}/β_{23}	14	0.927	$(\beta_{23})_{13C} = 15.7(\beta_{23})_{1H} - 2.4$
β_{32}/β_{34}	11^c	0.923	$\beta_{34} = 0.28\beta_{32} + 0.12$	δ_{25}/δ_{25}	14^d	0.933	$(\delta_{25})_{13C} = 13.8(\delta_{25})_{1H} + 0.1$
β_{23}/β_{32}	9^e	0.927	$\beta_{32} = 1.0\beta_{23}$	β_{32}/β_{32}	12^e	0.921	$(\beta_{23})_{13C} = 8.4(\beta_{32})_{1H} - 1.2$
β_{23}/γ_{24}	12^f	0.964	$\gamma_{24} = 0.31\beta_{23} - 0.01$	β_{23}/δ_{25}	11^g	0.978	$(\delta_{25})_{13C} = 4.9(\beta_{23})_{1H} + 0.2$
γ_{24}/δ_{25}	12^f	0.985	$\delta_{25} = 1.22\gamma_{24} + 0.02$	γ_{24}/β_{23}	11^h	0.949	$(\beta_{23})_{13C} = 3.3(\gamma_{24})_{1H} + 1.0$
β_{23}/β_{34}	9^e	0.977	$\beta_{34} = 0.39\beta_{23} + 0.04$	γ_{24}/δ_{25}	12^i	0.986	$(\delta_{25})_{13C} = 13.0(\gamma_{24})_{1H} + 0.1$
β_{23}/γ_{35}	9^j	0.956	$\gamma_{35} = 0.19\beta_{23} + 0.02$	δ_{25}/β_{23}	13^k	0.949	$(\beta_{23})_{13C} = 38.5(\delta_{25})_{1H} - 2.2$
γ_{24}/β_{34}	9^l	0.941	$\beta_{34} = 1.1\gamma_{24} + 0.06$	β_{23}/β_{32}	10	0.966	$(\beta_{32})_{13C} = 11.3(\beta_{23})_{1H} - 3.7$
γ_{24}/γ_{35}	9^l	0.965	$\gamma_{35} = 0.80\gamma_{24} - 0.02$	γ_{24}/β_{32}	9^e	0.947	$(\beta_{32})_{13C} = 24.2(\gamma_{24})_{1H} - 0.6$
δ_{25}/β_{34}	9^e	0.957	$\beta_{34} = 0.9\delta_{25} + 0.04$	δ_{25}/β_{32}	10^k	0.974	$(\beta_{32})_{13C} = 26.5(\delta_{25})_{1H} - 3.2$
δ_{25}/γ_{35}	8^m	0.944	$\gamma_{35} = 0.56\delta_{25}$	β_{32}/γ_{24}	8^n	0.992	$(\gamma_{24})_{13C} = 1.96(\beta_{32})_{1H} + 1.1$
				β_{32}/δ_{25}	8^o	0.940	$(\delta_{25})_{13C} = 4.5(\beta_{32})_{1H} + 0.5$
^{13}C–^{13}C				β_{32}/γ_{35}	10^p	0.952	$(\gamma_{35})_{13C} = 2.1(\beta_{32})_{1H} - 0.1$
β_{23}/δ_{25}	14^k	0.983	$\delta_{25} = 0.37\beta_{23} + 0.6$	β_{34}/δ_{25}	9^q	0.951	$(\delta_{25})_{13C} = 12.2(\beta_{34})_{1H} - 0.1$
a_2/a_3	11	0.961	$a_3 = 1.00a_2 + 7.9$	γ_{35}/β_{23}	9^q	0.977	$(\beta_{23})_{13C} = 41.6(\gamma_{35})_{1H} + 1.9$
β_{23}/β_{32}	11	0.951	$\beta_{32} = 0.62\beta_{23} - 1.6$	γ_{35}/δ_{25}	7^r	0.981	$(\delta_{25})_{13C} = 22(\gamma_{35})_{1H} + 0.2$
δ_{25}/β_{32}	11	0.961	$\beta_{32} = 1.66\delta_{25} - 2.7$				

[a] Number of points included in the regression analysis. [b] Correlation coefficient. [d] If the contribution of Et is excluded, a linear regression with a correlation coefficient of 0.985 was obtained: $(\delta_{25})_{13C} = 13.8(\delta_{25})_{1H} + 0.1$. Contributions removed: [c] OMe and Me; [e] OMe; [f] OMe and Br; [g] OMe, CN and Et; [h] Br, Et and OMe; [i] Et and OMe; [j] Cl; [k] Et; [l] Br; [m] OMe and Cl; [n] Cl, I and CN; [o] Br, I and OMe; [p] OMe, Cl and I; [q] OMe and I; [r] Br, Cl, I and OMe.

Table 9 Bilinear regressions between SCS values and *F* and *R* parameters of substituents

^1H SCS values	N^a	r^b	Equation	^{13}C SCS values	N^a	r^b	Equation
β_{23}	10^c	0.975	$\beta_{23} = 0.76F + 2.7R + 0.03$	β_{23}	9^j	0.937	$\beta_{23} = 5.5F + 50.8R + 0.3$
γ_{24}	10^c	0.853^d	$\gamma_{24} = 0.11F + 0.68R + 0.04$	γ_{24}	8^k	0.933	$\gamma_{24} = 3.5F + 1.0R + 0.6$
δ_{25}	10^c	0.951	$\delta_{25} = 0.26F + 1.13R + 0.02$	δ_{25}	8^l	0.954	$\delta_{25} = 3.7F + 18.6R - 0.1$
β_{32}	10^e	0.811^f	$\beta_{32} = 0.78F + 1.44R + 0.08$	β_{32}	11^m	0.927^n	$\beta_{32} = 3.3F + 32.1R + 0.36$
β_{34}	11^g	0.941	$\beta_{34} = 0.39F + 0.70R + 0.04$	β_{34}	7^o	0.986	$\beta_{34} = 5.1F - 15.8R + 0.4$
γ_{35}	10^h	0.873^i	$\gamma_{35} = 0.13F + 0.53R + 0.02$	γ_{35}	8^p	0.975	$\gamma_{35} = 2.0F + 3.1R + 0.1$

[a] Number of points included in the regression analysis. [b] Correlation coefficients. [c] Br, SMe, Me, CO_2H, Et, OMe, Cl, $COCH_3$, CN, H. [d] Without Br: $r = 0.917$, $\gamma_{24} = 0.20F + 0.59R + 0.02$; without the Br and Cl substituents: $r = 0.984$, $\gamma_{24} = 0.31F + 0.49R + 0.49$. [e] Br, SMe, Me, CO_2H, OMe, Cl, I, $COCH_3$, CN, H. [f] Without the OMe: $r = 0.961$, $\beta_{23} = 0.72F + 2.59R + 0.09$. [g] Br, SMe, Me, CO_2H, SH, OMe, Cl, I, $COCH_3$, CN, H. [h] Br, SMe, Me, CO_2H, OMe, Cl, I, $COCH_3$, CN, H. [i] Without the Cl: $r = 0.959$, $\gamma_{35} = 0.19F + 0.48R$. [j] Br, Me, CO_2H, Et, OMe, Cl, $COCH_3$, CN, H. [k] SMe, Me, CO_2H, OMe, Cl, I, $COCH_3$, H. [l] Br, Me, CO_2H, OMe, Cl, $COCH_3$, CN, H. [m] Br, SMe, Me, CO_2H, SH, OMe, Cl, I, $COCH_3$, CN, H. [n] Without the I: $r = 0.962$, $\beta_{32} = 1.4F + 34.3R + 0.8$. [o] Me, CO_2H, SH, I, $COCH_3$, CN, H. [p] SMe, Me, CO_2H, OMe, Cl, $COCH_3$, CN, H.

