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An unexpected aromatization during the N-alkylation reaction of 3,4-dihydro-1*H*-pyrazole derivatives: insight into the reaction mechanism

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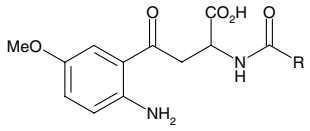
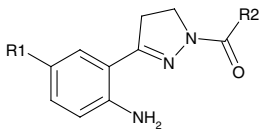
Abstract—In this letter we describe the unexpected aromatization that takes place during the N-alkylation reaction performed on several 3-(2-nitrobenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid methyl esters, giving rise to a mixture of 1-alkyl-3-(2-nitrobenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid methyl esters and 1-alkyl-3-(2-nitrobenzoyl)-1*H*-pyrazole-5-carboxylic acid methyl esters.

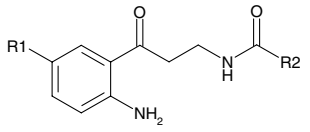
Several neurological diseases[1–3] and other types of physiological disorders[4–6] involve the overproduction of nitric oxide (NO) by the different nitric oxide synthase (NOS) isoforms. For this reason, the design of new NOS inhibitors is a matter of high potential therapeutic interest.



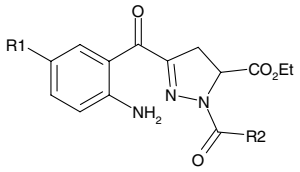
1a, R= Me
1b, R = Pr
(ref. 7)



2: R1= H, Cl, MeO
R2= Me, Et, Pr, etc.
(ref. 8)



3: R1= H, MeO
R2= Me, Et, Pr, etc.
(ref. 9)



4, R1 = H, Cl, OMe
R2 = Me, Et, Pr, etc.
(ref. 10)

We have recently synthesized and evaluated a series of NOS inhibitors with general structure **1**-**4**.[7–10] Among them, the 1-benzoyl-Δ^2-pyrazoline derivatives **4** have shown a moderate selectivity in the inhibition of the iNOS isoform.[10]

A key step in the synthesis of compounds **4** is the N-acylation of the appropriated 3-(5-substituted-2-nitrobenzoyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylic acid ethyl ester **5** (Scheme 1) to yield the nitro derivative **6** that was further reduced to the corresponding derivative **4**.

This synthetic scheme was followed to obtain 1-alkyl-Δ^2-pyrazoline analogues of **4** by N-alkylation of compound **5** (Scheme 1). In this reaction, besides the desired compound **7**, an important amount of the pyrazole derivative **8** is also obtained, as a consequence of an unexpected aromatization process.

The aromatization can be due to the action of the atmospheric oxygen, but the reaction was repeated under argon atmosphere with similar results, and a deeper investigation of the reaction mechanism was tackled.

Several methods have been described in the literature to oxidize the pyrazoline ring into the corresponding pyrazole. Among them, some inorganic compounds like bromine have been used in the synthesis of

