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Ring–Ring Interconversions of Nitrosoimidazoles. The Effect of some Condensed Six-Membered Rings on the Reactivity

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Abstract—The study of the effect of a condensed ring on the reactivity of nitrosoimidazoles with hydrochloric acid has been extended to some six-membered rings: thus, the reactivity of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (**6**), 6-chloro-2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*b*]pyridazine (**7**), 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrimidine (**8a**) and 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrazine (**9**) has been examined. The striking differences observed in the reactivity of compounds **6**–**9** (denitrosation, ring-opening with ammonia elimination, ring–ring interconversion with the *unexpected loss* of a C_3 fragment and decomposition, respectively) have been discussed.

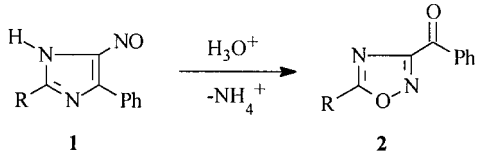
Introduction

The action of hydrochloric acid at room temperature on 4(5)-nitroso-5(4)-phenylimidazoles **1** affords 3-benzoyl-1,2,4-oxadiazoles **2** through a ring-opening/ring-closing process which involves elimination of ammonia (Scheme 1).[1]

We have also shown[2] that the course of this reaction can be affected by the presence of a ring condensed with the imidazole (at N-1 and C-2). Thus, by refluxing 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*][1,3]thiazole **3** (a compound with mutagenic activity)[3] in the presence of hydrochloric acid, a novel ring transformation is observed, with formation of 8-(4-chlorophenyl)-8-hydroxy-5-methyl-8*H*-[1,4]thiazino[3,4-*c*][1,2,4]oxadiazol-3-one **4**: also in this case the ring–ring interconversion is accompanied only by ammonia elimination (Scheme 2). Because **4** inhibited the cell growth of some tumour-derived cell lines (colon cancer, melanoma and breast cancer)[4a] and showed some interesting cardiovascular properties[4b] we have recently extended this ring–ring interconversion to several nitrosoimidazothiazoles substituted both in the 6-aryl[4a] and in the thiazole moiety[4c] with the aim of obtaining new suitable thiazinooxadiazolones for studies of structure/activity relationships. Moreover, by carrying out the reaction at room temperature we have been able to isolate the reaction intermediate **5**, so providing useful information on the reaction mechanism.[4a]

It is noteworthy that with both nitrosoimidazoles **1** and the nitrosoimidazothiazole **3** the rearrangement leads to products (**2** and **4**, respectively) which contain the same number of carbon atoms as the starting materials.

In the framework of our interest in nitrogen compounds with mutagenic activity,[3,5] in ring–ring interconversions[1a–c,6] and the study of the factors that can affect the course of ring transformations in derivatives of nitrosoimidazoles, we herein report on the results obtained when changing the ring condensed with the imidazole from the five-membered thiazole to some six-membered ones. Thus we have tested the reactivity of compounds **6**–**9**, and found significant differences between the selected systems, these being: in **6** the only heteroatom of the condensed ring is the common nitrogen atom, whereas compounds **7**–**9** possess a second nitrogen atom *ortho*, *meta* or *para* with respect to the bridge-head nitrogen; furthermore, it should be remarked that only **8** shows a situation similar to that of **3** as far as it concerns the presence of a heteroatom (a nitrogen atom vs. a sulphur atom in **3**) linked to the C-2 of the imidazole ring. For these reasons the systems **6**–**9** appear to be good probes



1 **2**

R = H, Me, Ph, NH_2

Scheme 1.

Keywords: ring–ring interconversions; heterocyclic rearrangements; condensed nitrosoimidazoles.