Table 10 Values of $\Delta^1J(^{13}C, ^1H)$ and SF parameters of furans **7**, **8**, **13**, **15**, **16**, **18**, **20**, **21**, **23**, **25**–**29**, **31**, **33**, **38** and **42**

Furan	SF	$\Delta^1J_{C2,H2}$	$\Delta^1J_{C3,H3}$	$\Delta^1J_{C4,H4}$	$\Delta^1J_{C5,H5}$	Furan	SF	$\Delta^1J_{C2,H2}$	$\Delta^1J_{C3,H3}$	$\Delta^1J_{C4,H4}$	$\Delta^1J_{C5,H5}$
7	0.332	3.5	—	2.3	2.4	**25**	0.280	−1.4	—	—	3.4
8	0.727	—	—	5.6	4.5	**26**	0.267	—	−1.8	1.3	1.5
13	0.602	6.5	—	5.3	3.5	**27**	0.267	—	−0.1	1.2	—
15	0.280	—	−1.1	0.8	—	**28**	0.280	—	—	—	−0.8
16	1.279	—	—	9.3	6.5	**29**	0.280	—	—	1.3	2.5
18	1.059	—	—	6.3	5.0	**31**	0.228	—	—	—	−0.6
20	0.675	7.0	—	—	1.5	**33**	0.215	—	—	—	−0.5
21	0.675	—	—	4.3	4.0	**38**	0.228	—	—	—	−1.6
23	1.059	9.5	—	—	3.5	**42**	0.228	—	—	−0.6	—

effects of the sulfur atom on ring *ipso*-carbons is incorrectly calculated.

Experimental

Tetrahydrofuran (THF) and Et_2O were distilled after refluxing over sodium–benzophenone under argon prior to use. Solutions of LiBu^n in hexane and LiBu^t in pentane were stored under argon prior to use.[73] Diisopropylamine was dried over NaOH and freshly distilled after refluxing over NaH under argon prior to use.[74] Dimethyl disulfide was filtered over neutral alumina prior to use. Diethyl sulfate was purified by washing with a 3% aqueous solution of sodium carbonate, distilled to remove water, dried over dry $CaCl_2$, and distilled at reduced pressure.[74] Dimethyl sulfate was dried over potassium carbonate and distilled at reduced pressure after refluxing over dry CaO.[74] Silica gel 60 F_{254} was used for TLC and the spots were detected with a UV lamp. Flash chromatography was carried out on silica gel (230–400 mesh). Kugelrohr distillations reflect the oven temperature and are listed as T_d/°C at *p*/mmHg. IR spectra were recorded as neat films between NaCl windows. ^1H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded in $CDCl_3$ solutions with $SiMe_4$ as internal reference. Chemical shifts are quoted as δ (ppm) and the full assignment of the ^{13}C NMR spectra was carried out with the aid of coupled spectra or 2D heteronuclear ^1H–^{13}C correlation spectra. *J* values are in Hz. Metallations were carried out under an argon atmosphere by using LiBu^n, LDA or LiBu^t for forming the lithium intermediate derivatives.

2-Methylthiofuran 4

To a stirred solution of furan (6.4 ml, 88.13 mmol) in dry Et_2O

(64 ml) at −20 °C was slowly added a solution (1.6 M) of LiBu^n (39.3 ml, 62.95 mmol) in hexane. Stirring was continued for 4 h, and the reaction mixture was then cooled at −78 °C and a solution of dimethyl disulfide (5.7 ml, 62.95 mmol) in dry Et_2O (60 ml) was slowly added. The reaction mixture was vigorously stirred at −78 °C for 0.5 h, the temperature was then successively allowed to rise to 0 °C for 0.5 h and to room temp. for 1 h. The reaction mixture was carefully quenched with distilled water (30 ml) and extracted with Et_2O–pentane (1:1, 3 × 50 ml). The combined organic layers were then washed with brine (3 × 50 ml), dried over Na_2SO_4 and evaporated under reduced pressure yielding a pale yellow oil (5.90 g) which was composed (^{1}H NMR) of a mixture of 2-methylthiofuran **4** (85%) and dimethyl disulfide (15%). A spectroscopically pure sample of furan **4** was obtained by distillation under reduced pressure (bp 75–77 °C at 180 mmHg) (lit., **4**,[36] bp 42–43 °C at 9 mmHg;[38] 139–140 °C at 771 mmHg[37]) and characterized by its IR, ^{1}H and ^{13}C NMR spectra. Spectroscopic yield: 70%. Found: C, 53.0; H, 5.4. Calc. for C_5H_6OS: C, 52.6; H, 5.3%. ν_{max}/cm^{-1} (film) 3120 (CH st), 1680 (C–C st), 1470 (C–C st) and 1155 (C–O–C st). δ_H(300 MHz, $CDCl_3$) 2.40 (s, 3H, SMe), 6.36 (dd, 1H, ^3J 3.3, ^3J 2.0, 4-H), 6.42 (dd, 1H, ^3J 3.3, ^4J 1.0, 3-H) and 7.47 (dd, 1H, ^3J 2.0, ^4J 1.0, 5-H). δ_C(75.5 MHz, $CDCl_3$) 18.7 (SMe), 111.3 (C-4), 114.1 (C-3), 144.7 (C-5) and 147.2 (C-2).

2-Phenylthiofuran 5

This compound was obtained as described above for 2-methylthiofuran **4** from furan (6.0 ml, 82.6 mmol) in Et_2O (60 ml), LiBu^n (0.9 M, 65.3 ml, 58.7 mmol) and diphenyl disulfide (12.81 g, 58.7 mmol). The pale yellow oil obtained (9.5 g) was composed (by ^{1}H NMR) of a mixture of 2-phenylthiofuran **5** (97%) and 2,5-bis(phenylthio)furan (3%). A spectroscopically pure sample of furan **5** was obtained by flash chromatography (pentane) and characterized by its IR, ^{1}H and ^{13}C NMR spectra (lit., **5**,[33–36] bp 119–120 °C at 8 mmHg,[33] 97–98 °C at 2.5 mmHg[34]). Spectroscopic yield: 90%. Found: C, 68.4; H, 4.6. Calc. for $C_{10}H_8OS$: C, 68.15; H, 4.6%. ν_{max}/cm^{-1} (film) 3130 (CH st), 1480 (C–C st), 1460 (C–C st), 1440 (C–C st) and 1150 (C–O–C st). δ_H(300 MHz, $CDCl_3$) 6.45 (dd, 1H, ^3J 3.3, ^3J 2.1, 4-H), 6.73 (dd, 1H, ^3J 3.3, ^4J 0.8, 3-H), 7.19 (m, 5H, SPh) and 7.55 (dd, 1H, ^3J 2.1, ^4J 0.8, 5-H). δ_C(75.5 MHz, $CDCl_3$) 111.7 (C-4), 119.4 (C-3), 126.2 (C_{para}), 127.3 (C_{meta}), 128.9 (C_{ortho}), 136.1 (C_{ipso}), 142.9 (C-2) and 146.4 (C-5).

