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On the reactivity of nitrosoimidazoles with acids (the Cusmano–Ruccia reaction): a continuous source of new ring-into-ring interconversion

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ABSTRACT

An extension of the 'Cusmano–Ruccia' reaction is reported. 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*]oxazole by the action of hydrochloric acid gives 3-(4-chlorobenzoyl)-5-methyl-1,2,4-oxadiazole (**13**); presumably via ammonium ion, CO_2 and methanol elimination. The relevance of the nature of the atom of the **B**-ring linked to C-2 of the imidazole for the occurrence of the ring-into-ring interconversion has been once more confirmed.

Studies on heterocyclic compounds cover more than half of the organic chemistry papers. Special interest is devoted to aromatic five- and six-membered ring derivatives containing nitrogen also because they carry out fundamental functions in a variety of life processes.[1] Moreover several and several drugs or promising hits contain their structures.[2] For all of these reasons we have been strongly involved in the study of ring-into-ring interconversion of heterocycles from different points of view (synthetic,[3,4] mechanistic,[3d,f,5] computational[6] and pharmacological[7]).

In the last two decades our research groups have been involved in attempts to extend the 'old' Cusmano–Ruccia reaction[8] (the conversion of some 4(or5)-aryl-5(or4)-nitrosoimidazoles **1** into 3-aroyl-1,2,4-oxadiazoles **2** by the action of acids; Scheme 1, route *a*) to several nitrosoimidazoles condensed with different five-(**3**; thiazole, Scheme 1, route *b*, formation of **4**)[7a,9] and six-membered heterocycles (**5**, **7** and **9**; pyridine, pyrimidine and pyridazine; Scheme 1, routes *c*–*e*, formation of **6**, **8** and **10**)[10] observing in every instance an unlikely behaviour.

Interestingly, several factors seem to affect the course of the occurring reactions, among them are the aromaticity of the **B**-ring condensed to imidazole, the nature of the C–X bond (see the general formula of the condensed imidazoles **BA**: X is the atom of the **B**-ring linked to C-2 of the imidazole ring; when X is a C-atom, the **B**-ring can stay unchanged, see route *c*, or can be only slightly modified, see route *e*), the stability of intermediates and/or final products. Indeed we have observed that the **B**-ring is strongly modified and involved in the interconversion only when X is a heteroatom (for example: X = S, route *b*; X = N, route *d*). Of peculiar interest is the reaction of 6-aryl-5-nitrosoimidazo[2,1-*b*]thiazoles **3** with acids: we obtained the 8-aryl-8-hydroxy-*8H*-[1,2,4]oxadiazolo[3,4-*c*][1,4]thiazinones **4**. Compound **4**, their acetals and some other derivatives obtained by ring opening of the thiazine ring show important pharmacological activities as LTCC (L-type calcium channel) blockers[7a–d,11] and as inhibitor of MDR1 (multidrug resistance of type 1) activity.[7e,f]

Following the above research line (Scheme 1) we have now enlarged our interest to the study of the reactivity with acid of 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*]oxazole **12**, $C_{12}H_8ClN_3O_2$, mp 140–142 °C dec., green: it represents the first example of this kind of nitroso compounds reported in the literature and strictly resembles **3** (the oxazole ring replacing the thiazole one, that is an oxygen atom substitutes a sulfur one in the condensed **B** ring). Compound **12** was obtained by nitrosation from the relevant 6-(4-chlorophenyl)-3-methylimidazo[2,1-*b*]oxazole (**11**).[12]

By heating (2–3 h) an ethanolic solution of **12** with hydrochloric acid (2 M) or by direct treatment of a solution of the non-isolated **12** in acetic acid/water with ethanol and hydrochloric acid we obtained from the reaction mixture by chromatographic separation on a silica gel column (eluant/petroleum ether/ethyl acetate from

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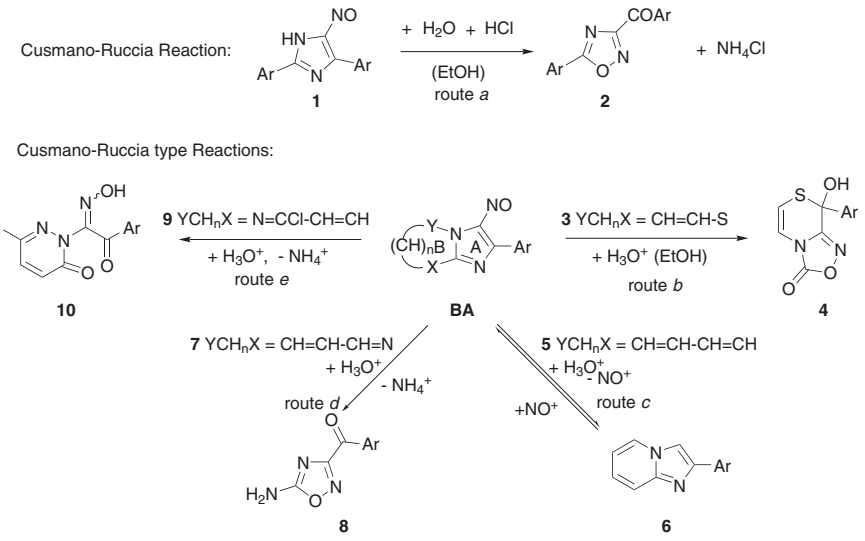
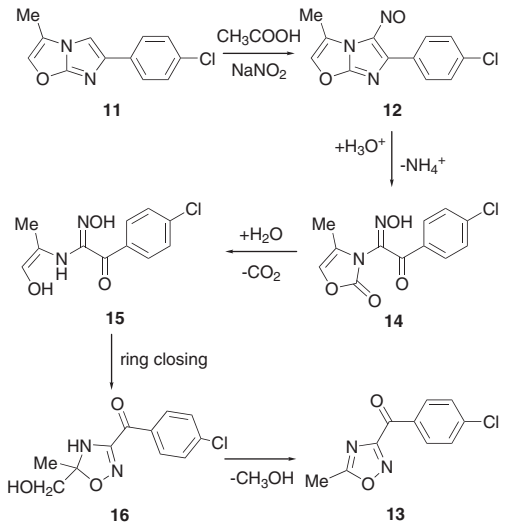


Scheme 1. Routes *a*, *b*, *d* and *e* are multi-step processes.

