Further reactions of furans with trithiazyl trichloride; mechanistic considerations

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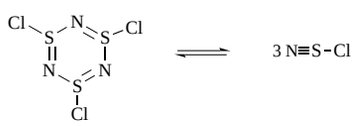
The reaction of 2,5-diarylfurans with trithiazyl trichloride 1 to give 5-aroyl-3-arylisothiazoles in a useful one-step synthesis of isothiazoles has been extended to both weakly and strongly polarised unsymmetrical 2,5-diarylfurans. These react in an entirely analogous manner; the more electron releasing aryl group becomes incorporated into the 5-aroyl group of the isothiazole as the exclusive (strong polarisation) or the major (weak polarisation) product. However, with 3-bromo-2-(4-methoxyphenyl)-5-(4-nitrophenyl)-furan 7, where the more reactive furan β-position is now substituted, this regiospecificity is reversed (to give isothiazole 8). When one of the α-aryl groups in the furan is replaced by methyl the same regiospecific isothiazole formation is now accompanied by some ring and side chain chlorination (15 ⟶ 16 + 17 + 18). All of these results can be explained by mechanisms (Schemes 2 and 5) which involve initial electrophilic attack of the furan to give a β-thiazyl derivative. This highly reactive (nitrenoid) substituent then induces a novel opening of the furan ring 21 to give a highly delocalised intermediate 22 which recyclises to the isothiazole.

Introduction

We have reported the reactions of 2,5-disubstituted furans with trithiazyl trichloride **1**, which is in equilibrium with the mono-



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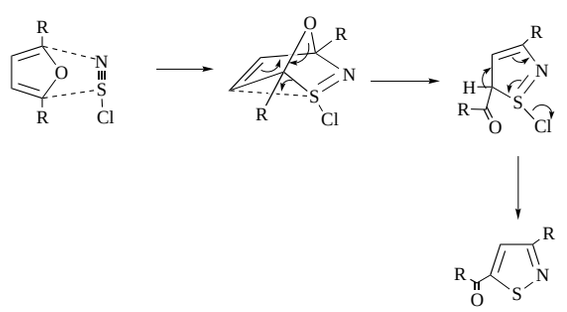
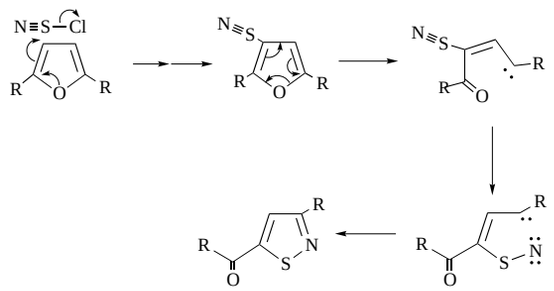
mer, thiazyl chloride N≡S−Cl to give isothiazoles regiospecifically and in good yields under mild conditions.[1] We proposed two possible mechanisms for this reaction, both initiated by the monomer as the reacting species; Diels–Alder cycloaddition of N≡S−Cl across the furan 2,5-positions (Scheme 1) or electro-



Scheme 1

philic substitution, *via* sulfur, at an unsubstituted β-position (Scheme 2). We have now investigated the scope of this reaction further, with emphasis on unsymmetrical furans, including some with alkyl substituents, and we produce evidence favouring the electrophilic substitution mechanism.

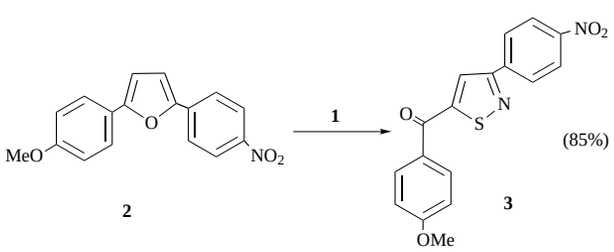
In order to distinguish between the proposed mechanisms, we have treated unsymmetrically 2,5-disubstituted and 2,3,5-trisubstituted furans with trithiazyl trichloride **1**. It was considered that the regiochemistry of these reactions with strongly polarised furans and those with only one free β-position would provide useful mechanistic information. We looked first at polarised 2,5-diarylfurans.



Scheme 2

Unsymmetrical 2,5-diarylfurans with trimer 1

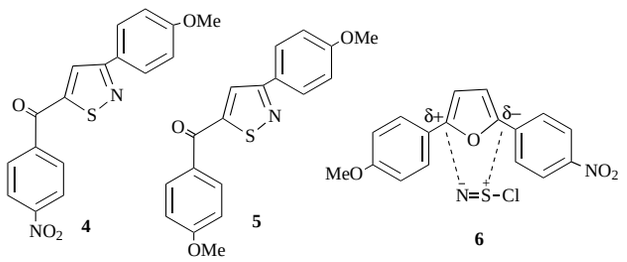
2-(4-Methoxyphenyl)-5-(4-nitrophenyl)furan **2** was synthesised from furan using the classical Gomberg reaction followed by a palladium-catalysed coupling reaction,[2] introducing the methoxyphenyl group first to faciliate the aryl bromide-palladium reaction. 4-Methoxyphenyldiazonium chloride and furan gave 2-(4-methoxyphenyl)furan in low yield (25%)[3] and this was treated with 4-bromonitrobenzene with a catalytic amount of $Pd(Ph_3P)_4$ to give **2** in 59% yield. Treatment of **2** with one equivalent of the trimer **1** in boiling THF cleanly gave one product (**3**) in 85% yield. HRMS and microanalysis indicated the molecular formula $C_{17}H_{12}N_2O_4S$. The ^1H and ^{13}C NMR spectra of the product were consistent with the two possible isomeric isothiazoles **3** and **4**. The IR spectrum showed a strong



2 **3**

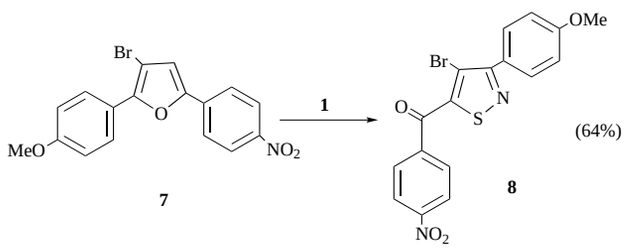
absorption at 1643 cm^{-1}, which is very similar to that of 5-(4-methoxybenzoyl)-3-(4-methoxyphenyl)isothiazole **5** (1645 cm^{-1}); isothiazole **5** was prepared in an analogous reaction between 2,5-bis(4-methoxyphenyl)furan and the trimer **1**.