Table 11 Linear regressions between $\Delta^1J(^{13}C, ^1H)$ and SF parameters

$\Delta^1J(^{13}C, ^1H)$	N[a]	r[b]	Equation
$\Delta^1J_{C2,H2}$	5[c]	0.950	$\Delta^1J_{C2,H2} = 9.23SF - 0.73$
$\Delta^1J_{C3,H3}$	—[d]	—	—
$\Delta^1J_{C4,H4}$	11	0.960	$\Delta^1J_{C4,H4} = 8.67SF - 1.35$
$\Delta^1J_{C5,H5}$	15[c,e]	0.900	$\Delta^1J_{C5,H5} = 7.81SF - 2.44$

[a] Number of points included in the regression analysis. [b] Correlation coefficients. [c] The contribution of furan **25** was excluded. [d] This linear regression has been excluded because there are only three points. [e] If the contribution of furans **7**, **21** and **29** are additionally excluded, a linear regression with a correlation coefficient of 0.940 was obtained (eqn.: $\Delta^1J_{C5,H5} = 7.87\Sigma F - 2.87$.

2,2′-Difuryl sulfide 6

To a stirred solution of furan (1 ml, 13.75 mmol), in dry Et_2O (10 ml) at −20 °C was slowly added a solution (1.15 M) of LiBu^n (8.5 ml, 9.82 mmol) in hexane. The reaction mixture was then cooled at −78 °C and sulfur (346 mg, 10.8 mmol) was added under an Ar atmosphere. The mixture was vigorously stirred at −78 °C for 0.5 h, the temperature was allowed to rise to 0 °C and KOH (857 mg, 13.75 mmol) and toluene-*p*-sulfonyl chloride (2.44 g, 12.77 mmol) in dry Et_2O (10 ml) were successively added, and the stirring was maintained for 3 h at 0 °C and overnight at room temp. After cooling the reaction mixture to 5 °C, distilled water (20 ml) and 1.8 M aqueous KOH (500 ml) were successively added. The mixture was extracted with Et_2O (3 × 100 ml) and the combined organic layers were washed with brine (3 × 100 ml) and distilled water (3 × 100 ml) and dried over $MgSO_4$. After concentration of the solution under reduced pressure, the pale yellow oily crude product was obtained (650 mg) and purified by flash chromatography (hexane–Et_2O, 95:5, v:v) yielding a colourless oil (480 mg) which was identified as 2,2′-difuryl disulfide **6** from its IR, ^{1}H, ^{13}C NMR and mass spectra (lit.,[73] 98–99 °C at 10 mmHg). Yield **6**: 50%. Found: C, 57.9; H, 3.6. Calc. for $C_8H_6O_2S$: C, 57.8; H, 3.6%. ν_{max}/cm^{-1} (film) 3145 (CH st), 3125 (CH st), 1450 (C–C st) and 1360 (C–C st). δ_H(300 MHz, $CDCl_3$) 6.36 (dd, 1H, ^3J 3.2, ^3J 2.1, 4-H), 6.61 (dd, 1H, ^3J 3.2, ^4J 1.0, 3-H) and 7.46 (dd, 1H, ^3J 2.1, ^4J 1.0, 5-H). δ_C(75.5 MHz, $CDCl_3$) 111.5 (ddd, ^1J 176.2, ^2J 13.1, ^2J 4.0, C-4), 116.7 (ddd, ^1J 179.3, ^2J 5.5, ^3J 3.6, C-3), 142.7 (q, $^2J_{C_2,H_3} = {}^3J_{C_2,H_4} = {}^3J_{C_2,H_5} = 8.4$ Hz, C-2) and 145.6 (ddd, ^1J 203.0, ^2J 10.1, ^3J 8.1, C-5). MS: *m*/*z* 168 (M + 2, 6%), 166 (M+, 99.5), 138 (100), 137 (94), 109 (43), 105 (41), 69 (39) and 55 (35).

2-Phenylthio-5-methylfuran 14

This compound was obtained as described above for 2-methylthiofuran **4** from 2-methylfuran (2.5 ml, 25.3 mmol) in dry Et_2O (20 ml), LiBu^n (1.6 M, 15.8 ml, 25.3 mmol) and diphenyl disulfide (5.51 g, 25.3 mmol). The crude pale yellow oil (4.24 g) was composed (by ^{1}H NMR) of a mixture of 2-phenylthio-5-methylfuran **14** (68%) and diphenyl disulfide (32%). A spectroscopically pure sample of furan **14** was obtained by flash chromatography (pentane) and characterized from its IR, ^{1}H and ^{13}C NMR spectra (lit., **14**,[35] bp 110 °C at 0.5 mmHg). Spectroscopic yield: 56%. Found: C, 69.1; H, 5.2. Calc. for $C_{11}H_{10}OS$: C, 69.4; H, 5.3%. ν_{max}/cm^{-1} (film) 3060 (CH st), 1705 (comb. ar.), 1580 (C–C st), 1470 (C–C st) and 1435 (CH_3). δ_H(300 MHz, $CDCl_3$) 2.31 (dd, 3H, ^4J 1.0, ^5J 0.4, Me), 6.06 (dq, 1H, ^3J 3.0, ^4J 1.0, 4-H), 6.60 (dq, 1H, ^3J 3.0, ^5J 0.4, 3-H) and 7.19 (m, 5H, SPh). δ_C(75.5 MHz, $CDCl_3$) 13.9 (Me), 108.0

Table 12 Net atomic charges on ring carbons, Q_C, of furans **4**–**8** and **11**–**45** calculated by the PM3 semiempirical molecular orbital formalism