4:1 to 1:1) a colourless compound (mp 109–110 °C) with moderate yield (global yield of the process **11** → **12** → **13**: 20%). HRMS gave for it an experimental MW 222.01964 versus the calculated value 222.01961 for $C_{10}H_7ClN_2O_2$. An accurate analysis of ^1H (two couples of aromatic protons, $\delta = 8.16$ and $\delta = 7.71$, and a singlet for three aliphatic protons, $\delta = 2.73$, accordingly with the presence of a 4-chlorophenyl ring and of a methyl group respectively), ^{13}C NMR (a signal coherent with a carbonyl group, $\delta = 181.85$ and two signals indicating the presence of two sp^2 carbons bound to electronegative atoms $\delta = 178.2$ and $\delta = 165.1$, that is the two C=N bonds of the oxadiazole ring) and the electron impact-mass spectra has allowed to assign it the structure of the already known 3-(4-chlorobenzoyl)-5-methyl-1,2,4-oxadiazole (**13**).[13]

A comparison between the formulas of **12** and **13** indicates that the reaction occurs, as expected (see Scheme 1, routes *a*, *b*, *d* and *e*) with the loss of a nitrogen atom of the starting imidazole ring (as ammonium ion),[8–10] but unexpectedly with the loss of two further carbon atoms, thus giving a derivative of 1,2,4-oxadiazole.

This behaviour in some way recalls the one observed while studying the reactivity of 2-(4-chlorophenyl)-3-nitrosoimidazo[1,2-*a*]pyrimidine **7**, which, by the action of hydrochloric acid, gives 5-amino-3(4-chlorobenzoyl)-1,2,4-oxadiazole. In this last instance



Scheme 2. Proposed mechanism for the **11** → **12** → **13** process.

the presumably first-formed product derived from an ammonium ion elimination collapses to an 1,2,4-oxadiazole derivative, which in turn by the loss of a three-carbon fragment furnishes the final product **8**.[10]

To understand the course of the reaction now examined one must take into account what it is already known about the reactivity of derivatives of nitrosoimidazoles. It is well known that compounds **1**, **3**, **7** and **9** by the action of hydrochloric acid gave a hydrolytic opening reaction of the imidazole ring with ammonium ion elimination.

Taking into account this information and considering the ability of linear polyfunctionalysed intermediates to give ring-closing reactions (particularly easy to take place, because of thermodynamic reasons, if five- or six-membered rings can be obtained) we can hypothesise that the reaction occurs according to the tentative pathway reported in Scheme 2: thus entering in the general scheme of an ANRORC process.[14]

In the instance of **12** the above ring-opening would provide in the first stage by losing an ammonium ion the oxazolone **14**, which in the experimental hydrolytic (acidic) conditions would furnish the intermediate **15** by carbon dioxide elimination. Compound **15** in turn by a ring-closing reaction could give the 1,2,4-oxadiazoline **16**: this non-aromatic intermediate by losing a molecule of methanol and aromatisation finally could supply the 1,2,4-oxadiazole **13**.

Interestingly, **13** and several other 3-aroyl-5-alkyl-1,2,4-oxadiazoles are intermediates (via a Boulton–Katritzky reaction)[3a,b,g] for the syntheses of many 3-amino-4-aryl-1,2,5-oxadiazoles known for their pharmacological properties as central suppressants, anticonvulsants and muscle relaxants.[15]

In summary, we can say that the Cusmano–Ruccia reaction extended to variously condensed nitrosoimidazoles can be an important source of new ring-into-ring interconversion was able to furnish new compounds that can show interesting pharmacological activities or can be intermediates for active compounds.

Moreover the reaction now observed once more confirms that only when in the C–X bond (see **BA**) X is a heteroatom, in the present instance oxygen, the **B**-ring is strongly involved in the evolution of the reaction.

Acknowledgments

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12. Synthesis of 6-(4-chlorophenyl)-3-methyl-5-nitrosoimidazo[2,1-*b*]oxazole **12**. A solution of sodium nitrite (0.6 g; 8.7 mmol) in water (10 mL) was added, under cooling and stirring, to a solution of 6-(4-chlorophenyl)-3-methylimidazo[2,1-*b*]oxazole (**11**, 1 g; 4 mmol) in acetic acid (20 mL). After 10 min at room temperature the green precipitate was collected and crystallized from ethanol (yield 35%). Mp 140–142 °C dec. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.48 (AA′ part of AA′XX′ system, H-2′ and H-6′); 7.97 (1H, H-2); 7.68 (XX′ part of AA′XX′ system, H-3′ and H-5′); 2.44 (3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ: 159.1; 156.7; 154.8; 137.9; 136.6; 131.4 (2C); 130.6; 129.2 (2C); 10.8. EI-MS (*m*/*z*,%): 261 (M^+, 100); 226 (45); 165 (88); 137 (27); 111 (25); 102 (34); 75 (30); 50 (12). HMRS calcd for $C_{12}H_8ClN_3O_2$: 261.03050. Found: 261.03039.
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