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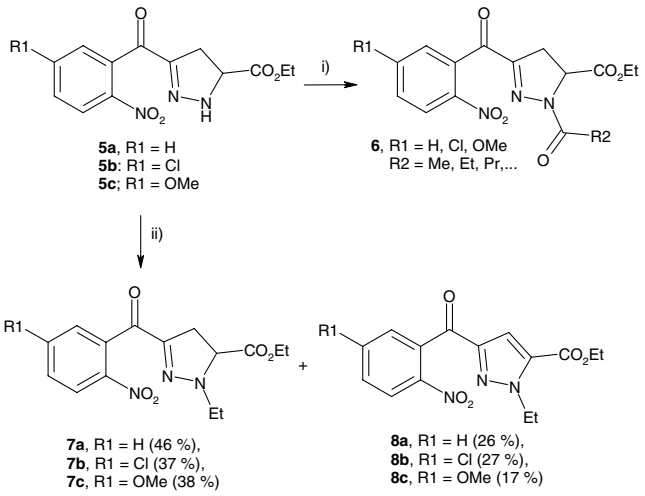
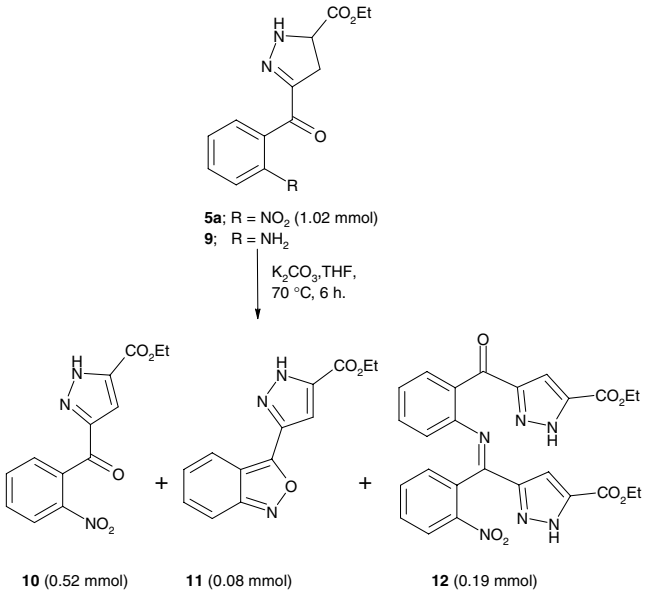


Scheme 1. Differences in the N-acylation and N-alkylation of 3-(5-substituted-2-nitrobenzoyl)-4,5-dihydro-1*H*-pyrazoles **5**. Reagents and conditions: (i) R2CO–Cl, Et_3N, CH_2Cl_2, room temperature, 3 h; (ii) $(EtO)_2SO_2$, K_2CO_3, THF, 70 °C, 22 h.



Scheme 2. Reaction product obtained in the treatment of the Δ^2-pyrazoline **5a**. Compound **9** does not react under the same conditions.

3,5-bis(ethoxycarbonyl)-1*H*-pyrazole from the corresponding Δ^2-pyrazoline.[11]

Metallic nitrates constitute another class of oxidizing reagents, and $Fe(NO_3)_3$ or $Cu(NO_3)_2$ deposited over an inert mineral support was employed in the oxidation of several 1-substituted Δ^1- or -Δ^2-pyrazolines.[12] More recently, $Zr(NO_3)_4$ has also been used in the synthesis of several 1*H*-pyrrole derivatives.[13]

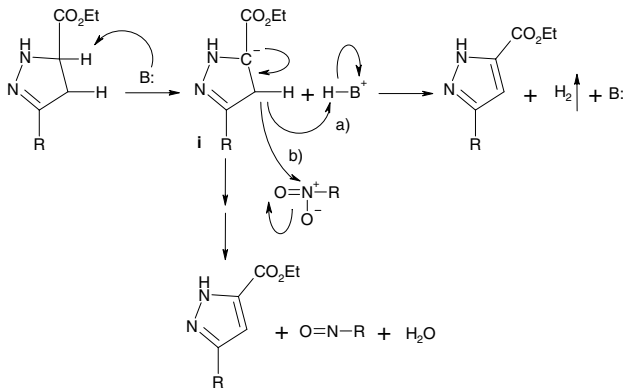
Organic compounds also constitute an important class of oxidizing agents. Among them, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) was used to oxidize condensed Δ^2-pyrazoline derivatives,[14] or in the synthesis of 5-acetyl-3-benzoyl-1*H*-pyrazole from the corresponding Δ^2-pyrazoline.[15] Chloranil (2,3,5,6-tetrachloro-2,5-cyclohexadiene-1,4-dione) has widely been used in the oxidation of Δ^2-pyrazoline rings, and a recent example is the synthesis of several 3-benzoyl-4-styryl-1*H*-pyrazole derivatives.[16] Recent papers describe the use of 4-(*p*-chlorophenyl)-1,2,4-triazole-3,5-dione as a reusable reagent in the oxidation of pyrazolines[17] and 1,4-dihydropyridines.[18]

