A New and Effective One-Pot Synthesis of Polysubstituted Carbazoles Starting from β-Nitro-β,γ-Unsaturated-Ketones and Indoles

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Abstract: Herein, we report a new one-pot synthesis of polysubstituted carbazoles starting from β-nitro-β,γ-unsaturated-ketones and indoles. The process is based on a Friedel-Crafts reaction of indoles to nitroolefins supported by 2,2,2-trifluoroethanol (TFE) followed by an acidic-promoted and microwave-assisted intramolecular cyclization, that involves the elimination of both nitrous acid and water molecules. Products were obtained in satisfactory to good overall yields (55–78%).

Carbazole alkaloids represent one of the most investigated nitrogen-containing heterocyclic systems characterized by two benzene rings fused to a central pyrrole unit.[1] Their importance is mainly due to the multitude of applications spanning from a plethora of biological activities such as the anti-tuberculosis, anti-viral, anti-cancer and anti-bacterial ones,[2] to the use of carbazole scaffold in material sciences and in particular as conductive polymers. In this regard, carbazole-based polymers have been successfully applied as transistors, smart windows, light emitting diode, etc.[3] Because of their versatility, over the years a growing number of studies concerning the preparation of polyfunctionalized carbazoles have been proposed in the literature. These methods can involve (i) the derivatization of a pre-existing carbazole scaffold,[4] or (ii) the ex-novo formation of carbazole structures starting from appropriate building blocks.[5] Generally, in the former case only simple substituents can be introduced and very often problems of regioselectivity occur. Contrarily, the second approach permits to achieve complex architectures in a simple way. However, this tactic requires the use of substrates having a properly functionalized carbon backbone, which availability strongly limits the corresponding synthetic strategy.

In this context, significant results were achieved using polyfunctionalized nitroolefins such as β-nitroacrylates and β-nitroenones, which have been profitably utilized for synthesizing structurally defined homo- and heteroaromatic substituted systems.[6] Stimulated by these structures, we have recently focused our attention on exploring the reactivity of β-nitro-β,γ-unsaturated ketones **1** and we found the latter to be precious precursors of the polysubstituted pyrroles **3** (Scheme 1).[7] The synthetic importance of **1** is due to the presence of two electrophilic centers in relative 1,4-positions and the opportunity to aromatize the intermediate **2** by the elimination of HNO_2 and H_2O. This peculiarity allows to use and consider **1** as useful source of 1,3-diene synthons.

Following this research trend, we have now disclosed a new application of **1**, in combination with indoles **4**, as key starting materials for the one-pot regioselective synthesis of polysubstituted carbazole derivatives **5**. The one-pot protocol involves two consecutive steps: (i) a Friedel-Crafts reaction between **1** and **4** to give the intermediates **6**, followed by (ii) a domino intramolecular Friedel-Crafts cyclization and aromatization process to provide the title compounds **5** (Scheme 2).

In order to find the best reaction conditions, we investigated the two steps separately. Concerning the Step I, we selected indole **4a** (R³=H) and nitroolefin **1a** (R=Ph, R¹=Me) as model substrates. In particular, based on our experience, we firstly attempted the synthesis of **6a** using basic alumina, under solvent-free conditions (SolFC) at 60 °C (Scheme 3, Eq. *a*).[8] Although the reaction was quite effective, the intermediate **6a** seemed unstable under the reaction conditions and the
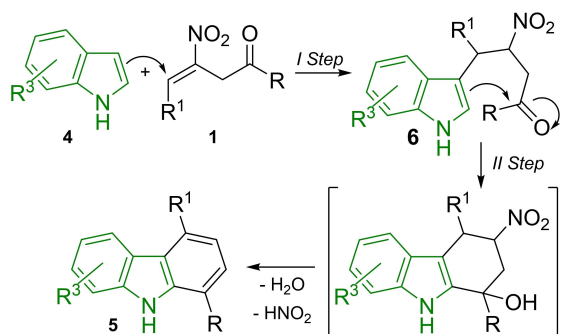
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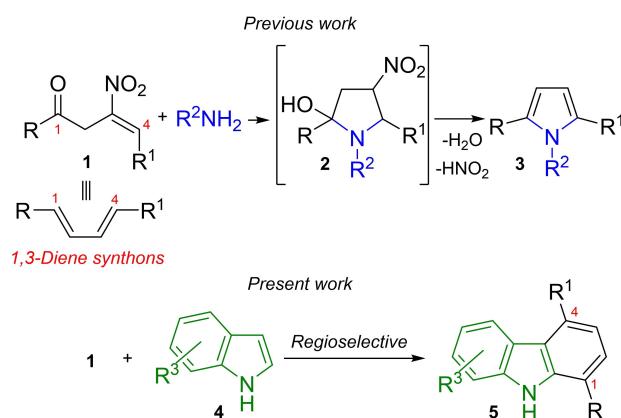
Scheme 1. Use of β-nitro-β,γ-unsaturated ketones **1** as 1,3-diene synthons.

