COMMUNICATION

Carbon–carbon bond formation *via* thermal intermolecular hydrogen atom transfer: two serendipitous heterocyclic examples

Richard J. Hamlyn, Richard H. Jones and Christopher A. Ramsden *

School of Chemistry and Physics, Keele University, Keele, Staffordshire, UK ST5 5BG

Received (in Cambridge, UK) 16th December 1999, Accepted 18th May 2000
Published on the Web 1st June 2000

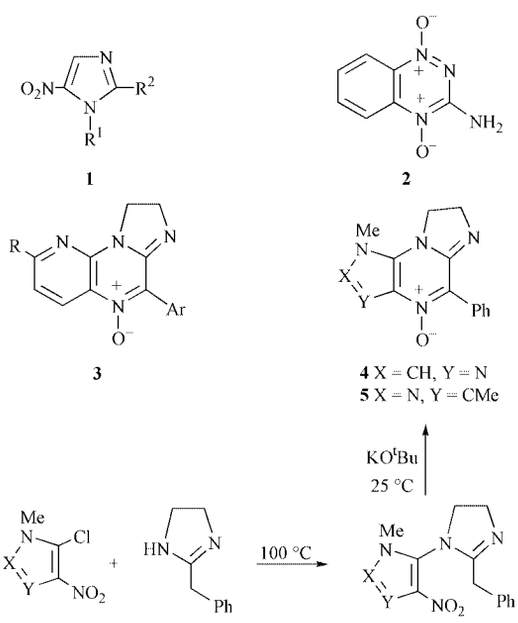
Formation of an anomalous 3-nitrothiophene product, encountered during the preparation of potential bioreductive anti-cancer agents, is rationalised in terms of a hydrogen atom transfer mechanism which also accounts for the unexpected formation of previously described 5,5′-biimidazoles.

Due to their fundamentally similar bonding, structurally diverse molecules containing three-centre, four-electron [3*c*–4*e*] bonds undergo similar modes of reaction, including *syn*-addition, ligand coupling and single electron transfer (SET).[1] For example, in terms of chemical bonding the nitro group ($-NO_2$) and xenon difluoride (XeF_2) are closely related and show similarities in chemical behaviour. We have recently defined conditions under which XeF_2 reacts by a SET mechanism ($XeF_2 \rightarrow XeF_2^{\bullet -}$)[2] and this mode of reaction to form the radical anions $RNO_2^{\bullet -}$ is also well known for nitro compounds. One-electron reduction of nitro compounds also has biological significance and is a key mechanistic step in the selective activity against anaerobic bacteria of the widely prescribed drug metronidazole **1** ($R^1 = CH_2CH_2OH$, $R^2 = CH_3$).[3]

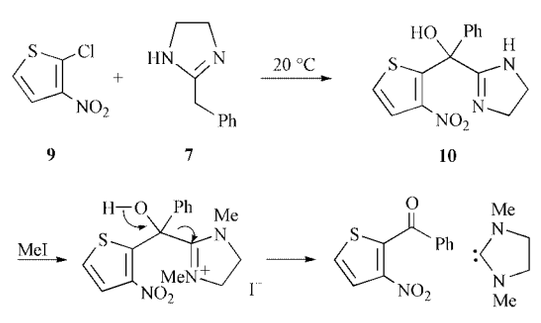
Selective bioreduction in the hypoxic environment of tumour cells, leading to formation of toxic products at the site of action, is also an attractive approach to cancer chemotherapy. In this context a number of heterocyclic *N*-oxides, which formally contain conjugated [3*c*–4*e*] bonds, have shown promising properties and these include the di-*N*-oxide **2** (SR-4233)[4] and the imidazo[1,2-*a*]pyrido[3,2-*e*]pyrazine 5-oxides **3** (Scheme 1).[5] Our general interest in molecules containing [3*c*–4*e*] bonds and their application to biological problems have led us to investigate heterocyclic modifications of the derivatives **3** which might result in increased potency and selectivity. We now report (i) the preparation of two analogues (**4** and **5**) of the derivatives **3**, (ii) an anomalous reaction which appears to proceed *via* a mechanism of synthetic and biological interest and (iii) a comparison of this mechanism with other examples from our previous studies. In particular we propose that these reactions proceed *via* a general mechanism [eqn. (1)] that is equivalent to intermolecular hydrogen atom transfer followed by radical coupling.

