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Synthesis and X-ray characterisation of a new polycondensed heterocycle obtained by a novel Mn(III)-mediated cascade reaction of 2-cyanophenyl isothiocyanate

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Abstract—2-Cyanophenyl isothiocyanate reacted with Mn(III) acetate in acetic acid or acetonitrile to give fair yields of a new polycondensed heterocycle arising from the joining together of two molecules of the starting isothiocyanate with loss of a CS moiety. The yields were close to 90% when the reaction was carried out in the presence of diethyl malonate. This compound was unambiguously identified by X-ray crystallography. Under the same conditions, 2-(methoxycarbonyl)phenyl isothiocyanate gave a quinazolinimine derivative instead which is likely to arise from cyclisation of an intermediate *N*,*N*′-diarylthiourea. The mechanism of formation of the former compound probably involves formation of a *N*,*N*′-bis(2-cyanophenyl)thiourea, followed by rearrangement and radical tandem ring closure of the corresponding cyclic imine derivative. This hypothesis is also supported by semiempirical calculations.

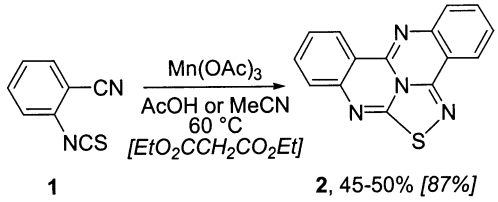
1. Introduction

The discoveries of the last two decades have convincingly located radical chemistry in the set of most powerful synthetic tools, and organic free-radicals are now playing a great role in the synthesis of many sorts of organic compounds. Our group has been studying a peculiar class of radical species, i.e. imidoyl radicals, for several years, which are key intermediates for the formation of various heterocyclic derivatives.[1] Recently, we turned our attention to α-thio-substituted imidoyl radicals. These species can be generated by addition of either sulphanyl radicals to isonitriles[2] or tin-, silicon-, and carbon-centred radicals to isothiocyanates.[3] In three recent papers[4] we have described the syntheses of benzothieno-fused quinoxalines[4a,b] and quinolines[4c] through cascade reactions of α-thioimidoyl radicals generated by addition of either 2-cyano- and 2-alkynyl-aryl radicals to aryl isothiocyanates,[4a,c] or (2-cyanophenyl)sulphanyl radicals to aryl isonitriles.[4b] These results prompted us to further investigate the reactivity and synthetic potential of isothiocyanates under various radical or electron-transfer conditions. Here we report the synthesis and X-ray characterisation of a new polycondensed heterocycle obtained from 2-cyanophenyl isothiocyanate through a novel cascade reaction initiated by manganese(III) acetate.

2. Results and discussion

When the isothiocyanate **1** (1 equiv.) was allowed to react with manganese(III) acetate (2 equiv.) in acetic acid or acetonitrile at 60°C, the reaction furnished a previously unreported aceanthrylene derivative **2** in 45–50% yield (Scheme 1). The structure of **2** was unambiguously established by X-ray diffraction (Fig. 1).

As can be noted, the skeleton of this compound formally involves the joining together of two units of **1** with loss of one CS molecule. It is worth noting that comparable yields of **2** were obtained both in acetic acid and in acetonitrile, whereas the presence of an enolisable compound such as diethyl malonate resulted in shorter reaction times and



Scheme 1.

Keywords: isothiocyanates; thioureas; manganese(III) acetate; X-ray diffraction; rearrangement; radicals.

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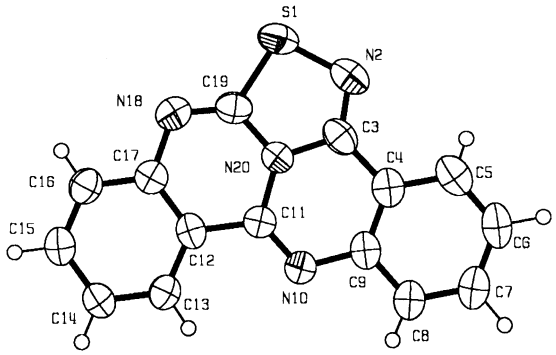
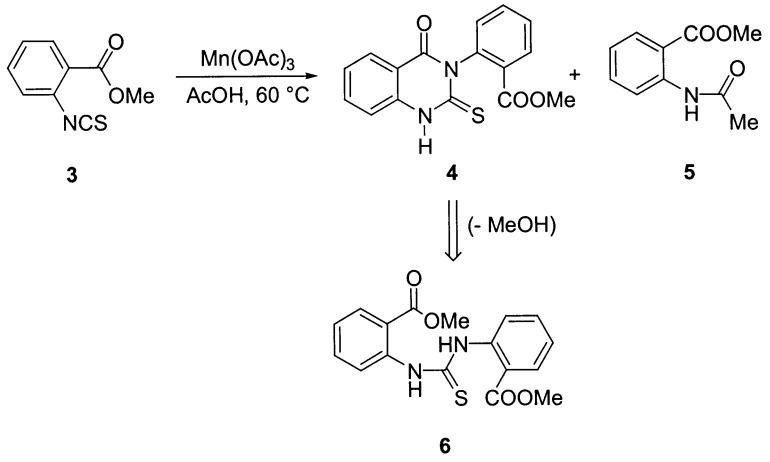


Figure 1. Molecular structure of **2**, showing the atom labelling scheme.

intermediate in the reaction of isothiocyanate **1** also, we tried to synthesise the 2,2′-dicyano derivative **7**. Analogous to what happened with **3**, any attempt to obtain compound **7** by usual methods resulted in isolation of the iminoquinazoline **8** in high yields (Fig. 2).[10] On the other hand, no traces of compound **2** were detected under these conditions. The structure of compound **8** was clearly suggested by ^{1}H and ^{13}C NMR analyses, which showed, respectively, two distinct N–H signals and the presence of seven quaternary and eight tertiary carbons: this data are clearly inconsistent with a symmetrical structure like **7**, but they perfectly fit the cyclised structure of **8**.

When imine **8** was treated at 60°C with manganese(III)



3 **4** **5** **6**

Scheme 2.

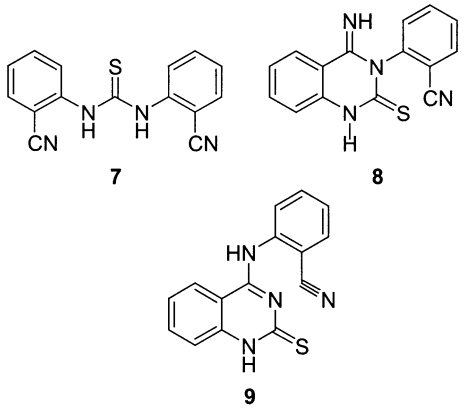
nearly quantitative yields (~90%).[5] At this stage it is not clear how diethyl malonate affects the reaction outcome; however, its importance most likely resides in its aptitude to give rise, by Mn(III) oxidation,[6] to carbon radicals that could somehow initiate or promote the cascade reaction.

To throw some light on the mechanism of formation of compound **2**, we allowed the methoxycarbonyl-substituted isothiocyanate **3** to react with manganese(III) acetate (2 equiv.) in acetic acid at 60°C in the presence or absence of diethyl malonate. In both cases, the reaction gave the quinazoline derivative **4** in ca. 30% yield, together with small amounts of *N*-acetylanthranilate **5** (Scheme 2).[7] As one can see, the reaction outcome is completely different with respect to isothiocyanate **1**; it is worth noting that the structure of product **4**, still containing the thiocarbonyl moiety, seems closely related to that of an intermediate, symmetrically disubstituted thiourea, viz. **6**.

Actually, compound **4** was the only product obtained from any attempt to independently synthesise thiourea **6** from methyl anthranilate, starting either from iodine and pyridine in carbon disulphide[8] or thiophosgene and pyridine in benzene.[9] Therefore, it may be reasonably inferred that thiourea **6** is initially formed by treatment of **3** with $Mn(OAc)_3$ and it then cyclises to **4** through an ionic and/or radical mechanism.

To test the possibility that a thiourea could be the same key acetate in acetic acid or acetonitrile and in the presence or absence of diethyl malonate (DEM), it systematically afforded the polycyclic compound **2**, although in variable yields. Table 1 shows that acetic acid is a good solvent as far as the reaction times are concerned; nevertheless, it gave much lower yields with respect to acetonitrile (entries a and c). Better yields were also ensured by the presence of DEM (entries b and d). The absence of the manganic salt caused instead the virtual disappearance of product **2**, even after 5 days at 60°C (entry e).

In light of these data, imine **8** can therefore be assumed as a



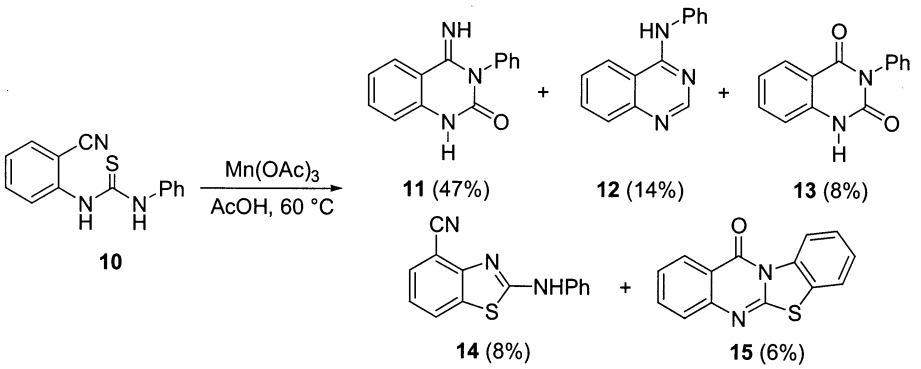
7 **8**

9

Figure 2.

