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Neighbouring Group Effects on Rates of Thermolysis of 4-Azidothiazoles

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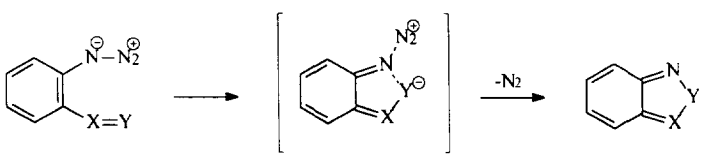
Dedicated to the memory of Prof. Gerrit L'abbé, who passed away unexpectedly while we were finishing this work.

Abstract: Rate measurements for thermolysis of 4-azidothiazoles in *p*-xylene solution have identified neighbouring group effects from nitro (19-fold rate increase), phenyliminomethyl (16), formyl (4.5) and acetyl (2.2) substituents in the 5-position. These effects are very similar in magnitude to those measured for 3-azidothiophenes, whereas in azidobenzenes the rate increases are much larger. 5-Substituents in 4-azidothiazole which are capable of conjugative donation (phenyl, ethyl propenoate) also increased the reaction rate. The reactions involving neighbouring group participation led to cyclized products from the 4-azidothiazoles though not all of these products were stable under the thermolysis conditions.

INTRODUCTION

When azidobenzenes are thermolysed in solution, *ortho* substituents such as acetyl and nitro increase the rate substantially, by 413- and 1060-fold, respectively.[1] These neighbouring group effects have been rationalized[2,3] in terms of a cyclic transition state (**1** in Scheme 1). One feature of this mechanism is that the negatively-charged terminal atom of the neighbouring group donates an electron pair to make a bond to the innermost of the three azido nitrogen atoms.



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Scheme 1

In a previous paper[4] we reported studies of the 3-azidothiophenes. The thermal reactions were already known to lead to cyclic products, analogous to Scheme 1, when the 2-substituent was formyl[5] or nitro,[6,7,8] but it had not been established whether the ring hetero-atom affected the ability of these 2-substituents to enhance the reaction rate. It was, however, known[9] that 3-azidothiophene thermolyses 31

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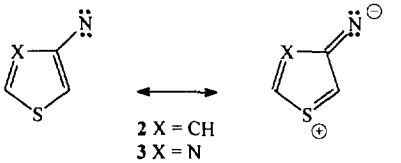
times faster than azidobenzene, and we attributed this result to substantial charge transfer from the ring sulfur atom to the partly-developed nitrene centre in the transition state. Structure **2** shows this transfer for the fully-developed nitrene.



2 X = CH
3 X = N

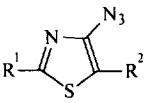
Our work[4] with 2-substituted-3-azidothiophenes revealed that neighbouring group effects on rate are quite small, being only 5- and 17-fold for acetyl and nitro, respectively. This outcome can be interpreted in terms of the transition state stabilizations represented by **1** and **2**. In **2** the nitrenoid nitrogen atom should bear appreciable negative charge whereas in **1** it is important that it should not; thus the two stabilizations cannot be additive.

In view of the dramatic change in neighbouring group effects between azidobenzenes and 3-azidothiophenes, we now turn our attention to 4-azidothiazoles **3**, in which the additional ring nitrogen may modify the influence of the ring sulfur atom on the neighbouring group effects exerted by 5-substituents. We have studied both reaction rates and products for these thermolyses of 4-azidothiazoles.

DISCUSSION

Rates of thermolysis

The 4-azidothiazoles **3a-h** were synthesized, and have been characterized by means of ^1H and ^{13}C NMR, IR, and mass spectra (see Experimental). All these azides decomposed slowly when heated in *p*-xylene at 80°C, the kinetic behaviour being cleanly first-order. The first-order rate constants are listed in Table 1.



3a : R^1 = Ph, R^2 = CN
3b : R^1 = Ph, R^2 = CHO
3c : R^1 = Ph, R^2 = COMe
3d : R^1 = Ph, R^2 = CH=NPh
3e : R^1 = Ph, R^2 = NO_2
3f : R^1 = R^2 = Ph
3g : R^1 = Ph, R^2 = (E)-CH=$CHCO_2Et$
3h : R^1 = H, R^2 = CHO

By analogy with the behaviour of azidobenzenes,[1] neighbouring group effects can be expected for those 4-azidothiazoles whose 5-substituents are formyl (**3b**), acetyl (**3c**), phenyliminomethyl (**3d**),

Table 1. First-Order Rate Constants for Thermal Decomposition of 4-Azidothiazoles in p-Xylene at 80.0°C

