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RADICAL CYCLIZATION AND 1,5-HYDROGEN TRANSFER IN SELECTED AROMATIC DIAZONIUM SALTS

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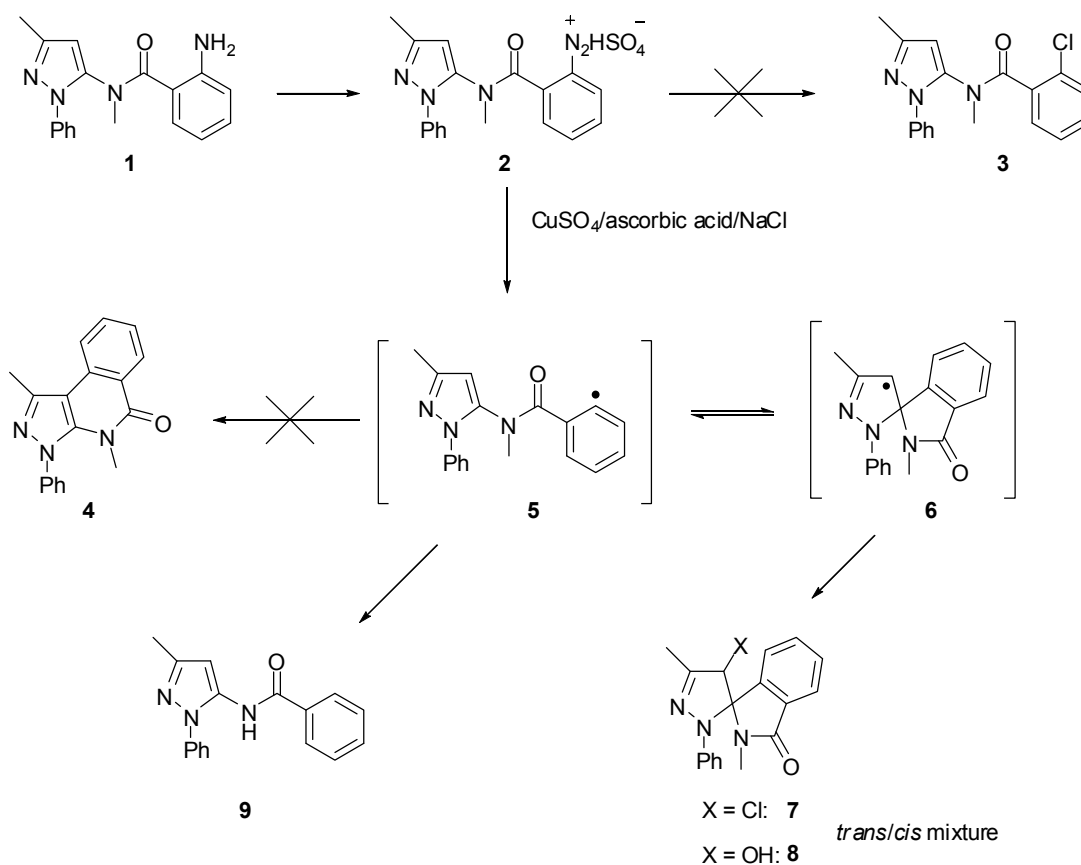
Abstract – 2-(Methyl-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)carbamoyl)thiophene-3-diazonium hydrogen sulfate **20**, 2-(methyl-(3-methylisoxazol-5-yl)carbamoyl)-benzenediazonium hydrogen sulfate **21** and 2-(methyl(phenyl)carbamoyl)-benzenediazonium hydrogen sulphate **22** were synthesized and reacted with a CuSO₄/NaCl/ascorbic acid combination to give complex mixtures. The structures of the reaction products were elucidated, depending upon the pathways followed. Compound **20** almost exclusively afforded an Ar-5 cyclization product and trace amounts of the product derived from a competing Ar-6 Pschorr closure. In the case of compound **21**, the Ar-6 cyclization was not observed, while the Ar-5 cyclization and 1,5-hydrogen radical transfer processes equally occurred. Finally, the Ar-6 cyclization was observed as the main process for compound **22**, accompanied by the Ar-5 cyclization and, in a much lesser extent, by an 1,5-hydrogen radical transfer process.

INTRODUCTION

Hanson and co-workers described the use of a combination of CuSO₄ and NaCl in the presence of ascorbic acid to perform the Sandmeyer reaction of 4-chlorobenzenediazonium chloride in a

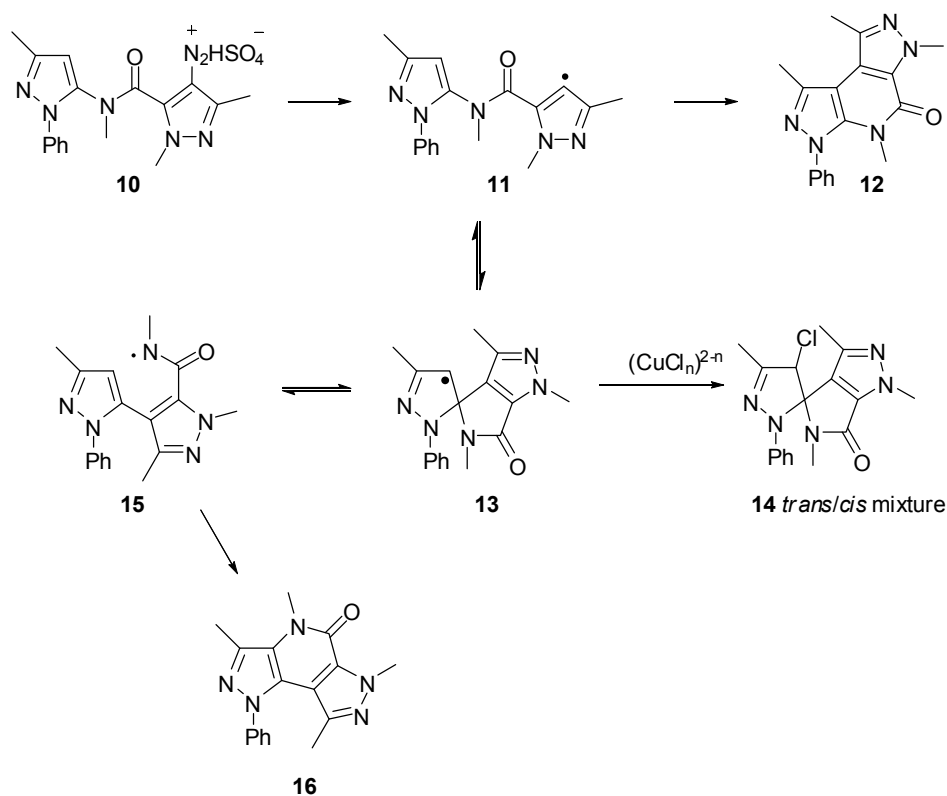
homogeneous aqueous phase, leading to 1,4-dichlorobenzene.¹ Ascorbic acid serves to reduce Cu(II) to Cu(I) which, in turn, reduces the diazonium ion to a diazenyl radical. The latter decomposes to dinitrogen and a 4-chlorophenyl radical. Complexes of Cu(II) ions with chloride ions then transfer a chlorine atom to the 4-chlorophenyl radical to afford the final product.