Table 1. Dependence of the yields of **2** on the reaction conditions

Entry	Mn(III) (equiv.)	DEM (equiv.)	Solvent	*t* (h)	**2** (%)
a	2	0	AcOH	14	25
b	2	1	AcOH	22	50
c	2	0	MeCN	48	70
d	2	1	MeCN	48	83
e	0	0	MeCN/H_2O	150	Trace amounts



Scheme 3.

viable intermediate for the conversion of **1** into **2**. It is necessary to explain the mechanism of formation of **2** from **8**, which entails a rearrangement of the iminoquinazoline with migration of the 2-cyanophenyl ring from the heterocyclic to the iminic nitrogen atom. Such a translocation would afford the amine **9** (Fig. 2), whose structure is much closer to that of the aceanthrylene and could quite easily account for the formation of **2** through a cascade cyclisation.

As a convincing evidence for the occurrence of a rearrangement, when thiourea **10** was allowed to react under the usual conditions it afforded amine **12** as one of the major products (Scheme 3). The structure of **12** was assigned by way of spectral analogies with an analogous compound, obtained from thiourea **30a**, whose structure was confirmed by X-ray diffraction (Fig. 6).

The most viable mechanism that might be envisaged to account for the migration is a Dimroth rearrangement.[11] This process has been usually encountered in 1-alkyl-2-iminopyrimidines **16**, which, in the presence of nucleophiles (typically water), give an apparent migration of the alkyl group from the heterocyclic to the iminic nitrogen atom. Since this mechanism has also been proposed for the rearrangement of **17**- and **18**-like substrates (Fig. 3),[11] it could be reasonable to postulate an analogous pathway for the conversion of imino- (**8**) into (arylamino)-quinazolines (**9**).

On the other hand, in our opinion, the Dimroth rearrangement is not likely to be the precise or the only mechanism operating in our reactions. Indeed, the reported rearrangements usually occur under very different conditions, i.e. in alkaline, aqueous solutions. Moreover, although imine **8** yielded amine **9** when kept at 60°C in acetonitrile/water in the absence of Mn(III), this reaction was very slow, requiring 150 h for converting 70% of the starting material. The same experiment performed in AcOH/water for 48 h resulted in hydrolysis of **8** to the corresponding ketone (27%).[12] Also the intervention of $Mn(OAc)_3$, together with its crystallisation water, as an acid catalyst should be discarded, since the acid catalysis seems to favour the unrearranged, hydrolysis products. This is proved, besides the result obtained in acetic acid, by treatment of **8** with hydrochloric acid in refluxing dioxane for 6 h, which afforded mainly two compounds (**19** and **20**, Fig. 3) derived from hydrolysis of the imine (**19**) and nitrile (**20**) moieties of **8**; compound **21**, arising from hydrolysis of the rearranged ketimine **9**, was only obtained in very small amounts (4%) (for a detailed discussion about identification of compound **20**, see Section 4).

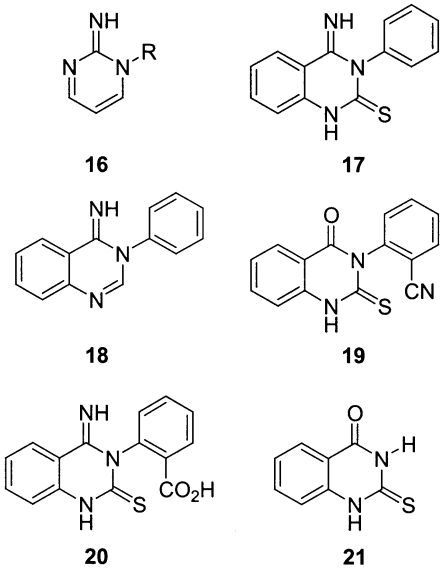


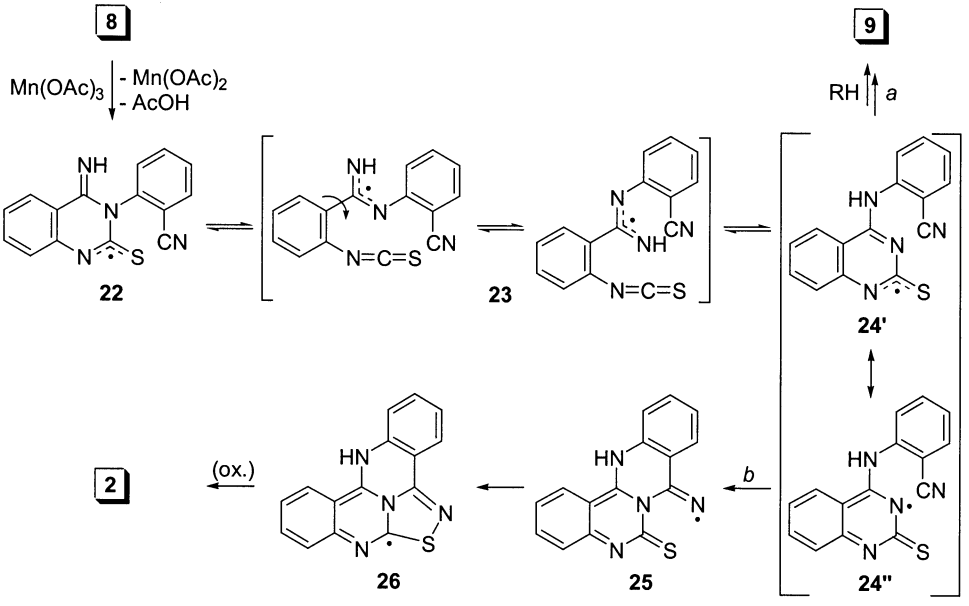
Figure 3.

Taking into account the overall above results, we can put forth a hypothesis, supported by literature precedents, that allows for the possibility that **8**-like thioxoquinazolines might be oxidised by Mn(III) to give thioamidyl radicals. Indeed, thiourea and *N*-substituted thioureas have been known for many years as corrosion inhibitors and redox components for vinyl polymerisation in the presence of a variety of oxidants. Several studies concerning the one-electron oxidation of thiourea derivatives with oxidising radicals or metal ions such as Ce(IV) or Mn(III) have been recently reported.[13] It is generally admitted that these derivatives are easily oxidised to give bidentate, resonance-stabilised radicals with an intramolecular three-electron bond between sulphur and nitrogen atoms. We can therefore surmise that imine **8** could be oxidised to radical **22**; the formation of the isothiocyanate moiety would hence be the result of a homolytic β-fragmentation with release of a reasonably stable anilino–amidino radical, viz. intermediate **23** (Scheme 4). Rotation around the Ar–C=N bond and re-cyclisation onto the NCS group would afford the rearranged product **9**. This would therefore be the radical version of the Dimroth rearrangement.

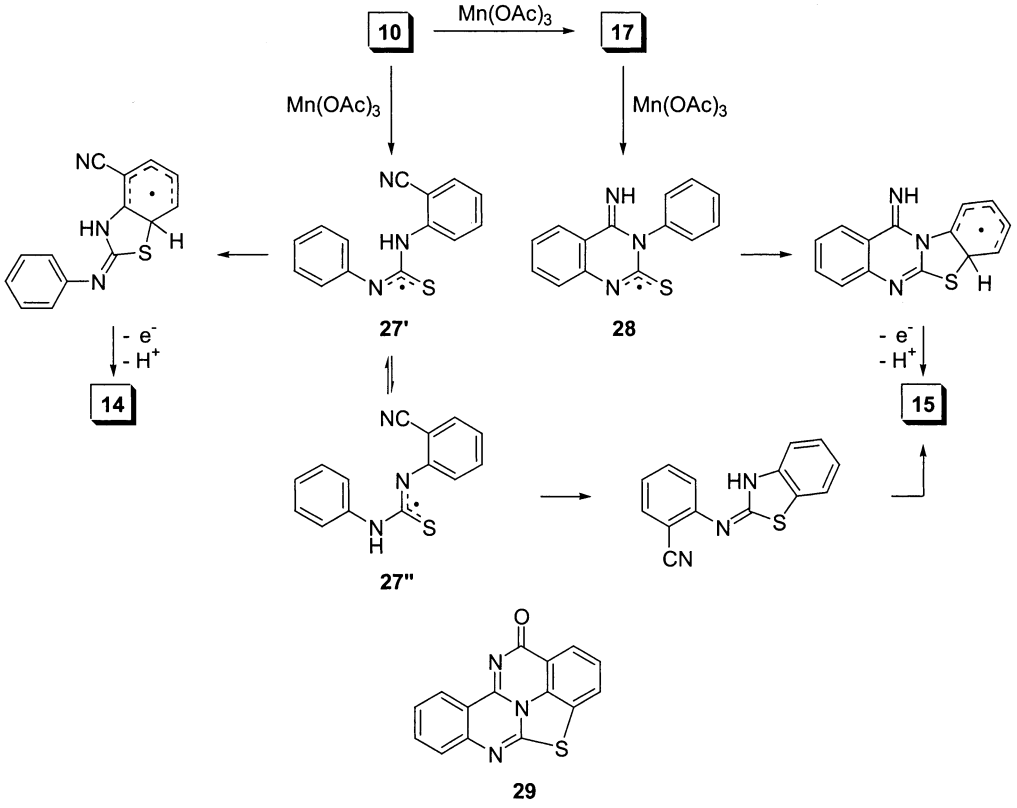
Besides explaining the rearranged product **9**, this mechanism can go further, giving on its own a full rationale of the entire process, including the formation of the polycyclic compound **2**. Indeed, radical **24**, through its mesomeric form **24″** can cyclise onto the cyano group to afford iminyl radical **25**. Ring closure of **25** onto the thiocarbonyl yields radical **26**, which furnishes the ultimate product **2** through (formal) loss of a hydrogen atom. The final step most likely involves oxidation of **26** by Mn(III) to the corresponding cation with subsequent loss of a proton; this can explain the need for two equiv. of $Mn(OAc)_3$, the former for generation of radical **22** and the latter for the final oxidation. It is therefore unnecessary to admit the intermediate formation of compound **9** by hydrogen abstraction from whatever species (Scheme 4, route *a*), since this would require two additional equiv. of Mn(III) to restart the cyclisation process. The tandem ring closure involving the cyano and thiocarbonyl groups (Scheme 4, route *b*) is probably the key process that shifts the equilibria towards the aceanthrylene derivative. In the absence of such a route only mixtures of rearranged and unrearranged compounds and their hydrolysis products can be obtained. The fact that **2** is quantitatively obtained with two equiv. of manganic salt also starting from **1** (rather than **8**) suggests that either the Mn(III)-catalysed cyclisation of thiourea to the corresponding imine is not a radical process or the result of that cyclisation is a radical species that reacts further to give **2** before being quenched by some atom-transfer reaction. The latter hypothesis could be supported by the important side-products always obtained when we treated **8** (instead of **1**) with $Mn(OAc)_3$ (see Section 4). At this stage we cannot say anything else about the mechanism; the issue of when and how DEM intervenes in the reaction remains an unsettled question as well.