This supported structure **3** over **4** for the first reaction product, and this was confirmed by comparison of the mass spectra of **3** and **5**, both of which showed a peak at *m*/*z* 135 (100%) for the 4-methoxybenzoyl group. None of the isomer **4** was



observed and the reaction of trimer with furan **2** is highly regioselective. This fits well for the electrophilic substitution mechanism (Scheme 2) since the electron releasing methoxyphenyl group at C-2 and the electron withdrawing nitrophenyl group at C-5 would both strongly direct substitution to C-3, which then leads on to formation of the observed product **3** with the 4-methoxybenzoyl group adjacent to sulfur. The formation of **3** is harder to accommodate on the Diels–Alder mechanism (Scheme 1) since the favoured orientation **6**, based on the polarities of the two components, would lead to the regioisomer **4**, which is not observed.

If electrophilic substitution of furan **2** does occur at C-3 as we propose, then this ring position could be 'blocked' by an alternative electrophilic substitution, such as bromination, and the consequences of this on the trimer reaction observed. We have already shown that 3-bromo-2,5-diphenylfuran reacts with the trimer **1** to give 5-benzoyl-4-bromo-3-phenylisothiazole regioselectively in the standard way, without any rearrangement.[1] Therefore furan **2** was treated with one equivalent of *N*-bromosuccinimide (NBS) to give a monobrominated product for which all the spectroscopic data indicated the expected 3-bromo structure **7**. For example, the ^{1}H NMR spectrum of the



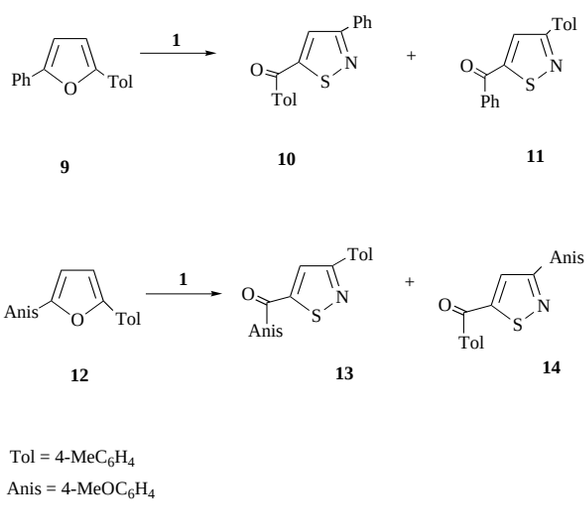
brominated furan **7** showed a singlet at 6.96 ppm, whereas that of the unbrominated compound **2** showed two doublets at 6.67 and 6.94 ppm, corresponding to the ring protons at C-3 and C-4 respectively. 3-Bromo-2-(4-methoxyphenyl)-5-(4-nitrophenyl)furan **7** was then treated with trimer under the same conditions as above (boiling THF). Monitoring by TLC showed the reaction to be considerably slower than that of furan **2**, but after refluxing the reaction mixture for 1 h, chromatography gave a yellow product (**8**) in 64% yield. This had a molecular ion at *m*/*z* 420 with a typical isotope pattern for one bromine. HRMS and microanalysis showed the molecular formula to be $C_{17}H_{11}BrN_2O_4S$. The ^{1}H NMR spectrum showed the absence of a proton on the isothiazole ring and no bromination had occurred in the benzene rings. The mass spectrum showed a fragment peak for 4-nitrobenzoyl and not for 4-methoxybenzoyl, and structure **8** was further supported by the $\nu_{C=O}$ absorption at 1670 cm^{-1} compared with 1643 and 1645 cm^{-1} for the 4-methoxybenzoyl compounds **3** and **5**. Structure **8** was finally confirmed by X-ray crystal structure determination.[4]

Thus, in comparison with the conversion of furan **2** into the isothiazole **3** by trimer, furan **7** has given, more slowly, a product **8** with the regiochemistry reversed. This result fits well for the β-substitution mechanism of Scheme 2, with substitution of the furan by SN at the only available site (C-4). The reaction is distinctly slower because this position is deactivated by the nitrophenyl group.†

As for the Diels–Alder cycloaddition mechanism, product **8** would indeed arise from furan **7** by way of the favoured orientation shown in **6** for the unbrominated furan. However, it is difficult to rationalise the complete reversal of this orientation on passing from furan **2** to furan **7**, as would be required in this mechanism. Bulky substituents at the furan 2,5-positions would also be expected to reduce the rate of cycloaddition more than the rate of β-substitution, yet 2,5-di-*tert*-butylfuran reacts well with the trimer **1** to give the corresponding isothiazole in only slightly reduced yield.[1]

Other 2,5-diarylfurans with trimer 1

We have already seen that highly polarised 2,5-disubstituted furans react with the trimer **1** to give only one isothiazole. We assumed that if the electronic properties of the substituents were more evenly balanced then both isomeric isothiazoles might be formed, and the ratio of these products could shed further light on the reaction mechanism. Therefore 2-(4-methylphenyl)-5-phenylfuran **9** and 2-(4-methoxyphenyl)-5-(4-methylphenyl)furan **12** were prepared by the same method as described above for compound **2**. Methyl and methoxy substituents were chosen to facilitate the determination of the product ratios by ^{1}H NMR spectroscopy. The furans **9** and **12** were treated with one equivalent of the trimer in boiling THF and the expected isothiazoles were obtained in each case (Scheme 3), as shown by HRMS and the other spectral data.