We found in previous studies that, under the foregoing conditions, diazonium salt **2** (Scheme 1) affords neither the product of the classical Sandmeyer reaction, chloro-derivative **3**, nor the expected product of a competing Pschorr ring closure, tricyclic derivative **4**. On the contrary, a mixture of epimeric products **7**, presumably via radical intermediates **5** and **6**, were obtained as the major reaction products.² We also isolated the derivative **9**, due to a 1,5-hydrogen atom transfer process, and trace amounts of the hydroxy spiro epimers **8**.³



Scheme 1

When we transformed, under the above conditions, the diazonium salt **10** (Scheme 2) derived from 4-amino-*N*-1,3-trimethyl-*N*-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)-1*H*-pyrazole-5-carboxamide,⁴ a different reaction pattern was observed. In fact, in this case we isolated the chlorinated spiro derivatives **14** and the product of the Pschorr ring closure **12** together with its structural isomer **16**.



Scheme 2

In continuing research on this type of reaction,²⁻⁵ and in order to establish the role of the aromatic moieties, linked by the amide bridge on the reaction pathway we became interested in investigating the transformation of diazonium salts **20–22** derived from the corresponding amines **17–19** (Figure 1).

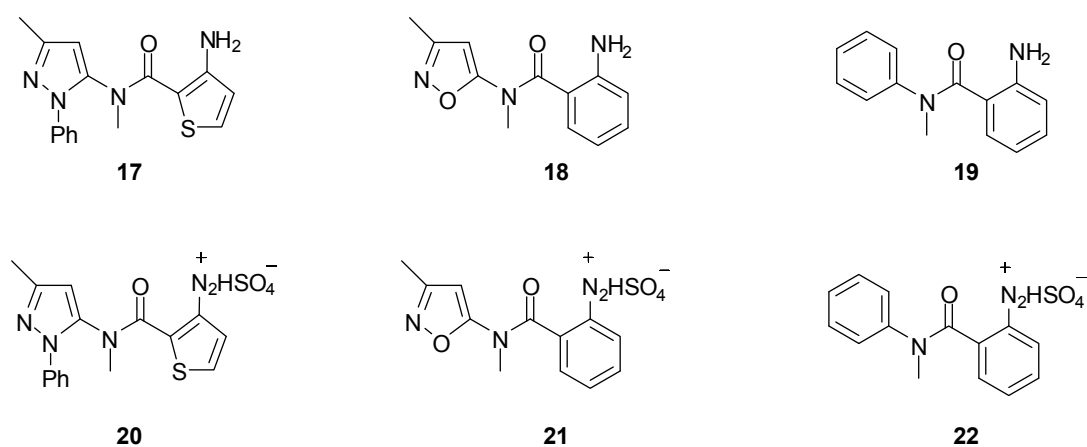
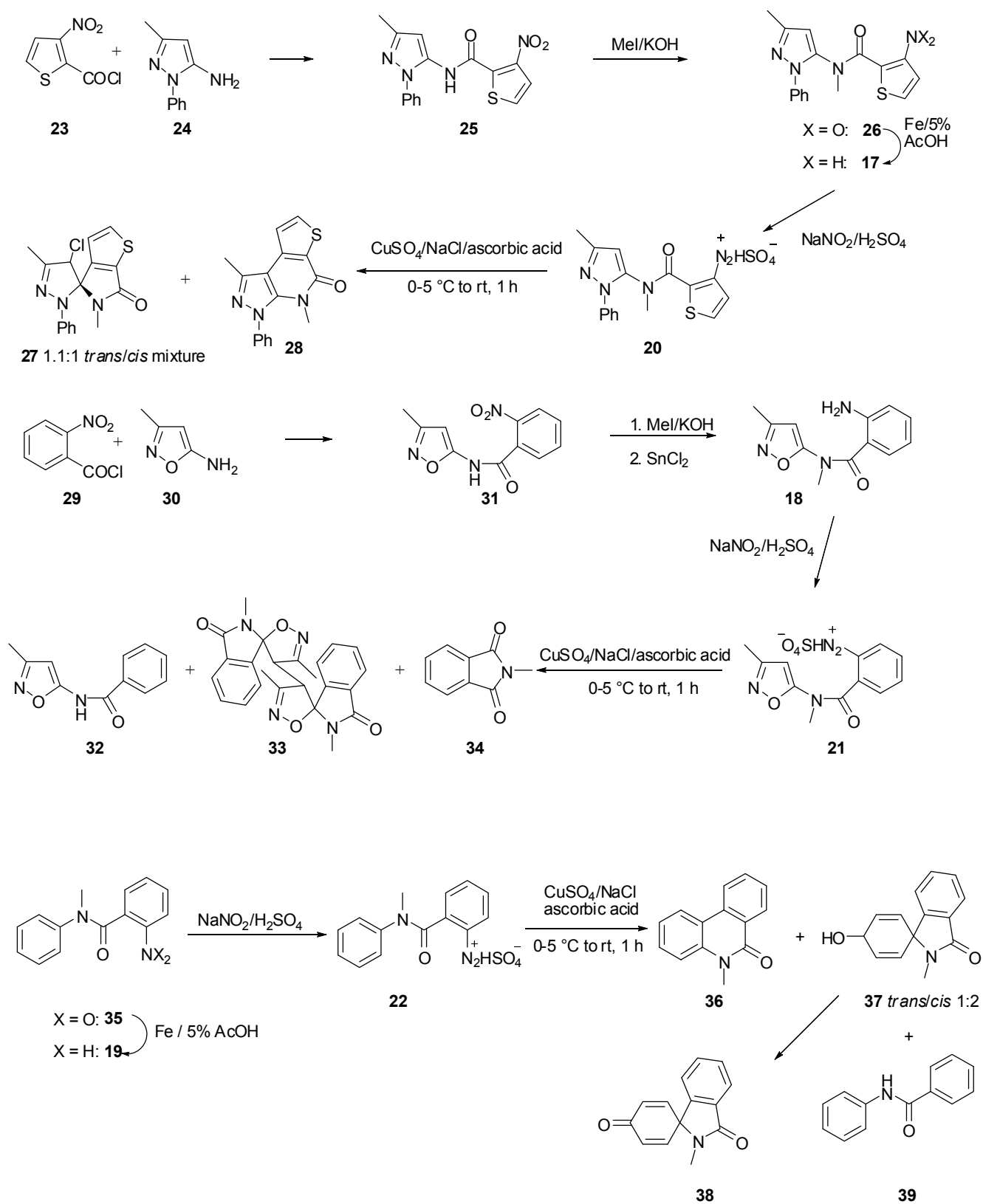


Figure 1

RESULTS AND DISCUSSION

The amino-derivatives **17–19** were synthesized accordingly to Scheme 3.



