On the Regioselectivity of Imidoyl Radical Cyclisations

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Dedicated to the memory of Professor Antonino Fava (1923–1997),
Emeritus Professor of the University of Bologna

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The previously reported tandem cyclisation of *N*-aryl α-(2-cyanophenyl)sulfanyl imidoyl radicals affords one quinoxaline derivative arising from exclusive 1,6-cyclisation of the final iminyl radical onto the *N*-aryl ring. When the imidoyl radicals are generated by addition of photolytically generated (2-cyanophenyl)sulfanyl radicals to isocyanides, the reaction also gives small amounts of a by-product that is formed by an analogous route and whose X-ray crystallographic data are reported here. The formation of this product entails a rare *ortho*-selective photo-Fries rearrangement of the starting disulfide, followed by addition to the isocyanide and regioselective 1,5-cyclisation of the resulting imidoyl onto only one of the two available radical acceptors, i.e. the cyano group and the sulfide moiety. Semiempirical MNDO-d calculations were performed in order to throw some light on the factors affecting these competitive cyclisations.

Introduction

α-Thio-substituted imidoyl radicals can be generated either by addition of carbon,[1] tin, or silicon[2] radicals to isothiocyanates or by reaction of sulfanyl radicals with isocyanides.[2h–2j,3] Although they have been known for quite a long time, applications of these species in synthetically useful transformations are still somewhat rare.[2f–2j,3d] However, remarkable procedures have been accomplished starting from alkenyl and alkynyl isocyanides[2h,3d] and isothiocyanates,[2g,2h] including the stereoselective synthesis of α-kainic acid.[2i–2l] Recently, we have reported novel radical cascade reactions involving α-thioimidoyl radicals generated by addition of either 2-cyanoaryl radicals to aryl isothiocyanates,[4] or (2-cyanoethyl)- or (2-cyanophenyl)sulfanyl radicals to aryl isocyanides.[5] In both cases, the radical addition/tandem cyclisation strategy leads to quinoxaline derivatives through an exclusive six-membered cyclisation of an intermediate iminyl radical.[6] Here we report the X-ray crystal data of a reaction by-product – formed through an analogous mechanism – whose structure confirms that, under our conditions, the iminyl radical is unable to give 5-membered cyclisation products. This compound is formed by a noteworthy regioselective cyclisation of an imidoyl radical onto only one of two available radical acceptors.

Results and Discussion

When imidoyl radicals **4** were produced from isocyanides **3** and photolytically generated sulfanyls **2**, the reactions gave, besides the expected quinoxaline **6** (Scheme 1, route *a*), small amounts (5–10%) of a by-product **9** as a single structural isomer. Its structure was eventually fully established by X-ray crystallography (Figure 1, and Table 1).

Compound **9** can be accounted for through a photo-Fries rearrangement of the starting disulfide **1** (Scheme 1, route *b*) followed by annulation between isocyanide **3** and the rearranged intermediate **7**. The photo-Fries reaction is fairly general for aromatic systems and usually leads to compounds derived from rearrangement of the initially formed biradicals to *ortho* and *para* products in a solvent cage.[7] The photo-Fries rearrangement is rather common with esters and amides and, as far as sulfur compounds are concerned, it has been observed with thiol esters[8] and sulfenanilides.[9] On the other hand, examples concerning aromatic disulfides are very rare;[10] it is also extremely unusual to encounter rearrangements exclusively affording *ortho* products. As far as we know, if we exclude a few examples dealing with cyclodextrin encapsulation[11] where, of course, supramolecular aspects play a crucial role, the only reported example concerns the photolysis of 2,2'-dithio-bis(acetanilides), which selectively yield products derived from intermolecular *ortho* rearrangement and intramolecular trapping of the resulting thiol.[10b] The present case is similar, but even more uncommon, as the rearranged product is trapped by an intermolecular reaction, i.e. addition to the isocyanide.