Scheme 3

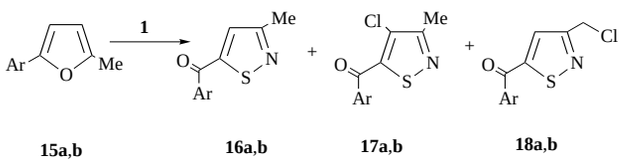
However, the ^{1}H NMR spectra showed that each reaction had indeed given two isomeric products, as chromatographically inseparable mixtures. By careful spectroscopic analysis and comparison with the isothiazoles described above and the 'symmetrical' 5-(4-methylbenzoyl)-3-(4-methylphenyl)isothiazole, the products were shown to be **10** + **11** and **13** + **14** respectively, in ratios of 3.3:1 (56% total yield) and 3.9:1 (65% total yield). Thus in each case the more electron releasing aryl group in the furan becomes part of the 5-aroyl group of the major isothiazole product (Scheme 3). This is in agreement with the reaction of the more highly polarised furan **2** above, where only the 'major' isomer was observed. These results also fit the electrophilic mechanism (Scheme 2) more readily than the cycloaddition mechanism (Scheme 1). For the former, substitu-

† This result argues against another possible mechanism, considered before,[1] which involves electrophilic substitution by NSCl *via* nitrogen at a furan α-position since, although C-5 is activated by the methoxyphenyl group, no products derived from this process were observed.

tion of SN should predominate at the more nucleophilic β position of the furan, adjacent to the more electron releasing group; this group is then incorporated into the aroyl group at the isothiazole 5-position, as shown in Scheme 2. By the same reasoning as before, the orientation which is expected to predominate in the Diels–Alder cycloaddition process (*cf.* **6**) leads, in both cases, to the minor rather than the major isomer. All the furan substituents are sufficiently similar for us to assume that the same mechanism is operating throughout.

2-Aryl-5-methylfurans with trimer 1

To test the generality of this isothiazole synthesis further we studied the reactions of 2-(4-methoxyphenyl)-5-methylfuran **15a** and 2-methyl-5-phenylfuran **15b** with the trimer **1** (1 equiv. in refluxing THF) (Scheme 4). The furans were prepared by the method of Girault *et al*.[5]



15a,**b** **16a**,**b** **17a**,**b** **18a**,**b**

a, Ar = 4-MeOC$_6$H$_4$ **b**, Ar = C$_6$H$_5$

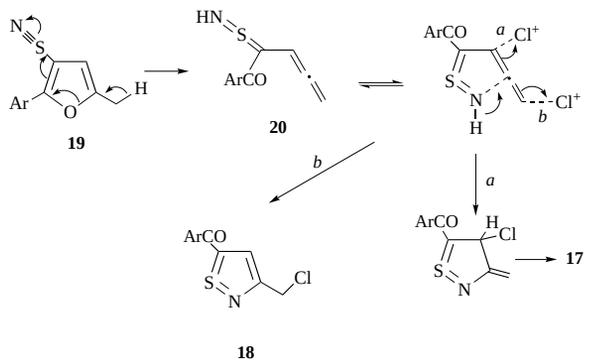
Scheme 4

The furan **15a** gave three products: the expected isothiazole **16a** (33%) and two of its mono-chloro derivatives **17a** and **18a** in approximately equal amounts, in a chromatographically inseparable mixture (28%). HRMS indicated the expected molecular formula of $C_{12}H_{11}NO_2S$ for **16a**, and a strong carbonyl stretch at 1636 cm^{-1} suggested the presence of an aryl ketone rather than an acetyl group. The ^{1}H and ^{13}C NMR spectra were also consistent with structure **16a**. In the mass spectrum of the isomeric mixture (**17a** + **18a**) the molecular ion had the characteristic isotope pattern for one chlorine atom, and the molecular formula (HRMS) was $C_{12}H_{10}ClNO_2S$. The ^{1}H NMR spectrum showed the presence of two compounds, and comparison with the spectrum of **16a** revealed the presence of the ring chlorinated product **17a**; the spectra of **16a** and **17a** were very similar, apart from the absence of the heterocyclic ring proton signal in the latter. The structure of the chloromethyl compound **18a** was determined from the ^{1}H and ^{13}C NMR spectra; a singlet at 7.70 ppm was observed for the isothiazole C-4 proton together with a singlet for the methylene protons at 4.72 ppm which is in the typical range for a chloromethyl group attached to an aromatic system. Analysis of the ^{13}C NMR spectrum of the mixture using the DEPT-135 technique revealed the methylene carbon at 41 ppm. Although the formation of these chloro compounds (**17a**, **18a**) is an added complexity, the isothiazole forming reaction is still highly regioselective since none of the corresponding 5-acetyl-3-arylisothiazoles were observed.

2-Methyl-5-phenylfuran **15b** and trimer **1** gave very similar results (Scheme 4). 5-Benzoyl-3-methylisothiazole **16b** was obtained as an oil in 40% yield, together with an inseparable mixture of the ring chlorination **17b** (29%) and side chain chlorination **18b** (10%) products. Structures were assigned by spectroscopic comparison with the 4-methoxyphenyl compounds.

Thus the reactions of 2-aryl-5-methylfurans with the trimer give isothiazoles, just like 2,5-diarylfurans, and with the same regioselectivity. Again, for the same reasons, these results fit the electrophilic substitution mechanism (Scheme 2) better than the Diels–Alder mechanism (Scheme 1).