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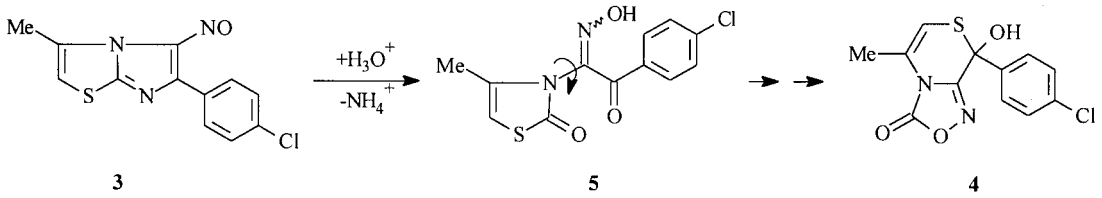
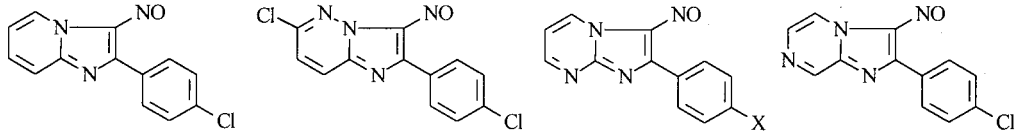


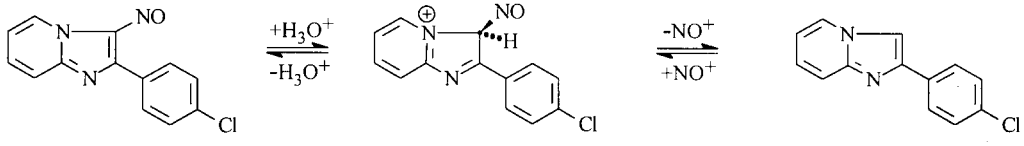
3 5 4

Scheme 2.



6 7 **8a** X = Cl **8b** X = H 9

Figure 1.



6 σ-complex 10

Scheme 3.

for the study of the influence of the structure of a condensed ring on the reactivity of nitrosoimidazoles (Fig. 1).

Results

Reactivity of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]-pyridine (6) with hydrochloric acid

In experimental conditions similar to those used for the **3→4** rearrangement (i.e. 3 h reflux in ethanol with excess hydrochloric acid) **6** (coloured product) remained practically unchanged (recovered: ca. 90%). By prolonged reflux (7 days) **6** gave high yields (ca. 85%) of a colourless product identified as 2-(4-chlorophenyl)-imidazo[1,2-*a*]pyridine **10** on the basis of its ^{1}H and ^{13}C NMR, and MS spectra and by comparison with an authentic sample:[7] a behaviour which well matches both the high reactivity of the imidazole ring towards electrophiles[†] and the essential characteristics of nitrosation–denitrosation reactions.[‡] On the other hand, the stability of the imidazopyridine ring system with respect to ring–ring interconversions can be related both to the low electrophilic character of the carbon atom (i.e. C-8*a*) which should be attacked by the water nucleophile and to the fact that a carbon–carbon bond breaking would be eventually required herein instead of the heteroatom (sulphur)–carbon bond breaking undergone by **3** (Scheme 3).[2,4a]

The behaviour of **6** well fits in with known properties of imidazo[1,2-*a*]pyridines such as those reported hereinafter. First of all, X-ray structural investigations on the latter compounds have pointed out[10] the overall aromatic character of the condensed system, as indicated by the coplanarity of the two heterocyclic rings and by the carbon–carbon bond lengths, that never exceed 1.42 Å (observed range: 1.35–1.42 Å). Moreover the Dimroth rearrangement occurs only when the imidazo[1,2-*a*]pyridine system is activated by a nitro group at the 6- or 8-position,[11] which deeply increases the electrophilic character of the pyridine ring enabling it to react with the strongly nucleophilic hydroxide ion.