Furan	C-2	C-3	C-4	C-5	Furan	C-2	C-3	C-4	C-5	Furan	C-2	C-3	C-4	C-5
4	−0.163	−0.176	−0.173	−0.058	**20**	−0.031	−0.213	−0.123	−0.069	**33**	0.024	−0.282	−0.148	−0.034
5	−0.163	−0.138	−0.172	−0.057	**21**	−0.008	−0.215	−0.150	−0.063	**34**	−0.062	−0.133	−0.180	−0.114
6	−0.167	−0.137	−0.177	−0.050	**22**	−0.018	−0.257	−0.153	−0.053	**35**	−0.136	−0.170	−0.197	−0.021
7	−0.065	−0.271	−0.142	−0.060	**23**	−0.028	−0.190	−0.241	−0.068	**36**	−0.139	−0.179	−0.119	−0.062
8	−0.031	−0.218	−0.151	−0.061	**24**	−0.067	−0.234	−0.234	−0.067	**37**	−0.005	−0.179	−0.196	−0.009
11	−0.057	−0.267	−0.146	−0.056	**25**	−0.068	−0.113	−0.265	−0.068	**38**	−0.156	−0.131	−0.157	−0.055
12	−0.019	−0.289	−0.140	−0.063	**26**	−0.058	−0.149	−0.259	−0.036	**39**	−0.033	−0.254	−0.120	−0.065
13	−0.058	−0.271	−0.142	−0.053	**27**	−0.041	−0.169	−0.174	−0.165	**40**	−0.024	−0.263	−0.113	−0.072
14	−0.157	−0.164	−0.179	−0.031	**28**	−0.161	−0.174	−0.149	−0.061	**41**	−0.012	−0.245	−0.163	−0.028
15	−0.165	−0.173	−0.174	−0.038	**29**	−0.031	−0.262	−0.149	−0.056	**42**	−0.032	−0.257	−0.150	−0.036
16	−0.072	−0.134	−0.181	−0.019	**30**	−0.011	−0.256	−0.154	−0.029	**43**	−0.124	−0.181	−0.181	−0.124
17	−0.150	−0.147	−0.217	−0.017	**31**	−0.042	−0.264	−0.143	−0.037	**44**	−0.007	−0.197	−0.197	−0.007
18	−0.139	−0.184	−0.149	−0.053	**32**	0.068	−0.353	−0.119	−0.067	**45**	−0.001	−0.201	−0.222	−0.022
19	−0.027	−0.201	−0.201	−0.027										

Table 13 Linear correlations relating ^{13}C NMR chemical shifts (δ) and net atomic charges localized on ring furan carbons (Q_C) calculated by PM3 ($\delta_C = mQ_C + n$)

Type of furan	N[a]	r[b]	Slope (m)	Independent term (n)
All	125	0.928	249	155.0
Monosubstituted	25	0.964	289	160.0
Disubstituted	51	0.933	242	155.0
Trisubstituted	40	0.926	259	154.9
Tetrasubstituted	9	0.984	248	151.8

[a] Number of points included in the regression analysis. [b] Correlation coefficient.

(C-4), 121.1 (C-3), 125.9 (C$_{para}$), 126.9 (C$_{meta}$), 128.9 (C$_{ortho}$), 136.9 (C$_{ipso}$), 140.1 (C-2) and 156.7 (C-5).

2-Methylthio-5-methylfuran 15

This compound was obtained as described above for 2-methylthiofuran **4** from 2-methylfuran (8.7 ml, 88.13 mmol) in dry Et$_2$O (64 ml), LiBu^n (1.6 M, 55.1 ml, 88.13 mmol) and dimethyl disulfide (7.9 ml, 88.13 mmol). The crude pale yellow oil (8.40 g) was composed (by ^{1}H NMR) of a mixture of 2-methylthio-5-methylfuran **15** (81%) and dimethyl disulfide (19%). A spectroscopically pure sample of furan **15** was achieved by distillation under reduced pressure (bp 80–82 °C at 47 mmHg) and characterized from its IR, ^{1}H and ^{13}C NMR spectra.[39,40] Spectroscopic yield: 60%. Found: C, 56.6; H, 6.5. Calc. for C_6H_8OS: C, 56.2; H, 6.3%. ν_{max}/cm^{-1} (film) 3120 (CH st), 1670 (C–C st), 1590 (C–C st), 1500 (C–C st) and 1450 (CH$_3$). δ_H(300 MHz, CDCl$_3$) 2.30 (dd, 3H, ^4J 1.2, ^5J 0.3, Me), 2.38 (s, 3H, SMe), 5.95 (dq, 1H, ^3J 3.3, ^4J 1.2, 3-H) and 6.35 (dq, 1H, ^3J 3.3, ^5J 0.3, 4-H). δ_C(75.5 MHz, CDCl$_3$) 13.8 (q, ^1J 128.6, Me), 19.5 (q, ^1J 140.3, SMe), 107.5 (d of quint., ^1J 173.9, $^2J_{C_3,H_4} = {}^3J_{C3,Me} = 3.8$, C-4), 116.2 (dd, ^1J 175.8, ^2J 4.6, C-3), 144.5 (m, C-2) and 154.9 (m, C-5).

3-Bromo-2-furoic acid 16

To a solution of diisopropylamine (1.0 ml, 6.80 mmol) in THF (7 ml) at −78 °C was added a 1.6 M solution of LiBu^n in hexane (4.25 ml, 6.80 mmol) dropwise, and the solution was stirred for 10 min at −78 °C. 3-Bromofuran (0.6 ml, 6.80 mmol) was then slowly added, and the solution was stirred for 150 min at −78 °C. After addition of dry ice (0.15 g, 34.0 mmol), stirring was maintained at −78 °C for 15 min and the temperature was allowed rise to room temp., and the solvents were eliminated under reduced pressure. The crude reaction product obtained was dissolved in the minimum amount of water and extracted with Et$_2$O (3 × 50 ml). The aqueous phase was decanted, a 1 M HCl solution was then added to pH 1 and the solution was then extracted with Et$_2$O (3 × 50 ml). These combined organic layers were dried over Na$_2$SO$_4$. After concentration of the solution, the resulting white solid (1.10 g) was purified by recrystallization from Et$_2$O–pentane giving a white solid (0.909 g) which was identified as 3-bromo-2-furoic acid **16** from its IR, ^{1}H and ^{13}C NMR spectra. Yield: 70%. Mp 150–152 °C (lit.,[29a] 163 °C). Found: C, 31.7; H, 1.8. Calc. for $C_5H_3BrO_3$: C, 31.4; H, 1.6%. ν_{max}/cm^{-1} (KBr) 3300–2100 (CO$_2$H), 1670 (C–C st), 1560 (C–C st) and 1470 (C–C st). δ_H(300 MHz, CDCl$_3$) 6.68 (d, 1H, ^3J 1.8, 4-H), 7.60 (d, 1H, ^3J 1.8, 5-H) and 11.29 (br s, 1H, CO$_2$H). δ_C(75.5 MHz, CDCl$_3$) 111.0 (d, ^2J 8.1, C-3), 117.3 (dd, ^1J 184.3, ^2J 13.1, C-4), 140.2 (s, C-2), 146.8 (dd, ^1J 207.5, ^2J 10.0, C-5) and 162.8 (s, CO$_2$H).