For the conversion of the methylfuran **15a** into **16a**, **17a** and **18a**, it was found that the unchlorinated isothiazole **16a** is *not* a precursor of the chlorinated products **17a** and **18a**: treatment of **16a** with excess of trimer in refluxing THF did not yield any observable amount of either **17a** or **18a**. A possible mechanism to account for their formation is proposed, tentatively, in Scheme 5. An alternative mode of ring opening (arrows in **19**) is



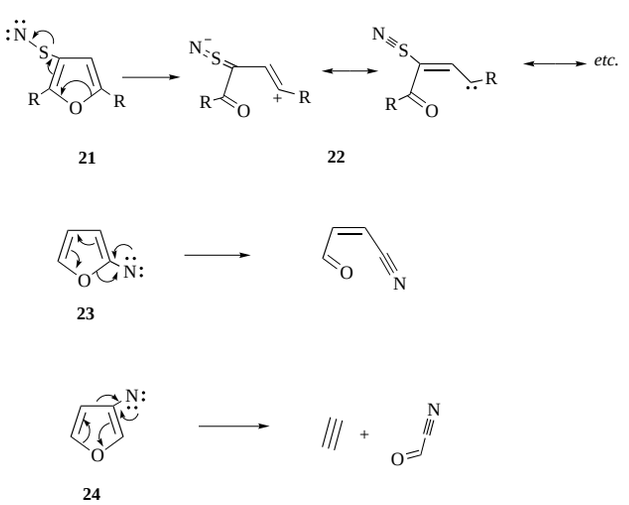
19 **20** **18** **17**

Scheme 5

now available to the initial electrophilic substitution product. This would give the allene **20** which could be intercepted by chlorination (presumably by the trimer **1**) at either terminus; concomitant cyclisation *via* routes *a* and *b* would then give the ring chlorinated **17** and the chloromethylisothiazole **18**. In the analogous reaction of 2,5-di-*tert*-butylfuran with trimer **1** under the same, and more vigorous conditions (refluxing toluene), no ring chlorinated isothiazole product was observed.[1] This lends some support to a mechanism such as that shown in Scheme 5 which involves the reactivity of the furan methyl hydrogen atoms (**19**).

Conclusion

We have shown in this and an earlier paper[1] that the reaction of di- and tri-substituted furans with the trimer **1** provides a direct one-step, regioselective synthesis of isothiazoles. In the presence of a 2-methyl substituent, however, chlorinated by-products are also formed. All of the (qualitative) evidence available so far supports the reaction mechanism shown in Scheme 2. The initially puzzling step in this mechanism is the ready opening of the furan ring once it is substituted by the β-thiazyl group. This is possibly more comprehensible when the nitrenoid contribution **21** to this intermediate is considered.‡ It is proposed that this highly reactive substituent induces a new



21 **22** **23** **24**

‡ We thank a referee for the alternative suggestion that the initially formed nitrene, before proton loss from the ring, could undergo intramolecular cycloaddition to the carbon–carbon double bond of the furan ring, followed by rearrangement to the isothiazole product.

cleavage of the furan ring (arrows in **21**) to give a highly delocalised intermediate **22**. This ring opening reaction is somewhat analogous to the well known cleavage processes[6] that result from the generation of α- and β-nitrenes (and carbenes) in furans and related five-membered heterocyclic rings, as summarised in **23** and **24**.

Experimental

For general details see ref. 1, except that light petroleum refers to the fraction bp 40–60 °C. Flash chromatography refers to the technique described by Still *et al.*[7] using medium pressure by a hand bellows or small air compressor and was used throughout, except where noted otherwise. Dry flash chromatography was carried out with suction using a water pump according to the technique described by Harwood.[8] Merck Kieselgel 60H silica gel was used for flash column chromatography and Merck Kieselgel 25H silica gel was used for dry flash chromatography. Preparative thin layer chromatography was carried out with Whatman K4F silica gel G (40 Å) precoated plates (20 × 20 cm, 250 μm thickness). Commercial aluminium backed thin-layer chromatography (TLC) plates (Merck Kieselgel 60F254) were used. The TLC plates were visualised under UV light at 254 and 350 nm, or by development in iodine vapour.

2-(4-Methoxyphenyl)-5-methylfuran 15a and 2-methyl-5-phenylfuran 15b

2-(4-Methoxyphenyl)-5-methylfuran **15a** was prepared by the method of Ayres and Smith[3] using 4-methoxyaniline (12.3 g, 0.1 mol) and 2-methylfuran (150 ml). Column chromatography of the concentrated extract of the steam distillate on silica with light petroleum–dichloromethane (DCM) (9:1) afforded the title compound as a light yellow solid (2.14 g, 11%), mp 44–45 °C (lit.,[5] 45–46 °C); *m*/*z* 188 (M^+, 95%), 173 (100, M − Me) and 145 (30, M − MeCO).

2-Methyl-5-phenylfuran **15b** was prepared by the same method using aniline (9.3 g, 0.1 mol) and 2-methylfuran (150 ml). Column chromatography of the concentrated extract of the steam distillate on silica with light petroleum–DCM (9:1) afforded 2-methyl-5-phenylfuran as a light yellow solid (2.34 g, 15%), mp 38–39 °C (lit.,[5] 38–39 °C); *m*/*z* 158 (M^+, 100%), 129 (12) and 115 (44, M − MeCO).