Azide	2-Substituent	5-Substituent	$10^5k_1/s^{-1}$	k_{rel}
3a	Ph	CN	0.160	1
3b	Ph	CHO	0.723[A]	4.52
3c	Ph	$COCH_3$	0.352[B]	2.20
3d	Ph	CH=NPh	2.16	16.3
3e	Ph	NO_2	3.06	19.1
3f	Ph	Ph	1.09	6.8
3g	Ph	(E)-CH=CHCO_2Et	2.62	16.4
3h	H	CHO	0.504	-

[A] The decay of the carbonyl band gave $10^5k_1 = 0.720\ s^{-1}$.
[B] The decay of the carbonyl band gave $10^5k_1 = 0.336\ s^{-1}$.

and nitro (**3e**). The parent compound, 4-azido-2-phenylthiazole, is not available for lack of a suitable precursor, but the 5-cyano derivative **3a** provides a suitable reference rate. The cyano group cannot, because of its linear geometry, provide the bridging bond in the transition state depicted in Scheme 1, but it does exert inductive and resonance effects similar to those of the four neighbouring groups listed above. In 3-azidothiophenes, it is known that a 2-cyano group speeds up the thermolysis by a very small factor (1.5-fold)[4], and in azidobenzene by 1.8-fold.[1]

The rate constants in p-xylene at 80°C relative to 4-azido-5-cyano-2-phenylthiazole are shown in Table 1. All the potentially effective neighbouring groups have caused significant rate enhancements, which are quite small for formyl and acetyl but, appreciable (16.3 and 19.1) for phenyliminomethyl and nitro, respectively. These neighbouring group effects are also measured in decalin solution at 120°C (Table 2), so that comparison can be made with the published data for both azidobenzenes[1] and 3-azidothiophenes[4] (see Table 3). The 3-azidothiophenes are the only other family of β-azidoheterocycles for which data exist. Some new data for this family appear in Table 4.

Table 2 First-Order Rate Constants for Thermal Decomposition of 4-Azido-2-phenylthiazoles in Decalin at 120.0°C

Azide	5-Substituent	Azide band used (cm^{-1})	Inhibitor[A] mol/mol azide	$10^4k_1/s^{-1}$	k_{rel} (mean)
3a	CN	2124	7	1.66	1
3b	CHO	2125	4	6.91	4.16
3c	COMe	2117	3	3.81	2.30
		2138	3	3.83	
3d	CH=NPh	2124	3	14.6	8.80
3e	NO_2	2125	5	18.6	11.0
		2162	5	17.8	

[A] The radical chain inhibitor was 2,6-di-*tert*-butyl-4-methylphenol

Table 3 Comparison of the Neighbouring Group Effects on Rates of Thermolysis of 4-Azidothiazoles, 3-Azidothiophenes and Azidobenzenes

Parent azide	Conditions	α-Substituents and k_{rel} values				
		2-CN	2-CHO	2-Ac	2-CH=NPh	2-NO_2
Azidobenzene[A]	decalin 120°C	1	16.2	232	33.8	596
		5-CN	5-CHO	5-Ac	5-CH=NPh	5-NO_2
4-Azido-2-phenylthiazole	*p*-xylene 80°C	1	4.6	2.5	16	19
	decalin 120°C	1	4.2	2.3	8.8	11
3-Azidothiophene[B]		2-CN	2-CHO	2-Ac	2-CH=NPh	2-NO_2
	decalin 120°C	1	3.7	3.3	7.9	11.6

[A] Data from reference 1.
[B] Data from reference 4 or the present paper (Table 4).

The comparison of relative rates made in Table 3 draws attention to two factors. The first factor is that neighbouring group effects are generally much smaller in the two families of β-azido heterocycles than they are in azidobenzenes. That the effects are small has already been explained by us for the 3-azidothiophenes[4] and is outlined in terms of the structures **1** and **2** in the Introduction. This explanation readily extends to the 4-azidothiazoles. The other factor is that the order of neighbouring group abilities in azidobenzene thermolyses (nitro > acetyl > phenyliminomethyl > formyl) differs from the one we find for β-azidoheterocycles (nitro > phenyliminomethyl > formyl > acetyl). The reason for this is still unclear.

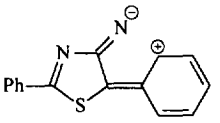
It will be noted (Table 1) that the 2-substituent has little influence on the reaction rate for 4-azidothiazole-5-carbaldehydes (compare azides **3b** and **3h**).