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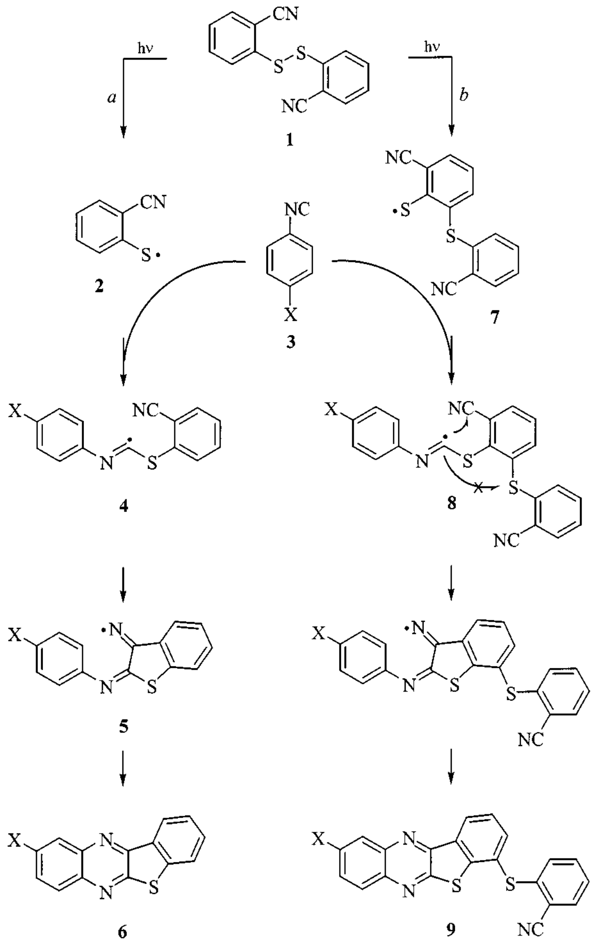


Scheme 1. Reaction of disulfide **1** with isocyanides **3**

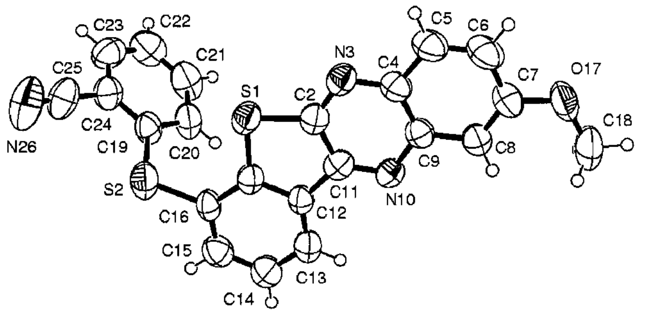


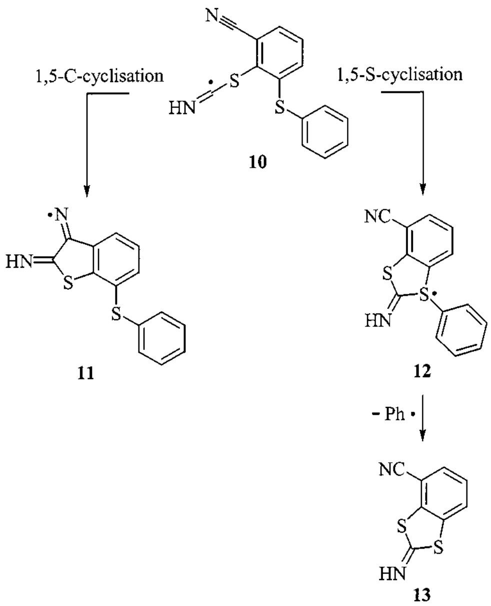
Figure 1. Molecular structure of **9** (X = MeO), showing the atom labelling scheme

The formation of compound **9** – whose X-ray structure confirms once again that **5**-like iminyls are unable to give 1,5-ring closure – is noteworthy from another point of view. As a matter of fact, **9** is formed by a regioselective cyclisation process of radical **8** onto the cyano group in the presence of another good radical acceptor, i.e. the arylthio moiety.[12] At first sight, this preference might be ascribed to polar rather than stereoelectronic factors, since imidoyls are supposed to be nucleophilic radicals[4] and their addition to the electrophilic nitrile carbon should in principle be faster than cyclisation onto a substantially nucleophilic sulfur atom.