Scheme 3

Table 1. Results of the radical mediated transformations of compounds **2**, **10**, **20–22**

Entry	Compound	Path a Products (%)	Path b Products (%)	Path c Products (%)
1	2	7 ⁷ (37)	0	9 (< 1)
2	10	14 ⁷ + 16 (15)	12 (7)	0
3	20	27 ⁷ (28)	28 (2)	0
4	21	33 (6), 34 (14)	0	32 (13)
5	22	37 ⁷ (9), 38 (3)	36 (25)	39 (3)

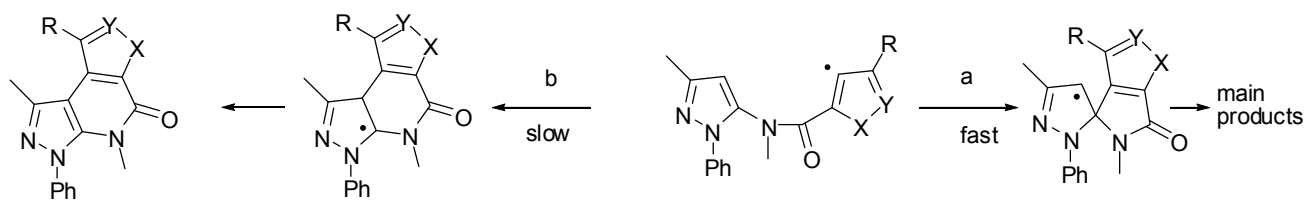
Compound **17** was obtained by reduction of nitro-derivative **26** with Fe/5% AcOH; compound **26** is the product of the methylation of **25**, which in turn arises from the coupling reaction between amine **24** and the acyl chloride **23**.

A slightly modified procedure in which the final reduction step was performed with SnCl₂, was employed for the synthesis of the amine **18**. Finally, the known amine **19** was prepared from the nitro-derivative **35** accordingly to a reported procedure.⁶

The diazonium compounds **20–22** were prepared from the corresponding amines and subsequently subjected *in situ* to the reaction conditions suitable for the generation of the aryl radical (CuSO₄, NaCl, ascorbic acid).^{1,2} After stirring 1 hour at rt, the products reported in Scheme 3 and Table 1 were isolated. Together with some data already reported by some of us,^{2,4} the following discussion also includes new computational data concerning compounds **2** and **10** for an useful comparison.

From the analysis of the structures of reaction products it is possible to gain information on the chemical behavior of the radical intermediates involved in the reaction pathways.

The initially originated 2-aryl radicals **40–42**, subsequently follow the transformations depicted in Scheme 4. The intramolecular cyclization, to give second generation tricyclic radicals, can follow two possible paths: a 5-*exo-trig* closure (path a) giving rise to the spiro systems **6**, **43–45** (in the following discussion collectively referred to as **I**) and a 6-*endo-trig* closure (path b) giving rise to the tri-cyclic systems **46–48** (**II**). Another possibility is the occurrence of a 1,5-hydrogen shift (path c) from the *N*-methyl group to the aryl center to give the methylene radicals **49–51** (**III**).