Finally, nitrobenzene has been used as a reagent for the oxidation of several condensed pyrazoline to obtain the corresponding pyrazole.[19,20] This reagent constitutes a mild oxidant that has been used to dehydrogenate several organic systems under acidic and basic conditions.[21,22]

This background and the fact that compounds **5** bear a nitro group on the benzene ring suggest that the Δ^2-pyrazoline aromatization could be due to the action of the 2′-NO_2 group. One experiment, consisting in heating compound **5a** (1.02 mmol) under the same conditions used in the N-alkylation reaction (THF, K_2CO_3, 70 °C, 6 h, argon atmosphere) without the alkylating agent, was carried out in order to confirm this hypothesis. Scheme 2 shows all the obtained compounds. Besides the expected pyrazole **10** (0.052 mol), a mixture of compounds **11** (0.08 mmol) and **12** (0.12 mmol) was isolated.

Formation of pyrazole **10** implies the loss of a hydrogen molecule in Δ^2-pyrazoline **5a**, and this aromatization could take place through the evolution of molecular hydrogen, in a similar way to the Chichibabin reaction.[23] So, the reaction begins when the base takes the C_5–H atom yielding the stabilized carbanion **i** (Scheme 3), which can further transfer a hydride ion to the conjugated acid HB^+ (route a), and a hydrogen molecule is formed.

The molecular hydrogen formed could also be responsible for the formation of the two reduction products **11** and **12** isolated in this reaction. Nevertheless, this route does not seem to be correct since when 2′-amino analogue **9** is treated under the same conditions no transfor-



Scheme 3. Possible routes for the hydride ion transfer in the Δ^2-pyrazoline aromatization.

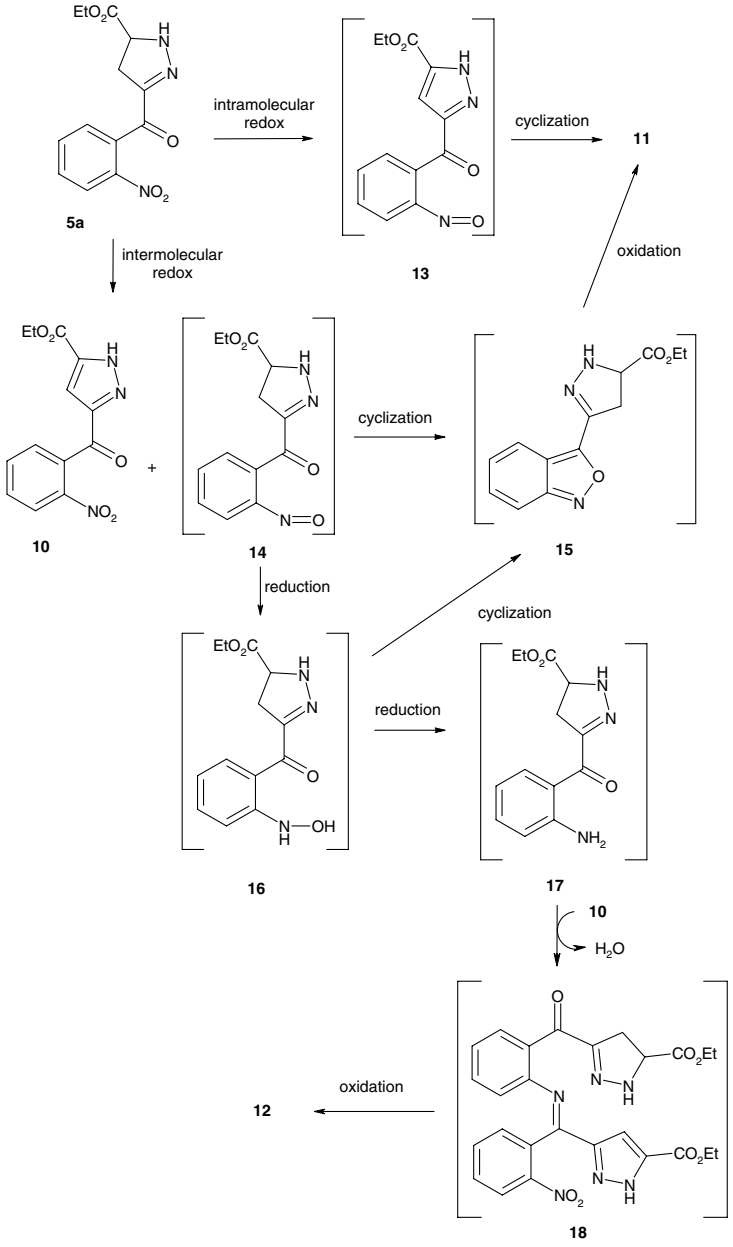
mation was observed, indicating the importance of the 2′-NO_2 group in the mechanism of the reaction.