Table 1 also presents data for two 5-substituents (phenyl and ethyl propenoate) which are not likely to act as neighbouring groups in the manner implied by Scheme 1, but which do increase the reaction rate. These increases probably represent additional stabilization of the nitrenothiazoles (see structures **4** and **5**). We have recently drawn attention to this kind of stabilization for the transition states in the thermolysis of 2-methoxyazidobenzene and 2-(methylthio)azidobenzene.[10]

Table 4 Rate Constants at 120.0°C for Thermolysis of some 2-Substituted-3-Azidothiophenes

Substituent in 3-azidothiophene	Solvent	Inhibitor[A] mol/mol azide	$10^4 k_1/s^{-1}$
2-CH=NPh	decalin	3.0	8.91
2-CHO	decalin	3.7, 2.5	4.23, 4.17
	p-xylene	0	4.92, 4.53

[A] The radical chain inhibitor was 2,6-di-*tert*-butyl-4-methylphenol.



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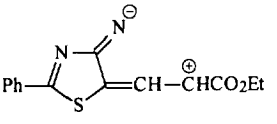

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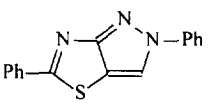
Finally, we can compare rates for 3-azidothiophenes and 4-azidothiazoles. At this moment, 4-azidothiazole is not a known compound. However, there are rates available for 2-cyano-3-azidothiophene (k_1 = 1.13 x 10^{-4} s^{-1} , decalin solvent at 120°C)[4] and 4-azido-5-cyano-2-phenylthiazole (k_1 = 1.66 x 10^{-4} s^{-1}, same conditions). The phenyl group in the latter compound possibly exerts some minor influence, but in approximate terms we can say there is little difference in rate. We have already seen that the neighbouring group effects are very similar in these two families of β-azidoheterocycles. Thus, one must conclude that modifying the thiophene ring into a thiazole ring has made very little difference to the thermal behaviour of these β-azides.

Products of thermolysis

In view of the significant level of neighbouring group participation which has been identified in the kinetic studies, one would expect bicyclic thermolysis products to be obtained (see Scheme 1 for analogy). Iddon and coworkers[11] have already reported two examples of 4-azido-5-(tolyliminomethyl)thiazoles yielding 2*H*-pyrazolo[3,4-d]thiazoles in good yield, and we now report a similar cyclization from 2-phenyl-5-phenyliminomethyl-4-azidothiazole **3d** to yield compound **6**. In a similar way, the azide **3f** was cyclized to give the tricyclic product **7**.



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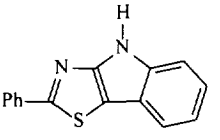

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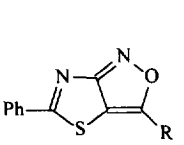
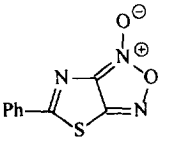
Attempts to obtain cyclic products from the azides **3b** and **3c** were not successful. When **3b** was thermolysed in *p*-xylene at 80°C, the azido band at 2126 cm^{-1} in the IR spectrum initially diminished at the same rate as the carbonyl band at 1666 cm^{-1}, which is consistent with the formation of the cyclic product **8a**.



8a: R = H
8b: R = Me



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However, at 40% reaction new carbonyl bands appeared, at 1689, 1706, and 1729 cm^{-1}, and thereafter increased in intensity. At the same time, new bands appeared in the N-H stretching region (at 3549, 3485, 3355 and 3315 cm^{-1}). However, these latter bands became very broad as the reaction entered its fourth half-life. The growth of the well-defined carbonyl bands did not parallel the decay of the azido band. When the azide decay was 50% and 75% complete, the development of the three carbonyl bands was only 33% and 50% complete, respectively. These results indicate that the carbonyl species are not the primary products of the azide decomposition, but arise in the decomposition of some such primary product as **8a**. A thin layer chromatogram on the reaction mixture after eight half-lives indicated there are at least ten products, and we therefore made no attempt to identify these. Isoxazolothiazoles related to **8a** have previously been reported by Athmani, Farhat and Iddon[11] to be unstable.

In the case of 5-acetyl-4-azido-2-phenylthiazole, the IR monitor during the thermolysis found that new carbonyl bands appeared at 1690, 1706, 1728, and 1745 cm^{-1} shortly after 20% reaction. Initially, these new bands grew about twice as fast as the azide decay, but by the time the azide band was 75% decayed these bands had ceased to intensify. Again, this behaviour suggests cyclization in the early stages of the reaction, however, that the cyclised product is unstable.

In a final experiment we did not succeed to obtain the expected thiazolofurazan **9** from the thermolysis of 4-azido-5-nitro-2-phenylthiazole (**3e**).