Scheme 2. One-pot synthesis of carbazoles **5**.
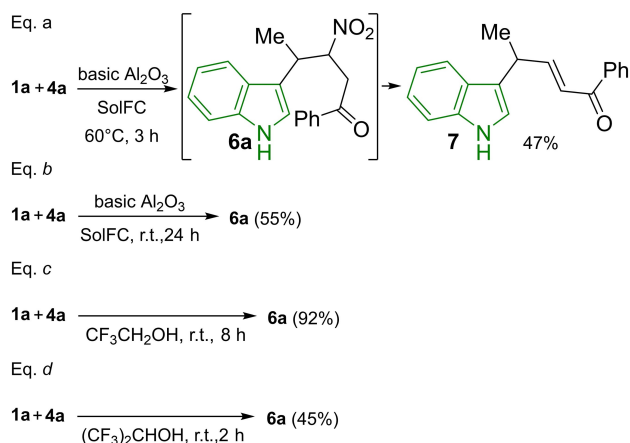
Scheme 3. Investigation on the Friedel-Crafts reactions between **1a** and **4a**.

unsaturated ketone **7** was directly isolated in 47% of yield. It is important to point out that, due to the *E*-configuration of the double bond, **7** was hardly suitable for the next cyclization (Step II). Repeating the reaction at room temperature, the desired intermediate **6a** was obtained in 55% yield after 24 hours (Scheme 3, Eq. *b*). The presence of unreacted substrates was observed, and no reaction improvement was possible even modifying the amount basic alumina. At this point, inspired by the article published by Crousse et al.[9] concerning the use of fluorinated solvents to promote the Friedel-Crafts reaction between indoles and nitroolefins, we explored this type of solvents for our process. In particular, we tested trifluoroethanol (TFE) and hexafluoro-2-propanol (HFIP). The reaction conducted in TFE was complete after 8 hours providing **6a** in 92%, whilst using HIFP the substrates were consumed just in two hours giving only 45% of **6a** and a complex mixture of inseparable by-products (Scheme 3, Eq. *c* and *d*). The origin of the observed regioselectivity can be rationalized considering the enhancement of the reactivity of nitroolefins provided by fluorinated solvents.

Delighted by the result obtained with TFE, we moved our attention to the conversion of **6a** into the carbazole **5a**. With this aim and following our previous research on similar cyclizations promoted by Amberlyst 15,[5a,10] we initially directly added this heterogeneous acid to the trifluoroethanolic solution deriving from the reaction of **1a** with **4a**. The reaction at room

temperature was totally ineffective, while upon warming a mixture of degradation by-products was obtained.

Then, searching for the best reaction conditions, TFE was evaporated under vacuum and replaced with other solvents (Table 1). The best result (**5a**, 75%) was obtained in 2-MeTHF at 100 °C (microwave irradiation), in the presence of 1.2 g/mmol of Amberlyst 15 and with a reaction time of 3 hours. A slightly worse result was obtained using *p*-toluenesulfonic acid (57%), while other solid acids such as acidic alumina, montmorillonite K10 and zeolite HSZ-320 were rather ineffective. In detail, acidic alumina provided the unsaturated ketone **7** as main product (61%), while montmorillonite K10 and zeolite HSZ-320 furnished **5a** in 19% and 11% of yield respectively (for both reactions unreacted adduct **6a** was recovered > 75%). No conversion of **6a** was observed in the absence of an acid species.

