Reaction of furans with trithiazyl trichloride: new synthesis of isothiazoles

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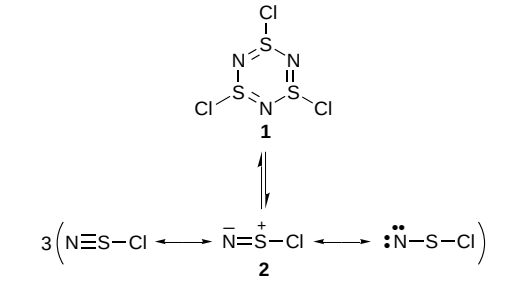
Trithiazyl trichloride 1 converts 2,5-disubstituted furans into isothiazoles (*e.g.* 3, 6, 7) regiospecifically and in good yield, providing a new, one-step synthesis of isothiazoles, for which a novel mechanism involving formation and ring-opening of a β-thiazylfuran 4 is proposed.

Trithiazyl trichloride **1**[1] is a stable but moisture-sensitive, yellow crystalline solid, prepared by heating ammonium chloride and sulfur with disulfur dichloride, and chlorination of the resulting salt, $S_3N_2Cl_2$.[2] The cyclic trimer **1** is in thermal equilibrium with the highly reactive monomer, thiazyl chloride **2** (Scheme 1). It is reactive towards many simple organic substrates and has considerable potential in the synthesis of sulfur-nitrogen compounds.[3]

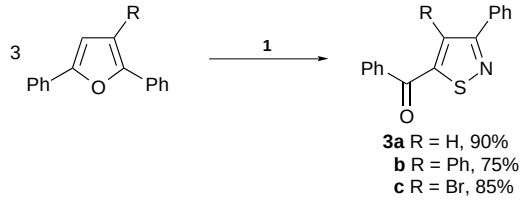
We thought that the monomer **2** might be selectively intercepted by furans in a Diels–Alder reaction.[4] Trithiazyl trichloride **1** reacted very cleanly with 2,5-diphenylfuran in boiling CCl_4, converting 3 equiv. into 5-benzoyl-3-phenylisothiazole **3a** in high yield (90%) (Scheme 2). 2,3,5-Triphenylfuran and 3-bromo-2,5-diphenylfuran reacted similarly to give the analogous isothiazoles **3b** (75%) and **3c** (85%). No isomers of the products were detected and so cleavage of the furan ring and incorporation of the S–N unit is apparently regiospecific. This represents a new opening of the furan ring and a new, mild, one-step synthesis of isothiazoles. Closely related, but fully substituted furans, such as 3,4-dibromo-2,5-diphenyl- and 3-bromo-2,4,5-triphenyl-furan did not react with the reagent **1**; clearly a ring hydrogen is required for the formation of HCl, which is evolved during the reactions. 2,5-Bis-(4-methylphenyl)-, 2,5-bis(4-methoxyphenyl)- and 2,5-di-*tert*-butylfuran all gave the analogous isothiazoles in boiling CCl_4 or toluene, although in somewhat lower yields (50–60%).

All of these products could have been formed by Diels–Alder reactions with thiazyl chloride **2**, followed by rearrangement of the adduct with loss of HCl,[3] but the above results led us to consider an alternative mechanism. This is based upon electrophilic substitution of the furan ring at an unsubstituted β-position to give a β-thiazyl derivative **4**, which could then rearrange to the isothiazole by a ring-opening, ring-closing mechanism (Scheme 3). We hoped to distinguish between these mechanisms by reacting the trimer **1** with polarised, unsymmetrical 2,5-disubstituted and 2,3,5-trisubstituted furans.

2-(4-Methoxyphenyl)-5-(4-nitrophenyl)furan **5a** in boiling THF gave 5-(4-methoxybenzoyl)-3-(4-nitrophenyl)isothiazole **6** (85%) very cleanly and regiospecifically (Scheme 4). This agreed well with the substitution mechanism (Scheme 3) since the aryl groups at C-2 and C-5 would strongly direct electrophilic attack to C-3, which leads to the observed isomer **6**. However, this result is harder to reconcile with the Diels–Alder mechanism since the expected orientation, based on the polarities of the furan **5a** and thiazyl chloride ($N^+{=}S^-{-}Cl$) would most reasonably lead to the undetected isothiazole isomer. The more nucleophilic furan ring position (C-3) of **5a** was then 'blocked' by bromination to give **5b**, which was treated with the trimer **1** under the same conditions. The reaction of **5b** was considerably slower than that of **5a**, but it too gave only one product, 4-bromo-2-(4-methoxyphenyl)-5-(4-nitrobenzoyl)isothiazole **7** (65%) with the *opposite* regiochemistry. This follows from the substitution mechanism, where the thiazyl substituent is introduced at the only available (deacti-