$$A + DH \longrightarrow A^{\bullet -} + DH^{\bullet +} \longrightarrow HA^{\bullet} + D^{\bullet} \longrightarrow HA\text{–}D \longrightarrow \text{products} \quad (1)$$

Reaction of 5-chloro-1-methyl-4-nitroimidazole **6** (X = CH, Y = N)[6] with 2-benzylimidazoline **7** (2-benzyl-4,5-dihydro-1*H*-imidazole) (2 equiv.) in hot propiononitrile gave the S_NAr product **8** (X = CH, Y = N) (69%), mp 185–186 °C† (Scheme 1). Cyclisation of this product at 25 °C using KO^{t}Bu or DBU gave the *N*-oxide **4** (13%), mp 195–198 °C as bright red needles together with the *N*-deoxy derivative (26%), mp 189–192 °C as orange crystals. In a similar sequence, 5-chloro-1,3-dimethyl-4-nitropyrazole[6] **6** (X = N, Y = CMe) gave the *N*-oxide **5** (26%), mp 224–226 °C as yellow needles and the *N*-deoxy derivative (29%), mp 198–201 °C as yellow needles. When 2-chloro-3-nitrothiophene[7] **9** was treated with the imidazoline **7** (Scheme 2) in propiononitrile a dark red colouration occurred and the



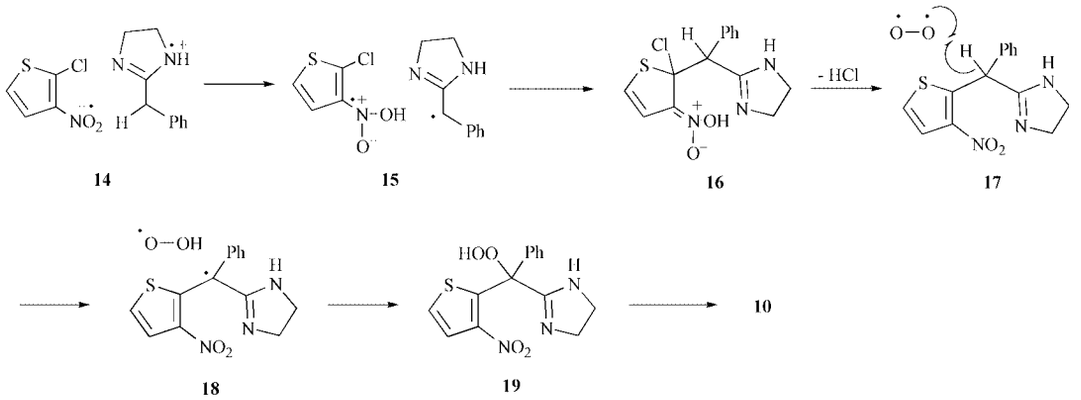
Scheme 1



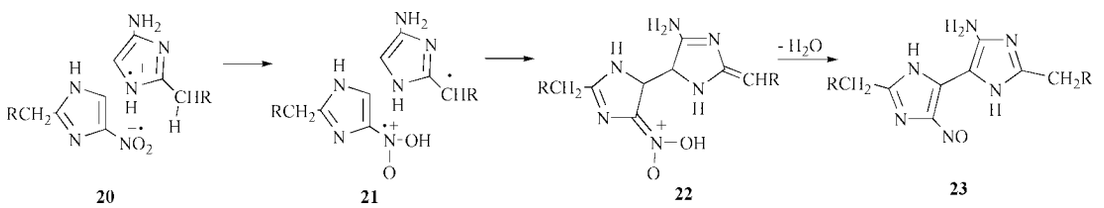
Scheme 2

product, which formed without heating, was isolated as fine beige needles, mp 140–142 °C and shown to have the constitution $C_{14}H_{13}N_3O_3S$ (62% yield). This compound was not the expected S_NAr product (*cf.* **8**) and requires the incorporation of additional oxygen. When the reaction was carried out under an oxygen free argon atmosphere no reaction was observed and product formation only occurred when dioxygen was introduced to the reaction mixture. Under anhydrous conditions the reaction proceeded to completion demonstrating that water is not a reactant. Initially the structure of this novel product was elusive due to its unexpected mode of formation and our failure to obtain crystals suitable for X-ray crystallography. Subsequently we have shown that this product is the tertiary alcohol **10** and this structure is fully supported by its spectroscopic properties. Furthermore, whereas treatment of compound **10** with one equivalent of MeI gave the expected *N*-methylimidazoline (86%), mp 186–189 °C, reaction with