Reactivity of 6-chloro-2-(4-chlorophenyl)-3-nitroso-imidazo[1,2-*b*]pyridazine (7) with hydrochloric acid

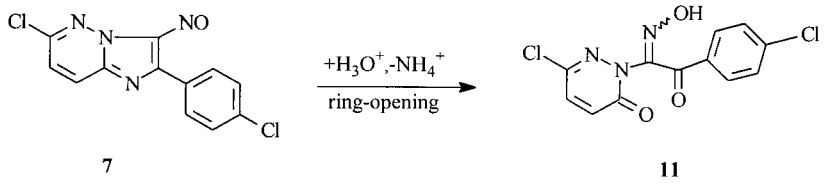
By 3 h reflux in ethanol with excess hydrochloric acid, compound **7** (green) gave a colourless product (yield: 54%), identified as 1-[3-chloro-6-oxo-1(6*H*)-pyridazinyl]-2-(4-chlorophenyl)-1,2-ethanedione 1-oxime **11** on the basis of its ^{1}H and ^{13}C NMR and mass spectra. The oxime proved stable also after prolonged reflux (18 h) (Scheme 4).

Reactivity of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrimidine (8a) with hydrochloric acid

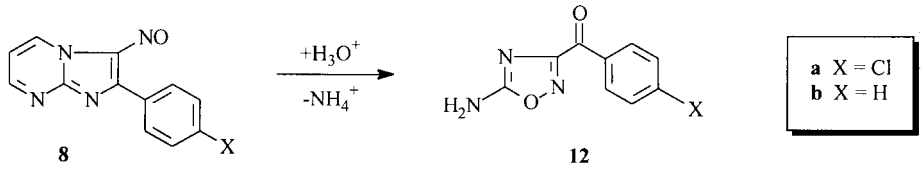
In experimental conditions similar to those used for the **3→4** rearrangement **8a** (green, $C_{12}H_7ClN_4O$) reacted giving a

[†] E.g. the imidazole can easily be brominated (formation of 2,4,5-tribromoimidazole)[8a] or nitrated (formation of 4-nitroimidazole).[8b]

[‡] The reversibility of aromatic nitrosation, due to the low electrophilic character of the nitrosonium ion, is clearly evidenced by sizeable kinetic isotope effects (k_H/k_D 1.3–4.5) mirroring a slow deprotonation of the intermediate σ-complex.[9]



Scheme 4.



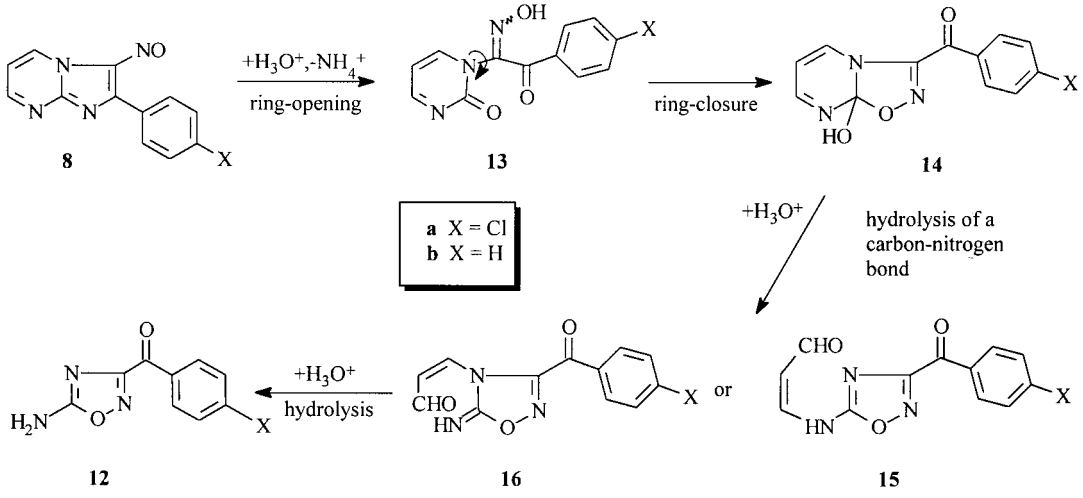
Scheme 5.

colourless product (yield: 40%), whose high-resolution mass spectrum and elemental analysis are in agreement with the molecular formula $C_9H_6ClN_3O_2$. The formation of such a compound thus implies the expected elimination of ammonia together with the *unexpected loss* of a three-carbon fragment with respect to the starting material. On the grounds of its spectral properties and by comparison with literature data the product has been identified as the known 5-amino-3-(4-chlorobenzoyl)-1,2,4-oxadiazole **12a**[12–14] (Scheme 5).