4-Bromo-2-phenylthiofuran 17

To a solution of 3-bromo-5-phenylthiofuran-2-carboxylic acid **34** (156 mg, >96% pure, 0.5 mmol) in quinoline (1 ml) was added under an Ar atmosphere bronze copper powder (71 mg, 1.1 mmol). The reaction mixture was vigorously stirred at 130–150 °C for 2 h and the temperature was then allowed to rise to room temp. The reaction mixture was diluted with Et$_2$O (25 ml), filtered, and the organic phase was successively washed with 1 M HCl solution (3 × 50 ml) and brine (3 × 50 ml), and dried over Na$_2$SO$_4$. After concentration of the solution, the pale yellow oil was purified by flash chromatography (pentane) giving an oil (74 mg) which was identified as 4-bromo-2-phenylthiofuran **17** from its IR, ^{1}H and ^{13}C NMR spectra. Yield: 58%. ν_{max}/cm^{-1} (NaCl) 3120 (CH st), 1470 (C–C st), 1455 (C–C st), 1430 (C–C st) and 1160 (C–O–C st). δ_H(300 MHz, CDCl$_3$) 6.75 (d, 1H, ^4J 1.2, 3-H), 7.23 (m, 5H, SPh) and 7.55 (d, 1H, ^4J 1.2, 5-H). δ_C(75.5 MHz, CDCl$_3$) 100.5 (C-4), 121.3 (C-3), 126.8 (C$_{para}$), 128.3 (C$_{meta}$), 128.1 (C$_{ortho}$), 134.8 (C$_{ipso}$), 142.3 (C-2) and 144.5 (C-5).

3-Bromo-2-methylthiofuran 18

To a solution of diisopropylamine (8.0 ml, 57.02 mmol) in dry THF (57 ml) at −78 °C was added a 1.25 M solution of LiBu^n (45.6 ml, 57.02 mmol) dropwise, and the solution was stirred at −78 °C for 10 min. 3-Bromofuran (4.7 ml, 51.84 mmol) and dimethyl disulfide (4.6 ml, 51.84 mmol) were successively added; the stirring was continued at −78 °C for 1 h and the temperature was kept at 0 °C for 1 h and then at room temp. for 12 h. The reaction mixture was carefully quenched with distilled cold water (160 ml) and extracted with Et$_2$O (3 × 50 ml). The combined organic layers were successively washed with a 2 M solution of NaOH (3 × 50 ml), a 2 M solution of HCl (3 × 50 ml) and brine (3 × 50 ml), dried over MgSO$_4$ and evaporated under reduced pressure yielding a pale yellow oil (6.06 g) which was composed (by ^{1}H NMR) of a mixture of 3-bromo-2-methylthiofuran **18** (49%), 3-bromofuran (23%) and 2-methylthiofuran **4** (6%). A spectroscopically pure sample of 3-bromo-2-methylthiofuran **18** was obtained by flash chromatography (hexane) and characterized from its IR, ^{1}H, ^{13}C NMR and mass spectra (lit.,[4] 79–81 °C at 14 mmHg). Spectroscopic yield: 30%. Found: C, 30.9; H, 2.8. Calc. for C_5H_5BrOS: C, 31.1; H, 2.6%. ν_{max}/cm^{-1} (film) 3120 (CH st), 1535 (C–C st), 1460 (C–C st), 1430 (C–C st) and 1350 (CH$_3$). δ_H(300 MHz, CDCl$_3$) 2.40 (s, 3H, SMe), 6.47 (d, 1H, ^3J 2.1, 4-H) and 7.44 (d, 1H, ^3J 2.1, 5-H). δ_C(75.5 MHz, CDCl$_3$) 17.9 (q, ^1J 141.7, SMe), 106.2 (d, ^2J 8.1, C-3), 115.0 (dd, ^1J 181.3, ^2J 13.1, C-4), 144.9 (dd, ^1J 206.0, ^2J 9.6, C-5) and 145.6 (sext, $^3J_{C2,Me} = {}^3J_{C2,H4} = {}^3J_{C2,H5} = 5.5$, C-2). MS: *m/z* 194 (89%), 192 (85), 179 (34), 177 (33), 151 (32), 149 (31), 85 (55), 70 (34), 69 (100) and 47 (76).

3,4-Bis(methylthio)furan 24

This compound was obtained as a crude by-product in the reaction of 3-bromo-4-methylthiofuran[20] (over 87% pure by ^{1}H NMR) from 3,4-dibromofuran **19** and dimethyl disulfide using LiBu^t as metallating reagent, and it was characterized from its ^{1}H and ^{13}C NMR spectra. δ_H(300 MHz, CDCl$_3$) 2.38 (s, 6H, 2 × SMe) and 7.36 (s, 2H, 2-H and 5-H). δ_C(75.5 MHz, CDCl$_3$) 17.9 (2 × SMe), 128.7 (C-3 and C-4) and 142.6 (C-2 and C-5).

2-Ethyl-5-methylthiofuran 27

To a solution of 3-bromo-2-methylthiofuran **18** (250 mg, 1.30 mmol) in dry Et$_2$O was added under an Ar atmosphere a 1.15 M solution of LiBu^t (1.3 ml, 1.43 mmol) in pentane dropwise, and the resulting solution was stirred for 30 min at −78 °C. HMPA (0.25 ml, 1.43 mmol) and a solution of ethyl iodide (1.0 ml, 13.0 mmol) in dry THF (6 ml) was added. Stirring was continued for 24 h at −78 °C and the temperature was then allowed to rise slowly to room temp. The reaction mixture was quenched with a cold saturated aqueous solution of ammonium chloride and extracted with Et$_2$O (3 × 25 ml). The organic combined layers were washed with brine (6 × 25 ml) and dried over MgSO$_4$. After concentration of the solution under reduced pressure, a crude pale yellow oil (68 mg) was obtained and purified by distillation under reduced pressure in a Kugelrohr oven: T_d 125 °C at 20 mmHg.[74] Spectroscopic yield: 16%. Found: C, 59.3; H, 6.9. Calc. for $C_7H_{10}OS$: C, 59.1; H, 7.1%. δ_H(300 MHz,

$CDCl_3$) 1.23 (t, 3H, ^3J 7.4, Me), 2.40 (s, 3H, SMe), 2.65 (m, 2H, CH_2), 5.96 (dt, 1H, ^3J 3.0, ^4J 1.1, 3-H) and 6.36 (dt, 1H, ^3J 3.0, ^5J 0.3, 4-H). δ_C(75.5 MHz, $CDCl_3$) 11.8 (qt, ^1J 127.1, ^2J 5.0, Me), 19.4 (q, ^1J 140.7, SMe), 21.6 (tq, ^1J 127.8, ^2J 4.5, CH_2), 105.7 (dq, ^1J 173.2, $^2J_{C3,H4} = {}^3J_{C3,CH_2} = 3.4$, C-3), 115.9 (dd, ^1J 176.2, ^2J 4.0, C-4), 144.6 (m, C-5) and 160.6 (m, C-2).