12: X = NMe, Y = N, R = Me

46a: X = NMe, Y = N, R = Me

40a: X = NMe, Y = N, R = Me

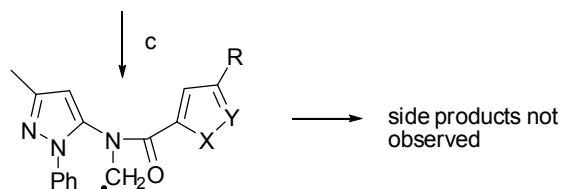
43a: X = NMe, Y = N, R = Me

28: X = S, Y = CH, R = H

46b: X = S, Y = CH, R = H

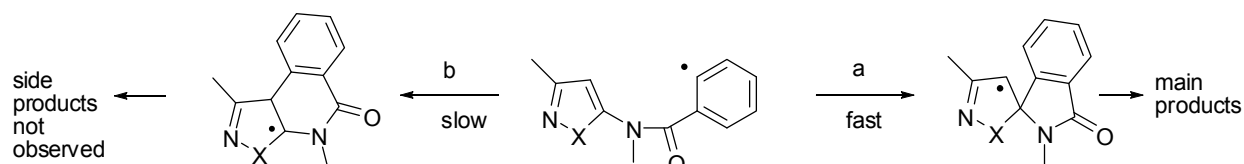
40b: X = S, Y = CH, R = H

43b: X = S, Y = CH, R = H



49a: X = NMe, Y = N, R = Me

49b: X = S, Y = CH, R = H



47a: X = NPh

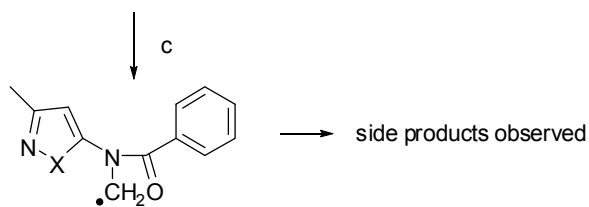
47b: X = O

41a: X = NPh

41b: X = O

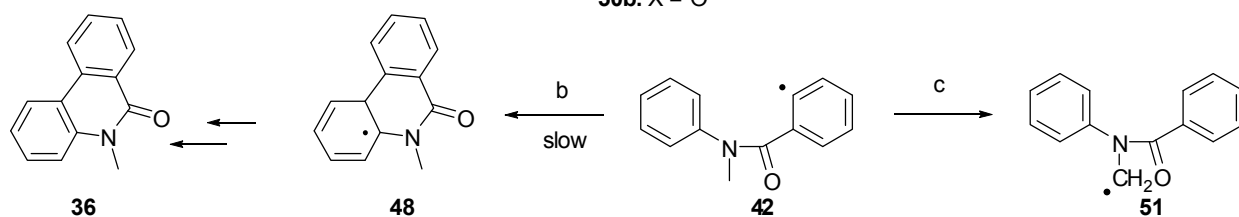
6: X = NPh

44: X = O



50a: X = NPh

50b: X = O



36

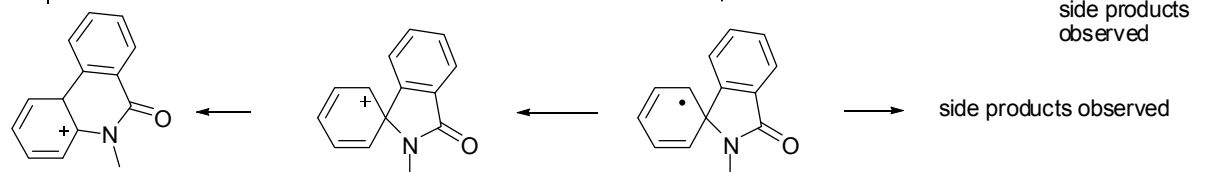
48

42

51

main product

side products observed



53

52

45

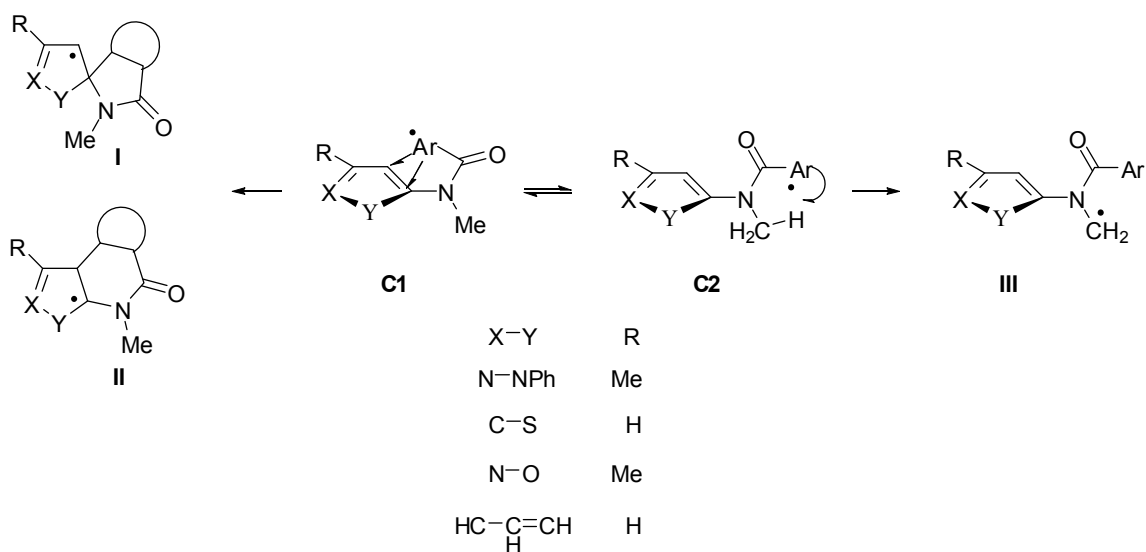
side products observed

Scheme 4

It was found that all of the diazonium salts **2**, **10**, **20–22** follow the path a whereas the path b is only followed by **10**, **20** and **22** (Schemes 1–4). Moreover, path a is the dominant one for all of the cases but the compound **22**, that mostly follows the way b giving compound **36** as major product, through the radical **48**. This result appears to be in accordance with the Baldwin's rules⁸ relying with the closure mode of simple aliphatic radicals, i.e. 5-*exo-trig* closure is dominant with respect to the 6-*endo-trig*, mainly on the ground of sterical reasons. When the cyclization process involves the radical's addition to an aromatic moiety, a competition between the two pathways does occur.^{9,10} In these cases, despite the 5-*exo-trig* – or “Ar-5” – cyclization is still the one kinetically preferred, 6-member rings containing final products of the type 6-*endo-trig* – or “Ar-6” – are obtained. This is likely due to the occurrence of alternative reaction pathways such as the oxidation of the radical to a cation, followed by a rearrangement of the latter. It is not surprising that in the case of the hetero-aromatic systems reported in this work the products derived from the spiro radicals are mainly obtained. This is due to the quite less aromatic character (and as a consequence the more localized nature of the π electron density in the C-4, C-5 formal double bond¹¹) of the hetero-aromatic ring acceptor. On the other hand, the Cu/promoted Pschorr radical 6-*endo-trig* cyclisation to give both phenanthrene⁹ and phenanthridone¹² systems are well documented.

It is worthy of further comment that we did not find products derived from a 6-*exo* (or “Ar-6”) mode of closure in the case of compound **2**² (Scheme 1), as instead is the case for the cited compound **22** and for compounds **10** and **20** (Schemes 2 and 3) that gave the “Ar-6” products **12** and **28** in trace amounts, through the radicals **46**. This is probably explainable with the oxidation by Cu^{2+} of the radical **45** to the corresponding spiro cation (Scheme 6), which can account for the formation of compound **36**. The higher reactivity of the electron-rich pyrazolinyl radicals **43a,b** and **6** makes the subsequent reaction with $(\text{CuCl}_n)^{2-n}$ complexes (see discussion below) faster than the oxidation.

In order to gain a better understanding of the radical's transformation processes described above, we evaluated the thermodynamic of the reaction courses depicted in the Scheme 4 by means of computational methods based on Density Functional theory. In particular the free energy variations (ΔG°) were evaluated by taking into consideration the conformations of the aryl radicals **40–42** with the higher degree of similarity between reactant and product (Scheme 5): **C1** is the conformation related to both the radical closures, while **C2** is the one related to the hydrogen shift process.



Scheme 5

Table 2 reports the estimation of the ΔG° values referred to the conformations **C1** and **C2**; the former is the one largely dominant in every case but for the radical **41b**; in this case both the conformations can be considered equally populated, within the accuracy limit of the computational method employed. From the data reported in Table 2, it is evident as the conclusion that can be inferred from a thermodynamical control of the investigated reactions are in line with those deduced from the kinetic behaviour.

Table 2. ΔG° s in KJ mol^{-1} for the conversions **C1** \rightarrow **C2**, **C1** \rightarrow **I**, **C1** \rightarrow **II** and **C2** \rightarrow **III** of the aryl radicals **40** - **42**

	41a	40a	40b	41b	42
$\Delta G^\circ(\text{C1} \rightarrow \text{C2})$	15.7	11.1	13.7	2.7	17.4
$\Delta G^\circ(\text{C1} \rightarrow \text{I})$	-123.7	-109.9	-107.3	-128.4	-88.1
$\Delta G^\circ(\text{C1} \rightarrow \text{II})$	-61.5	-84.9	-71.9	-81.4	-102
$\Delta G^\circ(\text{C2} \rightarrow \text{III})$	-72.3	-99	-80.6	-65.5	-75.5

The evolution of the cyclized radical is related to the relative trend to give one of the four possible radical quenching processes: i) The ligand transfer reaction with $(\text{CuCl}_n)^{2-n}$ complexes to give chloro-substituted derivatives. ii) The direct cyclization to give an aromatic system (Pschorr reaction). iii) The radical

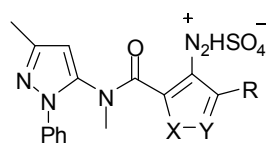
coupling to give a dimer. iv). The oxidation by Cu^{2+} , without Cl transfer, to give a cation. A “non-classical”² Sandmeyer reaction (i) is given by the radicals **I** arising from all of the compounds but **21** (Scheme 6). Further, while the compounds **2**, **10** and **20** give predominantly the chloro spiro-derivatives **7**, **14** and **27**, compound **22** give the 6-Ar cyclization compound **36** as the main product together with the epimeric alcohols *trans*- and *cis*-**37** and trace amount of the ketone **38** (Schemes 3 and 4).

This result reflects the relative electronic character, and as a consequence the nucleophilicity, of the radicals **I**. The fact that an alcohol is isolated in the case of **22**, without any trace of chloro compounds, can be rationalised by the intervention of a fast oxidation step. The formation of the product **36** is easily explained by the known tendency of the five member cyclic cation to quickly rearrange to the six member one.⁹ Further, the reaction pathway proposed in Scheme 6 for the intermediate **45** is supported by the reported evidence of a higher Cl/ H_2O^+ transfer ratio by any $[\text{Cu}(\text{II})\text{Cl}_n(\text{H}_2\text{O})_m]^{(2-n)}$ species.¹³ In the case of compound **21**, it can be argued that the reaction of the radical **44** (Schemes 4 and 3) with any Cu species is much slower than the dimerization, giving the product **33**. The formation of compound **34** is easily explained by the sequence reported in Scheme 6.