To our knowledge, additions of iminyl radicals to the sulphur atom of thiocarbonyls have never been observed. Nevertheless, very recently, we observed some homolytic intramolecular substitutions of iminyl radicals onto the sulphur atom of sulphide moieties resulting in the formation of benzoisothiazole rings.[14] This can definitely be mentioned as a good support for our hypothesis. Furthermore, it is worth pointing out that only a radical mechanism can conveniently explain the formation of a nitrogen–sulphur bond like that of **2**.

Additional support to the presence of radical mechanisms is also given by the side-products **14** and **15** (Scheme 3). These compounds can be easily rationalised by homolytic aromatic substitution of a thioamidyl radical on either aryl rings of the starting compound. More precisely, compound **14** can arise from cyclisation of thioamidyl **27** on the cyano-substituted aryl ring of thiourea **10**, whereas quinazolinothiophene **15** is the result of ring closure of thioamidyl **28** on the phenyl ring of the intermediate iminoquinazoline **17** (Scheme 5). Alternatively, **15** might also arise from prior cyclisation of thioamidyl **27** on the unsubstituted ring,



Scheme 4. Radical mechanism of formation of compound **2**.

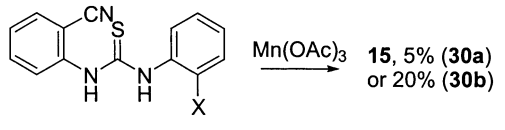


Scheme 5. Radical side-reactions of thioureido radicals.

followed by ring closure to the eventual iminoquinazoline. An analogous compound (**29**) was also obtained in ~30% yield in the reaction of imine **8** with Mn(III) and DEM in acetic acid (Table 1, entry b): its structure was confirmed by X-ray diffraction.

Homolytic aromatic substitution by sulphur-centred radicals is a reversible process[15] and substitution products are formed only in the presence of either a good radical leaving group, e.g. halogen atoms[16] or arylthio moieties,[17] or in a highly oxidising medium that is able to oxidise the intermediate cyclohexadienyl radical.[18] In our case, it is plausible that Mn(III) could be the oxidising agent for the cyclohexadienyls, thus shifting the equilibria towards the cyclisation products.

It is also worth noting that the reactions of the *N′*-substituted *N*-(2-cyanophenyl)thioureas **30a,b** with Mn(III) showed that the presence on the *N′*-ring of *ortho*-substituents such as chloro or methylsulphanyl again led to the formation of compound **15** (Scheme 6): this can be obviously rationalised by homolytic ipso-substitution of the thioamidyl **28** (or **27**) onto the C–Cl or C–SMe aromatic carbon. This result, together with the significant increase of the yield of **15** (20%) obtained with the SMe moiety, clearly stands for a radical mechanism.



Scheme 6.

With the aim of finding additional support to our hypothesis of a radical translocation (Scheme 4), we performed theoretical semiempirical calculations on the intermediates and transition states involved in the rearrangement of radical **28**. The results are summarised in Fig. 4.

Since semiempirical methods are not suitable to estimate *absolute* activation barriers, we should focus our attention to the *relative* quantities that were furnished by calculations. Those data clearly indicate that once radical **28** has fragmented, the resulting intermediate **31** (or **32**) can evolve into the cyclised structure **33** by surmounting an activation barrier (E_a=9.9 kcal/mol) that is 2.5 times lower than that of the reverse reaction (E_{ar}=24.4 kcal/mol). Therefore, in the absence of significant, fast side-reactions, it is conceivable to state that **28** can be totally converted into the thermodynamically preferred isomeric radical **33**. In the presence of a fast route that can transform the latter rearranged radical into another intermediate, like in the case of the formation of compound **2** (Scheme 4), the reaction is hence supposed to yield products not derived from **28** but instead from **33**. The results of calculations are therefore perfectly consistent with the proposed mechanism.

3. Conclusions

Treatment of 2-cyanophenyl isothiocyanate **1** with

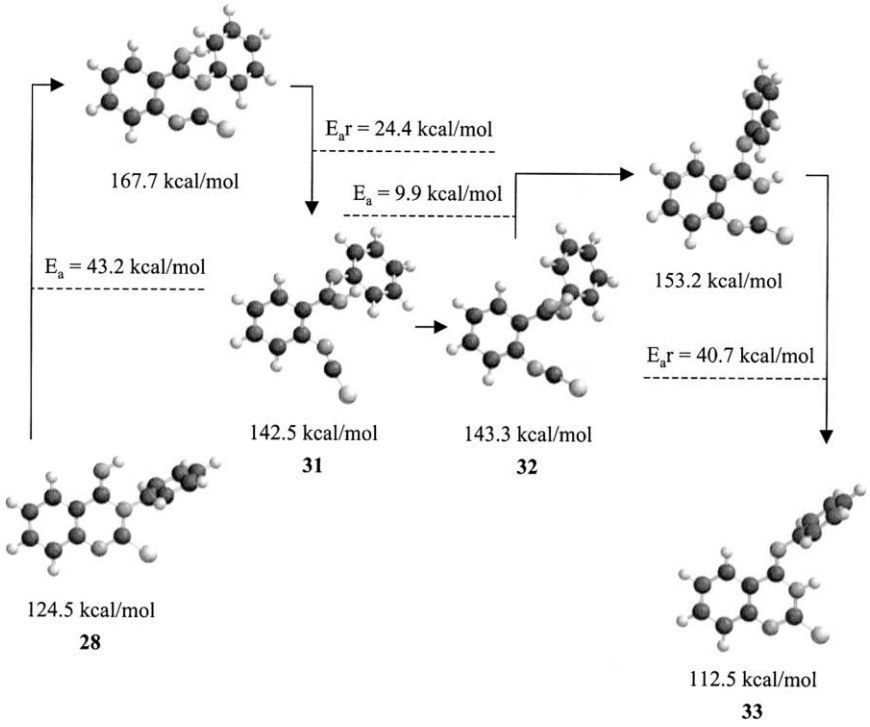


Figure 4. Reaction pathway (with calculated intermediates and transition states) for the rearrangement of radical **28**.

$Mn(OAc)_3$ in acetic acid or acetonitrile results in formation of the novel polycondensed nitrogen-heterocycle **2** in fair yields. The presence of diethyl malonate brings about a significant increase of the yield (~90%). The formation of **2** probably involves formation of a *N*,*N*′-bis(2-cyanophenyl)thiourea, cyclisation to an iminoquinazoline, and an (apparent) aryl translocation that resembles the Dimroth rearrangement but instead probably entails a radical mechanism initiated by Mn(III)-oxidation of the thioamido moiety. Eventually, a radical cascade reaction brings it to the final heterocycle.

The high efficiency of this process, which involves so many steps; the totally new structure of the aceanthrylene derivative **2** with an interesting N–S linkage; the novelty of the Dimroth-like radical rearrangement; the unprecedented radical addition of an iminyl to a thioureido group; in the end, the possibility that mild radical generation from thioamido moieties by $Mn(OAc)_3$ discloses novel synthetic routes; in our opinion, make this reaction remarkable. Studies are underway to exploit the potentialities in organic synthesis of the Mn(III)-mediated oxidation of thioureido compounds and their analogues.

4. Experimental

4.1. General procedures

Melting points were determined on an Electrothermal capillary apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in chloroform-d_1 (where not stated), deuterated dimethylsulphoxide (DMSO-d_6), or acetonitrile (MeCN-d_6) on Varian Gemini 200 (200 MHz) or 300 (300 MHz) instruments; the reference was tetramethylsilane with $CDCl_3$ and the solvent signal with DMSO and MeCN. Mass spectra (MS) and high-resolution mass spectra (HRMS) were performed with a VG 7070E spectrometer by electron impact with a beam energy of 70 eV. IR spectra were recorded in chloroform on a Perkin–Elmer 257 instrument or in nujol on a Perkin–Elmer Spectrum RX I FT-IR spectrophotometer. Column chromatography was carried out on silica gel (ICN Silica, 63–200, 60 Å) using light petroleum (40–70°C) and a light petroleum/diethyl ether (or dichloromethane) gradient (from 0 up to 100% more polar component) as eluant. Previously reported reaction products were identified by spectral comparison and/or mixed mp determination with authentic specimens.