2-Methylthio-4-methylfuran 28

The synthesis of this compound was performed as described above for *ipso*-metallation of 3(4)-bromofurans[20] from 3-bromo-4-methyl-2-methylthiofuran **36** (695 mg, 3.36 mmol) in dry Et_2O (7 ml), $LiBu^t$ (1.3 м, 2.8 ml, 3.69 mmol) and water (8 ml) as electrophile. The crude pale yellow oil (303 mg) was purified by distillation at reduced pressure in a Kugelrohr oven: T_d 70–85 °C at 20 mmHg.[75] Spectroscopic yield: 64%. Found: C, 56.0; H, 6.4. Calc. for C_6H_8OS: C, 56.2; H, 6.3%. ν_{max}(film)/cm^{-1} 3115 (CH st), 1780 (C–C st), 1760 (C–C st) and 1430 (CH_3). δ_H(300 MHz, $CDCl_3$) 1.99 (dd, 3H, ^4J 1.2, ^4J 0.3, Me), 2.38 (s, 3H, SMe), 6.29 (dq, 1H, ^4J 1.2, ^4J 0.3, 3-H) and 7.24 (quint., 1H, $^4J_{H5,H3} = {}^4J_{H5,Me} = 1.2$, 5-H). δ_C(75.5 MHz, $CDCl_3$) 9.6 (q, ^1J 127.6, Me), 18.7 (q, ^1J 141.0, SMe), 116.7 (d of quint., ^1J 174.9, $^3J_{C3,H5} = {}^3J_{C3,Me} = 4.5$, C-3), 121.6 (m, C-4), 141.4 (d of quint., ^1J 200.2, $^3J_{C5,H3} = {}^3J_{C5,Me} = 6.2$, C-5) and 146.9 (m, C-2).

2,5-Dimethyl-3-furyl thioacetate 30

Furan **30** was obtained from 2,5-dimethylfuran following the procedure described previously by Evers *et al.*[21] After concentration of the solution, the pale yellow reaction crude [2.76 g from 3.09 g of *S*-(2,5-dioxo-3-hexyl) ethanothioate] was purified by flash chromatography (hexane–ethyl acetate: 90 : 10 v : v) giving an oil (2.5 g) which was identified as *S*-(2,5-dimethyl-3-furyl) thioacetate **30**. Yield: 90%. Found: C, 57.1; H, 5.7. Calc. for $C_8H_{10}O_2S$: C, 56.45; H, 5.9%. ν_{max}/cm^{-1} (film) 3150 (CH st), 1720 (C–C st) and 1590 (C–C st). δ_H(300 MHz, $CDCl_3$) 2.21 (q, 3H, $^4J_{Me,H4} = {}^6J = 0.6$, 5-C$H_3$), 2.26 (q, 3H, $^5J = {}^6J = 0.6$, 2-CH_3), 2.36 (d, 3H, ^6J 0.6, CH_3–COS) and 5.90 (m, 1H, 4-H). δ_C(75.5 MHz, $CDCl_3$) 11.6 (Me), 13.3 (Me), 29.6 (*C*H_3–COS), 104.3 (C-3), 110.0 (C-4), 150.4 (C-5), 154.1 (C-2) and 194.3 (CO).

2,5-Dimethylfuran-3-thiol 31 and bis(2,5-dimethyl-3-furyl) disulfide 32

A stirred solution of *S*-(2,5-dimethyl-3-furyl) thioacetate **30** in 250 ml of 2 м aq. NaOH was refluxed for 1 h, and then was allowed to reach room temp. The rising pH was kept at 1 by adding 225 ml of 2 м aq. H_2SO_4 and the mixture was extracted with Et_2O (3 × 250 ml). The combined organic layers were then washed with brine (3 × 250 ml) and dried over $MgSO_4$. After careful concentration of the solution under reduced pressure, the reaction mixture was fractionated by distillation to obtain 7.09 g of an oil which contained a mixture of furan **31** (84%; yield: 30%) and the furan **32** (16%), originated from a spontaneous oxidation of thiol **31**. Both compounds were unequivocally characterized from their ^1H and ^{13}C NMR spectra (lit., **3**,[21f,g,77]). 2,5-Dimethylfuran-3-thiol **31**: δ_H(300 MHz, $CDCl_3$) 2.21 (m, 3H, Me), 2.26 (m, 3H, Me), 2.61 (m, 1H, SH), 5.87 (m, 1H, 4-H). δ_C(75.5 MHz, $CDCl_3$) 11.5 (Me), 13.2 (Me), 102.2 (C-3), 111.2 (C-4), 149.7 (C-5) and 151.7 (C-2). Bis(2,5-dimethyl-3-furyl) disulfide **32**: δ_H(300 MHz, $CDCl_3$) 2.07 (q, 3H, $^5J = {}^6J = 0.5$, Me), 2.23 (dc, 3H, ^4J 1.1, ^6J 0.5, Me) and 5.96 (m, 1H, H-4). δ_C(75.5 MHz, $CDCl_3$) 11.2 (Me), 13.3 (Me), 110.0 (C-4), 112.9 (C-3), 150.2 (C-5) and 155.0 (C-2).

S-(2,5-Dimethyl-3-furyl) thiobenzoate 33

To a stirred solution of 2,5-dimethylfuran-3-thiol **31** (5.0 g, 39.1 mmol) and pyridine (3.09 g, 39.1 mmol) in diethyl ether (60 ml) was slowly added benzoyl chloride (5.49 g, 39.1 mmol). After stirring at room temp. for 40 min, the reaction mixture was filtered through dry Na_2SO_4 and extracted with Et_2O (3 × 50 ml) and pentane (3 × 50 ml), washed with brine (3 × 50 ml), and dried over dry $MgSO_4$. After concentration of the solution under reduced pressure, the solid pyridinium chloride was eliminated by filtration and washed with pentane (2 × 25 ml), and a pale yellow oil product (8.93 g) was isolated by concentration of the solution under reduced pressure and purified by flash chromatography (hexane–ethyl acetate: 90 : 10, v : v) giving a colourless oil (7.94 g) which was identified as *S*-(2,5-dimethyl-3-furyl) thiobenzoate **33** from its IR, ^1H and ^{13}C NMR spectra (lit.,[21a] bp 118–122 °C at 0.5 mmHg). Yield: 94%. Found: C, 67.3; H, 5.1. Calc. for $C_{13}H_{12}O_2S$: C, 67.2; H, 5.2%. ν_{max}/cm^{-1} (film) 3070 (CH st), 1680 (C–C st), 1580 (C–C st) and 1450 (CH_3). δ_H(300 MHz, $CDCl_3$) 2.26 (br s, 3H, 2-Me), 2.29 (m, 3H, 5-Me), 5.99 (m, H-4), 7.46 (m, 2H, *ortho*-H), 7.59 (tt, 1H, ^3J 7.5, ^4J 1.5, *para*-H) and 8.00 (m, 2H, *meta*-H). δ_C(75.5 MHz, $CDCl_3$) 11.8 (Me), 13.4 (Me), 103.2 (C-3), 110.4 (C-4), 127.3 (C_{ortho}), 128.5 (C_{meta}), 133.4 (C_{para}), 136.3 (C_{ipso}), 150.6 (C-5), 154.7 (C-2) and 199.8 (CO).

