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Synthesis of indazole-*N*-oxides via the 1,7-electrocyclisation of azomethine ylides

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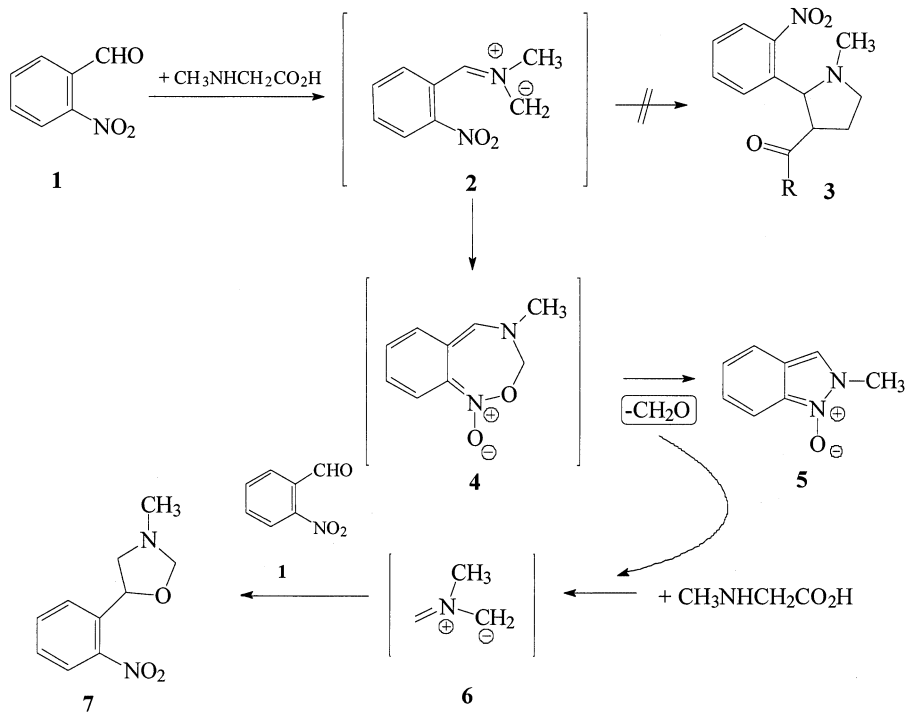
Abstract—The first example of the 1,7-electrocyclisation of a non-stabilised azomethine ylide, e.g. **2**, onto a nitro group, to give a 1,2,6-oxadiazepine intermediate, e.g. **4**, is reported. Subsequent ring contraction results in the formation of the indazole-*N*-oxides **5**, **12**, and **14**. © 2001 Elsevier Science Ltd. All rights reserved.

In the search for new syntheses of the pyrrolo[3,2-*c*]quinoline ring system of the bradykinin receptor antagonist martinelline alkaloids[1] we have studied the formation and reactions of the non-stabilised azomethine ylide **2** formed in the reaction of *o*-nitrobenzaldehyde **1** with sarcosine in refluxing benzene. To our surprise, in spite of the presence of a large excess of active dipolarophiles, such as ethyl acrylate or methyl



1 2 3 4 5 6 7

Scheme 1.

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vinyl ketone, we could not observe any trace of the expected cycloadducts **3** in the ^{1}H NMR spectrum of the crude reaction mixture. However, two products, an indazole-*N*-oxide **5** and an oxazolidine **7** were isolated after chromatographic separation (in 40 and 43% yields, respectively) and their structures confirmed by spectroscopic analysis.

The formation of these two compounds is probably due to the fragmentation of the unstable intermediate **4** shown in Scheme 1, in which the decarboxylative condensation[2] of *o*-nitrobenzaldehyde **1** and sarcosine is followed by a 1,7-electrocyclisation[3] of the non-stabilised azomethine ylide **2**. As such, this represents the first 1,7-electrocyclisation of an azomethine ylide onto a nitro group. The seven-membered ring of **4** subsequently undergoes a ring contraction, resulting in the elimination of formaldehyde and the production of 2-methyl-2*H*-indazol-*N*-oxide **5**. The formaldehyde by-product is then able to react with the excess sarcosine present in the reaction mixture, resulting in the formation of azomethine ylide **6**. This dipole could then react with the other starting material, *o*-nitrobenzaldehyde **1**, to yield the 3-methyl-5-aryloxazolidine **7** as the second product.

A similar process has been reported for the 1,7-electrocyclisation of the azomethine imine **8**, leading to the formation of the benzotriazole-*N*-oxide **9** (Scheme 2).[4]

We next chose to form the azomethine ylides from 6,7-dimethoxy - 3,4 - dihydro - *N* - (2 - nitrobenzyl)isoquinolinium chloride **10**[5] by dehydrohalogenation with triethylamine (Scheme 3).[6] In the presence of *N*-phenylmaleimide a 2:1 mixture of the cycloadduct **11** (as single isomer, proven by ^{1}H NOE experiments) and indazole-*N*-oxide **12** was obtained, while in the absence of the dipolarophile the *N*-oxide **12** was formed in quantitative yield. In contrast to the example described above, in this case the aldehyde arising from the fragmentation (which in this example is attached to the indazole component) is not sufficiently reactive to act as a dipolarophile in a 1,3-dipolar cycloaddition process in competition with the 1,7-electrocyclisation.