4.2. Starting materials

Thiophosgene, anthranilonitrile, methyl anthranilate, diethyl malonate (Aldrich), and manganese(III) acetate dihydrate (Acros) were commercially available.

4.3. Synthesis of the aryl isothiocyanates 1 and 3

4.3.1. General procedure.[19] A dichloromethane (25 mL) solution of anthranilonitrile or methyl anthranilate (0.1 mol) was added dropwise in 10 min at rt to a dichloromethane (15 mL)/water (35 mL) solution of thiophosgene (14.4 g, 0.125 mol). The mixture was stirred at rt for 3 h. Additional dichloromethane was added (50 mL) and the organic layer was separated and dried (sodium sulphate). The solvent was evaporated and the residue crystallised (**1**) or distilled (**3**) to give the title isothiocyanate.

4.3.2. 2-Isothiocyanatobenzenecarbonitrile (1).[19] Yield= 82%; mp=62–63°C (pale-yellow needles, from light petroleum); 200 MHz ^1H NMR δ 7.29–7.41 (2H, m),

7.55–7.62 (2H, m); 50 MHz ^{13}C NMR δ 109.87 (q), 115.89 (q), 127.45, 127.73, 133.81, 134.56, 141.06 (q, very broad, NCS) (one quat. carbon not apparent); ν_{max} 2220 (CN), 2020 (vs, NCS) cm^{-1}; MS *m/e* (rel inten) 160 (M^+, 100), 133 (6), 116 (8), 102 (40), 76 (17), 75 (30).

4.3.3. Methyl 2-isothiocyanatobenzenecarboxylate (3). Yield=80%; bp (6 mbar)=143–145°C [lit.[20] bp (0.35 mmHg)=100–102°C].

4.4. Reactions of the aryl isothiocyanates with manganese(III) acetate

4.4.1. General procedure. A mixture of aryl isothiocyanate **1** or **3** (5 mmol), diethyl malonate (DEM, 5 mmol), and manganese(III) acetate dihydrate (5 mmol) in acetic acid or acetonitrile (25 mL) was stirred at the appropriate temperature (60 or 80°C) until the starting brown colour of manganese(III) turned yellowish. Another equiv. (5 mmol) of $Mn(OAc)_3$ was then added and the mixture was stirred until reduction of additional Mn(III) was complete; at this point all the starting material was consumed as well. The mixture was poured into water, neutralised with 10% aqueous sodium carbonate, and then extracted with dichloromethane. The organic phase was dried (sodium sulphate), the solvent was evaporated, and the residue chromatographed on a silica gel column. The following reactions were performed according to this general procedure. All of the column chromatographies separated an initial fraction containing elemental sulphur.

It is worth noting that the starting material was entirely recovered by treatment of **1** in acetic acid or acetonitrile at 60°C in the absence of Mn(III) and/or diethyl malonate.

4.4.2. Reactions of 1 in acetic acid. After 38 h (18 h for the first equivalent of Mn(III) and 20 h for the second one), column chromatography of the crude (light petroleum/dichloromethane 80:20 v/v) afforded *6-thia-5,7,11c,12-tetraazabenzo[e]aceanthrylene* (**2**) (87%), pale-yellow solid, mp=224–227°C (from ethyl acetate); 200 MHz ^{1}H NMR δ 7.27–7.42 (3H, m), 7.55–7.65 (3H, m), 8.13 (1H, bd, J=7.5 Hz), 8.36 (1H, dd, J_1=7.8 Hz, J_2=1.4 Hz); 50 MHz ^{13}C NMR (DMSO-d_6) δ 124.24, 125.20, 126.10, 126.25, 127.14, 127.58, 134.47, 134.76;[21] ν_{max} 3000, 1630, 1610, 1590, 1470 cm^{-1}; MS *m/e* (rel inten) 276 (M^+, 100), 138 (11), 102 (15), 41 (23). Anal. calcd for $C_{15}H_8N_4S$: C, 65.20; H, 2.92; N, 20.28. Found: C, 65.38; H, 2.91; N, 20.24. See below for the X-ray characterisation of **2**.

In the absence of DEM the reaction was complete after 64 h, the yield of **2** dropped to ~50%, and some *N-(2-cyanophenyl)acetamide* (10%) was separated, mp=132–134°C (lit.[22] mp=133°C). At 80°C the reaction was complete after 10 h (4+6 h), but chromatography of the crude (light petroleum/dichloromethane 80:20 v/v) gave **2** in only 20% yield together with *N-(2-cyanophenyl)acetamide* (6%).

4.4.3. Reactions of 1 in acetonitrile at 60°C. After 38 h (18+20 h), column chromatography of the crude (light petroleum/dichloromethane 80:20 v/v) afforded **2** (87%) and anthranilonitrile (trace amounts). In the absence of DEM the reaction was complete after 64 h (28+36 h) and column chromatography of the crude (light petroleum/dichloromethane 80:20 v/v) yielded **2** (47%), anthranilonitrile (trace amounts), and *N-(2-cyanophenyl)acetamide* (31%).

4.4.4. Reaction of 3 with DEM in acetic acid at 60°C. After 24 h (12+12 h), column chromatography of the crude (light petroleum/diethyl ether 85:15 v/v) afforded *methyl 2-[4-oxo-2-thioxo-1,4-dihydro-3(2H)-quinazolinyl]-benzenecarboxylate* (**4**) (31%), mp=238–240°C (from ethyl acetate) [200 MHz ^{1}H NMR δ 3.75 (3H, s), 7.15 (1H, d, J=7.8 Hz), 7.27–7.38 (2H, m), 7.55–7.70 (3H, m), 8.17 (1H, dd, J_1=8.2 Hz, J_2=1.0 Hz), 8.24 (1H, dd, J_1=7.8 Hz, J_2=1.6 Hz), 10.60 (1H, bs); 50 MHz ^{13}C NMR δ 52.84, 115.45, 116.87 (q), 125.49, 127.72 (q), 129.24, 129.82, 130.86, 132.48, 134.37, 136.15, 139.38 (q), 139.72 (q), 160.81 (q), 165.09 (q), 176.88 (q); ν_{max} 3400, 3000, 1720, 1700, 1620 cm^{-1}; MS *m/e* (rel inten) 312 (M^+, 15), 281 (3), 253 (100), 162 (7), 90 (7). Anal. calcd for $C_{16}H_{12}N_2O_3S$: C, 61.52; H, 3.87; N, 8.96. Found: C, 61.80; H, 3.88; N, 9.00.], *methyl 2-(acetylamino)benzenecarboxylate* (**5**, 6%), mp=97–99°C (lit.[23] mp=101°C) [200 MHz ^{1}H NMR δ 2.09 (3H, s), 3.77 (3H, s), 6.92 (1H, td, J_t=7.2 Hz, J_d=0.8 Hz), 7.39 (1H, td, J_t=7.7 Hz, J_d=1.7 Hz), 7.88 (1H, dd, J_1=7.2 Hz, J_2=1.7 Hz), 8.56 (1H, dd, J_1=7.7 Hz, J_2=0.8 Hz), 10.91 (1H, bs); 50 MHz ^{13}C NMR δ 25.95, 52.77, 115.20 (q), 120.75, 122.87, 131.23, 135.11, 142.02 (q), 169.21 (q), 169.53 (q); ν_{max} 3320, 2960, 1710, 1690, 1610, 1590 cm^{-1}; MS *m/e* (rel inten) 193 (M^+, 32), 151 (64), 119 (100), 92 (8), 43 (29)], and a solid, mp=130–132°C, whose structure was not fully established but, since only three aromatic protons were observed, it is probably the result of some cyclisation of the isothiocyanato moiety on the benzenic ring [200 MHz ^{1}H NMR δ 3.98 (3H, s), 7.20 (1H, dd, J_1=J_2=7.9 Hz), 7.57 (1H, bd, J=7.9 Hz), 7.88 (1H, dd, J_1=7.9 Hz, J_2=1.0 Hz), 10.15 (1H, bs); 50 MHz ^{13}C NMR δ 53.10, 113.16 (q), 122.73, 126.78 (q), 127.75, 127.81 (q), 128.04, 166.92 (q), 170.15 (q); ν_{max} 3370, 3000, 1700 (b), 1600, 1450, 1290 cm^{-1}; MS *m/e* (rel inten) 209 (M^+, 51), 177 (100), 121 (32). HRMS calcd for $C_9H_7NO_3S$ 209.0147, found 209.0150]: we suggest the structure of (previously unreported) *methyl 2-oxo-2,3-dihydro-1,3-benzothiazole-4-carboxylate*.

The same compounds and yields were obtained by reacting **3** with Mn(III) in acetic acid in the absence of diethyl malonate. On the contrary, only the unreacted starting material was recovered after 48 h in the reaction of **3** with diethyl malonate in acetic acid in the absence of manganic acetate.

4.5. Synthesis of *N,N′*-diarylthioureas (or the corresponding imines)

4.5.1. General procedure. A toluene (25 mL) solution of arylamine (20 mmol) was added dropwise at 35°C to a toluene (25 mL) solution of isothiocyanate **1** (20 mmol) and cat. amount of *p*-toluenesulphonic acid. The resulting solution was stirred at 35°C for 24 h; then cooled and filtered to give the thiourea derivatives as highly insoluble solids. With 2-aminobenzonitrile the corresponding iminoquinazoline **8** was obtained instead of the expected thiourea **7**.

4.5.2. *N*-(2-Cyanophenyl)-*N′*-phenylthiourea (10). Yield=86%, mp=242–243°C (lit. mp=165–168°C[10a] and >300°C[22]); ν_{max} ($CHCl_3$) 3400, 3360, 2215, 1585 cm^{-1}; MS *m/e* (rel inten) 253 (M^+, 100), 252 (45), 220 (30), 195 (30), 93 (15), 77 (35).