In order to understand the course of the **8a→12a** conversion, it is first of all necessary to ascertain whether the loss of the three-carbon fragment precedes or follows the nitroso-imidazole ring-opening.

As a matter of fact it is well known that 1-alkyl-1,2-dihydro-2-iminopyrimidines can undergo addition of water, followed by a reversible ring fission which eventually leads to isomerisation products (Dimroth rearrangement).[15] It has also been reported that ring-opened intermediates can decompose giving malonodialdehyde (i.e. a three-carbon fragment) and substituted guanidines.[15] Actually, **8a** contains an atomic skeleton similar to that of the above-mentioned 1-alkyl-1,2-dihydro-2-iminopyrimidines, which is condensed with the nitrosoimidazole system; in principle, it is thus possible to hypothesise that the three-carbons loss precedes the opening of the nitrosoimidazole ring to **13**. Nonetheless, our experimental conditions (acidic solution) appear completely different from those used by Perrin and Pitman[15] (strongly alkaline solution) to decompose the above-mentioned ring-opened intermediates. Furthermore, in an independent experiment we have ascertained that an ethanolic solution of 2-(4-chlorophenyl)-imidazo[1,2-*a*]-pyrimidine remains essentially unaltered when treated with hydrochloric acid (8 h, 80°C): this observation suggests that, at least in acidic solution, opening of the imidazole ring, triggered by the 3-nitrosogroup, is a prerequisite for the three-carbon fragment loss.

Moreover by carrying out the reaction at room temperature in dioxane we have been able to isolate an intermediate which afforded **12a** by further reflux in ethanol. The structure of the intermediate obtained has been studied spectroscopically: its mass spectrum shows $M^{+\cdot}$ at 277 according with $C_{12}H_8ClN_3O_3$ and its ^1H and ^{13}C NMR spectra fit well with the structure of both (*Z*)-3-{[3-(4-chlorobenzoyl)-1,2,4-oxadiazol-5-yl]amino}-2-propenal **15a**



Scheme 6.

and (*Z*)-3-[3-(4-chlorobenzoyl)-5-imino-1,2,4-oxadiazol-4(5*H*)-yl]-2-propenal **16a**.

The latter observation allows us to definitively conclude that the loss of the three-carbon fragment follows the ring-opening of the nitrosoimidazole and, on the other hand, provides a significant insight into the reaction mechanism. Thus (Scheme 6), the first step of the overall transformation could well be a hydrolytic ring-opening of **8a** to **13a** analogous to the **3** to **5** process, accompanied by ammonia elimination: a hypothesis which is strongly supported by the observed formation of **11** from **7**. Conceivably, the reaction scheme is completed by (a) ring-closure of **13a** to the non-aromatic 3-(4-chlorobenzoyl)-8*a*-hydroxy-8*aH*-1,2,4-oxadiazolo[4,5-*a*]pyrimidine **14a**, (b) acidic hydrolysis of a carbon–nitrogen bond to the isolated **15a** or **16a**, and (c) further hydrolysis with loss of a three-carbon fragment and formation of the final compound **12a**. Unfortunately no choice could be made between structures **15a** and **16a**, both of which are compatible with the experimental ^{1}H and ^{13}C NMR spectra. With the aim to resolve the structure we have also performed a particular 2D NMR sequence (g-HNMQC)[16] to evidentiate any H–N coupling, but no correlation for the proton resonance at 12.27 ppm could be detected which would allow a definitive assignment.

Interestingly the reaction with 2-phenyl-3-nitroso-imidazo[1,2-*a*]pyrimidine **8b** similarly led to 3-benzoyl-5-amino-1,2,4-oxadiazole **12b** (yield: 54%) fostering the hope for a more general applicability of the process.

Reactivity of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrazine (9) with hydrochloric acid

In experimental conditions similar to those used for the **3→4** rearrangement, **9** gave only decomposition products; similar results were obtained at room temperature both in ethanol and in dioxane.