Consequently, the nitro group is necessary for the reaction and could act as an acceptor of the hydride ion (Scheme 3, route b), allowing the pyrazoline aromatization and giving rise to the corresponding 2′-nitroso derivative in several steps.

The transfer of the hydride ion can take place in an intramolecular manner, yielding the nitroso intermediate **13** that could cyclize[24] to give the final product 3-(benzo[*c*]isoxazol-3-yl)-1*H*-pyrazol-5-carboxylic acid ethyl ester **11** (Scheme 4). Nevertheless, this process does not explain the formation of compound **10** where the Δ^2-pyrazoline moiety is oxidized to the corresponding pyrazole with the 2′-NO_2 group still remaining unaffected.

On the other hand, an intermolecular redox can also be considered. The pyrazoline moiety of one molecule of **5a** aromatizes to yield compound **10**, and the hydride ion is transferred to the nitro group of another molecule of **5a** yielding the nitroso intermediate **14**. This nitroso-ketone **14** can easily cyclize to give benzoisoxazole **15** that is further oxidized to **11**.

The 2′-NO group of intermediate **14** can accept another hydride ion and the reduction process continues yielding hydroxylamine **16**. Cyclization of **16** to produce intermediate **15** can also take place easily. A further reduction of the hydroxylamine group of **16** can also take place by accepting the transfer of another hydride ion giving the intermediate amine **17**. Condensation of **17** with the nitropyrazole compound **10** yields the intermediate **18** that is finally oxidized to the final compound **12**.



Scheme 4. Possible whole mechanism for the formation of compounds **10**, **11**, and **12**.

In this scheme, the oxidation processes imply the transfer of one hydride ion from the Δ^2-pyrazoline moiety to an appropriate acceptor group that could be 2′-NO_2, 2′-NO or 2′-NHOH, which are reduced. Alternatively, a wider scheme can be drawn from the reduction of the nitroso intermediate **13**.

The reduction of a nitro group to the corresponding amino needs three hydride ions to be transferred from the Δ^2-pyrazoline moiety. At least two of these hydride ions must be transferred in an intermolecular manner, while the third one can be inter- or intramolecular.

The reason why this reaction takes place during the N-alkylation of compound **5** and not in the N-acylation seems to be due to both temperature and reaction time. Reaction of compound **5** with the more reactive acyl chloride takes place at room temperature and in a short period (3 h), while a higher temperature and a longer reaction time are needed for the N-alkylation process.

This hypothesis is confirmed by the fact that when compound **5a** is treated under the same conditions used in the N-acylation reaction (Et_3N, CH_2Cl_2, room temperature, 3 h) without the acylating agent, no reaction is observed.

An interesting and related transformation has been described in the condensation of 1,5-diketones with 2- and 4-nitroanilines.[25] In these reactions, the formation of 1,4-dihydropyridine system is expected. Nevertheless, the dihydropyridine moiety aromatizes until the corresponding pyridinium salt and a reduction is observed of the 2- or 4-nitro group to the corresponding amine.

In conclusion, the unexpected aromatization observed in the N-alkylation of Δ^2-pyrazoline derivative **5a** is due to the participation of the 2′-NO_2 group that acts as a hydride acceptor.

Acknowledgments

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Supplementary data

Supplementary data associated with this article for spectroscopic data (^1H, ^{13}C NMR, and MS LSIMS) of compounds **10**, **11**, and **12** can be found, in the online version, at doi:10.1016/j.tetlet.2006.06.141.

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