Table 1. Selected bond lengths [Å] and angles [°] for **9** (X = MeO)

Bond lengths			
S(1)–C(2)	1.741(4)	N(3)–C(4)	1.367(5)
S(1)–C(1)	1.743(4)	C(7)–O(17)	1.388(6)
S(2)–C(19)	1.771(4)	C(4)–C(9)	1.405(6)
S(2)–C(16)	1.774(4)	C(9)–N(10)	1.377(5)
C(1)–C(16)	1.395(6)	N(10)–C(11)	1.318(5)
C(1)–C(12)	1.413(5)	C(11)–C(12)	1.454(6)
C(2)–N(3)	1.316(6)	C(24)–C(25)	1.444(7)
C(2)–C(11)	1.424(6)	C(25)–N(26)	1.140(6)
Bond angles			
C(2)–S(1)–C(1)	90.1(2)	C(11)–N(10)–C(9)	115.1(4)
C(19)–S(2)–C(16)	102.3(2)	N(10)–C(11)–C(2)	122.4(4)
C(16)–C(1)–C(12)	120.0(4)	N(10)–C(11)–C(12)	125.9(4)
C(16)–C(1)–S(1)	125.4(3)	C(7)–O(17)–C(18)	116.3(4)
C(12)–C(1)–S(1)	114.6(3)	C(2)–C(11)–C(12)	111.6(4)
N(3)–C(2)–C(11)	123.3(4)	C(13)–C(12)–C(1)	119.4(4)
N(3)–C(2)–S(1)	123.3(4)	C(13)–C(12)–C(11)	130.4(4)
C(11)–C(2)–S(1)	113.4(4)	C(1)–C(12)–C(11)	110.2(4)
C(2)–N(3)–C(4)	115.5(4)	C(15)–C(16)–S(2)	120.4(3)
N(3)–C(4)–C(9)	121.4(4)	C(1)–C(16)–S(2)	120.5(4)
N(3)–C(4)–C(5)	119.9(5)	C(20)–C(19)–S(2)	123.8(4)
N(10)–C(9)–C(4)	122.3(4)	C(24)–C(19)–S(2)	117.6(3)
N(10)–C(9)–C(8)	117.4(4)	N(26)–C(25)–C(24)	179.0(7)

To verify this hypothesis, we performed semiempirical MNDO-d calculations for the transition states leading to the carbon- and sulfur-cyclised intermediates. From these calculations we unexpectedly found evidence that, in these cyclisations, polar effects do not seem to play a crucial role and the reaction products are determined by thermodynamic rather than kinetic factors. For the sake of simplicity, the calculations were performed on imidoyl radical **10** (Scheme 2 and Figure 2): this reduced problems in conformational analysis due to the additional aryl ring linked to the nitrogen.



Scheme 2. Competitive cyclisation pathways for radical **10**

The energy minimum of the starting imidoyl radical **10** was located at 150.0 kcal/mol and both cyclisations are exothermic, the energies of the iminyl (**11**) and sulfuranyl (**12**)