2,5-Diarylfurans

General procedure. 2,5-Diarylfurans were synthesized by a modification of the method described by Ohta *et al.* in their synthesis of 2-arylfurans.[2] The 2-arylfuran (1.2 equiv.) was treated with an aryl bromide (1.0 equiv.) in dimethylformamide (DMF) in the presence of tetrakis(triphenylphosphine)-palladium(0) catalyst (5 mol%) and potassium acetate (1.5 equiv.). The mixture was heated at 120 °C for 16 h. The reaction mixture was cooled to room temperature and DMF was removed under reduced pressure. The residue was dissolved in DCM, and the DCM solution was filtered through Celite. The filtrate was washed with water and the DCM solution was dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica with DCM–light petroleum afforded the product.

2-(4-Methoxyphenyl)-5-(4-nitrophenyl)furan 2

2-(4-Methoxyphenyl)furan (418 mg, 2.4 mmol) was treated with 4-bromonitrobenzene (404 mg, 2 mmol) in the presence of tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.1 mmol) and potassium acetate (294 mg, 3 mmol) in DMF (5 ml). Column chromatography on silica with DCM–light petroleum (1:1) gave the *title compound* (353 mg, 59%) as yellow needles, mp 168–170 °C (ethanol) (Found: C, 69.3; H, 4.45; N, 4.7; M^+, 295.0841. $C_{17}H_{13}NO_4$ requires C, 69.15; H, 4.4; N, 4.7%; *M*, 295.0845); ν_{max}(Nujol mull)/cm^{-1} 1604s, 1496s, 1332s and 1257s; δ_H(400 MHz; $CDCl_3$) 8.23 (2H, dt, *J* 9.1, 2.1), 7.80 (2H, dt, *J* 9.1, 2.1), 7.69 (2H, dt, *J* 8.9, 2.1), 6.96 (2H, dt, *J* 8.9, 2.1), 6.94 (1H, d, *J* 3.6, furan 4-H), 6.67 (1H, d, *J* 3.6, furan 3-H) and 3.86 (3H, s, OMe); δ_C(101 MHz; $CDCl_3$) 159.75, 155.76, 150.29, 145.95, 136.40, 128.28, 125.63, 124.38, 123.40, 114.31, 111.50 (furan C-4), 106.36 (furan C-3) and 55.40 (OMe); *m*/*z* 295 (M^+, 82%), 265 (100, M − NO) and 250 (88).

2-(4-Methylphenyl)-5-phenylfuran 9

2-Phenylfuran[3] (346 mg, 2.4 mmol) was treated with 4-bromotoluene (344 mg, 2 mmol) in the presence of the palladium catalyst (116 mg, 0.1 mmol) and potassium acetate (294 mg, 3 mmol) in DMF (5 ml). The title compound (99 mg, 21%) was obtained as a white solid, mp 98–99 °C (lit.,[9] 105.5 °C) (Found: M^+, 234.1045. Calc. for $C_{17}H_{14}O$: *M*, 234.1045); ν_{max}(Nujol mull)/cm^{-1} 1606s, 1499s, 1024s and 928s; δ_H(400 MHz; $CDCl_3$) 7.79–7.76 (2H, m, Ph), 7.67 (2H, d *J* 8.2, *p*-MeC_6H_4), 7.45–7.41 (2H, m, Ph), 7.32–7.27 (1H, m, Ph), 7.24 (2H, d, *J* 8.2, *p*-MeC_6H_4), 6.75 (1H, d, *J* 3.5, furan-H), 6.70 (1H, d, *J* 3.5, furan-H) and 2.40 (3H, s, Me); *m*/*z* 234 (M^+, 100%) and 220 (39, M − CH_2).

2-(4-Methoxyphenyl)-5-(4-methylphenyl)furan 12

2-(4-Methoxyphenyl)furan[3] (835 mg, 4.8 mmol) was treated with 4-bromotoluene (688 mg, 4 mmol) in the presence of the palladium catalyst (232 mg, 0.2 mmol) and potassium acetate (588 mg, 6 mmol) in DMF (8 ml). The *title compound* (315 mg, 30%) was obtained as a white solid, mp 150–152 °C (ethanol) (Found: M^+, 264.1152. $C_{18}H_{16}O_2$ requires *M*, 264.1150); ν_{max}(Nujol mull)/cm^{-1} 1610m, 1502m, 1297m, 1250s, 1177m, 1115m and 1029s; δ_H(400MHz; $CDCl_3$) 7.68 (2H, d, *J* 8.9), 7.63 (2H, d, *J* 8.2), 7.21 (2H, d, *J* 7.9), 6.95 (2H, d, *J* 8.9), 6.66 (1H, d, *J* 3.4, furan-H), 6.59 (1H, d, *J* 3.4, furan-H), 3.85 (3H, s, MeO) and 2.38 (3H, s, Me); *m*/*z* 264 (M^+, 100%), 249 (81, M − Me) and 235 (21).

2,5-Bis(4-methoxyphenyl)furan

2-(4-Methoxyphenyl)furan (835 mg, 4.8 mmol) was treated with 4-methoxybromobenzene (748 mg, 4 mmol) in the presence of the palladium catalyst (232 mg, 0.2 mmol) and potassium acetate (588 mg, 6 mmol) in DMF (8 ml). The *title compound* (278 mg, 25%) was obtained as a white solid, mp 197–198 °C (ethanol) (lit.,[10] 195–196 °C); δ_H(400 MHz; $CDCl_3$) 7.67 (4H, dt, *J* 8.9, 2.5), 6.94 (4H, dt, *J* 8.9, 2.5), 6.58 (2H, s, furan 3-H and 4-H) and 3.84 (6H, MeO); *m*/*z* 280 (M^+, 100%) and 265 (87, M − Me).

