



# A straight access to functionalized carbazoles by tandem reaction between indole and nitrobutadienes



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## ABSTRACT

As a continuation of our research on the synthetic exploitation of the nitrobutadienic building-blocks obtained from the ring-opening of nitrothiophenes, we herein report about their reaction with the  $\pi$ -nucleophilic indole. Thanks to their double Michael-acceptor nature, 2,3-dinitro and 2-nitro-3-phenylsulfonyl substituted 1,3-butadienes produce poly-functionalized carbazoles through a double (inter-+intra-molecular) conjugate addition, followed by aromatization of the newly built ring. Significance is attached to the results obtained in fluorinated solvents such as trifluoroethanol, whereby a mild process, with no need for catalysis, overcomes some practical difficulties otherwise limiting the scope of the reaction. Besides the mechanistic aspects, the reaction encompasses motifs for a synthetic interest, mainly in the field of further-tunable arylcarbazoles endowed with predictable applicative properties, e.g., as fluorescent devices.

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## 1. Introduction

In spite of aromaticity, adequately functionalized thiophenes can be effectively opened following the nucleophilic attack by a secondary amine,<sup>1</sup> providing a valuable access to synthetically useful, versatile, nitrobutadienic building-blocks (Scheme 1), some of which endowed with biological activity.<sup>2</sup> From these, during the years, we have obtained a wide collection of heterocyclic targets within metal-free overall ring-opening/ring-closing procedures characterized by a high atom economy.<sup>3</sup> Such targets encompass e.g., pyrroles, pyrazoles, isoxazoles and pyrazines, to cite only *N*-heterocycles, whose occurrence in biologically active molecules of both natural and synthetic origin is well-known and fosters continuing efforts in search for original preparative protocols.

Among more recent research lines in this particular field, we have investigated the behavior of some of our electrophilic building-blocks with the  $\pi$ -nucleophilic indole. Preliminary results have shown an intriguing variability in their reactivity, depending on the character, the number and the position of substituents on the nitrobutadienic fragment.<sup>3d</sup>

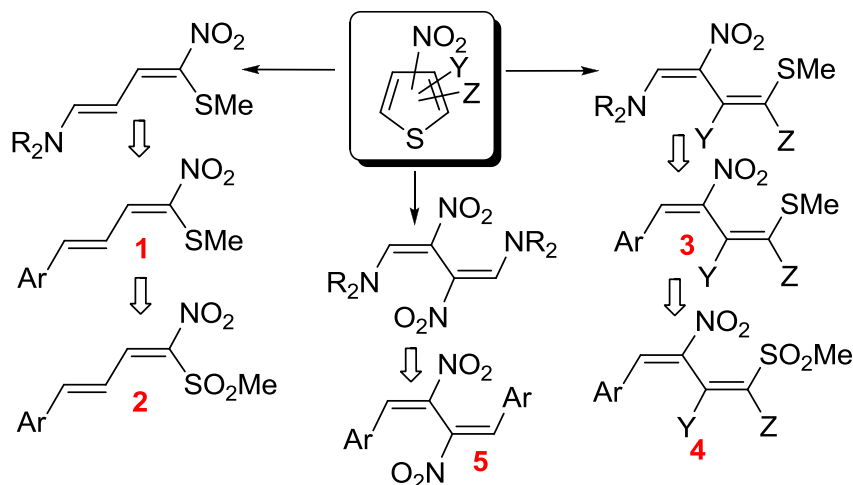
In particular, we reported that while model sulfides **1** and **3** (Scheme 1, Y=Z=H) react too sluggishly in Zn(OAc)<sub>2</sub>-catalyzed

reactions,<sup>4</sup> the corresponding sulfones **2** and **4** (Y=Z=H) undergo the expected indole addition to the nitrovinyl moiety, respectively producing the indole derivatives **6** and **7**, the latter as the result of a 1,4-Michael addition on the butadienic moiety (Scheme 2). More interestingly, when dinitrobutadienes **5** are reacted in the same conditions, 1,3,4- and 1,2,4-substituted carbazoles (Scheme 2, **8** and **9**, respectively) are isolated as the main products,<sup>3d</sup> together with minor amounts of the tetrasubstituted derivative **10**, as the final result of a double Michael addition.