DOI: 10.1039/a909891g



Scheme 3



Scheme 4

excess MeI gave 3-nitro-2-thienyl phenyl ketone **12** (62%), mp 140–144 °C. We propose that this reaction proceeds *via* the N^1,N^2-dimethylimidazolinium salt **11** and that the carbene **13**[8] acts as a leaving group (Scheme 2) which is rapidly protonated to form the imidazolinium salt.

The mechanism shown in Scheme 3 accounts for the formation of the alcohol **10**. Initial SET between the electron-rich imidazoline **7** and the electron-deficient nitrothiophene **12** gives the contact ion pair **14**. The basic radical anion then abstracts a proton from the acidic radical cation to give a radical pair **15**. At this stage the overall reaction is equivalent to hydrogen atom transfer ($1e^- + H^+$) to the nitroheterocycle **9**. One-electron reduction potentials of nitroimidazoles (*e.g.* **1**), as measured by the calculated LUMO energy, are known to be low. Using the AM1 method we have calculated the LUMO energies of the nitroimidazole **4** and the nitropyrazole **5** to be −0.82 and −0.87 eV respectively, in agreement with previous calculations on close analogues.[9] The calculated LUMO energy of the nitrothiophene **9** (−1.34 eV) is even lower and consistent with the proposed anomalous behaviour. The radical pair may then react together with C–C bond formation (**15**→**16**) and elimination of HCl to give the intermediate **17**. The molecule **17** can be expected to readily give the relatively stable conjugated radical **18** by reaction with dioxygen. The alcohol **10** is then formed *via* the peroxide **19**.

Indirect evidence for the involvement of the intermediate **17** in the mechanism of formation of compound **10** was obtained during attempts to determine structure **10** by X-ray crystallography of simple derivatives. From among unsuitable elongated needles the crystallographer selected a small cuboid crystal which was found to be the hydrobromide salt of compound **17**. Fig. 1 shows a perspective view and atom labelling of this salt.[10] Attempts to improve the yield of this product were unsuccessful.

We have previously reported[9] the formation of 5,5′-bi(imidazole) derivatives during catalytic reduction of 2-alkyl-4(5)-nitroimidazoles **1** (R^1 = H, R^2 = alkyl) to the corresponding aminoimidazoles. This novel dehydrodimerisation was limited to 2-alkyl derivatives and the substituent effect was difficult to rationalise. We now recognise that this reaction is probably also mediated by sequential SET and proton transfer, and that the proton is delivered from the essential 2-alkyl substituent (Scheme 4). We propose that initial electron transfer occurs between the electron-rich aminoimidazole (HOMO: *ca.* −8.2 eV)[9] and the electron-deficient 4-nitroimidazole precursor (LUMO: *ca.* −0.5 eV)[9] to give the contact ion pair **20**. Proton transfer may then take place from the acidic 2-alkyl group of the radical cation to the basic radical anion to give a pair of conjugated radicals **21** which combine to link the imidazole rings (**21**→**22**). Tautomerism with elimination of water (**22**→**23**) and further catalytic reduction of the nitroso derivative **23** then leads to the isolated bi(imidazole)s after subsequent condensation of the primary amines with diethyl ethoxymethylenemalonate.