Discussion

In the attempt to rationalise the striking differences in the reactivity of compounds **1**, **3**, **6–9** outlined above we can confidently assume that the first stage of the ring opening of nitrosoarylimidazoles in the presence of acids (i.e. in conditions where both arylimidazoles and condensed aryl-imidazoles should by themselves be stable) is represented by the protonation of the nitrosogroup.[§] This enhances the electrophilicity of the imidazole ring making it amenable to the attack of even such a weak nucleophile as water to C-2: the following ring opening easily occurs in the case of **1** (in a few minutes at room temperature),[1,17] while it requires refluxing (3 h or more) in the case of **3**,[2,4a] **7** and **8** indicating that the presence of a condensed ring significantly lowers the reactivity (for steric reasons and/or by increasing the stability of the heterocyclic systems). As expected, the presence of an electronegative heteroatom (sulphur or nitrogen) in the condensed ring (cf. compounds **3**, **7–9**) does favour the nucleophilic attack insofar as no imidazole ring opening occurs in **6**, which only undergoes proto-denitrosation (see Scheme 3).

Thus, in compounds **1**, **3**, **7** and **8** the nucleophilic attack of water causes the hydrolytic opening of the imidazole ring with elimination of ammonia. In the case of **3** and **8** the intermediates **5** and **13** eventually furnish by further heating **4** and **12**, respectively. In contrast, in the case of **7** the product of hydrolytic opening of the imidazole ring (i.e. **11**, structurally similar to **5**) is the final reaction product. Why does the reaction stop at this stage? Probably because the further evolution of the reaction would require, in **11**, the thermodynamically unfavourable carbon–carbon bond breaking between the primitive C-2 and C-3 ring positions.

The results herein should thus be of valuable help in focussing the factors that affect the ring–ring interconversion mechanism in condensed nitrosoimidazoles. One such factor can undoubtedly be identified in the presence of a low-energy heteroatom–carbon bond in the heterocycle originally condensed with the imidazole ring: as a matter of fact the feeble –CO–S– bond of **5**, the intermediate from ring-opening of **3**, most likely represents the driving force for an $S_{N_{ac}}$ process triggered by the oxime oxygen and eventually leading to the final product via opening of the thiazole ring. Likewise, **13**, structurally similar to **5**, can evolve (possibly via the formation of **14**) by hydrolysis of the N-1/C-6 or of the N3/C4 bond of the pyrimidine ring: the ensuing **15** or **16**, respectively, would then furnish the final product **12**.

Experimental

^{1}H and ^{13}CNMR spectra were recorded on a Varian Gemini 300 Instrument in the Fourier transform mode at 21±0.5°C in DMSO-d_6. Chemical shifts (δ) in ppm from tetramethylsilane and coupling constants in Hz, respectively, are reported. The g-HNMQC experiment[16] was performed using a Varian Unity PFG 400 instrument operating at a frequency of 399.94 MHz for ^{1}H observation. Pulses for ^{1}H and ^{15}N were calibrated at 9.2 and 36 μs, respectively. The long range delay in the sequence was optimised for 3.5 Hz. Mass spectra were recorded on a VG70 70E apparatus. All melting points were obtained with an Electrothermal apparatus. All new compounds gave satisfactory elementary analyses (C, H, N and halogens). Solvents were removed under reduced pressure. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck 230–400 mesh) were used for analytical TLC and for column-chromatography, respectively. Compounds **8a** and **8b** were obtained according to literature methods.[18]

2-(4-Chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (6). A solution of sodium nitrite (0.60 g, 8.7 mmol) in water (10 ml) was added, under cooling and stirring, to a solution of 2-(4-chlorophenyl)-imidazo[1,2-*a*]pyridine[7] (0.91 g, 4 mmol) in acetic acid (20 ml). After 2 h at room temperature, the mixture was neutralised with NaOH 2 M and the green precipitate was collected and crystallised from ethanol (mp 227–228°C, 0.62 g, 60%); [Found: C, 60,5; H, 3.2; N, 16.2. $C_{13}H_8ClN_3O$ requires C, 60.6; H, 3.1; N, 16.3%]. δ_H 9.82 (1H, ddd, $J_{5,6}$=6.6 Hz, $J_{5,7}$=1.2 Hz,

§ The same result would be obtained, of course, by ring protonation.