EXPERIMENTAL

General

Remarks regarding safety: Sodium azide is extremely poisonous and organic azides are potentially hazardous. Although we never had any explosions occuring with the heterocyclic azides described in this report, caution is always necessary when handling these compounds. Preparation should be carried out only in a fume cupboard (hood) provided with a powerfull exhaust system. The use of a screen of safety glass is recommended.

Mp's were determined using a Reichert Thermovar apparatus. IR spectra were recorded on a Perkin Elmer 1720 FT spectrometer, and NMR spectra on either a Bruker AMX-400 or a Bruker WM-250 instrument. The NMR spectra were measured with deuteriochloroform solutions unless otherwise specified. The *J* values are recorded in Hz. Low resolution mass spectra were measured with a Hewlett Packard 5989 A instrument, at 70 eV for EI spectra, and with methane as reagent gas for CI spectra. The high resolution mass spectra were recorded with a Kratos MS 50 TC machine.

Synthesis of 4-azidothiazoles

Through nucleophilic substitution of halogen by azide ion. Typical procedure.

*4-Azido-5-cyano-2-phenylthiazole (**3a**)* was obtained from 4-chloro-2-phenylthiazole-5-carbaldehyde.[12] A solution of this aldehyde (0.5 g, 2.2 mmol) in pyridine (5 ml) and hydroxylamine hydrochloride (0.16 g, 2.3 mmol) in water (5 ml) was stirred at room temperature for 1 h and then treated with copper(II)sulfate pentahydrate (0.11 g, 0.44 mmol). To the blue solution was added triethylamine (0.444 g, 4.4 mmol) in dichloromethane (2 ml) and dicyclohexylcarbodiimide (0.566 g, 2.7 mmol) in dichloromethane (8 ml). After stirring for 2 h at room temperature, formic acid (0.5 ml) was added to the solution in a dropwise manner.[13] The reaction mixture was then chromatographed as such on silica gel with dichloromethane as the eluent to give 4-chloro-5-cyano-2-phenylthiazole (0.42 g, 85%); mp 138-138.4°C (from methanol); Elemental analysis: found C, 54.6; H, 2.3 $C_{10}H_5ClN_2S$ requires C, 54.5; H, 2.3%; IR ν_{max}(KBr)/cm^{-1} 2215m (CN); ^{1}H-NMR (400 MHz) δ_H 7.4-7.6 and 7.93 (3 + 2 H, m + d, Ph); ^{13}C-NMR (100 MHz) δ_C 100.4 (C-5), 110.6 (CN), 126.8, 129.4, 131.1 and 132.7 (Ph), 149.6 (C-4) and 172.0 (C-2, t); LRMS: m/z 220 (M^+, 100%), 185 (M^+-Cl, 16), 117 (72), 82 (25), 77 (Ph^+, 11); HRMS: found M^+ 219.9871 $C_{10}H_5ClN_2S$ requires M^+ 219.9862.

This chloronitrile (300 mg, 1.35 mmol) and sodium azide (265 mg, 4.1 mmol) were heated together in DMSO (3 ml) for 3 h at 60°C. The cooled reaction mixture was poured into water (20 ml) and extracted with chloroform (3 x 30 ml). These extracts were combined, dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica gel with chloroform/n-hexane (2:1) as the eluent to give 4-azido-5-cyano-2-phenylthiazole (**3a**) (110 mg, 36%); mp 139-141°C (decomp); IR ν_{max}(KBr)/cm^{-1} 2217m (CN) and 2154s, 2129s (N_3); ^{1}H-NMR (400 MHz) δ_H 7.5-7.6 and 7.94 (3 + 2 H, m + d, Ph); ^{13}C-NMR (100 MHz) δ_C 86.8 (C-5), 110.8 (CN), 126.8, 129.4, 131.3 and 132.5 (Ph), 157.6 (C-4) and 171.5 (C-2); LRMS m/z 227 (M^+, 10%), 199 (M^+ - N_2, 12), 129 (50), 103 ($PhCN^+$, 100), 77 (Ph^+, 44), 76 (29), 70 (16) and 51 (33); HRMS: found M^+ 227.0259 $C_{10}H_5N_5S$ requires M^+ 227.0266.