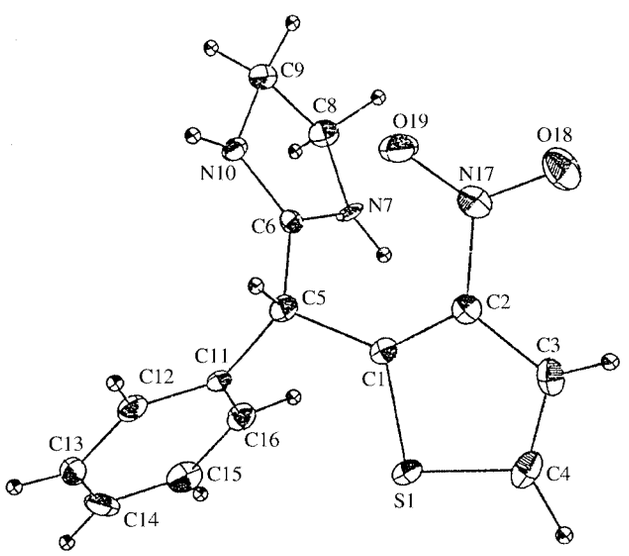
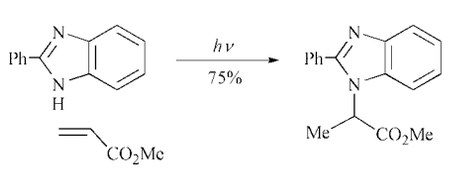


Fig. 1 Perspective view and atom labeling of the X-ray structure of the HBr salt of the imidazoline **17**.

In addition to the thermal examples described above, we have recently reported what we believe to be a photochemical example of this mode of reaction of a heterocycle.[11] Thus, the photoaddition of methyl acrylate to 2-phenylindole gives an adduct isomeric with the Michael adduct (Scheme 5). We have



Scheme 5

previously rationalised this reaction in terms of a formal hydrogen atom transfer followed by rapid radical coupling [eqn. (1)].[11]

We consider it unlikely that the thermal nitroheterocycle reactions described above occur *via* a hydride transfer mechanism ($2e^- + H^+$) analogous to that for quinone reactions which involve initial ion-pair formation.[12] It may well be that *some* quinone reactions under aprotic conditions also take place *via* hydrogen atom transfer ($1e^- + H^+$) (eqn. 1) to give a solvent caged semiquinone and donor radical: this pathway was first proposed by Becker.[13] Many quinone reaction products can be satisfactorily accounted for in terms of initial rate determining formation of a radical pair followed by regiospecific radical disproportionation (oxidised products)[14] or radical recombination (addition products).[13]

Experimental

The following procedure was used to prepare compound **10**. Calculations were carried out using the AM1 semi-empirical method[15] and energy was minimised with respect to all geometrical variables.

1-(4,5-Dihydro-1*H*-imidazol-2-yl)-1-phenyl-1-(3-nitro-2-thienyl)methanol 10

A solution of 2-chloro-3-nitrothiophene **9** (1.0 g, 6.0 mmol) in propiononitrile (30 ml) containing molecular sieves (4 Å) was stirred and 2-benzyl-4,5-dihydro-1*H*-imidazole **7** (1.93 g, 12.0 mmol) in propiononitrile (20 ml) was added dropwise. After maintaining stirring (24 h) at ambient temperature, the solution was filtered and evaporated under vacuum to give a dark red residue that was purified by flash chromatography on silica (9:1, ethyl acetate–MeOH as eluent) to give a single product that was recrystallised from EtOH and identified as *compound* **10** (1.13 g, 62%), fine beige needles, mp 140–142 °C (Found: C, 55.59; H, 4.33; N, 13.69. $C_{14}H_{13}N_3O_3S$ requires C, 55.43; H, 4.32; N, 13.85%); ν_{max}(KBr)/cm^{-1} 3428, 1613, 1534, 1496, 1446 and 1333; δ_H ($CDCl_3$) 1.65–1.85 (1H, br s, NH), 3.69 (4H, s, 2 × CH_2), 7.12 (1H, d, *J* 5.7 Hz, thiophene-H), 7.41–7.43 (3H, m, phenyl-H), 7.59 (1H, d, *J* 5.7 Hz, thiophene-H), 7.67–7.69 (2H, m, phenyl-H); δ_C (CD_3OD) 50.21 (2 × CH_2), 75.48 (C-OH), 125.81 (CH), 126.31 (CH), 127.91 (CH), 129.05 (CH), 130.18 (CH), 141.99 (C), 146.24 (C), 151.81 (C), 172.56 (C); *m*/*z* 303.0675 ($M^{\bullet+}$: $C_{14}H_{13}N_3O_3S$ requires 303.0678), 286 (M − OH) and 257 (M − NO_2).