4.5.3. *N*-(2-Cyanophenyl)-*N′*-(2-chlorophenyl)thiourea (30a). The general procedure was slightly modified by using dichloromethane (25 mL) to dissolve 2-chloroaniline and a dichloromethane/light petroleum 1:1 mixture (25 mL) to dissolve **1**. Yield=85%, mp=240–243°C; 300 MHz ^1H NMR (DMSO-d_6) δ 7.37 (1H, t, J=7.7 Hz), 7.43 (1H, d, J=8.0 Hz), 7.49–7.64 (3H, m), 7.65–7.79 (2H, m), 8.23 (1H, d, J=8.0 Hz), 12.30 (1H, bs, NH), one NH signal not apparent; both NH signals seem to be apparent, as a single peak, in acetonitrile solvent [300 MHz ^1H NMR (MeCN-d_3) δ 7.33–7.52 (3H, m), 7.55–7.76 (4H, m), 7.79 (1H, dd, J_1=7.7 Hz, J_2=1.6 Hz), 8.55 (2H, bs, NH); ν_{max} (nujol) 3331, 3216, 2238, 1638, 1615, 1544, 1466, 1415 cm^{-1}; MS *m/e* (rel inten) 289 (M^++2, 18), 287 (M^+, 50), 252 (100), 219 (7), 161 (8), 111 (10), 90 (11). Anal. calcd for $C_{14}H_{10}ClN_3S$: C, 58.43; H, 3.50; N, 14.60. Found: C, 58.63; H, 3.49; N, 14.65].

4.5.4. *N*-(2-Cyanophenyl)-*N′*-[2-(methylsulphanyl)phenyl]-thiourea (30b). Yield=85%, mp=224–226°C; ν_{max} (nujol) 3254, 3186, 2224, 1575, 1534, 1498 cm^{-1}; MS *m/e* (rel inten) 299 (M^+, 77), 266 (24), 252 (100), 220 (10), 161 (10), 106 (30), 102 (19). Anal. calcd for $C_{15}H_{13}N_3S_2$: C, 60.17; H, 4.37; N, 14.03. Found: C, 60.40; H, 4.39; N, 13.99. As soon as compound **30b** is dissolved in DMSO, it appears to cyclise to the corresponding iminoquinazoline; the following NMR spectrum is consistent with the latter structure (6:4 mixture of imine geometric isomers): 300 MHz ^1H NMR (DMSO-d_6) δ 6.60 (0.6H, bs, imine NH), 7.29–7.65 (6H, m), 7.71 (1H, t, J=7.5 Hz), 8.19 (1H, d, J=7.7 Hz), 9.28 (0.4H, bs, imine NH), 12.49 (1H, bs, thioamide NH);[24] attempts to record spectra in less polar solvents were unsuccessful, due to the extreme insolubility of **30b**. An IR spectrum recorded after the NMR experiment showed totally different NH and CN stretching regions, thus confirming complete conversion of **30b** to the corresponding iminoquinazoline: ν_{max} (nujol) 3213, 1636, 1614, 1543, 1414, 1304, 1259, 1229, 1183 cm^{-1}. This compound melts at 224–226°C, so that it is presumable that the mp reported above for **30b** is actually that of the cyclisation product.

4.5.5. 2-[4-Imino-2-thioxo-1,4-dihydro-3(2*H*)-quinazolinyl]benzonitrile (8). This product was always obtained by any attempt to synthesise thiourea **7** from **1** and 2-aminobenzonitrile. Yield=80%, mp=172–175°C (dec.); 300 MHz ^1H NMR (DMSO-d_6) δ 7.40 (1H, t, J=7.7 Hz), 7.46 (1H, d, J=8.0 Hz), 7.66–7.78 (3H, m), 7.93 (1H, ddd, J_1=J_2=8.0 Hz, J_3=1.4 Hz), 8.08 (1H, dd, J_1=7.7 Hz, J_2=1.1 Hz), 8.27 (1H, d, J=7.7 Hz), 9.35 (1H, bs, NH), 12.58 (1H, bs, NH); 75 MHz ^{13}C NMR (DMSO-d_6) δ 112.83 (q), 115.14 (q), 115.97, 116.31 (q), 124.31, 126.22, 128.84, 130.96, 133.23, 133.76, 134.33, 136.10 (q), 143.37 (q), 153.93 (q), 174.49 (q); ν_{max} (nujol) 3220, 2235, 1641, 1618, 1548, 1417, 1244, 1186 cm^{-1}; MS *m/e* (rel inten) 278 (M^+, 34), 277 (100), 139 (7), 102 (8). Anal. calcd for $C_{15}H_{10}N_4S$: C, 64.72; H, 3.62; N, 20.12. Found: C, 65.02; H, 3.61; N, 20.24.

4.5.6. Synthesis of 2-[(2-thioxo-1,2-dihydro-4-quinazolinyl)amino]benzonitrile (9). A solution of iminoquinazoline **8** (2.78 g, 10 mmol) in aqueous acetonitrile (0.4 mL of water in 50 mL of MeCN) was kept at 60°C for 150 h. The reaction mixture was cooled, the solvent was evaporated and the residue chromatographed to give the title compound, yield=70%, mp=324–326°C (dec.); 300 MHz ^1H NMR (DMSO-d_6) δ 7.15–8.45 (8H, m), 10.62 (1H, bs, NH), 11.35 (1H, bs, NH), 12.54 (1H, bs, NH), 12.91 (1H, bs, NH); ν_{max} (nujol) 3260, 2215, 1625, 1610 cm^{-1}; MS *m/e* (rel inten) 278 (M^+, 34), 277 (100), 139 (9), 102 (8), 76 (4). Anal. calcd for $C_{15}H_{10}N_4S$: C, 64.72; H, 3.62; N, 20.12. Found: C, 65.05; H, 3.60; N, 20.26. The ^1H NMR spectrum shows that compound **9** exists as a nearly 1:1 mixture of isomers arising from tautomerism of the –NH–C=N– moiety. The reported spectrum is not a mixture of **8** and **9**, since the higher-field NH signal of **8** clearly disappeared. The formation of a new species was clearly evidenced as well by the significantly different absorptions showed by the IR spectrum. The structure of **9** was also confirmed by its hydrolysis with dioxane/HCl, which yielded *2-thioxo-2,3-dihydro-4(1H)-quinazolinone* (**21**) in ~70% yield (identified by comparison with an authentic, commercial sample [Aldrich]).

4.6. Reactions of iminoquinazoline 8

4.6.1. Reaction of 8 with $Mn(OAc)_3$ in acetic acid (Table 1, entry a). Following the general procedure in Section 4.4.1, after 14 h column chromatography separated **2** (25%), mp=224–226°C (spectral data identical to those reported in Section 4.4.2) and *13H-quinazolino[3,4-a]quinazolin-13-one* (5%), mp=112–115°C (dec.) [ν_{max} ($CHCl_3$) 1693 cm^{-1}; MS *m/e* (rel inten) 247 (M^+, 100), 219 (85), 129 (18), 119 (25), 102 (35), 76 (23); HRMS calcd for $C_{15}H_9N_3O$ 247.0746, found 247.0752]; the latter compound could not be purified, but its 300 MHz ^1H NMR spectrum (DMSO-d_6) clearly showed the signal due to the H-2 proton (δ 8.53, s); the structure was also deduced by its analogies with compound **29** (see below), which it can derive from by desulphuration.[25] The reaction also afforded major amounts of an unidentifiable product with (apparent) *m/e* 259, which proved to be completely insoluble in all of the most common solvents.

4.6.2. Reaction of 8 with $Mn(OAc)_3$ and DEM in acetic acid (Table 1, entry b). Following the general procedure in Section 4.4.1, after 22 h column chromatography afforded **2** (50%) and *11H-4-thia-5,10,11c-triazacyclopenta[def]chrysen-11-one* (**29**, 30%), mp=295–300°C [300 MHz ^1H NMR (DMSO-d_6) δ 7.86 (1H, t, J=7.5 Hz), 7.95–8.03 (2H, m), 8.12 (1H, d, J=7.7 Hz), 8.17 (1H, d, J=8.0 Hz), 8.49 (1H, d, J=7.7 Hz), 8.75 (1H, d, J=7.7 Hz); ν_{max} (nujol) 1657, 1595, 1511 cm^{-1}; MS *m/e* (rel inten) 277 (M^+, 58), 249 (100), 217 (7). Anal. calcd for $C_{15}H_7N_3OS$: C, 64.97; H, 2.54; N, 15.15. Found: C, 65.41; H, 2.54; N, 15.19.]. The structure of **29** was confirmed by X-ray diffraction (Fig. 5).

4.6.3. Reaction of 8 with $Mn(OAc)_3$ in acetonitrile (Table 1, entry c). Following the general procedure in Section 4.4.1, after 48 h column chromatography afforded **2** (70%) together with traces of some unidentified products.

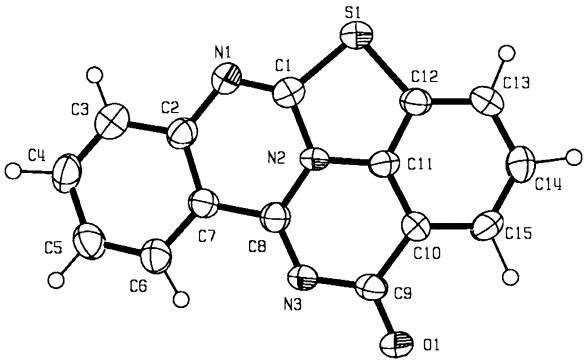


Figure 5. Molecular structure of **29**, showing the atom labelling scheme.