$J_{5,8}$=1.2 Hz, H-5), 8.59 (2H, AA′ part of AA′XX′ system, H-2′ and 6′), 8.08 (2H, m, H-7 and H-8), 7.70 (2H, XX′ part of AA′XX′ system, H-3′ and 5′), 7.53 (1H, ddd, $J_{5,6}$=6.6 Hz, $J_{6,7}$=6.4 Hz, $J_{6,8}$=2.2 Hz, H-6). δ_C 157.13 (C-2), 153.07 (C-3), 145.26 (C-8*a*), 137.71 (C-7), 136.65 (C-4′), 131.72 (C-2′/6′), 130.24 (C-1′), 129.05 (C-3′5′), 126.24 (C-5), 120.94 (C-6), 117.35 (C-8). MS *m/z* 257 (M^+, 100%), 194 (60), 192 (68), 123 (17), 78 (61). HRMS 257.03588, $C_{13}H_8ClN_3O$ requires 257.03559 (Cl-35 isotope).

6-Chloro-2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*b*]pyridazine (7). A mixture of 3-amino-6-chloropyridazine (1.04 g, 8 mmol) and 2-(4-chlorophenyl)-*N*-hydroxy-2-oxoethanimidoyl chloride[19] (0.87 g, 4 mmol) in ethanol (100 ml) was stirred at room temperature for 30 min and then left for 3 h. The green precipitate was collected and crystallised from ethanol (mp 219–220°C, 0.64 g, 55%); [Found: C, 49.3; H, 2.2; N, 19.2. $C_{12}H_6Cl_2N_4O$ requires C, 49.2; H, 2.1; N, 19.1%]. δ_H 8.61 (1H, d, $J_{7,8}$=9.5 Hz, H-7), 8.52 (2H, AA′ part of AA′XX′ system, H-2′ and 6′), 8.05 (1H, d, $J_{7,8}$=9.5 Hz, H-8), 7.72 (2H, XX′ part of AA′XX′ system, H-3′ and 5′). MS *m/z* 292 (M^+, 99%), 278 (37), 275 (47), 263 (17), 241 (35), 229 (100), 227 (50), 149 (21), 114 (84), 75 (25), 73 (74), 63 (19). HRMS 291.99228, $C_{12}H_6Cl_2N_4O$ requires 291.99187 (Cl-35 isotope).

2-(4-Chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrazine (9). A mixture of 2-aminopyrazine (0.76 g, 8 mmol) and 2-(4-chlorophenyl)-*N*-hydroxy-2-oxoethanimidoyl chloride[19] (0.87 g, 4 mmol) in ethanol (100 ml) was stirred at room temperature for 30 min and then left for 3 h. The green precipitate was collected and crystallised from ethanol (mp 203–204°C, 0.41 g, 40%) [Found: C, 55.6; H, 2.6; N, 21.5. $C_{12}H_7ClN_4O$ requires C, 55.7; H, 2.7; N, 21.7%]. δ_H 9.62 (1 H, d, $J_{8,6}$=1.5 Hz, H-8), 9.48 (1H, dd, $J_{6,5}$=4.3 Hz, $J_{6,8}$=1.5 Hz, H-6), 8.64 (2H, AA′ part of AA′XX′ system, H-2′ and 6′), 8.59 (1H, d, $J_{5,6}$=4.3 Hz, H-5), 7.75 (2H, XX′ part of AA′XX′ system, H3′ and 5′). δ_C 156.48 (C-2), 153.14 (C-3), 144.01 (C-8), 139.49 (C-6) 137.01 (C-8*a*), 136.78 (C-4′), 131.79 (C-2′/6′), 129.98 (C-1′), 129.36 (C-3′/5′), 117.26 (C-5). MS *m/z* 258 (M^+, 98%), 241 (15), 223 (18), 203 (18), 195 (100), 193 (41), 123 (19), 114 (18), 103 (20), 98 (26), 79 (34), 52 (27). HRMS 258.03066, $C_{12}H_7ClN_4O$ requires 258.03084 (Cl-35 isotope).