3-Bromo-5-phenylthio-2-furoic acid 34

To a solution of diisopropylamine (0.5 ml, 3.67 mmol) in THF (3.7 ml) at −78 °C was added a 1.6 м solution of $LiBu^n$ in hexane (2.3 ml, 3.67 mmol) dropwise, and the solution was stirred for 10 min at −78 °C. Solutions of 3-bromo-2-furoic acid **16** (250 mg, 1.83 mmol) in THF (3 ml) and diphenyl disulfide (400 mg, 1.83 mmol) in THF (3 ml) were successively added and the temperature was then allowed to rise to room temp. Stirring was continued for 12 h at room temp. and the solvent was eliminated under reduced pressure. The crude reaction was dissolved in the minimum amount of water and extracted with Et_2O (3 × 50 ml). The aqueous phase was decanted, 1 м HCl was then added to pH 1 and the solution was extracted with Et_2O (3 × 50 ml). These combined ethereal layers were dried over Na_2SO_4. After concentration of the solution, the resulting white solid (430 mg) was purified by recrystallization in chloroform–pentane giving a white solid (400 mg) which was characterized (^1H NMR) as a mixture of 3-bromo-5-phenylthio-2-furoic acid **34** (96%) and 3-bromo-2-furoic acid **16** (4%) and used without further purification. Spectroscopic yield: 67%. Spectroscopic data of **34**: δ_H(300 MHz, $CDCl_3$) 6.58 (s, 1H, 4-H), 7.40 (m, 5H, SPh) and 7.98 (br s, 1H, CO_2H). δ_C(75.5 MHz, $CDCl_3$) 111.4 (C-3), 120.6 (C-4), 128.4 (C_{para}), 129.5 (C_{meta}), 131.3 (C_{ortho}), 131.9 (C_{ipso}), 142.0 (C-2), 152.8 (C-5) and 161.8 (CO_2H).

3,4-Dibromo-2-methylthiofuran 35 and 3,4-dibromo-2,5-bis(methylthio)furan 43

These compounds were obtained as described above for 3-bromo-2-methylthiofuran **18** from 3,4-dibromofuran **19** (1.0 g, 4.43 mmol) and dimethyl disulfide (0.4 ml, 4.43 mmol). The crude pale yellow oil (1.02 g) was composed (^1H NMR) of a mixture of 3,4-dibromo-2-methylthiofuran **35** (68%), 3,4-dibromo-2,5-bis(methylthio)furan **43** (19%), 3-bromo-2-methylthiofuran **18** (6%) and 3,4-dibromofuran **19** (7%). The purification of this crude mixture by flash chromatography (pentane) allowed the isolation of two fractions which were identified as 3,4-dibromo-2-methylthiofuran **35** (530 mg) and 3,4-dibromo-2,5-bis(methylthio)furan **43** (140 mg) from their IR, ^1H and ^{13}C NMR spectra. Yields: **35**, 44; **43**, 9.9%. Spectroscopic data for **35**: Found: C, 22.2; H, 1.6. Calc. for $C_5H_4OSBr_2$: C, 22.1; H, 1.5%. ν_{max}/cm^{-1} (film) 3120 (CH st), 1770 (C–C st), 1530 (C–C st) and 1305 (CH_3). δ_H(300 MHz, $CDCl_3$) 2.42 (s, 3H, SMe) and 7.54 (s, 1H, 5-H). δ_C(75.5 MHz, $CDCl_3$) 17.7 (q, ^1J 141.7, SMe), 104.6 (d, ^2J 10.1, C-4), 109.5 (d, ^3J 6.1, C-3), 142.9 (d, ^1J 212.6, C-5) and 146.7 (quint., $^3J_{C2,H5} = {}^3J_{C2,Me}$ 5.5, C-2). Spectroscopic data of **43**. Found: C, 22.8; H, 2.0. Calc. for $C_6H_6OS_2Br_2$: C, 22.7; H, 1.9. ν_{max}/cm^{-1} (film) 1520 (C–C st), 1420 (C–C st) and 1410 (C–C st). δ_H(300 MHz, $CDCl_3$) 2.45 (s, 3H, SMe). ^{13}C NMR: 17.6 (SMe), 109.7 (C-3 and C-4) and 148.0 (C-2 and C-5).

3-Bromo-4-methyl-2-methylthiofuran 36

This compound was obtained as described above for 3-bromo-

2-methylthiofuran **18** from 3-bromo-4-methylfuran **20** (10.35 g, 64.3 mmol) and dimethyl disulfide (5.7 ml, 64.3 mmol). The crude pale yellow oil (11.26 g) was purified by distillation at reduced pressure in a Kugelrohr oven yielding a fraction of the title compound (8.66 g) which was characterized from its IR, ^{1}H and ^{13}C NMR spectra. T_d 150 °C at 20 mmHg. Yield: 65%. Found: C, 34.7; H, 3.2%. Calc. for C_6H_7OSBr: C, 34.8; H, 3.4. ν_{max}/cm^{-1} (film) 3120 (CH st), 1585 (C–C st) and 1430 (CH_3). δ_H(300 MHz, $CDCl_3$) 1.98 (d, 3H, ^{4}J 1.2, Me), 2.38 (s, 3H, SMe) and 7.28 (q, 1H, ^{4}J 1.2, 5-H). δ_C(75.5 MHz, $CDCl_3$) 9.3 (q, ^{1}J 128.6, Me), 17.9 (q, ^{1}J 141.4, SMe), 110.0 (dq, ^{3}J 7.8, ^{3}J 4.7, C-3), 122.6 (dq, ^{2}J 12.8, ^{2}J 6.5, C-4), 141.1 (dq, ^{1}J 203.7, ^{3}J 6.0, C-5) and 144.9 (q, $^{3}J_{C2,H5} = {}^{3}J_{C2,SMe} = 5.0$, C-2).

3,4-Dimethyl-2-methylthiofuran 38

The synthesis was performed as described above for *ipso*-metallation of 3(4)-bromofurans[20] from 3-bromo-4-methyl-2-methylthiofuran **36** (900 mg, 4.35 mmol) in dry Et_2O (9 ml), LiBu^{t} (1.25 M, 3.8 ml, 4.79 mmol) and dimethyl sulfate (0.9 ml, 9.58 mmol). The crude pale yellow oil (344 mg) was purified by distillation at reduced pressure in a Kugelrohr oven (T_d 140–170 °C at 20 mmHg) yielding a fraction which contained a mixture of 3,4-dimethyl-2-methylthiofuran **38** (88%; spectroscopic yield: 49%) and of 4-methyl-2-methylthiofuran **28** (12%). Spectroscopic data of furan **38**: δ_H(300 MHz, $CDCl_3$) 1.93 (d, 3H, ^{4}J 1.2, 4-Me), 2.00 (d, 3H, ^{5}J 0.6, 3-Me), 2.29 (s, 3H, SMe) and 7.22 (qq, 1H, ^{4}J 1.2, ^{5}J 0.6, 5-H). δ_C(75.5 MHz, $CDCl_3$) 8.4 (q, ^{1}J 126.9, Me), 8.5 (q, ^{1}J 127.6, Me), 18.8 (q, ^{1}J 140.7, SMe), 121.7 (m, C-4), 125.8 (m, C-3), 140.6 (dq, ^{1}J 199.4, ^{3}J 6.1, C-5) and 142.5 (m, C-2).