3-Bromo-2-(4-methoxyphenyl)-5-(4-nitrophenyl)furan 7

2-(4-Methoxyphenyl)-5-(4-nitrophenyl)furan **2** (295 mg, 1 mmol) and *N*-bromosuccinimide (178 mg, 1 mmol) were dissolved in benzene (10 ml) and heated under reflux for 2 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue on silica with DCM–light petroleum (1:1) afforded the *title compound* (164 mg, 44%) as yellow needles, mp 160–162 °C (ethanol) (Found: C, 54.85; H, 3.3; N, 3.7. $C_{17}H_{12}BrNO_4$ requires C, 54.6; H, 3.2; N, 3.7%); ν_{max}(Nujol mull)/cm^{-1} 1603s, 1516s, 1497s, 1337s and 1259s; δ_H(300 MHz; $CDCl_3$) 8.25 (2H, dt, *J* 9.0, 2.2), 7.98 (2H, dt, *J* 9.0, 2.1), 7.77 (2H, dt, *J* 9.0, 2.3), 7.00 (2H, dt, *J* 9.0, 2.1), 6.96 (1H, s, furan 4-H) and 3.87 (3H, s, OMe); δ_C(76 MHz; $CDCl_3$) 160.00, 150.48, 149.56, 146.61, 135.26, 127.38, 124.42, 123.73, 121.82, 114.94, 114.12, 96.91 and 55.36 (OMe); *m*/*z* 375 (M^+, 100%), 360 (16, M − Me), 345 (32, M − NO) and 329 (29, M − NO_2).

5-(4-Methoxybenzoyl)-3-(4-nitrophenyl)isothiazole 3

To a refluxing solution of 2-(4-methoxyphenyl)-5-(4-nitrophenyl)furan **2** (295 mg, 1 mmol) in THF (10 ml), trithiazyl trichloride **1** (245 mg, 1 mmol) in THF (10 ml) was added dropwise. The mixture was heated under reflux for 30 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the

residue with DCM–light petroleum (1:1) gave the *title compound* (289 mg, 85%) as light yellow needles, mp 158–160 °C (ethanol) (Found: C, 59.7; H, 3.5; N, 8.0; M^+, 340.0523. $C_{17}H_{12}N_2O_4S$ requires C, 60.0; H, 3.55; N, 8.2%; *M*, 340.0518); ν_{max}(Nujol mull)/cm^{-1} 1643vs (C=O), 1598vs, 1519vs and 1386vs; δ_H(300 MHz; $CDCl_3$) 8.32 (2H, dt, *J* 8.9, 2.0), 8.16 (2H, dt, *J* 8.9, 2.0), 8.07 (1H, s, isothiazole 4-H), 8.00 (2H, dt, *J* 8.9, 2.0), 7.04 (2H, dt, *J* 8.9, 2.0) and 3.92 (3H, s, OMe); δ_C(76 MHz; $CDCl_3$) 184.21 (C=O), 166.47, 165.02, 164.43, 148.27, 139.53, 131.90, 129.41, 127.70, 124.47, 124.26, 114.29 and 55.61 (OMe); *m*/*z* 340 (M^+, 15%), 310 (30, M − NO) and 135 (100, $MeOC_6H_4CO$).

4-Bromo-3-(4-methoxyphenyl)-5-(4-nitrobenzoyl)isothiazole 8

To a refluxing solution of 3-bromo-2-(4-methoxyphenyl)-5-(4-nitrophenyl)furan **7** (188 mg, 0.5 mmol) in THF (10 ml), trithiazyl trichloride **1** (122 mg, 0.5 mmol) in THF (5 ml) was added dropwise. The mixture was heated under reflux for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue with DCM–light petroleum (1:1) gave the *title compound* (134 mg, 64%) as yellow needles, mp 134–135 °C (ethanol) (Found: C, 48.6; H, 2.65; N, 6.7; M^+, 419.9620. $C_{17}H_{11}BrN_2O_4S$ requires C, 48.7, H, 2.6; N, 6.7%; *M*, 419.9602); ν_{max}(Nujol mull)/cm^{-1} 1670vs (C=O), 1526vs and 1393vs; δ_H(400 MHz; $CDCl_3$) 8.38 (2H, dt, *J* 8.9, 2.2), 8.09 (2H, dt, *J* 8.9, 2.2), 7.82 (2H, dt, *J* 8.9, 2.2), 7.01 (2H, dt, *J* 8.9, 2.2) and 3.88 (3H, s, OMe); δ_C(101 MHz; $CDCl_3$) 185.60 (C=O), 166.85, 160.92, 158.14, 150.85, 140.70, 130.88, 130.51, 125.74, 124.06, 113.81, 109.56 and 55.38 (OMe); *m*/*z* 420 (M^+, 23%), 390 (11, M − NO), 150 (9, $O_2NC_6H_4CO$), 133 (9, $MeOC_6H_4CN$) and 120 (100).

5-(4-Methoxybenzoyl)-3-(4-methoxyphenyl)isothiazole 5

To a refluxing solution of 2,5-bis(4-methoxyphenyl)furan (280 mg, 1 mmol) in refluxing THF (10 ml), trithiazyl trichloride **1** (245 mg, 1 mmol) in THF (10 ml) was added dropwise. The mixture was heated under reflux for 30 min. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue with DCM–light petroleum (1:1) gave the *title compound* (189 mg, 58%) as a light yellow oil (Found: M^+, 325.0764. $C_{18}H_{15}NO_3S$ requires *M*, 325.0773); ν_{max}(neat)/cm^{-1} 1645vs (C=O), 1600s and 1507s; δ_H(400 MHz; $CDCl_3$) 8.00 (2H, dt, *J* 8.9, 2.9), 7.93 (1H, s, isothiazole 4-H), 7.92 (2H, dt, *J* 8.9, 2.9), 7.02 (2H, dt, *J* 8.9, 2.9), 6.98 (2H, dt, *J* 8.9, 2.9), 3.91 (3H, s, OMe) and 3.86 (3H, s, OMe); δ_C(101 MHz; $CDCl_3$) 184.91 (C=O), 167.47, 164.97, 164.18, 160.76, 131.91, 129.84, 128.38, 127.19, 123.98, 114.28, 114.15, 55.64 (OMe) and 55.39 (OMe); *m*/*z* 325 (M^+, 36%) and 135 (100, $MeOC_6H_4CO$).