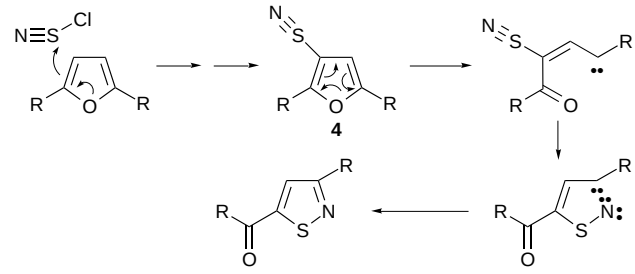


Scheme 1

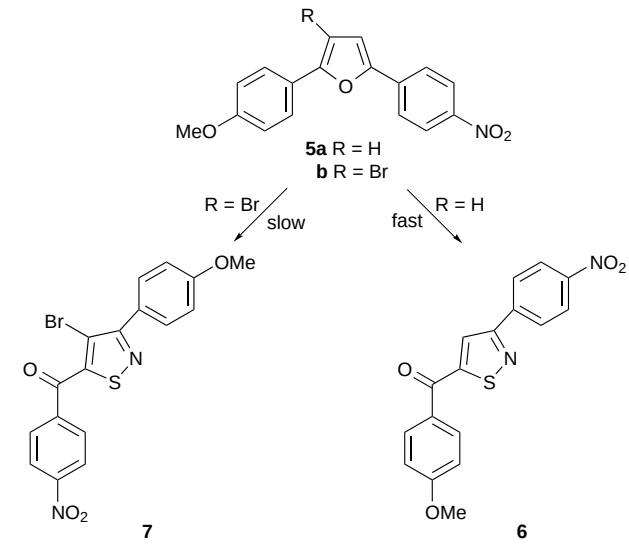


3a R = H, 90%
b R = Ph, 75%
c R = Br, 85%

Scheme 2



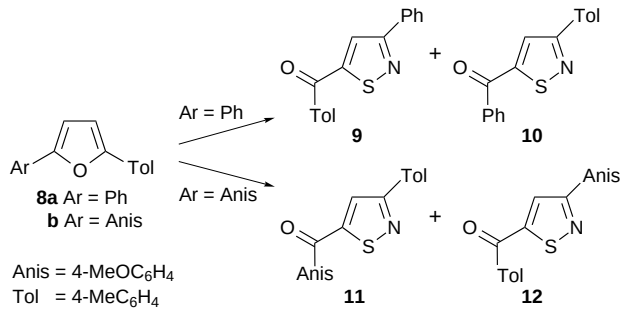
Scheme 3



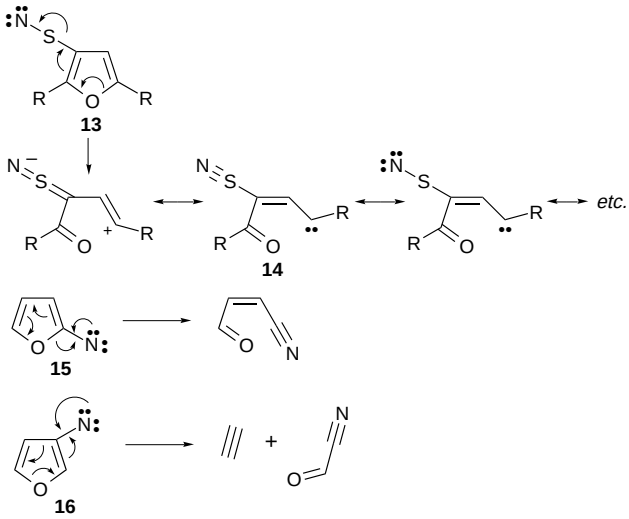
Scheme 4

vated) site, which leads to the observed isomer (Scheme 3). The Diels–Alder mechanism would require the complete reversal of orientation of cycloaddition, on passing from furan **5a** to **5b**, which seems unlikely.

Each of these highly polarised furans gave only one isothiazole; it seemed likely that if the degree of polarisation was reduced both possible isomeric isothiazoles might be formed, and this proved to be so. Thus 2-(4-methylphenyl)-5-phenylfuran **8a** and 2-(4-methoxyphenyl)-5-(4-methylphenyl) furan **8b** were treated with the trimer in boiling THF



Scheme 5



Scheme 6

(Scheme 5). Detailed analysis of the ^{1}H NMR spectra showed that each gave mixtures of two isomeric isothiazoles which were inseparable by chromatography; these were **9** and **10** (3.3 : 1) (56%) and **11** and **12** (3.9 : 1) (65%) respectively. Thus in each case the more electron-releasing aryl group in the furan becomes part of the 5-aroyl group of the major isomer, in agreement with the reaction of the more highly polarised furan **5a**, where only the 'major' isomer was observed. On the mechanism of Scheme 3, substitution of SN should predominate at the ring position adjacent to the more electron-releasing group, which then transforms into the 5-aroyl group, as observed. The expected orientation in the Diels–Alder reaction would have led to the minor rather than the major isomer.

From all this evidence we favour the mechanism of Scheme 3. The initially puzzling step, ready opening of the β-thiazyl furan ring, is comprehensible when the nitrenoid character **13** of this intermediate is considered. The highly reactive thiazyl substituent could induce cleavage of the furan ring (arrows in **4** ≡ **13**) to give the delocalised intermediate **14** which then collapses to the isothiazole (Scheme 6). This unusual ring-opening is somewhat analogous to the well established cleavage reactions of nitrenes (and carbenes) directly attached to furan and other five-membered heterocyclic rings (*cf.* **15** and **16**).[5]

The structures of all the new compounds reported here are based on a detailed analysis and comparison of their spectra, particularly NMR and mass spectra, with model compounds. These data, and syntheses of the compounds, will be presented in a full paper.

We thank Zeneca Specialities, the Commonwealth Scholarship Commission and MDL Information Systems (UK) Ltd for financial support, and the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College.

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Received, 12th December 1996; Com. 6/08345E