The reaction pathway c – 1,5-hydrogen atom shift – is mainly followed by the radical **41b** arising from the precursors **21** and, in a much lower extent, by the radical **42** formed from **22** (Schemes 4 and 3). Both the radicals **50b** and **51** given by **41b** and **42** bring to the *N*-demethylated products **32** and **39** through one or both the mechanisms depicted in Scheme 7.

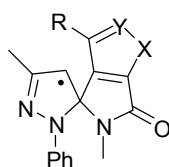
The ionic mechanism should be favored by the intrinsic stability of the immonium ion¹⁴ originated by the Cu(II) oxidation of the radicals **50b** and **51**. In the case of **21**, this process completely outclasses the oxidation/rearrangement steps, that are instead dominant in the case of **22**. This significant difference can be explained on the ground of the above cited conformational freedom of the radicals arising from **21** with respect to **22** (Schemes 3 and 4). The calculated data reported in tab. 2: $\Delta G^\circ (\text{C1} \rightarrow \text{C2})$ 2.7 KJ mol^{-1} for **41b** vs. 17.4 KJ mol^{-1} for **42**, support this statement.

Type I radicals



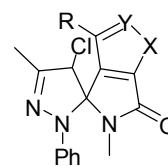
10: X = NMe, Y = N, R = Me

20: X = S, Y = CH, R = H



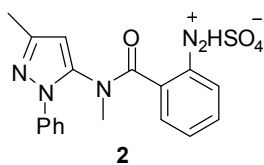
43a: X = NMe, Y = N, R = Me

43b: X = S, Y = CH, R = H

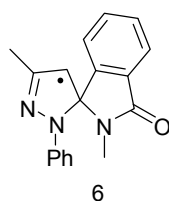


14: X = NMe, Y = N, R = Me

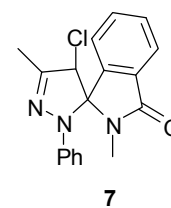
27: X = S, Y = CH, R = H



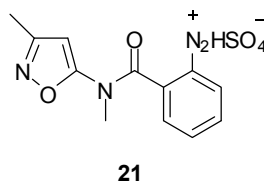
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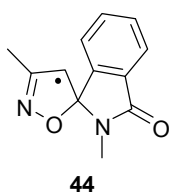
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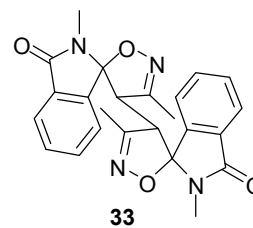
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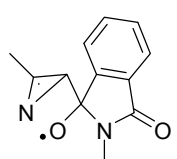
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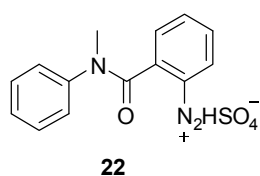
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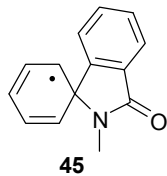
33



34

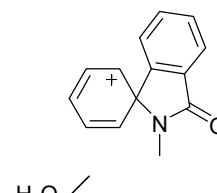


22

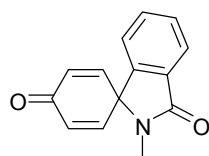


45

Cu(II)
fast

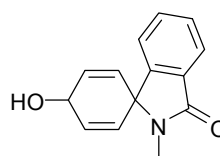


H₂O



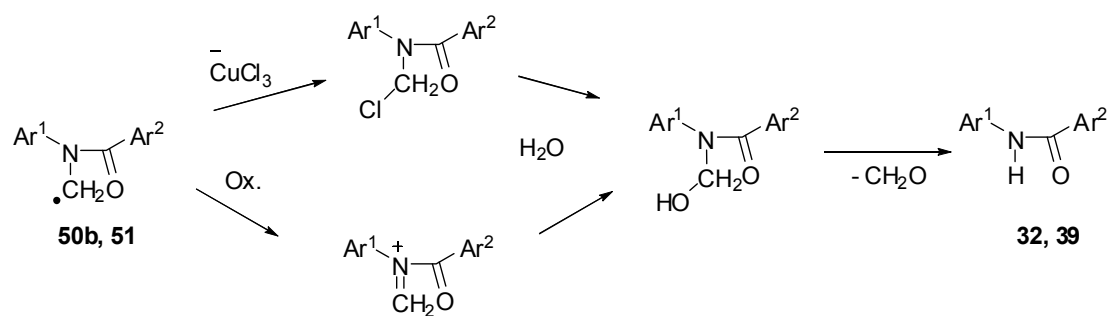
38

Cu(II)



37

Scheme 6



Scheme 7

CONCLUSIONS

The products distribution of the radicals mediated transformation of a set of aromatic diazonium compounds is fairly complex but explainable on the ground of the several reaction pathways accessible by the intermediates involved.

The initial aryl radical gives rise mainly to a 5-*exo-trig* (or Ar-5) cyclisation when the radical attacks a hetero-aromatic system (compounds **2**, **10**, **20**, **21**). On the other hand, when the attack involves a benzenic ring (compound **22**), the intervention of a more complex oxidative pathway makes the Ar-6 cyclization mode the one dominant, yielding the phenanthridone-like compound **36** as the main reaction product. An 1,5-hydrogen shift side reaction occurs in some cases and is quite relevant in the case of compound **21**. Both kinetic and thermodynamic based arguments can account for the experimental evidences collected. The final products structure depends also on the particular reaction course followed by the radical intermediates.

Despite its complexity, the reaction pattern described in the present study is on the whole internally coherent, rightly integrated within the body of literature evidences concerning the diazonium compound's radical chemistry and give a further insight into the class of the hetero-aromatic systems. A contribution to the general radical cyclisation rules can be added, i.e. radicals of the general pattern showed below follow the "Ar-5" closure path rather than the "Ar-6" one (Figure 2).

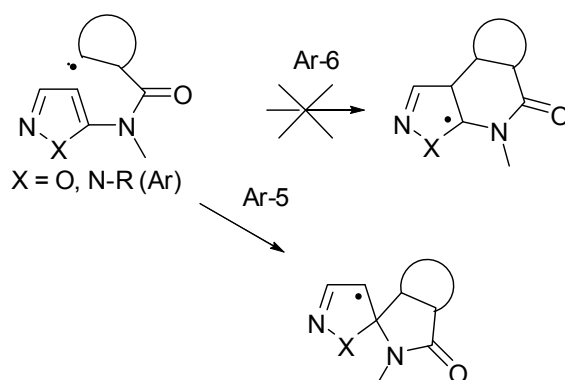


Figure 2

Finally, all of the spiro derivatives reported in the present study can be considered as potentially active biological agents because many compounds that possess a spirooxyindole moiety were shown to exhibit significant biological activity.¹⁵

EXPERIMENTAL

Generals

Reaction progress was monitored by TLC on silica gel plates (Merck 60, F₂₅₄, 0.2 mm). Organic solutions were dried over Na₂SO₄. Evaporation refers to the removal of solvent on a rotary evaporator under reduced pressure. All melting points were determined on a Büchi 530 capillary melting point apparatus and are uncorrected. IR spectra were recorded with a Perkin Elmer Spectrum RXI FT-IR System spectrophotometer as solid in KBr disc or nujol. ¹H NMR and ¹³C NMR spectra of all compounds but **27-cis/trans** were obtained in CDCl₃ or DMSO-*d*₆ solutions on a Bruker AC 250 F or Bruker AC series 300 spectrometers. ¹H NMR and ¹³C NMR spectra of compounds **27-cis/trans** were obtained on a Bruker Avance II 400 spectrometer. In all cases tetramethylsilane was used as an internal standard; chemical shifts are expressed in δ values (ppm). Mass spectra at 70 eV were obtained using an 3400-CX Varian gas chromatograph fitted with a Saturn 3 mass spectrometer. For compound **33** the mass spectra was obtained by a Shimadzu LCMS2010 apparatus. Merck silica gel (Kieselgel 60/230-400 mesh) was used for flash chromatography (FC) columns. Yields refer to products after one crystallization. The name of the compounds were obtained using the ChemDraw Ultra 12.0 software.