Crystal data. $C_{14}H_{14}BrN_3O_2S$, *M* 368, monoclinic, *a* = 9.051(2), *b* = 13.430(2), *c* = 12.144(4) Å, *β* = 99.870(2)°, *U* = 1454.3(6) Å^3, *T* = 150(2) K, space group $P2_1/n$, *Z* = 4, *μ* = 2.977 mm^{-1}, *R* values wR_2 = 0.0877, *R* = 0.0369 (1820 reflections with $F > 4\sigma(F)$), reflections: measured 6383, independent 2281; R_{int} = 0.0872.

Acknowledgements

We thank the Cancer Research Campaign for the award of a Project Grant to support this work, the EPSRC Crystallography Service (Cardiff) for collection of X-ray data and Professor Gurnos Jones (Keele) for his interest and suggestions.

Notes and references

† All new compounds were characterised by spectroscopy and elemental analysis.

1 J. I. Musher, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 54; C. A. Ramsden, *Chem. Soc. Rev.*, 1994, **23**, 111; C. A. Ramsden, *J. Heterocycl. Chem.*, 1999, **36**, 1573.
2 C. A. Ramsden and R. G. Smith, *J. Am. Chem. Soc.*, 1998, **120**, 6842; C. A. Ramsden and R. G. Smith, *Org. Lett.*, 1999, **1**, 1591.
3 *Nitroimidazoles: Chemistry, Pharmacology and Clinical Applications*, eds. G. E. Adams, A. Breccia and B. Cavalleri, Nato Advanced Study Institutes Series, Series A: Life Sciences, Plenum Press, New York and London, 1982, vol. 42; J. A. McFadzean, *Flagyl: The Story of a Pharmaceutical Discovery*, Parthenon Publishing Group Ltd., 1986.
4 E. M. Zeman, J. M. Brown, M. J. Lemmon, V. K. Hirst and W. W. Hirst, *Int. J. Radiat. Oncol. Biol. Phys.*, 1986, **12**, 1239.
5 M. A. Naylor, M. A. Stephens, J. Nolan, B. Sutton, J. H. Tocher, E. M. Fielden, G. E. Adams and I. J. Stratford, *Anti-Cancer Drug Des.*, 1993, **8**, 439.
6 J. Sarasin and E. Wegmann, *Helv. Chim. Acta*, 1924, **7**, 713; 5-chloro-1,3-dimethyl-4-nitropyrazole was purchased from Maybridge Chemical Co. Ltd.
7 C. D. Hurd and K. L. Kreuz, *J. Am. Chem. Soc.*, 1952, **74**, 2965; G. Consiglio, V. Frenna, C. Arnone, E. Mezzina and D. Spinelli, *J. Chem. Soc., Perkin Trans. 2*, 1994, 2187.
8 A. J. Arduengo, III, *Acc. Chem. Res.*, 1999, **32**, 913; A. J. Arduengo, III, J. R. Goerlich and W. J. Marshall, *J. Am. Chem. Soc.*, 1995, **117**, 11027; A. J. Arduengo, III, H. V. R. Dias, R. L. Harlow and M. Kline, *J. Am. Chem. Soc.*, 1992, **114**, 5530.
9 A. H. M. Al-Shaar, D. W. Gilmour, D. J. Lythgoe, I. McClenaghan and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2779; A. H. M. Al-Shaar, R. K. Chambers, D. W. Gilmour, D. J. Lythgoe, I. McClenaghan and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2789.
10 G. M. Sheldrick, SHELX-93, University of Göttingen, 1986.
11 R. H. Jones, C. A. Ramsden and H. L. Rose, *J. Heterocycl. Chem.*, 1996, **33**, 1031.
12 B. M. Trost, *J. Am. Chem. Soc.*, 1967, **89**, 1847.
13 H.-D. Becker, *J. Org. Chem.*, 1969, **34**, 1203.
14 W. Brown and A. B. Turner, *J. Chem. Soc. C*, 1971, 2057.
15 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.