Reaction of 2-(4-methylphenyl)-5-phenylfuran 9 with trithiazyl trichloride 1

To a refluxing solution of 2-(4-methylphenyl)-5-phenylfuran **9** (100 mg, 0.43 mmol) in THF (5 ml), trithiazyl trichloride **1** (105 mg, 0.43 mmol) in THF (5 ml) was added dropwise. The mixture was heated under reflux for 30 min. The mixture was then cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue on silica with DCM–light petroleum (1:1) gave a 3.3:1 mixture of two inseparable isomers **10** and **11** (65 mg, 56%) as a colourless oil (Found: M^+, 279.0722. $C_{17}H_{13}NOS$ requires *M*, 279.0719); ν_{max}(neat)/cm^{-1} 1651vs (C=O), 1605s, 1274s and 1182; δ_H(400 MHz; $CDCl_3$), the major isomer, 5-(4-*methylbenzoyl*)-3-*phenylisothiazole* **10**, 8.025 (1H, s, isothiazole 4-H), 8.01–7.98 (2H, m, Ph), 7.92 (2H, d, *J* 8.2, Tol), 7.59–7.56 (1H, m Ph), 7.51–7.44 (2H, m, Ph), 7.37 (2H, d, *J* 7.9, Tol) and 2.49 (3H, s, Me); the minor isomer, 5-*benzoyl*-3-(4-*methylphenyl*)*isothiazole* **11**, 8.03 (1H, s, isothiazole 4-H), 8.01–7.98 (2H, m, Ph), 7.88 (2H, d, *J* 8.2, Tol), 7.70–7.68 (1H, m, Ph), 7.51–7.44 (2H, m, Ph), 7.29 (2H, d, *J* 7.9, Tol) and 2.42 (3H, s, Me); δ_C(101 MHz; $CDCl_3$) 186.22 (C=O), 185.84 (C=O) 167.88, 167.76, 165.06, 164.84, 144.73, 139.77, 134.41, 134.06, 133.61, 133.56, 129.63, 129.58, 129.50, 129.46, 129.24, 128.88, 128.81, 126.85, 126.76, 124.75, 124.64, 124.56, 21.70 (Me) and 21.34 (Me); *m*/*z* 279 (M^+, 49%), 265 (38, M − CH_2), 202 (3, M − Ph), 188 (18, M − MeC_6H_4), 176 (2, M − PhCN), 160 (4, M − MeC_6H_4CO), 119 (82, MeC_6H_4CO), 105 (100, PhCO), 91 (40, MeC_6H_4) and 77 (90, Ph).

Reaction of 2-(4-methoxyphenyl)-5-(4-methylphenyl)furan 12 with trithiazyl trichloride 1

To a refluxing solution of the 2-(4-methoxyphenyl)-5-(4-methylphenyl)furan **12** (135 mg, 0.5 mmol) in THF (5 ml), trithiazyl trichloride **1** (122 mg, 0.5 mmol) in THF (5 ml) was added dropwise. The mixture was heated under reflux for 30 min. The mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue on silica with DCM–light petroleum (1:1) gave a 3.9:1 mixture of two inseparable isomers **13** and **14** as a white solid (102 mg, 65%) (Found: M^+, 309.0822. $C_{18}H_{15}NO_2S$ requires *M*, 309.0824); ν_{max}(Nujol mull)/cm^{-1} 1645vs (C=O), 1597s and 1385s; δ_H(500 MHz; $CDCl_3$), the major isomer, 5-(4-*methoxybenzoyl*)-3-(4-*methylphenyl*)*isothiazole* **13**, 8.00 (2H, dt, *J* 8.9, 2.0), 7.96 (1H, s, isothiazole 4-H), 7.86 (2H, d, *J* 8.2), 7.27 (2H, d, *J* 8.2), 7.02 (2H, dt, *J* 8.9, 2.0), 3.91 (3H, s, OMe) and 2.40 (3H, s, Me); the minor isomer, 5-(4-*methylbenzoyl*)-3-(4-*methoxyphenyl*)*isothiazole* **14**, 8.00 (2H, m), 7.93 (1H, s, isothiazole 4-H), 7.90 (2H, dt, *J* 8.9, 2.1), 7.34 (2H, d, *J* 8.0), 6.98 (2H, dt, *J* 8.5, 2.0), 3.86 (3H, s, OMe) and 2.47 (3H, s, Me); δ_C(126 MHz; $CDCl_3$) 185.95 (C=O), 184.78 (C=O), 167.77, 167.52, 165.27, 165.04, 164.13, 160.74, 144.67, 139.71, 131.84, 131.53, 129.71, 129.58, 129.49, 129.47, 128.90, 128.31, 126.90, 126.79, 124.27, 124.17, 114.23, 114.10, 55.57 (OMe), 55.31 (OMe), 21.70 (Me) and 21.31 (Me); *m*/*z* 309 (M^+, 37%), 295 (9, M − CH_2), 202 (2, M − $MeOC_6H_4$), 192 (3, M − MeC_6H_4CN), 174 (1, M − $MeOC_6H_4CO$), 135 (100, $MeOC_6H_4CO$), 119 (16, MeC_6H_4CN), 107 (7, $MeOC_6H_4$) and 91 (12, MeC_6H_4).