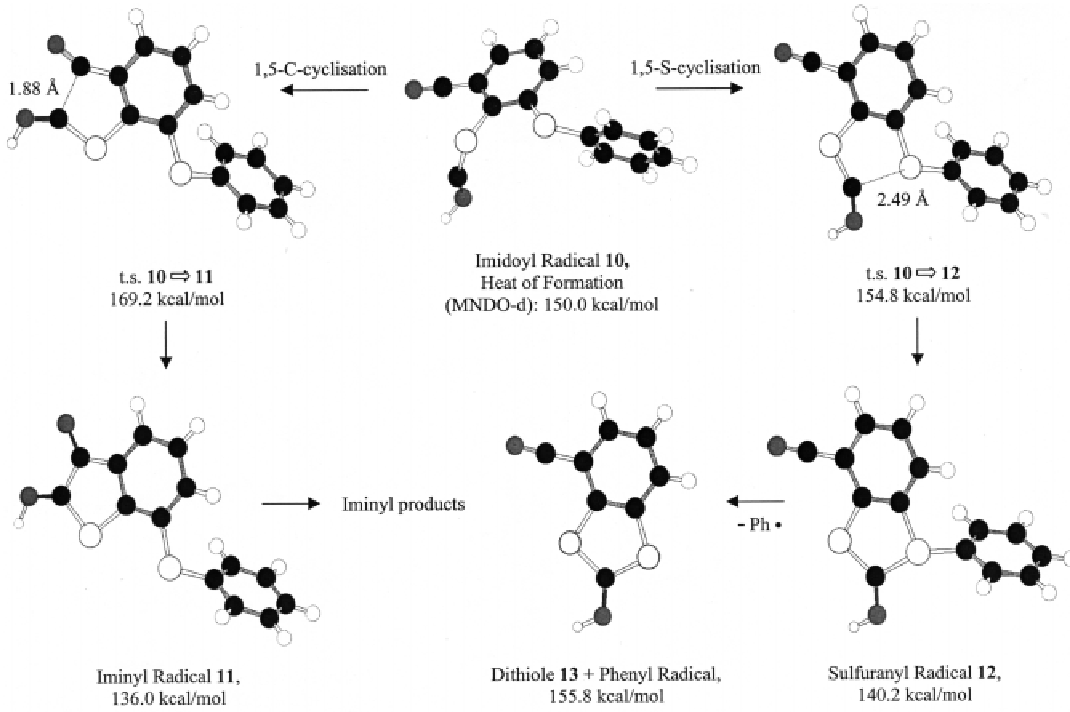


Figure 2. Reaction paths for the C- and S-cyclisation of imidoyl radical **10**, reporting the energies of the intermediates and transition states (t.s.)

radicals being 136.0 kcal/mol and 140.2 kcal/mol, respectively.[13] Whereas iminyl **11** appears to be thermodynamically favoured, cyclisation onto the sulfur atom to give **12** is predicted to be kinetically preferred, since the activation barrier is much lower (4.8 kcal/mol vs. 19.2 kcal/mol for the 1,5-C-cyclisation). Nevertheless, sulfuranyl **12** could afford dithiole **13** only by overcoming an energy barrier that, although not calculated, is certainly higher than that of the reverse ring opening to imidoyl **10**. In fact, the loss of a phenyl radical from **12** to give **13** was calculated to be endothermic by 15.6 kcal/mol, against an activation energy for the reverse reaction of 14.6 kcal/mol. We therefore suggest that the formation of the sulfuranyl radical **12** is very fast compared to iminyl **11**, but, due to the relatively small activation barrier for the reverse reaction and the unfavourable activation energy of the subsequent reaction, **12** is in equilibrium with the open radical **10**. On the other hand, the more stable iminyl **11** is not likely to revert to the open imidoyl, since the activation barrier for this reaction is 33.2 kcal/mol. In the usual reactions, subsequent cyclisation processes consume the iminyl radical, so that the equilibrium is shifted towards iminyl-derived products. A rough estimate of the equilibrium constant ratio for the two competitive reactions (S- and C-cyclisation), obtained from the kinetic data reported in Figure 2, gave a $K_{(S-cyc.)}/K_{(C-cyc.)}$ ratio of about 0.09. This means that, in our reactions, the yields of **13** (or **13**-derived products) are expected to be lower than 1%; indeed, we were not able to detect any such compounds.

Conclusions

Compound **9** is the result of an unusual *ortho*-selective photo-Fries rearrangement of disulfide **1** with subsequent trapping by isocyanide **3**. The resulting imidoyl radical affords **9** through an apparently regioselective cyclisation onto the cyano group. Semiempirical calculations explained this result in terms of a thermodynamically-controlled reaction, in which the very fast (and reversible) cyclisation of the imidoyl radical onto the sulfur atom is balanced by the slower (but practically irreversible) cyclisation onto the cyano group. The resulting iminyl radical affords **9** through another regioselective 1,6-ring closure which is analogous to that observed for the other quinoxaline derivatives **6**.[4][5] The X-ray data reported here confirm the structures expected for both **6** and **9**. Further studies are underway to attempt to throw more light on the reactivity of imidoyl, iminyl, and vinyl radicals and the stereoelectronic and/or polar factors affecting their cyclisation onto unsaturated bonds and aromatic rings.