*4-Azido-2-phenylthiazole-5-carbaldehyde (**3b**)* was obtained by reacting 4-chloro-2-phenylthiazole-5-carbaldehyde[12] with sodium azide in DMSO; mp 133°-135°C (lit.[12] 136°C); IR ν_{max}(KBr)/cm^{-1} 2159m and 2130s (N_3), 1661s (CHO); ^{1}H-NMR (250 MHz) δ_H 7.4 - 7.6 and 8.0 (3 + 2 H, m + d, Ph) and 9.8 (1 H, s, CHO); ^{13}C-NMR (62.5 MHz) δ_C 119.5 (C-5, d, ^2J 34), 127.0, 129.2, 131.9 and 132.4 (Ph), 155.7 (C-4, s), 173.7 (C-2, t), and 178.9 (CHO, d, ^1J 182.5); LRMS m/z 230 ($M^{\cdot+}$, 3.4%), 202 ($M^{\cdot+}$ - N_2, 3.8), 129 (17), 104 ($PhCNH^+$, 100), 103 ($PhCN^{\cdot+}$, 45), 77 (Ph^+, 48), 76 (27), 71 (29), 70 (27), and 51 (31); HRMS: found $M^{\cdot+}$ 230.0249 $C_{10}H_6N_4OS$ requires $M^{\cdot+}$ 230.0262.

*5-Acetyl-4-azido-2-phenylthiazole (**3c**)* was synthesized from 4-chloro-2-phenylthiazole-5-carbaldehyde.[12] A solution of this chloroaldehyde (1 g, 4.6 mmol) in THF (30 ml) was treated with diazomethane (0.36 g, 9 mmol). After stirring for 1 h at 0°C and 3 days at room temperature[14], the solvent was evaporated under reduced pressure and the residu purified by chromatography on silica gel with ether/n-hexane (1:1) as the eluent to give 5-acetyl-4-chloro-2-phenylthiazole (850 mg, 78%); mp 144.8-145.3°C (MeOH); IR ν_{max}(KBr)/cm^{-1} 1654s (CO); ^{1}H-NMR (400 MHz) δ_H 2.73 (3 H, s, Me), 7.45 - 7.55 and 7.95 (3 + 2 H, m + d, Ph); ^{13}C-NMR (100 MHz) δ_C 29.7 (Me), 126.7, 129.2, 131.9 and 132.0 (Ph), 133.1 and 141.6 (C-4 and C-5), 171.3 (C-2) and 189.8 (CO); LRMS m/z 237 ($M^{\cdot+}$, 81%), 222 ($M^{\cdot+}$ - CH_3, 100), 194 ($M^{\cdot+}$ - CH_3 - CO, 39), 93 (23), 92 (20), 91 (54), 77 (Ph^+, 16), 43 (Ac^+, 49); HRMS: found $M^{\cdot+}$ 237.002 $C_{11}H_8ClNOS$ requires $M^{\cdot+}$ 237.0015.

This chloroketone (500 mg, 2.2 mmol) and sodium azide (444 mg, 6.6 mmol) were heated together in DMSO (20 ml) at 60°C for 3 h. The cooled solution was poured into water (80 ml) and extracted with chloroform (3 x 50 ml). These extracts were combined, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with diethyl ether/n-hexane (1:1) as the eluent gave 5-acetyl-4-azido-2-phenylthiazole (0.2 g, 37%); mp 118-119°C (decomp); IR ν_{max}(KBr)/cm^{-1} 2142s and 2119s (N_3), 1651s (CO); ^{1}H-NMR (400 MHz) δ_H 2.57 (3 H, s, Me), 7.45 - 7.54 and 7.97 (3 + 2 H, m + d, Ph); ^{13}C-NMR (100 MHz) δ_C 28.8 (Me), 122.1 (C-5), 126.7, 129.2, 131.9, and 132.1 (Ph), 150.6 (C-4), 171.2 (C-2) and 189.8 (CO); LRMS m/z 244 ($M^{\cdot+}$, 3%), 216 ($M^{\cdot+}$ - N_2, 6), 104 ($PhCNH^+$, 11), 77 (Ph^+, 14) and 43 ($MeCO^+$, 100); HRMS: found $M^{\cdot+}$ 244.0408 $C_{11}H_8N_4OS$ requires $M^{\cdot+}$ 244.0419.

*4-Azido-5-nitro-2-phenylthiazole (**3e**)* was obtained in two steps from 4-chloro-2-phenylthiazole. A solution of this chloro compound[15] (1.0 g, 5.1 mmol) in acetic anhydride (15 ml) was cooled in ice and treated dropwise with concentrated nitric acid (1.0 ml, 20 mmol) while keeping the temperature below 5°C. The reaction mixture was then brought to room temperature and poured into ice-water (50 ml). The precipitated product was collected and chromatographed on silica gel. Elution with light

petroleum/diethyl ether (2:1) gave 4-chloro-5-nitro-2-phenylthiazole (0.7 g, 57%); mp 146-148°C (from methanol); IR ν_{max}(KBr)/cm^{-1} 1518s and 1320s (NO_2); ^{1}H-NMR (400 MHz) δ_H 7.53 (2 H, t), 7.61 (1 H, t) and 7.97 (2 H, d); ^{13}C-NMR (100 MHz) δ_C 112.9 (C-5), 126.8, 129.5, 131.1, and 133.2 (Ph), 140.5 (C-4), and 169.0 (C-2); LRMS m/z 240 (M^+, 90%), 194 (M^+ - NO_2, 84), 175 (M^+ -NO - Cl, 44), 159 (25), 133 (35), 121 (27), 77 (Ph^+, 35), 76 (27); HRMS: found M^+ 239.9758 $C_9H_5ClN_2O_2S$ requires M^+239.9760.