The direct conversion of **1a** and **4a** into **5a** was also investigated under the optimized reaction condition of Step 2. At room temperature the reaction between **1a** and **4a** resulted completely ineffective, whilst at 100 °C **5a** was obtained in only 9% of yield.

Finally, in order to demonstrate the generality of our protocol the optimized reaction conditions were applied to a variety of nitroolefins **1** and indoles **4**, providing in all cases from good to very good overall yields for the two coupled steps (55–78%, Scheme 4). All reactions were performed on 1 mmol scale; for compound **5a** the reaction was also repeated on 2 mmol scale leading to a comparable result (73% *vs* 75%). Indoles functionalized at different positions of the benzene unit were proved reactive under our reaction conditions, including 7-alkylindoles.

The electrophilic reactants **1** used in these trials can be diversified exploiting terminal unsaturation or alkyl groups at the nitroalkene moiety (**1**, $R^1 = H$, alkyl). A somewhat limitation

Table 1. Optimization studies concerning the Step II.

Acidic species [g/mmol]	Solvent	Temp. [°C]	Time [h]	Yield [%][a] of **5a**
Amberlyst 15 (1)	TFE	90	2	–
Amberlyst 15 (1)	EtOH	90	4	54
Amberlyst 15 (1)	*i*-PrOH	90	4	60
Amberlyst 15 (1)	2-MeTHF	90	3	63
Amberlyst 15 (1)	EtOAc	90	4	36
Amberlyst 15 (1)	MeCN	90	4	18
Amberlyst 15 (1)	DCM	90	4	19
Amberlyst 15 (1)	Toluene	90	4	26
Amberlyst 15 (1.2)	2-MeTHF	90	3	68
Amberlyst 15 (1.4)	2-MeTHF	90	3	67
Amberlyst 15 (1.2)	2-MeTHF	100	3	75
Amberlyst 15 (1.2)	2-MeTHF	110	3	73
p-TsOH·H₂O (0.29)	2-MeTHF	100	3	57
Acidic Al₂O₃ (1.2)	2-MeTHF	100	3	Traces
Mont. K10 (1.2)	2-MeTHF	100	3	19
Zeolite HSZ-320 (1.2)	2-MeTHF	100	3	11
–	2-MeTHF	100	3	–