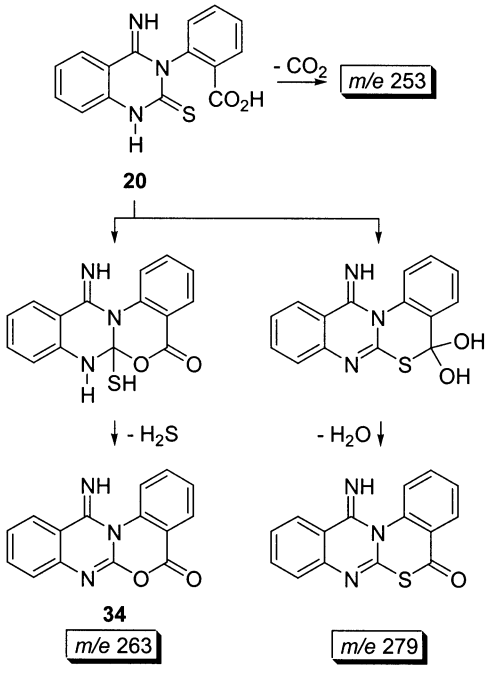
4.6.4. Reaction of 8 with $Mn(OAc)_3$ and DEM in acetonitrile (Table 1, entry d). Following the general procedure in Section 4.4.1, after 48 h column chromatography afforded **2** (83%) together with traces of some unidentified products.

4.6.5. Reaction of 8 in acetonitrile/water in the absence of $Mn(OAc)_3$ (Table 1, entry e). Following the general procedure in Section 4.4.1, after 150 h column chromatography separated compound **9** (40%) and **2** (trace amounts), together with 33% of unreacted starting material.

4.6.6. Reaction of 8 in acetic acid/water in the absence of $Mn(OAc)_3$. Following the general procedure in Section 4.4.1, after 48 h column chromatography yielded *2-[4-oxo-2-thioxo-1,4-dihydro-3(2H)-quinazolinyl]benzonitrile* (**19**, 27%), mp=293–296°C [300 MHz ^{1}H NMR (DMSO-d_6) δ 7.20 (1H, bd, J=8.0 Hz), 7.36 (1H, ddd, J_1=7.9 Hz, J_2=7.5 Hz, J_3=0.9 Hz), 7.47 (1H, ddd, J_1=8.0 Hz, J_2=1.1 Hz, J_3=0.5 Hz), 7.62 (1H, ddd, J_1=J_2=7.7 Hz, J_3=1.1 Hz), 7.72 (1H, ddd, J_1=8.2 Hz, J_2=7.3 Hz, J_3=1.3 Hz), 7.79 (1H, dd, J_1=7.8 Hz, J_2=1.6 Hz), 7.87 (1H, bdd, J_1=7.4 Hz, J_2=1.6 Hz), 8.19 (1H, ddd, J_1=7.9 Hz, J_2=1.3 Hz, J_3=0.3 Hz), 10.75 (1H, bs, NH); 75 MHz ^{13}C NMR (DMSO-d_6) δ 112.59 (q), 115.95 (q), 116.47, 125.58, 128.05, 130.10, 131.09, 133.73, 135.05, 136.94, 140.04 (q), 142.03 (q), 160.08 (q), 175.63 (q) (one quaternary carbon not apparent); ν_{max} ($CHCl_3$) 3400, 2220, 1710, 1625, 1610 cm^{-1}; MS *m/e* (rel inten) 279 (M^+, 100), 278 (46), 246 (15), 220 (8), 162 (12), 145 (26), 119 (43), 90 (18). Anal. calcd for $C_{15}H_9N_3OS$: C, 64.50; H, 3.24; N, 15.04. Found: C, 64.85; H, 3.23; N, 15.10]. The reaction also afforded major amounts of an unidentifiable compound with (apparent) *m/e* 278.

4.6.7. Hydrolysis of 8 in dioxane/HCl. A solution of **8** (1.11 g, 4 mmol) in a mixture of 1,4-dioxane (30 mL) and 10% aqueous hydrochloric acid (20 mL) was refluxed for 6 h. The mixture was then poured into an aqueous solution of ammonium hydroxide and extracted with dichloromethane. The organic phase was separated and dried, the solvent was evaporated and the residue chromatographed to give **19** (20%), mp=293–296°C (spectral data identical to those reported in Section 4.6.6), *2-[4-imino-2-thioxo-1,4-dihydro-3(2H)-quinazolinyl]benzoic acid* (**20**, 28%), mp=278–280°C (dec.) [200 MHz ^{1}H NMR (DMSO-d_6) δ 7.17 (1H, bs, imine NH), 7.38–7.50 (2H, m), 7.55 (1H, d, J=8.2 Hz), partially overlapped with 7.59 (1H, ddd, J_1=J_2=7.4 Hz, J_3=1.4 Hz), 7.65–7.80 (1.3H, bs+ddd, J_1=J_2=7.3 Hz, J_3=1.5 Hz), 7.82–7.94 (2H, m), 8.05 (1H, dd, J_1=7.9 Hz, J_2=0.9 Hz), 12.98 (0.7H, bs) (carboxylic OH not apparent). This compound seems to show significant tautomerism of the NHCS moiety, since the signal at 12.98 ppm is clearly ascribable to less than one proton; the remaining part appears as a very broad singlet at ~7.7 ppm, partially overlapped with the aromatic protons. 50 MHz ^{13}C NMR (DMSO-d_6) δ 119.48, 119.92 (q), 128.05, 131.30, 132.15, 132.46, 134.57, 134.79, 136.60 (q), 139.28, 141.67 (q), 143.45 (q), 163.58 (q), 171.00 (q), 179.70 (q); ν_{max} (nujol) 3396, 1680, 1652, 1538, 1406, 1202 cm^{-1}; MS *m/e* (rel inten) 297 (M^+, 1), 279 (1), 263 (13), 253 (100), 235 (6), 145 (4), 134 (11), 92 (15), 90 (47), 64 (28). HRMS calcd for $C_{15}H_{11}N_3O_2S$ 297.0572, found 297.0585], and *2-thioxo-2,3-dihydro-4(1H)-quinazolinone* (**21**, 4%), mp=295–300°C (identified by comparison with a commercial sample).

Compound **20** was identified on the basis of the following reasoning. The MS spectrum of **20** shows a very low molecular ion (*m/e* 297 [<1]) but the two observed main fragments (*m/e* 263 [13%] and 253 [100%]) definitely originate from it. Those peaks derive from the molecular ion by loss of H_2S and CO_2, respectively. This was proved by a B/E experiment, which also showed significant loss of water (*m/e* 279) from the M^+. At the beginning of the MS analysis, before vaporisation of the sample, thermal fragmentation with loss of H_2S occurs as a minor reaction since a clean spectrum of a compound with M^+ 263 and main fragments at *m/e* 235, 207, 145, and 90 (100%) appears at T~200°C; further heating brings about volatilisation of the compound with concomitant major loss of CO_2. The base peak at *m/e* 253 in the MS spectrum and the decomposition observed during melting point determination, together with the other IR and NMR spectral data, clearly stand for the presence of a carboxylic group. On the other hand, the facile loss of H_2S



Scheme 7. Fragmentation pattern of compound **20**.

and H_2O can only be explained by a structure in which the carboxyl and thiocarbonyl groups are close enough to react with each other in the way shown in Scheme 7.

As a further evidence, when **20** was allowed to react again for several hours in a refluxing dioxane/conc. hydrochloric acid solution, it afforded a mixture containing compound **34** as the major product. This was proved by MS and IR analyses of the crude. The former revealed a compound substantially identical in molecular ion and fragments to that obtained from **20** at the beginning of the MS analysis (M^+ 263); the latter showed an unambiguous new absorption at 1724 cm^{-1} due to the new lactone carbonyl group of **34**. These data are altogether clearly consistent with a structure still containing the aryl ring linked to the N-3 atom. Therefore, they confirm that no significant rearrangement occurred during the reaction under investigation.[26]

4.7. Reactions of the *N,N′*-diarylthioureas 10, 30a, and 30b with $Mn(OAc)_3$

4.7.1. General procedure. The general procedure described for the reactions of isothiocyanates **1** and **3** with $Mn(OAc)_3$ was used (Section 4.4.1). However, thioureas **10** and **30b** required three equiv. of Mn(III) instead of two for complete disappearance of the starting material.