Computational Details

All calculations have been performed in the framework of density functional theory by using the Gaussian 09 software.¹⁶ The Becke 3-parameters hybrid functional B3LYP,¹⁷ consisting of Becke exchange functional plus the Lee, Yang and Parr correlation functional has been used joined with the Dunning's correlation consistent polarized valence double zeta (cc-pVDZ). The geometry optimizations have been followed by the calculation of the harmonic frequencies, in order to verify the nature of minimum in the potential energy surface of the structure obtained and to calculate the zero-point vibrational contribution to the energy. The molecular Gibbs free energies of formation have been calculated by adding the estimated zero-point, thermal and entropic contributions (T = 298 K, p = 1 bar) to the SCF energy.

N-(3-Methyl-1-phenyl-1*H*-pyrazol-5-yl)-3-nitrothiophene-2-carboxamide (**25**)

To a solution of commercially available 3-methyl-1-phenyl-1*H*-pyrazol-5-amine (17.3 g, 0.1 mol) in dry CHCl₃ (450 mL), 3-nitrothiophene-2-carbonyl chloride (19.2 g, 0.1 mol) was added; the resulting solution

was refluxed for 5 h. After the first hour, triethylamine (14 mL) was added in four portions (7, 3.5, 2 x 1.75 mL respectively, with intervals of 1 h between additions). Then the reaction was quenched with ice cold water. The organic phase was dried onto Na₂SO₄ and solvent was evaporated. The residue was crystallized from EtOH to give compound **25** (50%); a yellow orange solid; mp 140–143 °C (EtOH); IR (*Nujol*) cm⁻¹ 3193 (NH), 1678 (CO); ¹H NMR (250 MHz, CDCl₃) δ 2.36 (3H, s, Me), 6.72 (1H, s, pyrazole H-4), 7.46-7.66 (7H, m, phenyl and thienyl protons), 10.75 (1H, br s, exchangeable with D₂O); ¹³C NMR (75 MHz, CDCl₃) δ 13.49, 98.42, 124.95 (2C), 126.43, 128.31, 129.13, 129.29 (2C), 134.97, 136.93, 139.41, 142.85, 149.21, 154.09; MS *m/z* 328 (M⁺). Anal. Calcd for C₁₅H₁₂N₄O₃S: C, 54.87; H, 3.68; N, 17.06). Found: C, 55.01; H, 3.81; N, 17.26.

3-Amino-*N*-methyl-*N*-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)thiophene-2-carboxamide (**17**)

In a three neck round bottomed flask, compound **25** (32.8 g, 0.1 mol) was solubilized in hot acetone (360 mL), then KOH (21.87 g, 0.39 mol) was added in one portion and a solution of methyl iodide (9.27 mL) in acetone (50 mL) was added dropwise. The reaction mixture was refluxed for 1 h. The resulting suspension was filtered off and the obtained solution evaporated. Finally, the solid residue was crystallized from EtOAc to give *N*-methyl-*N*-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)-3-nitrothiophene-2-carboxamide (**26**) (23%) as a yellow solid (mp 90–93 °C) and directly employed in the subsequent step after partial characterization by proton NMR. ¹H NMR (250 MHz, CDCl₃) δ 2.21 (3H, s, Me), 3.46 (3H, s, Me), 6.08 (1H, s, pyrazole H-4), 7.30-7.44 (7H, m, phenyl and thienyl protons).

Powdered Fe (80 g, 1.4 mol) was added to 100 mL of a 5% (v/v) aqueous acetic acid solution and stirred at 100 °C for 15 min. Then *N*-methyl-*N*-(1-phenyl-3-methyl-1*H*-pyrazol-5-yl)-3-nitrothiophene-2-carboxamide (**26**) (44.5 g, 0.13 mol) was added within 1 h. The reaction mixture was stirred for 1 h more and then the pH was raised to 8 by adding aq. NaHCO_{3(sat.)}. The mixture was filtered, the solid material washed with water until neutrality, dried by standing overnight at rt and extracted with boiling CHCl₃ (3 x 150 mL). The solution was dried onto sodium sulphate and evaporated. The solid residue was crystallized from EtOH to give compound **17** (80%); a pale yellow solid; mp 120–122 °C; IR (*nujol*) cm⁻¹ 3488 and 3371 (NH₂), 1618 (CO); ¹H NMR (250 MHz, CDCl₃) δ 2.37 (3H, s, Me), 3.17 (3H, s, Me), 4.16 (2H, s br. exchangeable with D₂O, NH₂); 6.20 (1H, s, pyrazole H-4), 6.43-7.44 (7H, m, phenyl and thienyl protons); ¹³C NMR (75MHz, CDCl₃) δ 14.22, 37.36, 100.95, 106.31, 119.12, 122.88 (2C), 127.38, 129.11, 131.01 (2C), 138.40, 141.16, 149.29, 155.96, 165.92; MS *m/z* 312 (M⁺). Anal. Calcd for C₁₆H₁₆N₄OS: C, 61.52; H, 5.16; N, 17.93. Found: C, 61.72; H, 5.32; N, 18.17.

2-Amino-*N*-methyl-*N*-(3-methylisoxazol-5-yl)benzamide (**18**)

N-Methyl-(3-methylisoxazol-5-yl)-2-nitrobenzamide (6.70 g, 0.026 mol), previously prepared following the literature procedure,¹⁸ were added to a continuously stirred suspension of SnCl₂ (14.60 g, 0.077 mol) in HCl_{conc.} (30 mL) while keeping the reaction temperature below 10 °C with an ice bath. The final suspension was further stirred for 24 h. Then the reaction was quenched with iced water (300 mL) and basified by adding 125 mL of a 40% (w/v) NaOH solution. Then the reaction mixture was extracted with EtOAc (3 x 250 mL), and the organic phase was washed with water, dried with Na₂SO₄ and evaporated. The solid residue was crystallized from EtOH to give compound **18** (65%), a colourless solid; mp 70–73 °C; IR (KBr) cm⁻¹ 3481 and 3369 (NH₂), 1648 (CO); ¹H NMR (250 MHz, CDCl₃) δ 2.19 (s, 3H, Me), 3.45 (s, 3H, Me), 4.78 (br s, 2H, exchangeable with D₂O, NH₂), 5.77 (s, 1H, isoxazole 4-H), 6.65–7.27 (m, 4H, C₆H₄); ¹³C NMR (75 MHz, CDCl₃) δ 11.91, 35.54, 93.89, 116.94, 117.07, 117.11, 128.88, 132.21, 147.10, 163.34, 164.73, 170.00; MS *m/z* 231 (M⁺). Anal. Calcd for C₁₂H₁₃N₃O₂: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.51; H, 5.90; N, 18.40.