Experimental Section

General Remarks: UV photolyses of disulfides were performed with a Heraeus TQ 150 high-pressure mercury lamp (150 W). Details on the starting materials and experimental procedures of the reactions affording compounds **6** and **9** are reported in our previous paper.[5] The homogeneity of the column fractions containing products **9**

was confirmed by ^{1}H NMR spectroscopy: this proved that our samples were formed by a unique substance and they were not a mixture of isomers bearing the X-group and/or the (2-cyanophenyl)sulfanyl substituent in positions different from those shown in structure **9**. Identification of **9** (X = MeO) was based on the X-ray crystallographic analysis reported below and that of **9** (X = Cl, Ph) on spectral analogies. The spectroscopic data of products **9** (X = MeO, Cl, Ph) have been previously reported.[5]

X-ray Crystallographic Study. – Analysis of the Crystal Structure of 2-[(9-methoxy[1]benzothieno[2,3-*b*]quinoxalin-4-yl)sulfanyl]-benzonitrile (9, X = MeO)

Crystal Data: Empirical formula $C_{22}H_{13}N_3OS_2$, formula weight 399.48, monoclinic, space group $C2/c$, a = 21.558(5), b = 15.074(3), c = 14.077(2) Å, β = 122.10(5)°, V = 3875(2) Å^3, Z = 8, D_c = 1.3694 Mg/m^3, μ (Cu-K_α) = 2.5815 mm^{-1}, F(000) = 1648.

Data Collection and Processing: Siemens AED diffractometer, radiation Cu-K_α (λ = 1.54178 Å), T = 24 °C, crystal size 0.7 × 0.14 × 0.12 mm, max. and min. transmission factors 1.00 and 0.921, no absorption correction, collection range $3.80 \leq \theta \leq 69.58°$, index ranges $-26 \leq h \leq 20$, $-18 \leq k \leq 18$, $0 \leq l \leq 17$, reflections collected 3785, independent reflections 3634 [R_{int} = 0.0202].

Structure Analysis and Refinement: The structure was solved by direct methods with SIR97[14] and refined by full-matrix least-squares on F^2 with SHELX93.[15] 553 Reflections with negative F^2 were omitted in the refinement. All atoms, except hydrogen atoms, were refined with anisotropic thermal parameters. Hydrogen atoms were located in a ΔF map and refined with isotropic thermal parameters fixed at 1.2 times the U_{iso} of the bonded carbon atom. Final agreement factors were R_1 = 0.0540 [$I > 2\sigma(I)$], wR_2 = 0.1635 [all data] and g.o.f = 0.787 for 3081 data and 254 parameters. Largest diffraction peak and hole were 0.406 and –0.268 e.A^{-3}. The molecular structure and selected bond lengths and angles are shown in Figure 1[16] and Table 1. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-125734. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Semiempirical Calculations: Semiempirical calculations on radicals **10**, **11**, **12**, phenyl radical, and compound **13**, as well as the search for the reaction paths connecting **10–11** and **10–12** were carried out with the *CS MOPAC* routine included in the CambridgeSoft *ChemOffice Pro* 4.0 package. After a careful conformational search, the geometries of the open-shell intermediates were fully optimised following the MNDO-d parameterisation. A rough estimate of the transition-state geometry was then located with the "SADDLE" algorithm as programmed in the *CS MOPAC* routine, fixing the geometries of the open (imidoyl **10**) and cyclised radical (iminyl **11** or sulfuranyl **12**) and varying by steps of 0.15 the scalar of the calculated vector defining the difference between the starting and final radical. The transition state geometry and energy were finally refined with the "OPTIMISE" option of the MOPAC routine. Geometries and energies for radicals **10**, **11**, **12**, phenyl radical, dithiole **13**, and the transition states connecting **10–11** and **10–12** are shown in Figure 2. The transition states are characterised by a single imaginary vibrational frequency (780.6 cm^{-1} and 186.5 cm^{-1} for the transition states leading to **11** and **12**, respectively) resulting from a negative force constant in the diagonal form of the Hessian; they both collapse to the starting radicals when optimised without the "SADDLE" option.

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