A solution of this chloronitro compound (0.7 g, 3 mmol) and sodium azide (0.95 g, 15 mmol) in DMF (30 ml) was stirred at room temperature for 15 min then poured into ice-water (100 ml). Chloroform extracts (3 x 50 ml) were combined, dried ($MgSO_4$), and evaporated. Chromatography of the residue on silica gel with light petroleum/diethyl ether (1:1) as the eluent gave 4-azido-5-nitro-2-phenylthiazole (0.4 g, 56%), mp 111-114°C (decomp); IR ν_{max}(KBr)/cm^{-1} 2163m, 2131s (N_3), 1527s, 1354s and 1318s (NO_2); ^{1}H-NMR (400 MHz) δ_H 7.51 (2 H, t), 7.60 (1 H, t) and 7.97 (2 H, d); ^{13}C-NMR (100 MHz) δ_C 126.9, 129.5, 131.1 and 133.2 (Ph), 127.8 (C-5), 148.8 (C-4) and 169.0 (C-2); LRMS m/z 247 (M^+, 33%), 221 (13), 189 (M^+ - N_2 - NO, 27), 173 (10), 159 (M^+ - N_2 - 2NO, 23), 129 (PhC=N^+-CN, 32), 121 (22), 105 (35), 104 (21), 103 ($PhCN^+$, 93), 77 (Ph^+, 63), 76 (42), 72 (17), 70 (M^+ - N_2 - NO_2 - PhCN, 100) and 51 (38); HRMS: found M^+ 247.0166 $C_9H_5N_5O_2S$ requires M^+ 247.0164.

*4-Azidothiazole-5-carbaldehyde (**3h**)* was prepared by a published procedure[11], mp 82-83°C (decomp) (lit.[11] 81.5-82.5°C); IR ν_{max}(KBr)/cm^{-1} 2134s, 2162sh (N_3) and 1666s (CO); ^{1}H-NMR (400 MHz) δ_H 8.94 (1 H, d, ^5J 1, H-2), and 9.94 (1 H, d, ^5J 1, CHO); ^{13}C-NMR (100MHz) δ_C 119.7 (C-5, $^2J_{CH}$ 34, $^3J_{CH}$ 2), 155.9 (C-4, $^3J_{CH}$ 16), 159.3 (C-2, $^1J_{CH}$ 212) and 180.2 (CHO, $^1J_{CH}$ 184); LRMS m/z 154 (M^+, 33%), 126 (M^+ - N_2, 30), 83 (13), 71 (M^+ - N_2 - CO - HCN, 100), 70 (62), 53 (15), 45 (50), and 44 (33); HRMS: found M^+ 153.9951 $C_4H_2N_4OS$ requires M^+ 153.9949.

By diazotization of the corresponding amine. Typical procedure.

*4-Azido-2,5-diphenylthiazole (**3f**)* was obtained from 4-amino-2,5-diphenylthiazole.[16] A solution of the amine (0.9 g, 3.5 mmol) in trifluoroacetic acid (6 ml) was diazotized by addition of sodium nitrite (1.2 g, 17 mmol), the temperature being kept below 5°C with an ice-bath. The mixture was then cooled below -30°C before a tenfold excess of sodium azide (2.3 g) was added, after which stirring was maintained 4 h at room temperature. The reaction mixture was then diluted with water (100 ml) and extracted with chloroform (4 x 50 ml). The chloroform extracts were combined, dried ($MgSO_4$) and evaporated to yield the crude azide. Chromatography on silica gel with light petroleum/diethyl ether (2:1) as the eluent gave 4-azido-2,5-diphenylthiazole (0.80 g, 82%); mp 96-97°C (decomp);

IR ν_{max}(KBr)/cm^{-1} 2150m and 2117s (N_3); ^{1}H-NMR (400 MHz) δ_H 7.28, 7.40 and 7.68 (1 + 2 + 2 H, tt + t + d, Ph), 7.42-7.45 and 7.92-7.96 (3 + 2 H, 2m, Ph); ^{13}C-NMR (100 MHz) δ_C($CDCl_3$) 120.1 (C-5), 126.0, 127.5, 127.7, 128.8, 129.0, 130.3, 130.5, and 132.8 (2 Ph), 142.9 (C-4) and 163.7 (C-2); LRMS m/z 278 (M^+, 2.4%), 250 (M^+ - N_2, 20), 147 ($PhCSCN^+$, 86), 146 (43), 121 ($PhCS^+$, 100), 120 (58), 103 ($PhCN^+$, 49), 77 (Ph^+, 87), 76 (39), and 51 (65); HRMS: found M^+ 278.0621 $C_{15}H_{10}N_4S$ requires M^+278.0626.