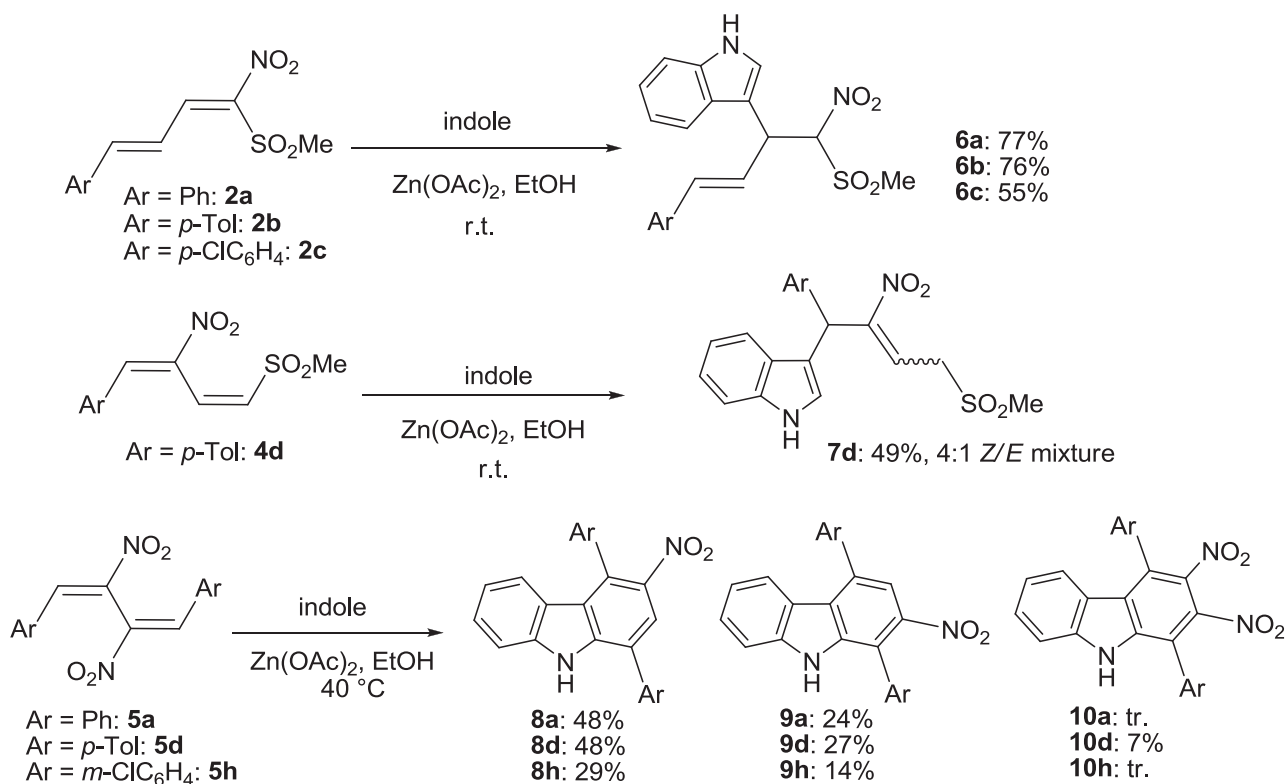
The carbazole nucleus is a key structural motif present in a variety of biologically important compounds either of natural or of synthetic origin<sup>5</sup> endowed with e.g., antimalarial, antitumor, antiplasmodial, and antitrypanosomal activities. Besides, carbazoles have recently assumed growing importance also in the field of materials science,<sup>6</sup> due to their photorefractive, photoconductive, hole-transporting and light-emitting properties. Accordingly, the synthesis of carbazoles,<sup>7,8</sup> including naturally occurring ones, has received considerable attention and the development of green and efficient approaches to such core structure with different functional groups is a major objective in organic synthesis currently, as testified by the impressive number of publications in the field.

In consideration of the interest of the subject, it seemed worthwhile to explore more deeply the behavior of derivatives **5**, in order to better define the scope of the process and to improve its efficiency.

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Scheme 1. Ring-opening derivatives of nitrothiophenes.

Scheme 2. Preliminary results from our previous work on the subject.<sup>3d</sup>

## 2. Results and discussion

The conditions for the reactions reported in Scheme 2 [2 equiv of indole, 1 equiv of Zn(OAc)<sub>2</sub> in EtOH, 40 °C, followed by quenching in water] have been extended to the series of 1,4-diaryl derivatives **5a–i**, spanning from electron-rich to electron-poor and hindered aromatic moieties, and the results are reported on the left side of Table 1.

The 3-nitrocarbazole **8** is the main product in all examples, in a ratio, with respect to the 2-nitro derivative **9**, ranging from 1.5 to 2, while the 2,3-dinitrocarbazole **10** is generally present only in traces. Reactions are usually rather slow, particularly in the presence of steric hindrance (**b**, **e**, **j**) or of an electron-releasing

substituent on the aryl moiety (**f**, **g**). Yields too are influenced by steric effects, as evident for **b** versus **c** and versus **d**; **h** versus **i**; **j** versus **k**. In the case of the particularly hindered mesityl derivative **5e**, not even traces of nitrocarbazoles can be observed, with total substrate recovery.

For the reaction under study we suggested<sup>3d</sup> a sequence of two Michael additions of indole to the nitrovinyl moieties (the first inter- and the second intra-molecular), each followed by restoration of the aromaticity of the indole ring, eventually leading to the double addition product, the tetrahydrocarbazole **11** (Scheme 3). As recently reported in similar cases,<sup>9</sup> the second participation of the indole nucleus could involve the same C(3) rather than the C(2) position, to generate a spiro intermediate that in acidic media can

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