4.7.2. Reaction of 10. After 30 h column chromatography separated *12H-[1,3]benzothiazolo[2,3-b]quinazolin-12-one* (**15**, 6%), mp=190–192°C (lit.[27a] mp=193°C) [the structure of **15** was confirmed by spectral comparison with an authentic specimen prepared according to the literature:[27a] 300 MHz ^{1}H NMR δ 7.42–7.56 (4H, m), 7.64 (1H, dd, J_1=7.5 Hz, J_2=1.5 Hz), 7.69 (1H, bd, J=8.2 Hz), 7.81 (1H, ddd, J_1=8.4 Hz, J_2=7.3 Hz, J_3=1.5 Hz), 8.45 (1H, dd, J_1=8.0 Hz, J_2=1.6 Hz), 9.05 (1H, dd, J_1=8.1 Hz, J_2=1.6 Hz); ν_{max} (nujol) 1785, 1595, 1580, 1555 cm^{-1}; MS *m/e* (rel inten) 252 (M^+, 100), 224 (21), 134 (6), 90 (11)], *2-anilino-1,3-benzothiazole-4-carbonitrile* (**14**, 8%), mp=184–186°C [200 MHz ^{1}H NMR δ 7.24–7.40 (4H, m), 7.51–7.62 (3H, m), 7.66 (1H, dd, J_1=7.5 Hz, J_2=0.6 Hz), 8.10 (1H, dd, J_1=7.9 Hz, J_2=0.6 Hz); in $CDCl_3$ the NH proton gives a signal overlapped with the aromatic system, whereas in DMSO-d_6 it is significantly deshielded (~11 ppm); 50 MHz ^{13}C NMR δ 105.62 (q), 117.27 (q), 123.87, 126.22, 129.06, 130.19, 130.66, 131.19, 134.63 (q), 139.86 (q), 148.50 (q), 171.83 (q); ν_{max} ($CHCl_3$) 3420, 2220, 1690, 1600, 1560 cm^{-1}; MS *m/e* (rel inten) 251 (M^+, 100), 250 (44), 225 (9), 121 (8), 77 (16).[28] Anal. calcd for $C_{14}H_9N_3S$: C, 66.91; H, 3.60; N, 16.72. Found: C, 67.21; H, 3.58; N, 16.82], *N-phenyl-4-quinazolinamine* (**12**, 14%), mp=215–218°C (lit.[11a] mp=220–221°C)[29] [300 MHz ^{1}H NMR (DMSO-d_6) δ 7.12 (0.9H, bt, J=7.0 Hz), 7.21 (0.1H, bt, J=7.8 Hz), 7.30–7.50 (m), 7.62 (0.9H, ddd, J_1=7.8 Hz, J_2=7.2 Hz, J_3=1.2 Hz), 7.68 (0.1H, bt, J=7.8 Hz), 7.75–7.95 (m), 8.52–8.62 (2H, s [H-2]+d [J=7.8 Hz] of the major isomer overlapped with the corresponding signals of the minor one), 9.80 (0.9H, bs, NH), 11.58 (0.1H, bs, NH);[30] 75 MHz ^{13}C NMR (DMSO-d_6) δ 114.29 (q, minor), 115.14 (minor), 115.16 (q, major), 122.44 (major), 122.96 (major), 123.70 (major), 126.17 (major), 127.53 (minor), 127.78 (major), 128.04 (minor), 128.41 (major), 128.74 (minor), 129.05 (minor), 132.94 (major), 135.13 (minor, H-2), 135.72 (q, minor), 139.11 (q, major), 139.78 (q, minor), 149.66 (q, major), 150.17 (q, minor), 154.48 (major, H-2), 157.74 (q, major);[30] ν_{max} ($CHCl_3$) 3455, 1720, 1670, 1620, 1600, 1570 cm^{-1}; MS *m/e* (rel inten) 221 (M^+, 38), 220 (100), 102 (8), 92 (8), 77 (7)], *4-imino-3-phenyl-3,4-dihydro-2(1H)-quinazolinone* (**11**, 47%), mp=214–218°C (lit.[11a] mp=222–223°C) [300 MHz ^{1}H NMR (DMSO-d_6) δ 6.50 (0.8H, bs), 7.08–7.17 (2H, m), 7.27–7.65 (5H, m), 8.12 (1H, d, J=7.5 Hz), 8.85 (0.2H, bs), 11.03 (1H, bs); ν_{max} ($CHCl_3$) 3420, 3300, 1700, 1620 cm^{-1}; MS *m/e* (rel inten) 237 (M^+, 18), 236 (100), 118 (10), 91 (8)], and *3-phenyl-2,4(1H,3H)-quinazolinedione* (**13**, 8%), mp=277–279°C (lit.[11a] mp=278–281°C).

4.7.3. Reaction of 30a. After 72 h column chromatography separated **15** (5%), *2-(2-chloroanilino)-1,3-benzothiazole-4-carbonitrile* (3%), mp=175–178°C [300 MHz ^{1}H NMR (DMSO-d_6) δ 7.20–7.90 (6 H, m), 8.28 (1H, dd, J_1=8.0 Hz, J_2=1.2 Hz), 11.00 (1H, bs, NH); ν_{max} ($CHCl_3$) 3410, 2210, 1630, 1590 cm^{-1}; MS *m/e* (rel inten) 287 (M^++2, 5), 285 (M^+, 15), 250 (100), 235 (13), 207 (8), 90 (7).[28] Anal. calcd for $C_{14}H_8ClN_3S$: C, 58.84; H, 2.82; N, 14.70. Found: C, 59.02; H, 2.81; N, 14.78], *N-(2-chlorophenyl)-4-quinazolinamine* (15%), mp=106–109°C[31] [300 MHz ^{1}H NMR δ 7.08 (1H, ddd, J_1=J_2=7.7 Hz, J_3=1.4 Hz), 7.38 (1H, ddd, J_1=J_2=7.9 Hz, J_3=1.4 Hz), 7.46 (1H, dd, J_1=8.2 Hz, J_2=1.2 Hz), 7.61 (1H, ddd, J_1=8.2 Hz, J_2=7.0 Hz, J_3=1.1 Hz), 7.82 (1H, ddd, J_1=8.3 Hz, J_2=7.1 Hz, J_3=1.4 Hz), 7.92–7.98 (2H, m), 8.13 (1H, bs, NH), 8.80 (1H, dd, J_1=8.2 Hz, J_2=1.4 Hz), 8.84 (1H, s, H-2); ν_{max} (nujol) 3415, 1730, 1680, 1620, 1600 cm^{-1}; MS *m/e* (rel inten) 257 (M^++2, 4), 255 (M^+, 11), 254 (10), 220 (100), 102 (7), 92 (8). Anal. calcd for $C_{14}H_{10}ClN_3$: C, 65.76; H, 3.94; N, 16.43. Found: C, 66.08; H, 3.92; N, 16.52. The structure of this compound was confirmed by X-ray diffraction (Fig. 6)], *3-(2-chlorophenyl)-4(3H)-quinazolinone* (6%), mp=160–165°C (lit.[32] mp=170°C) [300 MHz ^{1}H NMR (DMSO-d_6) δ 7.65–7.77 (3H, m), 7.80–7.91 (3H, m), 8.02 (1H, ddd, J_1=8.2 Hz, J_2=7.9 Hz, J_3=1.4 Hz), 8.31 (1H, dd, J_1=8.0 Hz, J_2=1.1 Hz), 8.43 (1H, s, H-2); ν_{max} ($CHCl_3$) 1790, 1620, 1590 cm^{-1}; MS *m/e* (rel inten) 258 (M^++2, 2), 256 (M^+, 7), 221 (100), 111 (9), 76 (6)], and *3-(2-chlorophenyl)-4-imino-3,4-dihydro-2(1H)-quinazolinone* (16%), mp=202–204°C [300 MHz ^{1}H NMR (DMSO-d_6) δ 6.61 (0.4H, bs, imine NH), 7.17–7.30 (2H, m), 7.45–7.90 (5H, m+t, J=8.0 Hz), 8.20 (1H, d, J=8.0 Hz), 9.00 (0.6H, bs, imine NH), 11.12 (1H, bs, amide NH); ν_{max} (nujol) 3300, 3190, 1720, 1620 cm^{-1}; MS *m/e* (rel inten) 273 (M^++2, 2), 271 (M^+, 4), 270 (7), 236 (100), 118 (4), 91 (11). Anal. calcd for $C_{14}H_{10}ClN_3O$: C,

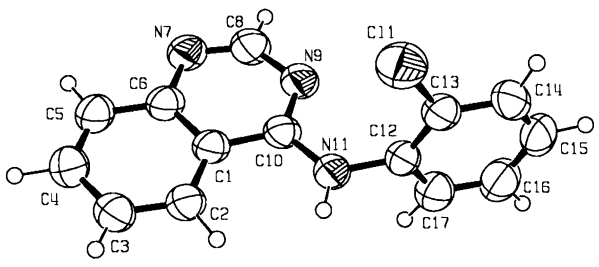


Figure 6. Molecular structure of *N*-(2-chlorophenyl)-4-quinazolinamine, showing the atom labelling scheme.

61.88; H, 3.70; N, 15.46. Found: C, 62.12; H, 3.67; N, 15.53].

4.7.4. Reaction of 30b. After 48 h column chromatography separated **15** (20%) and *4-imino-3-[2-(methylsulphanyl)-phenyl]-3,4-dihydro-2(1H)-quinazolinethione* (20%), mp=224–226°C [MS *m/e* (rel inten) 299 (M^+, 75), 253 (100), 266 (38), 252 (95), 237 (16), 102 (19); the melting point and the ^{1}H NMR spectrum of this compound are identical to those obtained for the cyclisation product of **30b** in DMSO (see Section 4.5.4)]. The reaction also afforded very minor amounts of unidentified compounds.

4.8. X-Ray crystal structure analysis of 6-thia-5,7,11c,12-tetraazabenzo[e]aceanthrylene (2)

Crystal data. Empirical formula $C_{15}H_8N_4S$, formula weight 276.32, temperature 293 K, wavelength CuK_α (1.54178 Å), crystal system monoclinic, space group $P2_1/c$, unit cell dimensions a=15.302(2), b=4.904(1), c=16.582(2) Å, β=107.46(5)°, volume 1187.0(5) Å^3 (by least squares fitting of the setting angles of 28 automatically centred reflections in the range $15.7\leq\theta\leq31.1°$), Z=4, density (calculated) 1.5462 Mg/m^3, absorption coefficient 2.3112 mm^{-1}, F(000) 568.0.