Ethyl 3-(4-azido-2-phenylthiazol-5-yl)propenoate (3g) was synthesized in two steps from 4-azido-2-phenylthiazole-4-carbaldehyde (**3b**). A solution of **3b** (2.3 g, 10 mmol) and triethylphosphonoacetate (2.24 g, 10 mmol) in tetrahydrofuran (10 ml) was added to a suspension of powdered potassium hydroxide (1 g, 18 mmol) in tetrahydrofuran (30 ml). The mixture was stirred at room temperature for 2.5 h, then filtered, and the filtrate was evaporated. The residual oil was suspended in water (200 ml) and extracted with chloroform (3 x 50 ml); these extracts were combined, washed with water (3 x 50 ml), dried ($MgSO_4$) and evaporated. Chromatography of the crude product on silica gel with light petroleum/diethyl ether (2:1) as the eluent gave ethyl 3-(4-amino-2-phenylthiazol-5-yl)propenoate (0.9 g, 33%); mp 161-162°C (from MeOH); IR ν_{max}(KBr)/cm^{-1} 3443m, 3311m, 3202m (NH_2), 1700m (CO) and 1635s (C=C); ^{1}H-NMR (400 MHz) δ_H 1.32 (3 H, t, Me), 4.24 (2 H, q, CH_2), 4.79 (2 H, br s, NH_2), 5.86 and 7.70 (2 H, 2d, *J* 15.2, CH=CH), 7.4-7.46 and 7.85-7.9 (3 + 2 H, 2m, Ph); ^{13}C-NMR (100 MHz) δ_C 14.4 and 60.3 (Et), 105.2 (C-5), 113.2 and 133.1 (CH=CH), 126.4, 129.0, 130.9 and 132.8 (Ph), 158.3 (C-4), 167.3 (CO, m) and 167.5 (C-2, t). LRMS m/z 274 (M^+, 74%) 257 (M^+-OH, 13), 229 (M^+-OCH_2CH_3, 100), 202 (18), 126 (25), 104 (42), 98 (31), 77 (Ph^+, 15); HRMS: found M^+ 274.0778 $C_{14}H_{14}N_2O_2S$ requires M^+ 274.0776.

This amine (0.9 g, 3.3 mmol) in trifluoroacetic acid (15 ml) was treated with sodium nitrite (1.15 g, 16 mmol) with the temperature held below 5°C. After cooling the mixture to -30°C, a tenfold excess of sodium azide (2.15 g) was added and stirring was maintained at room temperature for 4 h. The reaction mixture was then diluted with water (50 ml) and extracted with diethyl ether (3 x 50 ml), the extracts being combined, dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with light petroleum/diethyl ether (2:1) as eluent to obtain the azide **3g** (0.4 g, 20%); mp 98-99°C (decomp); IR ν_{max}(KBr)/cm^{-1} 2156m and 2115s (N_3), 1702s (CO), 1619 s (C=C); ^{1}H-NMR (400 MHz) δ_H 1.33 (3 H, t, Me), 4.24 (2 H, q, CH_2), 6.1 and 7.67 (2 H, 2d, *J* 15.7, CH=CH), 7.4-7.5 and 7.92 (3 + 2 H, m + d, Ph); ^{13}C-NMR (100 MHz) δ_C 14.3 and 60.6 (Et), 116.3 (C-5), 118.3 and 131.4 (CH=CH), 126.5, 129.1, 131.4 and 132.3 (Ph), 149.6 (C-4), 166.3 (CO, m) and 167.3 (C-2, t); LRMS m/z 300 (M^+, 21%), 272 (M^+ - N_2, 38), 227 (17), 226 (M^+ - N_2 - EtOH, 34), 213 (13), 200 (m/z 272 - C_2H_4 - CO_2, 100), 199 (33),

149 (18), 141 (19), 129 (80), 124 (18), 121 (80), 104 (PHCNH$^+$, 27), 103 (PhCN$^{\cdot+}$, 48), 96 (45), 77 (Ph$^+$, 73) and 51 (36); HRMS: found M$^{\cdot+}$ 300.0678 $C_{14}H_{12}N_4O_2S$ requires M$^{\cdot+}$ 300.0681.