Preparation and transformation of 2-(methyl-(3-methyl-1-phenyl-1*H*-pyrazol-5-yl)carbamoyl)-thiophene-3-diazonium hydrogen sulfate (**20**)

The solution of compounds **20** was prepared from the corresponding amines **17** (2 g, 6.41 mmol) by treating with 2.5 M H₂SO₄ (12.8 mL) and 2.5 M NaNO₂ (2.65 mL) while keeping temperature at 0–5 °C. The transformation reaction was carried out following the procedure of Hanson¹ which has been modified by us.² After 15 min the resulting solution of **20** was diluted with 305 mL of a cold (0–5 °C) solution of CuSO₄·5H₂O (0.3 M) and sodium chloride (0.75 M). Ascorbic acid was then added (0.28 g, 1.59 mmol) and stirring was continued for 1 h at room temperature. The suspension was filtered off and the solid residue was dried between porous plates and subsequently chromatographed following the FC procedure:¹⁹ external diameter column 5 cm, EtOAc/light petroleum (bp 40–70 °C) (3:7 v/v) as eluent, silica gel (170 g), fractions each 50 mL. Fractions 16–38 were evaporated, and the residue was crystallized to give compounds **27** (*trans/cis* 1.2:1 mixture).

The partial separation of the epimers was obtained operating a very fast FC with a Biotage® apparatus, using Et₂O/light petroleum (bp 40–70 °C) as eluent. Compound *cis*-**27** was obtained pure, whereas *trans*-**27** was contaminated with about 15% of *cis* isomer, as judged by ¹H NMR.

cis-4-Chloro-5,5'-dimethyl-2-phenyl-2,4-dihydrospiro[pyrazole-3,4-thieno[2,3-*c*]pyrrol]-6(5'*H*)-one (*cis*-**27**):²⁰ 16%; a pale yellow solid; mp 178–180 °C (EtOH); IR (KBr) cm⁻¹ 1697 (CO); ¹H NMR (400 MHz, CDCl₃) δ 2.25 (s, 3H, Me), 2.67 (s, 3H, Me), 5.25 (s, 1H, pyrazoline H-4), 6.79 (d, *J* = 7.0 Hz, 2H), 6.90 (t, *J* = 5.9 Hz, 1H), 7.09–7.15 (m, 3H), 7.76 (d, *J* = 4.5 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.39, 27.27, 67.35, 86.58, 115.68 (2C), 119.52, 122.28, 129.05 (2C), 136.44, 136.73, 143.06,

146.97, 153.95, 162.57. Anal. Calcd for C₁₆H₁₄ClN₃OS: C, 57.91; H, 4.25; N, 12.66. Found: C, 57.75; H, 4.50; N, 12.50.

***trans*-4-Chloro-5,5'-dimethyl-2-phenyl-2,4-dihydrospiro[pyrazole-3,4-thieno[2,3-*c*]pyrrol]-6(5'*H*)-one (*trans*-27):**^{20,21} IR (*Nujol*) cm⁻¹ 1702 (CO); ¹H NMR (400 MHz, CDCl₃) δ 2.26 (s, 3H, Me), 2.80 (s, 3H, Me), 4.94 (s, 1H, pyrazoline H-4), 6.72 (d, *J* = 7.1 Hz, 2H), 6.89 (t, *J* = 6.0 Hz, 1H), 7.07-7.17 (m, 3H), 7.66 (d, *J* = 4.3 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 13.43, 25.69, 66.76, 87.86, 116.24 (2C), 122.29, 122.46, 128.95 (2C), 134.57, 136.44, 142.39, 146.85, 151.17, 162.30. Anal. Calcd for C₁₆H₁₄ClN₃OS: C, 57.91; H, 4.25; N, 12.66. Found: C, 57.85; H, 4.54; N, 12.52.

Fractions 66-94 of the first chromatographic procedure afforded a residue which was crystallized from EtOH to give **1,4-dimethyl-3-phenyl-3*H*-pyrazolo[3,4-*b*]thieno[3,2-*d*]pyridine-5(4*H*)-one (28)** (2.1%); a colourless solid, mp 195–196 °C; IR(KBr) cm⁻¹ 1636 (CO); ¹H NMR (250 MHz, (CDCl₃) δ 2.63 (3H, s, Me), 3.29 (3H, s, Me), 7.44-7.84 (7H, m, C₆H₅ and thiophene protons); ¹³C NMR (75MHz, CDCl₃) δ 13.74, 31.76, 102.74, 121.52, 125.14, 127.54 (2C), 129.28 (2C), 129.47, 134.89, 138.33, 139.67, 142.16, 143.19, 158.55; MS *m/z* 295 (M⁺). Anal. Calcd for C₁₆H₁₃N₃OS: C, 65.06; H, 4.44; N, 14.23. Found: C, 65.16; H, 4.62; N, 14.37.

Preparation and transformation of 2-(methyl-(3-methyl-isoxazol-5yl)carbamoyl)benzenediazonium hydrogen sulfate (21)

The solution of compounds **21** was prepared from the corresponding amine **18** (3 g, 12.98 mmol) by treating with 2.5 M H₂SO₄ (26 mL) and 2.5 M NaNO₂ (5.37 mL) while keeping temperature at 0–5 °C. The transformation reaction was carried out following the procedure of Hanson¹ which has been modified by us.² After 15 min the resulting solution of **21** was diluted with 620 mL of a cold (0–5 °C) solution of CuSO₄·5H₂O (0.3 M) and sodium chloride (0.75 M). Ascorbic acid was then added (0.57 g, 3.24 mmol) and stirring was continued for 1 h at room temperature. The mixture was extract with EtOAc (3 x 250 mL) and the organic phase was washed with water, dried with Na₂SO₄ and evaporated. The residue was washed with EtOAc (2.5 mL) and the suspension filtered off affording a quasi-pure solid product which was crystallized from EtOH to give **4'-(2,3'-dimethyl-3-oxo-4'*H*-spiro[isindoline-1,5'-isoxazol]-4'-yl)-2,3'-dimethyl-4'*H*-spiro[isindoline-1,5'-isoxazol]-3-one (33)** (6.4%); a colourless solid; mp > 270 °C; IR (KBr) cm⁻¹ 1724, 1711; ¹H NMR (250 MHz, CDCl₃) δ 2.34 (s, 6H, 2x Me), 2.81 (s, 6H, 2xMe), 3.83 (s, 2H, isoxazolines 4-H), 7.37-7.52 (m, 8H, 2xC₆H₄); ¹³C NMR (75MHz, CDCl₃) δ 14.54, 24.37, 52.75, 101.11, 123.47, 124.53, 130.98, 131.93, 132.25, 138.04, 155.88, 164.86; MS *m/z* 431 (M+1). Anal. Calcd for C₂₄H₂₂N₄O₄: C, 66.97; H, 5.15; N, 13.02. Found: C, 66.75; H, 5.20; N, 13.29.