Reaction of 2-(4-methoxyphenyl)-5-methylfuran 15a with trithiazyl trichloride 1

To a refluxing solution of 2-(4-methoxyphenyl)-5-methylfuran **15a** (376 mg, 2 mmol) in THF (15 ml), trithiazyl trichloride **1** (489 mg, 2 mmol) in THF (15 ml) was added dropwise. The mixture was heated under reflux; after 15 min no starting material **15a** was observed (TLC). The mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue on silica with DCM–light petroleum (3:1) gave a 1:1 mixture of 4-*chloro*-5-(4-*methoxybenzoyl*)-3-*methylisothiazole* **17a** and 3-*chloromethyl*-5-(4-*methoxybenzoyl*)*isothiazole* **18a** as a brown oil (145 mg, 27%) (Found: M^+, 267.0100. $C_{12}H_{10}ClNO_2S$ requires *M*, 267.0121); ν_{max}(neat)/cm^{-1} 1651vs (C=O), 1599s, 1573s, 1510s, 1422, 1314s, 1261s and 1171s; δ_H(400 MHz; $CDCl_3$) 7.94 (2H, dt, *J* 9.0, 2.5, 2′-H), 7.88 (2H, dt, *J* 9.0, 2.5, 2′-H), 7.70 (1H, s, isothiazole 4-H, **18a**), 7.00 (2H, dt, *J* 9.0, 2.1, 3′-H), 6.97 (2H, dt, *J* 9.0, 2.1, 3′-H), 4.72 (2H, s, CH_2Cl, **18a**), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe) and 2.52 (3H, s, Me, **17a**); δ_C(126 MHz; $CDCl_3$) 184.69 (C=O), 184.28 (C=O), 166.00, 165.84, 164.77, 164.63, 164.26, 155.86, 132.42, 131.86, 129.28, 129.14, 126.18, 123.55, 114.16, 114.08, 55.59 (OMe), 41.04 (CH_2Cl, **18a**) and 17.53 (Me, **17a**); *m*/*z* 267 (M^+, 18%), 135 (100, $MeOC_6H_4CO$) and 77 (20, Ph). Further elution with DCM afforded 5-(4-*methoxybenzoyl*)-3-*methylisothiazole* **16a** as a light brown solid (154 mg, 33%), mp 81–83 °C (DCM–light petroleum) (Found: M^+, 233.0509. $C_{12}H_{11}NO_2S$ requires *M*, 233.0511); ν_{max}(Nujol mull)/cm^{-1} 1636vs (C=O), 1597vs, 1509vs and 1261vs; δ_H(400 MHz; $CDCl_3$) 7.96 (2H, dt, *J* 8.9, 2.5, 2′-H), 7.43 (1H, s, isothiazole 4-H), 7.00 (2H, dt, *J* 8.9, 2.5, 3′-H), 3.90 (3H, s, OMe) and 2.57 (3H, s, Me); δ_C(126 MHz; $CDCl_3$) 184.90 (C=O), 167.21, 164.48,

164.07, 131.85, 129.78, 127.17, 114.03, 55.59 (OMe) and 19.05 (Me); *m*/*z* 233 (M^+, 35%), 192 (3, M – MeCN) and 135 (100, $MeOC_6H_4CO$).

Reaction of 2-methyl-5-phenylfuran 15b with trithiazyl trichloride 1

To a refluxing solution of the furan **15b** (316 mg, 2 mmol) in THF (15 ml), trithiazyl trichloride **1** (489 mg, 2 mmol) in THF (15 ml) was added dropwise. The mixture was heated under reflux; after 15 min, no starting material **15b** was observed (TLC). The mixture was cooled to room temperature and concentrated under reduced pressure. Column chromatography of the residue on silica with DCM–light petroleum (75:25) gave a 3:1 mixture of 5-*benzoyl*-4-*chloro*-3-*methylisothiazole* **17b** and 5-*benzoyl*-3-*chloromethylisothiazole* **18b** as a brown oil (187 mg, 39%) (Found: M^+, 237.0016. $C_{11}H_8ClNOS$ requires *M*, 237.0015); ν_{max}(neat)/cm^{-1} 1661vs (C=O), 1635vs, 1607vs and 1283vs; δ_H(400 MHz; $CDCl_3$) 7.91–7.85 (2H, m, **17b** and **18b**), 7.71 (1H, s, isothiazole 4-H, **18b**), 7.65–7.61 (1H, m, **17b** and **18b**), 7.53–7.47 (2H, m, **17b** and **18b**), 4.70 (2H, s, CH_2Cl, **18b**) and 2.51 (3H, s, Me, **17b**); δ_C(126 MHz; $CDCl_3$) 186.06 (C=O), 185.74 (C=O), 166.01, 165.48, 165.01, 155.14, 136.55, 136.32, 134.15, 134.09, 133.69, 129.64, 129.17, 128.78, 128.69, 126.69, 40.94 (CH_2Cl, **18b**) and 17.48 (Me, **17b**); *m*/*z* 237 (M^+, 18%), 160 (7, M − Ph), 105 (100, PhCO) and 77 (46, Ph).

Further elution with DCM gave 5-*benzoyl*-3-*methylisothiazole* **16b** as a light brown solid (163 mg, 40%), mp 28–30 °C (DCM–light petroleum) (Found: M^+, 203.0411. $C_{11}H_9NOS$ requires *M*, 203.0405); ν_{max}(Nujol mull)/cm^{-1} 1657vs (C=O), 1598vs and 1402vs; δ_H(400 MHz; $CDCl_3$) 7.91–7.87 (2H, m), 7.63–7.59 (1H, m), 7.50–7.46 (2H, m), 7.41 (1H, s, isothiazole 4-H) and 2.53 (3H, s, Me); δ_C(126 MHz; $CDCl_3$) 186.22 (C=O), 167.32, 163.98, 136.95, 133.40, 129.11, 128.62, 127.59 and 18.93 (Me); *m*/*z* 203 (M^+, 38%), 162 (5, M − MeCN), 126 (32, M − Ph), 105 (100, PhCO) and 77 (69, Ph).

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