Other methods

*4-Azido-2-phenyl-5-phenyliminomethylthiazole (**3d**)* was obtained from the corresponding azidoaldehyde (**3b**) by reaction with aniline;[12] mp 136.9-139.6°C (lit.[12], 133-134°C); IR ν_{max}(KBr)/cm^{-1} 2122s (N_3) and 1613m (C=N); ^{1}H-NMR (400 MHz) δ_H 7.18 - 7.25, 7.36, 7.4 - 7.5 and 8.0 (10 H, m + t + m + d, 2 Ph) and 8.49 (1 H, s, CH=N); ^{13}C-NMR (100 MHz) δ_C 119.4 (C-5, d, ^2J 18), 121.1, 126.4 - 132.5 and 151.1 (2 Ph), 148.6 (CH=N, ^1J 165, *E*-isomer), 150.8 (C-4, d, ^3J<1), and 169.6 (C-2, t).

Synthesis of 3-azidothiophenes

3-Azidothiophene-2-carbaldehyde[17] and 3-azido-2-(phenyliminomethyl)thiophene[18] were prepared by literature methods.

Products of thermolysis

The azide **3d** (0.5 g) was refluxed in carbon tetrachloride (20 ml) for 2 days. After cooling, the precipitate (0.33 g) was collected and boiled with ethanol (30 ml) for 30 min to extract impurities from the insoluble thiazoloindazole **6** (0.28 g, 63%); mp 170-172°C; IR ν_{max}(KBr)/cm^{-1} 1594m, 1500s; ^{1}H-NMR [$(CD_3)_2SO$, 400 MHz] δ_H 7.38 (1 H, t), 7.5 - 7.6 (5 H, m), 7.95 (2 H, d), 8.07 (2 H, d) and 8.83 (1 H, s, 6-H); ^{13}C-NMR [$(CD_3)_2SO$, 100MHz] δ_C 114.4, (C-6a, ^2J 6), 120.5 (C-6, ^1J 200), 119.1, 127.0, 127.1, 129.4, 129.7, 131.9, 133.0 and 140.1 (2 Ph), 170.6 (C-3a, ^3J 8) and 174.3 (C-2); LRMS m/z 277 (M$^{\cdot+}$, 100%), 251 (13), 174 (M$^+$ - PhCN, 7), 147 (23), 104 (PhN=CH$^+$, 68), 77 (Ph$^+$, 76) and 51 (37); HRMS: found M$^{\cdot+}$ 277.0683 $C_{16}H_{11}N_3S$ requires M$^{\cdot+}$ 277.0674.

The azide **3f** (0.3 g, 1.08 mmol) was refluxed in carbon tetrachloride (20 ml) for 18h. After cooling the precipitated **7** was filtered off and purified by chromatography on silica gel and ether/petroleumether (1:2) as the eluent (0.16 g, 59%); mp 255-256°C; IR ν_{max}(KBr)/cm^{-1} 3248m, 2921m, 1457s; ^{1}H-NMR (400MHz) δ_H 7.20-7.28 (1 H, tr), 7.29-7.34 (1 H t), 7.41-7.52 (3 H + 1 H, m + d), 7.73 (1 H, d), 8.02-8.05 (2 H, d), 8.9 (1 H, broad s, NH); ^{13}C-NMR [$(CD_3)_2SO$, 62.5 MHz] δ_C 112.5 (C-5), 119.4, 119.7 and 123.0 (C-6, C-7, C-8), 119.5 (C-8b), 125.7, 129.2, 130.1 and 135.2 (2 Ph), 128.0 (C-8a), 139.6 (C-4a), 148.7 (C-3a), 162.2 (C-2); LRMS m/z 250 (M$^{\cdot+}$, 100%), 146 (M$^{\cdot+}$-PhCHN, 23), 120 (M$^{\cdot+}$-PhCHN-CN, 30), 10311), 77 (Ph$^+$, 17); HRMS: found M$^{\cdot+}$ 250.0574 $C_{15}H_{10}N_2S$ requires M$^{\cdot+}$ 250.0565.

Kinetic measurements

Rates were measured by our usual method,[4] the decay of the azido band in the IR spectrum being monitored. The reactions were followed for at least two half-lives, and the plots of ln(absorbance) versus time were strictly first-order (correlation coefficients 0.999 or better). With decalin solvent, a radical chain inhibitor was added to suppress the induced decomposition of the azide which might occur in this solvent.[1]

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