[a] Yield of the pure isolated product.
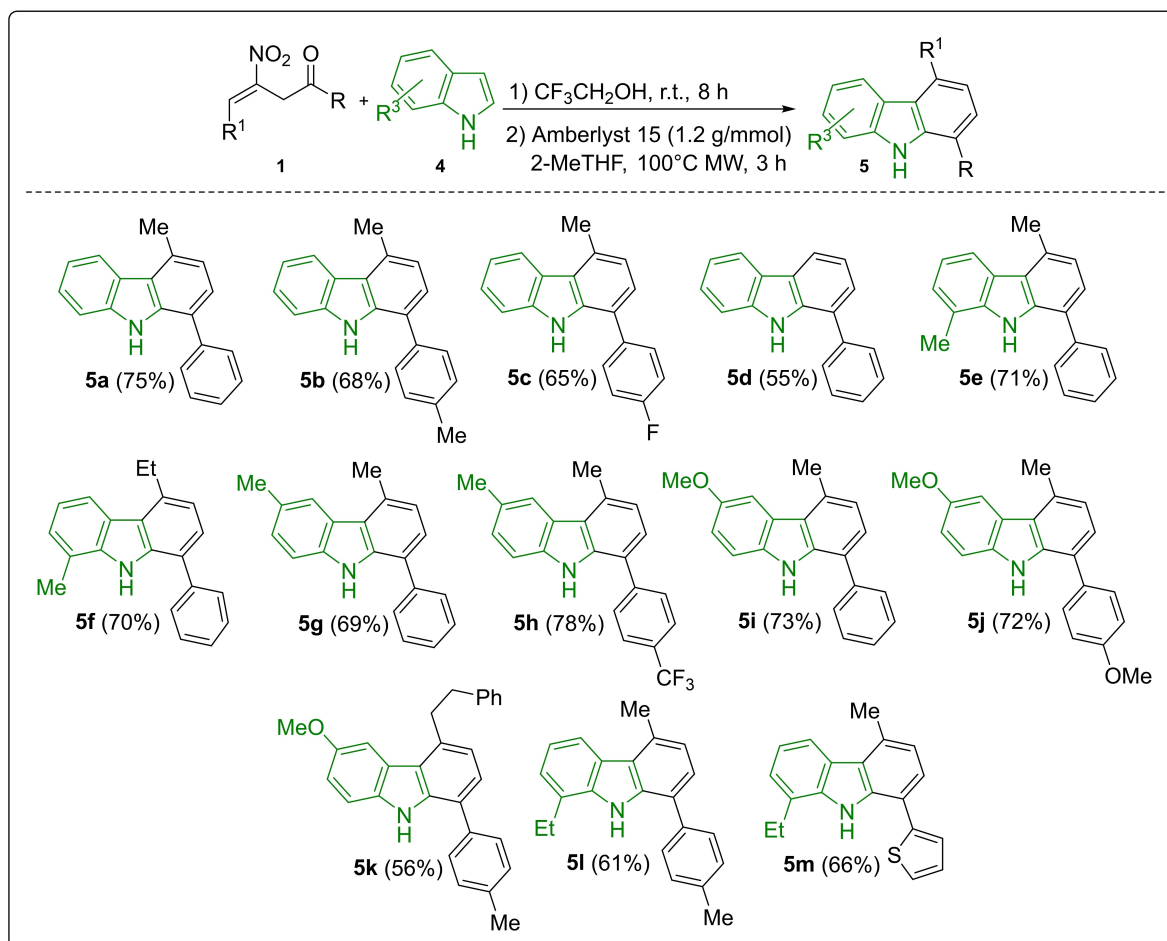
Scheme 4. Substrate scope demonstration.

has been observed in the nature of the substituents present in the ketone unit which supports for aryl groups (**1**, R=aryl, heteroaryl) but not alkyl frameworks (**1**, R=alkyl). In spite of this, combining different attributes, a structurally significant array of various 1,4-disubstituted carbazole derivatives **5** can be efficiently prepared using the present procedure.

In conclusion, we developed a new efficient one-pot synthesis of polysubstituted carbazoles starting from easily accessible starting materials such as indoles and β-nitro-β,γ-unsaturated ketones. The protocol well fits with the modern concept of green chemistry, since two sustainable solvents such as trifluoroethanol[11] and 2-methyltetrahydrofuran[12] were used for the two steps. Moreover, the use of a solid supported acid (Amberlyst 15) in the second step, permits to minimize the typical wasteful aqueous work-up to a simple filtration with a consequent minimization of material and energy consumptions, with evident benefits from a sustainable viewpoint.

General procedure for the synthesis of compounds 5a–m.

A trifluoroethanolic solution (4 mL) of the proper indole **4** (1.2 mmol) and nitroolefin **1** (1 mmol) was stirred, in a 20 mL microwave vial, at room temperature for 8 hours. Then, the solvent was removed under vacuum and the residue intermediate **6** was resolubilized in 2-MeTHF (10 mL), treated with

Amberlyst 15 (1.2 g) and irradiated by means of a Biotage® Initiator at 100 °C for 3 hours. Finally, Amberlyst 15 was filtered off and washed with EtOAc (20 mL), the solvent was evaporated under reduced pressure and the crude product **5** was purified by flash column chromatography (hexane:ethylacetate=95:5).

Acknowledgements

Conflict of Interest

The authors declare no conflict of interest.

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