The mother liquors of the above suspension were evaporated and the residue chromatographed following the FC procedure:¹⁹ external diameter column 5 cm, EtOAc/light petroleum (bp 40–70 °C) (3:7 v/v) as eluent, silica gel (192 g), fractions each 50 mL. Fractions 15–23 were evaporated, and the residue was crystallized from EtOAc/light petroleum to give a compound which was identical in all respects (MS, ¹H-NMR, mixed mp, TLC) with an authentic specimen of *N*-methylphthalimide (**34**) (14.4%). Fractions 31–36 left a residue which was crystallized from EtOH to give *N*-(3-methyl-isoxazol-5-yl)benzamide (**32**)²² (13.3%); mp 144–146 °C; IR (KBr) cm⁻¹ 3344 (NH), 1677 (CO); ¹H NMR (250 MHz, CDCl₃) δ 2.28 (s, 3H, CH₃), 6.39 (s, 1H, pyrazole H-4), 7.47–7.92 (m, 5H, C₆H₅), 9.08 (br s, 1H, exchangeable with D₂O, NH); MS *m/z* 203 (M+1).

Preparation and transformation of 2-(methyl(phenyl)carbamoyle)benzenediazonium hydrogen sulphate (**22**)

The solution of compounds **22** was prepared from the corresponding amine **19** (3.39 g, 15 mmol) by treating with 2.5 M H₂SO₄ (30 mL) and 2.5 M NaNO₂ (6.21 mL) while keeping temperature at 0–5 °C. The transformation reaction was carried out following the procedure of Hanson¹ which has been modified by us.² After 15 min the resulting solution of **22** was diluted with 714 mL of a cold (0–5 °C) solution of CuSO₄·5H₂O (0.3 M) and sodium chloride (0.75 M). Ascorbic acid was then added (0.66 g, 3.75 mmol) and stirring was continued for 1 h at room temperature. The mixture was extracted with EtOAc (3 x 250 mL) and the organic phase was washed with water, dried with Na₂SO₄ and evaporated. The residue was chromatographed following the FC procedure¹⁸: external diameter column 5 cm, EtOAc/light petroleum (bp 40–70 °C) (4:6 v/v) (3 L) and 6:4 v/v (3 L) as eluents, silica gel (230 g), fractions each 50 mL.

Fractions 15–23 were evaporated, and the residue was crystallized from cyclohexane to give 5-methylphenanthridine-6(5*H*)-one (**36**)⁶ (25%); mp 104–105 °C (benzene/light petroleum (bp 40–70 °C)); ¹H NMR (250 MHz, DMSO-*d*₆) δ 3.72 (s, 3H, Me), 7.32–8.52 (m, 8H, 2 x C₆H₄); MS *m/z* 209 (M+).

Fractions 24–33 left a residue which was crystallized from EtOAc to give *N*-phenylbenzamide (**39**) (3.4%); mp 156–58 °C (lit.,²⁴ 160–161 °C from EtOH); ¹H NMR (300 MHz, DMSO-*d*₆) δ 7.07–7.97 (m, 10H, 2 x C₆H₅), 10.23 (s, 1H, exchangeable with D₂O, NH); MS *m/z* 197 (M⁺).

Further elution gave fractions 46–58 from which a residue was obtained. Crystallization of the residue gave 2-methylspiro[cyclohexa[2,5]diene-1,1'-isoindoline]-3',4-dione (**38**) (3%); a colourless solid, mp 213–215 °C (EtOAc/light petroleum bp 40–70 °C); IR (KBr) cm⁻¹ 1708, 1664 (CO). ¹H NMR (300 MHz, CDCl₃) δ 2.88 (s, 3H, Me), 6.51 (d, *J* = 8.1 Hz, 2H, cyclohexadiene protons), 6.75 (d, *J* = 8.2 Hz, 2H, cyclohexadiene protons), 7.38 (d, *J* = 5.7 Hz, 1H, phenyl proton), 7.63 (m, 2H, phenyl protons), 7.82 (d, *J*

= 7.8, 1H, phenyl proton); ^{13}C NMR (300 MHz, CDCl_3) δ 25.69, 64.29, 122.87, 123.57, 129.63, 131.16 (2C), 131.80, 132.50, 141.37, 147.64 (2C), 166.91, 184.17. Anal. Calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_2$: C, 74.65; H, 4.92; N, 6.22). Found: C, 74.42; H, 5.06; N, 6.30.

Continuing elution, fractions 70-81 and 82-114 were collected. Evaporation left residues which were crystallized from EtOAc to give epimers *trans*-37 and *cis*-37 respectively.

***trans*-4-Hydroxy-2'-methylspiro[cyclohexa[2,5]diene-1,1'-isoindolin]-3'-one (*trans*-37):**²⁰ (3%); a colourless solid, mp 120–122 °C (EtOAc); IR (KBr) cm^{-1} 1665 (CO); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.74 (s, 3H, Me), 4.55 (m, 1H, cyclohexadiene proton), 5.35 (m, 3H, one exchangeable with D_2O , OH and cyclohexadiene protons), 6.28 (dd, $J = 8.5, 1.9$ Hz, 2H, cyclohexadiene protons), 7.42-7.71 (ABCD m, 4H, C_6H_4); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 24.67, 59.78, 62.69, 122.58, 123.27, 126.93 (2C), 128.63, 131.06, 131.83, 134.81 (2C), 147.42, 166.44. Anal. Calcd for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.12; H, 5.96; N, 6.30.

***cis*-4-Hydroxy-2'-methylspiro[cyclohexa[2,5]diene-1,1'-isoindolin]-3'-one (*cis*-37):**²¹ (6%); a colourless solid, mp 189–191 °C (EtOAc); IR (KBr) cm^{-1} 1682 (CO); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 2.82 (s, 3H, Me), 4.69 (br s, 1H, cyclohexadiene proton), 5.38 (d, $J = 9.9$ Hz, 2H, cyclohexadiene protons), 5.42 (d, $J = 6.6$ Hz, 1H, exchangeable with D_2O , OH), 6.23 (d, $J = 9.9$ Hz, 2H, cyclohexadiene protons), 7.26 (d, X part of an ABCX pattern, $J = 9.0$ Hz, 1H, phenyl proton), 7.53-7.75 (ABC part m, 3H, phenyl protons); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 24.71, 59.68, 62.41, 122.29, 122.65, 125.85 (2C), 128.30, 130.69, 131.58, 133.74 (2C), 147.43, 166.18. Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{NO}_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.01; H, 5.86; N, 6.35.

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20. The relative stereochemistry was deduced on the ground of the supposed deshielding effect due to the magnetic anisotropy of the aromatic ring on the *CHOH* and *CHCl* protons of *cis-37* and *cis-27*

respectively, compared with the *trans* isomers. This hypothesis was supported by the values of ^1H shielding tensor computed for the four compounds at the optimized geometry (available in the supporting material) by using the B3LYP/aug-cc-pvdz level: observed vs calculated proton $\Delta\delta$: 0.12 vs. 0.13 ppm for **37** and 0.50 vs. 0.31 for **27**.

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