2-Ethyl-4-methyl-3-methylthiofuran 40

The synthesis was performed as described above for 3-bromo-2-methylthiofuran **18** from diisopropylamine (1.8 ml, 12.8 mmol) in dry THF (14 ml), LiBu^{n} (1.1 M, 11.6 ml, 12.8 mmol), 3-methyl-4-methylthiofuran **25** (1.62 g, 9.62 mmol, over 96% pure) in dry THF (30 ml), and diethyl sulfate (3.4 ml, 25.6 mmol). The crude pale yellow oil (2.84 g) was purified by a flash chromatography (pentane) yielding an oil (225 mg) which was identified as 2-ethyl-4-methyl-3-methylthiofuran **40** from its IR, ^{1}H and ^{13}C NMR spectra. Yield: 13%. Found: C, 61.4; H, 7.7. Calc. for $C_8H_{12}OS$: C, 61.5; H, 7.7%. ν_{max}/cm^{-1} (film) 1730 (comb. ar), 1550 (C–C st), 1450 (C–C st) and 1110 (C–O–C st). δ_H(300 MHz, $CDCl_3$) 1.20 (t, 3H, ^{3}J 7.5, CH_3CH_2), 2.04 (d, 3H, ^{4}J 1.2, 4-CH_3), 2.17 (s, 3H, SMe), 2.75 (q, 2H, ^{3}J 7.5, CH_2CH_3) and 7.12 (q, 1H, ^{4}J 1.2, 5-H). δ_C(75.5 MHz, $CDCl_3$) 8.5 (q, ^{1}J 127.4, CH_3-C4), 12.8 (qt, ^{1}J 127.6, ^{2}J 5.1, CH_3CH_2), 19.6 (q, ^{1}J 139.5, SMe), 19.9 (tq, ^{1}J 127.5, ^{2}J 4.5, CH_2CH_3), 112.3 (m, C-3), 123.1 (m, C-4), 137.0 (dq, ^{1}J 200.5, ^{3}J 6.1, C-5) and 160.0 (q, $^{2}J_{C2,H6} = {}^{3}J_{C2,H5} = 5.9$, C-2).

2,5-Dimethyl-3-phenylthiofuran 41

The synthesis was performed as described above for 3-bromo-2-methylthiofuran **18** from diisopropylamine (1.6 ml, 11.18 mmol) in dry THF (13 ml), LiBu^{n} (1.1 M, 10.2 ml, 11.18 mmol) in hexane, 3-phenylthio-2-methylfuran **22** (1.77 g, 9.32 mmol) in dry THF (20 ml) and dimethyl sulfate (2.1 ml, 22.36 mmol). The crude pale yellow oil was purified by distillation at reduced pressure in a Kugelrohr oven, T_d 65 °C at 0.015 mmHg, yielding an oil (857 mg) which was identified as 2,5-dimethyl-3-phenylthiofuran **41** from its IR, ^{1}H and ^{13}C NMR spectra. Yield: 50%. Found: C, 70.7; H, 6.1. Calc. for $C_{12}H_{12}OS$: C, 70.55; H, 5.9%. ν_{max}/cm^{-1} (film) 3120 (CH st), 3060 (CH st), 1610 (C–C st), 1590 (C–C st), 1480 (C–C st) and 1440 (CH_3). δ_H(300 MHz, $CDCl_3$) 2.26 (dq, 3H, ^{4}J 1.2, ^{6}J 0.5, 5-CH_3), 2.30 (quint., 3H, $^{5}J_{CH_3\text{-}C2,H4} = {}^{6}J_{CH_3\text{-}C2,H6} = 0.5$, 2-$CH_3$), 5.99 (qq, 1H, ^{4}J 1.2, ^{5}J 0.5, 4-H) and 7.15 (m, 5H, SPh). δ_C(75.5 MHz, $CDCl_3$) 11.7 (q, ^{1}J 128.6, CH_3-C5), 13.5 (q, ^{1}J 128.3, CH_3-C2), 107.6 (quint., $^{2}J_{C3,H4} = {}^{3}J_{C2,Me} = 3.4$, C-3), 110.8 (dq, ^{1}J 176.3, ^{3}J 3.5, C-4), 124.9 (dt, ^{1}J 161.5, ^{2}J 7.3, C_{para}), 126.0 (dt, ^{1}J 161.5, ^{2}J 6.8, C_{meta}), 128.7 (dd, ^{1}J 160.2, ^{2}J 8.0, C_{ortho}), 138.2 (t, ^{2}J 9.1, C_{ipso}), 150.6 (dq, ^{2}J 9.4, ^{2}J 6.9, C-5) and 154.9 (q, $^{2}J_{C2,Me} = {}^{3}J_{C2,H4} = 7.1$, C-2).

2,5-Dimethyl-3-methylthiofuran 42

The synthesis was performed as described above for 3-bromo-2-methylthiofuran **18** from diisopropylamine (0.6 ml, 4.11 mmol) in dry THF (5.2 ml), LiBu^{n} (1.05 M, 3.9 ml, 4.11 mmol) in hexane, 2-methyl-3-methylthiofuran **29** (430 mg, 2.86 mmol) and dimethyl sulfate (0.8 ml, 8.22 mmol). The crude pale yellow oil (356 mg) was purified by flash chromatography (pentane) yielding an oil (0.162 mg) which was identified as 2,5-dimethyl-3-methylthiofuran **42** from its IR, ^{1}H and ^{13}C NMR spectra (lit., **42**,[39,73,77]; bp[39] 62–64 °C at 10 mmHg). Yield: 40%. Found: C, 59.0; H, 6.9. Calc. for $C_7H_{10}OS$: C, 59.1; H, 7.1%. ν_{max}/cm^{-1} (film) 1610 (C–C st), 1570 (C–C st) and 1430 (CH_3). δ_H(300 MHz, $CDCl_3$) 2.23 (dq, 3H, ^{4}J 1.1, ^{6}J 0.5, 5-CH_3), 2.24 (s, 3H, SMe), 2.28 (quint., 3H, $^{5}J_{CH_3\text{-}C2,H4} = {}^{6}J_{CH_3\text{-}C2,H6} = 0.5$, 2-$CH_3$) and 5.94 (qq, 1H, 4 J 1.1, ^{5}J 0.5, 4-H). δ_C(75.5 MHz, $CDCl_3$) 11.6 (q, ^{1}J 128.6, CH_3-C2), 13.4 (q, ^{1}J 128.3, CH_3-C5), 19.3 (q, ^{1}J 139.7, SMe), 109.4 (dq, ^{1}J 174.4, ^{3}J 3.6, C-4), 112.3 (m, C-3) and 149.9 (quint., $^{2}J_{C2,Me} = {}^{3}J_{C2,H4} = 8.1$, C-2).

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