Reaction of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine (6) with hydrochloric acid. Hydrochloric acid (2 M; 4 ml) was added to a stirred solution of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyridine **6** (1.03 g, 4 mmol) in 60 ml of ethanol and refluxed for 3 h without valuable transformation of **6.** After refluxing until complete disappearance of the green colour (ca. 7 days), the removal of the solvent left a solid which after purification by flash-chromatography (ethyl acetate/benzene, 1:5, v/v) was identified as 2-(4-chlorophenyl)-imidazo[1,2-*a*]pyridine **10** (0.78 g, 85%). Mp 208–209°C (lit.[7] 208°C). δ_H 8.53 (1H, ddd, $J_{5,6}$=6.7 Hz, $J_{5,7}$=1.1 Hz, $J_{5,8}$=1.1 Hz, 5-H), 8.44 (1H, d, $J_{3,8}$=1.1 Hz, H-3), 7.99 (2H, AA′ part of AA′XX′ system, H-2′ and 6′), 7.58 (1H, dddd, $J_{7,8}$=9.1 Hz, $J_{6,8}$=1.1 Hz, $J_{5,8}$=1.1 Hz, $J_{3,8}$=1.1 Hz, H-8), 7.50 (2H, XX′ part of AA′XX′ system, H-3′ and 5′), 7.26 (1H, ddd, $J_{7,8}$=9.1 Hz, $J_{6,7}$=6.7 Hz, $J_{5,7}$=1.1 Hz, H-7), 6.91 (1H, ddd, $J_{5,6}$=6.7 Hz, $J_{6,7}$=6.7 Hz, $J_{6,8}$=1.1 Hz, H6). δ_C 144.85 (C-8*a*), 143.10 (C-2), 132.82 (C-1′), 132.09 (C-4′), 128.74 (C-3′/5′), 127.22 (C-2′/6′), 126.97 (C-5), 125.22 (C-7), 116.65 (C-8), 112.45 (C-6), 109.49 (C-3). HRMS 228.04619, $C_{13}H_9ClN_2$ requires 228.04543 (Cl-35 isotope).

Reaction of 6-chloro-2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*b*]pyridazine (7) with hydrochloric acid. Hydrochloric acid (2 M; 4 ml) was added to a stirred solution of 6-chloro-2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*b*]pyridazine **7** (1.17 g, 4 mmol) in 80 ml of ethanol and refluxed for 9 h. Removal of the solvent left a solid, which was washed with water and identified as 1-[3-chloro-6-oxo-1(6*H*)pyridazinyl]-2-(4-chlorophenyl)-1,2-ethanedione 1-oxime **11** (0.66 g, 53%), that did not change by further refluxing (18 h). Mp 168–170°C [Found: C, 46.4; H, 2.3; N, 13.3. $C_{12}H_7Cl_2N_3O_3$ requires C, 46.2; H, 2.3; N, 13.5%]. δ_H 13.81 (1H, s, exch., OH), 8.00 (2H, AA′ part of AA′XX′ system, H-2′ and 6′), 7.73 (1H, d, $J_{4,5}$=9.9 Hz, H-4), 7.66 (2H, XX′ part of AA′XX′ system, H-3′ and 5′), 7.25 (1H, d, $J_{4,5}$=9.9 Hz, H-5). δ_C 183.74 (C-2), 156.92 (C-6), 143.93 (C-3), 138.74 (C-1), 138.52 (C-4′), 135.70 (C-5/4), 133.70 (C-1′), 132.53 (C-4/5), 131.85 (C-2′ and C-6′), 128.58 (C-3′ and C-5′). HRMS 310.98583, $C_{12}H_7Cl_2N_3O_3$ requires 310.98645 (Cl-35 isotope).