Data collection and processing. Siemens AED diffractometer, $\theta-2\theta$ scan, scan width 1.2+0.34 tg θ°, scan speed 0.05–0.16° s^{-1}, graphite monochromated CuK_α radiation (λ=1.54178 Å). Pale-yellow prismatic crystal, crystal size 0.50×0.35×0.31 mm, theta range for data collection 3.03–70.13°, index ranges $-18\leq h\leq17$, $-5\leq k\leq5$, $-7\leq l\leq20$, reflections collected 2305, independent reflections 2235 [R(int)=0.0201], no absorption correction performed, max. and min. transmission 1.0 and 0.886.

Structure analysis and refinement. The structure was solved by direct methods with SIR92[33] and refined by full matrix least squares on F^2 with SHELX93.[34] The hydrogen atoms were located in a ΔF map and refined isotropically. Data/restraints/parameters 2235/0/213, goodness-of-fit on F^2 0.986, final R indices [$I>2\sigma(I)$] R_1=0.0501, wR_2=0.1602. Maximal Δ/σ=−0.001 and 0.044 for non-hydrogen and hydrogen atoms respectively, maximum and minimum residual peak in the final difference Fourier map 0.319 and −0.318 e A^{-3}. The molecular structure is shown in Fig. 1.

4.9. X-Ray crystal structure analysis of 11H-4-thia-5,10,11c-triazacyclopenta[def]chrysen-11-one (29)

Crystal data. Empirical formula $C_{15}H_7N_3OS$, formula weight 277.30, temperature 293 K, wavelength CuK_α (1.54178 Å), crystal system monoclinic, space group $P2_1/c$, unit cell dimensions a=9.815(2), b=15.854(3), c=7.571(2) Å, β=101.68(2)°, volume 1153.7(5) Å^3 (by least squares fitting of the setting angles of 24 automatically centred reflections in the range $18.2\leq\theta\leq33.5°$), Z=4, density (calculated) 1.5965 Mg/m^3, absorption coefficient 2.4217 mm^{-1}, F(000) 568.0.

Data collection and processing. Siemens AED diffractometer, $\theta-2\theta$ scan, scan width 1.2+0.34 tg θ°, scan speed 0.05–0.16° s^{-1}, graphite monochromated CuK_α radiation (λ=1.54178 Å). Pale-yellow prismatic crystal, crystal size 0.48×0.30×0.28 mm, theta range for data collection 4.60–69.98°, index ranges $0\leq h\leq11$, $0\leq k\leq19$, $-9\leq l\leq9$, reflections collected 2309, independent reflections 2186 [R(int)=0.0456], no absorption correction performed, max. and min. transmission 1.0 and 0.931.

Structure analysis and refinement. The structure was solved by direct methods with SIR92[33] and refined by full matrix least squares on F^2 with SHELX93.[34] The hydrogen atoms were located in a ΔF map and refined isotropically. Data/restraints/parameters 1837/0/209, goodness-of-fit on F^2 0.853, final R indices [$I>2\sigma(I)$] R_1=0.0532, wR_2=0.1332. Maximal Δ/σ=0.000 for both non-hydrogen and hydrogen atoms, maximum and minimum residual peak in the final difference Fourier map 0.379 and −0.249 e A^{-3}. The molecular structure is shown in Fig. 5.

4.10. X-Ray crystal structure analysis of *N*-(2-chlorophenyl)-4-quinazolinamine

Crystal data. Empirical formula $C_{15}H_{10}Cl_1N_3$, formula weight 255.71, temperature 293 K, wavelength CuK_α (1.54178 Å), crystal system monoclinic, space group $P2/c$, unit cell dimensions a=11.230(3), b=9.101(2), c=13.173(3) Å, β=112.91(2)°, volume 1240.1(6) Å^3 (by least squares fitting of the setting angles of 24 automatically centred reflections in the range $20.4\leq\theta\leq38.6°$), Z=4, density (calculated) 1.3696 Mg/m^3, absorption coefficient 2.6164 mm^{-1}, F(000) 528.0.

Data collection and processing. Enraf–Nonius CAD4 diffractometer, $\theta-2\theta$ scan, scan width 1.2+0.34 tg θ°, scan speed 0.05–0.16° s^{-1}, graphite monochromated CuK_α radiation (λ=1.54178 Å). Pale-yellow prismatic crystal, crystal size 0.45×0.22×0.18 mm, theta range for data collection 4.27–69.98°, index ranges $-13\leq h\leq12$, $0\leq k\leq11$, $0\leq l\leq16$, reflections collected 2448, independent reflections 2350 [R(int)=0.0191], no absorption correction performed, max. and min. transmission 1.0 and 0.855.

Structure analysis and refinement. The structure was solved by direct methods with SIR92[33] and refined by full matrix least squares on F^2 with SHELX93.[34] The hydrogen atoms were located in a ΔF map and refined isotropically. Data/restraints/parameters 2217/0/204, goodness-of-fit on F^2 0.853, final R indices [$I>2\sigma(I)$] R_1=0.0786, wR_2=0.2128. Maximal Δ/σ=0.000 and −0.001 for non-hydrogen and hydrogen atoms respectively, maximum and minimum residual peak in the final difference Fourier map 0.523 and −0.573 e A^{-3}. The molecular structure is shown in Fig. 6.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 161826 (**2**), CCDC 161827 (**29**), and CCDC 161828 [*N*-(2-Chlorophenyl)-4-quinazolinamine]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road,

Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.11. Semiempirical calculations

Semiempirical calculations on radicals **28**, **31**, **32**, and **33** as well as the search for the reaction paths connecting **28**–**31** and **32**–**33** were carried out with the semiempirical program included in the Wavefunction *PC Spartan Pro 1.0.3* 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 by calculating the energy profile obtained by fixing the geometries of the starting and final radical and varying in 20 steps the distance between the two atoms involved in the reaction (ring opening or ring closure). The transition state geometry and energy were finally refined with the 'Transition-State-Geometry' option of the semiempirical routine.

Ring opening of **28** to **31** was found to be endothermic by 18 kcal/mol, with an activation barrier of 43.2 kcal/mol. Structure **31** is the absolute minimum for the isothiocyanate radical; the intermediate **32**, which has a *s-cis*-like structure and is therefore more suitable to study the subsequent ring closure to **33**, lies in a local minimum only 0.8 kcal/mol higher than **31**. For our purposes, the rotation barrier around the C–NCS bond can be hence considered negligible. Rotation of the C–amidine bond produces two virtually degenerate minima, giving two structures with nearly identical geometries in which the plane containing the disubstituted aromatic ring contains the isothiocyanate moiety as well and is orthogonal to the plane containing the amidino group. The two amidine nitrogen atoms, both of them bearing spin density, are therefore practically equidistant from the isothiocyanate carbon atom. Ring closure of **32** was calculated to be exothermic by 30.8 kcal/mol, with an activation barrier of only 9.9 kcal/mol. The whole rearrangement process (**28→33**) was hence found to be exothermic by 12 kcal/mol.

Energy values for radicals **28**, **31**, **32**, and **33**, and activation barriers for ring opening of **28** and ring closure of **32** are reported in Fig. 4, together with the optimised geometries. All of the transition states are characterised by a single imaginary vibrational frequency (376.8 and 364.2 cm^{-1} for the transition states leading to **31** and **33**, respectively) resulting from a negative force constant in the diagonal form of the Hessian; all of them collapse to the starting radicals when optimised without the 'Transition-State-Geometry' option.

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6. Treatment of an enolisable compound with Mn(III) is a

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24. As a general rule, all the iminoquinazoline compounds (e.g. **30b**) show, besides the characteristic peak of the thioamide proton (12.5–13 ppm), two NMR absorptions at 6.5–7.2 and 8.8–9.4 ppm ascribable to the imine proton and probably due to *E*/*Z* isomerism of the imine moiety (the sum of those two signals always corresponds to one proton). On the contrary, the IR spectra show only one significant, generally sharp NH band in the range 3220–3320 cm^{-1}. This behaviour was observed with other analogous imines synthesised in our laboratory (unpublished results). Compounds **8** and **20** seem to exist as single geometric isomers.
25. Desulphurated products are usually always obtained in the reactions of thioureas or their derivatives with $Mn(OAc)_3$.
26. The crude also contained a minor product whose structure was not fully established, but certainly included a cyano-group: this was probably formed through hydrolytic fragmentation of the N-3–C-4 bond. This is an additional proof in favour of structure **20**, since formation of a nitrile moiety should not be expected from a rearranged ketimine derivative.
27. (a) Katz, L. *J. Am. Chem. Soc.* **1953**, *75*, 712. (b) Muthusamy, S.; Ramakrishnan, V. T. *Synth. Commun.* **1992**, *22*, 519.
28. The formation of anilinobenzothiazoles was unquestionably confirmed by reacting *N*,*N*′-diphenylthiourea under the usual conditions. The resulting 2-anilino-1,3-benzothiazole was compared (mixed mp determination, spectral comparison, and GC–MS analysis) with an authentic sample prepared according to the literature (Hofmann, A. W. *Chem. Ber.* **1879**, *12*, 1126).
29. Although compound **12** has been reported in several papers, its NMR and MS spectral data are not available anywhere. However, our spectral data, particularly the NMR absorptions of the NH and H-2 protons, are consistent with those of analogous compounds, see: Szczepankiewicz, W.; Suwinski, J. *Tetrahedron Lett.* **1998**, *39*, 1785.
30. ^1H NMR spectrum shows that this compound is a 1:9 mixture of tautomers: the signal at 9.80 ppm is probably due to the major, aromatic form (**12**, see Ref. 26), whereas that at 11.58 due to the ketimine form. The presence of two structures is also evidenced by the ^{13}C NMR spectrum (2 CH signals overlapped). The assignments were made on the basis of spectral calculations, which perfectly predicted the consistent shift to higher fields of the H-2 (more than 15 ppm) by passing from structure **2** to the ketimine form.
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