With regard to the proposed mechanism we performed the next series of experiments with 6,7-diethoxy-3,4-dihydro-1-(2-nitrophenyl)-*N*-substituted-isoquinolinium bromides (prepared from the corresponding halide and 3,4-dihydroisoquinoline[7]) (Scheme 4). In all cases the isoquinoline fused indazole-*N*-oxide was formed. In one case (**13c** R = CO_2CH_3) the competitive formation of the 1,3-dipolar cycloadduct **15** as a single isomer (proven again by ^{1}H NOE experiments) was observed (ratio of **14**:**15** is approx. 3:1) due to the high reactivity of the electron-deficient C=O double bond of the by-product aldehyde.

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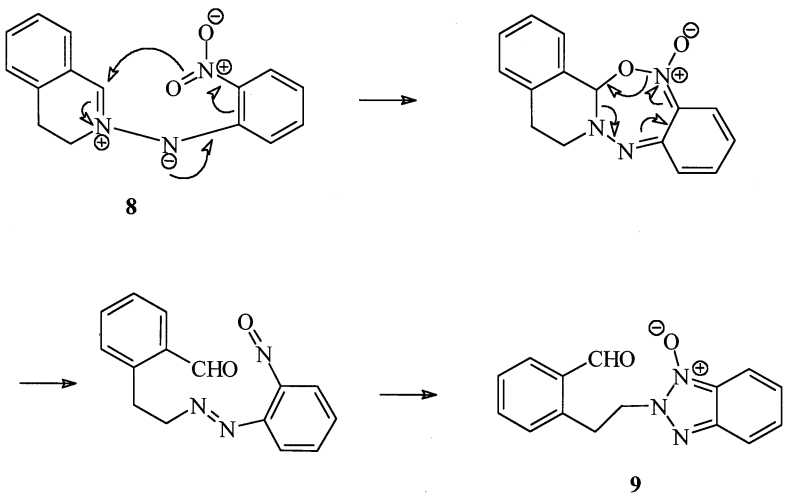
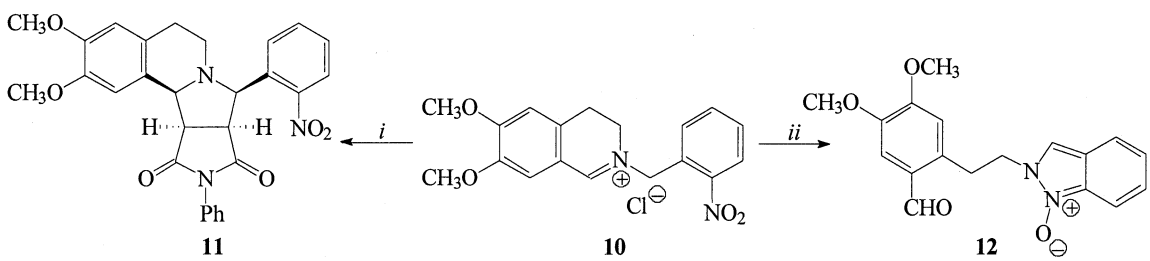
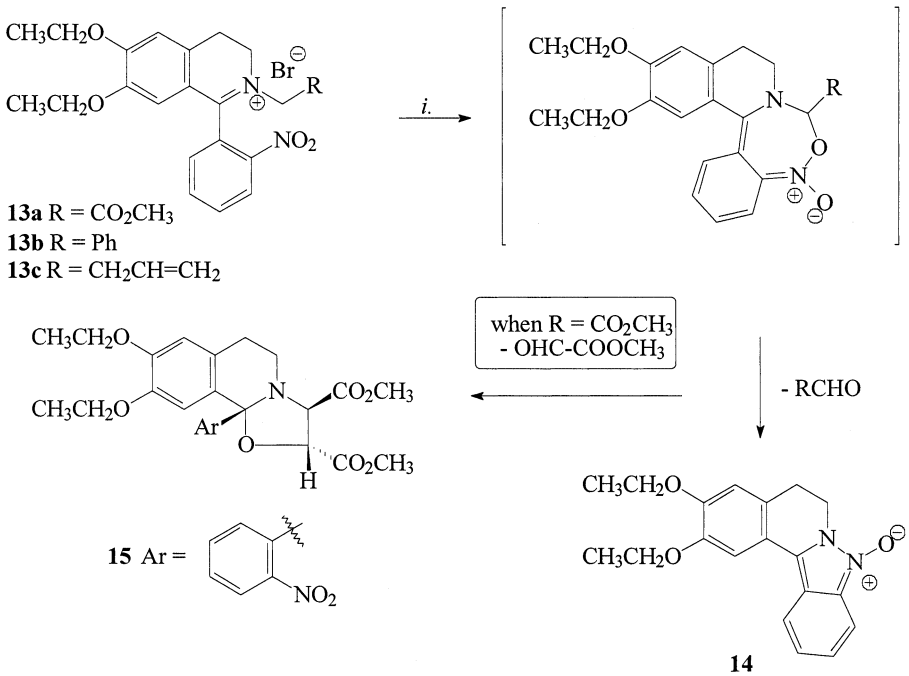


Scheme 2.



Scheme 3. *Reagents and conditions*: (i) *N*-phenylmaleimide, Et_3N, MeOH, rt; (ii) Et_3N, MeOH, rt.



Scheme 4. *Reagents and conditions*: (i) Et_3N, MeOH, rt.

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