Reaction of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-a]pyrimidine (8a) with hydrochloric acid. *(A) 5-Amino-3-(4-chlorobenzoyl)-1,2,4-oxadiazole **12a**.* Hydrochloric acid (2 M; 4 ml) was added to a stirred solution of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrimidine **8a** (1.03 g, 4 mmol) in 60 ml of ethanol. The reaction mixture was refluxed until complete disappearance of the green colour (ca. 1.5 h). Removal of the solvent left a solid which gave 5-amino-3-(4-chlorobenzoyl)-1,2,4-oxadiazole **12a** (0.36 g, 40%) after purification by flash-chromatography (ethyl acetate/petroleum ether 40–60°C, 1:1, v/v). Mp 234–235°C (lit[1d,12] 236–237°C). δ_H 8.28 (2H, br s, exch., NH_2), 8.15 (2H, AA′ part of AA′XX′ system, H2′ and 6′), 7.67 (2H, XX′ part of AA′XX′ system, H-3′ and 5′). δ_C 183.19 (CO), 172.45 (C-5), 165.77 (C-3), 139.68 (C-4′), 133.91 (C-1′), 132.11 (C-2′ and C-6′), 129.08 (C-3′ and C-5′). MS *m/z* 223 (M^+, 46%), 152 (16), 139 (100), 111 (57), 75 (35). IR (KBr) 1665 cm^{-1}. HRMS 223.01468, $C_9H_6ClN_3O_2$ requires 223.01485 (Cl-35 isotope). The ^{13}C NMR and mass spectra well compare with the reported ones[13,14] (e.g. the medium and the largest ^{13}C chemical shift differences being 0.12 and 0.26 ppm, respectively).

*(B) (Z)-3-{[3-(4-chlorobenzoyl)-1,2,4-oxadiazol-5-yl]amino}-2-propenal **15a** or (Z)-3-[3-(4-chlorobenzoyl)-5-imino-1,2,4-oxadiazol-4(5H)-yl]-2-propenal **16a**.* Hydrochloric acid (2 M; 4 ml) was added to a stirred solution of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrimidine **8a** (1.03 g, 4 mmol) in 60 ml of dioxane; after 5 h at room temperature the removal of the solvent left a solid containing unchanged **8a**, the intermediate **15a** or **16a** and the final product **12a**. The mixture was separated by column-chromatography. In the presence of hydrochloric acid by refluxing in ethanol (1 h) the intermediate gave **12a**. Spectral data for intermediate **15a** or **16a**: δ_H 12.27 (1H, br s, exch., NH), 9.49 (1H, d, $J_{1,2}$=8.2 Hz, H-1), 8.18 (2H, AA′ part of AA′XX′ system, H-2′ and 6′), 7.93 (1H, d, $J_{2,3}$=13.7 Hz, H-3), 7.70 (2H, XX′

part of AA′XX′ system, H-3′ and 5′); 5.91 (1H, dd, $J_{2,3}$=13.7 Hz, $J_{1,2}$=8.2 Hz, H-2). δ_C 191.93 (C-1), 181.90 (CO), 168.18 (C-5″), 165.13 (C-3″), 148.14 (C-3), 139.75 (C-4′), 133.37 (C-1′), 131.99 (C-2′ and C-6′), 128.95 (C-3′ and C-5′), 113.73 (C-2). MS *m/z* 277 (M^+, 1%), 223 (18), 207 (9), 139 (100), 111 (55), 75 (33).

Reaction of 2-phenyl-3-nitrosoimidazo[1,2-*a*]pyrimidine (8b) with hydrochloric acid→5-amino-3-benzoyl-1,2,4-oxadiazole 12b. Operating as reported under A, **8b** (0.90 g, 4 mmol) gave **12b** (0.41 g, 54%) after purification by flash-chromatography (ethyl acetate/petroleum ether 40–60°C, 1:1, v/v). Mp 193–194°C (lit[1d] 193°C).

Reaction of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrazine (9) with hydrochloric acid. Hydrochloric acid (2 M; 4 ml) was added to a stirred solution of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrazine **9** (1.03 g, 4 mmol) in 60 ml of ethanol and refluxed for 3 h. Removal of the solvent left an untreatable tar. Similar results were obtained also by working either at room temperature or in dioxane.

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