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A Two-Step Synthesis of Unsymmetrical 1,4-Disubstituted Carbazoles from Sulfonylindoles Under Heterogeneous Catalysis

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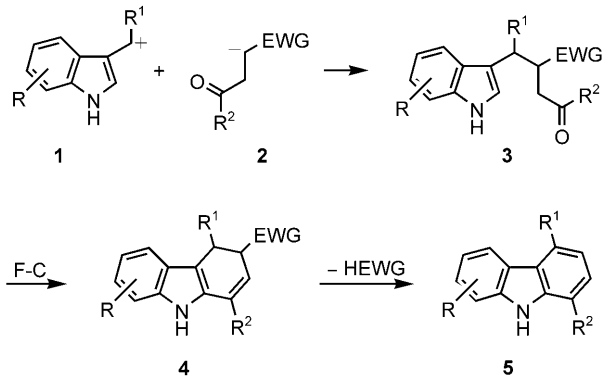
Abstract: Reaction of sulfonylindoles with protected β-nitro ketones affords the corresponding 3-(2-nitroalkyl)indoles that, under acidic conditions, undergo a sequence of cascade processes finally leading to unsymmetrical 1,4-disubstituted carbazoles.

Keywords: carbazoles; electrophilic substitution; heterogeneous catalysis; nitro compounds

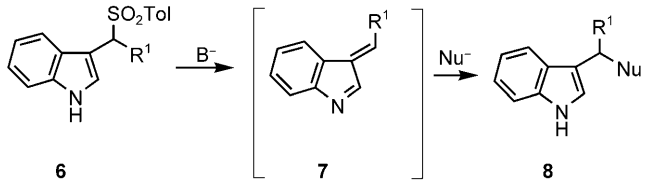
Carbazoles are tricyclic heteroaromatic compounds featured by a central pyrrole ring, which are endowed of a considerable practical interest. Many natural products embedding the carbazole moiety as the main core structure, present an enhanced pharmacological profile as effective antibiotic and antiviral agents.[1] Furthermore, the carbazole unit is easily recognizable in many polymeric materials that evidence particular physical properties.[2] From a synthetic standpoint, the formation of the carbazole system can be carried out exploiting two main general procedures.The first one is based on the direct formation of the tricyclic system starting from functionalized benzene precursors. The second approach employs indole derivatives as substrates on which the third benzene ring is built up. Metal-catalyzed coupling reactions of anilines with functionalized arenes, followed by an oxidative ring closure, belong to the former approach.[3] Similarly, reductive ring closures of nitrogenated biphenyl derivatives[4] and cycloaddition reactions of diyne compounds,[5] allow the preparation of carbazoles from functionalized benzene systems. Conversion of indoles to carbazole derivatives can be achieved exploiting Diels–Alder processes or related pericyclic reactions such as electrocyclizations.[6] The Friedel–Crafts reaction is widely used for the synthesis of 3-substituted indoles and this process carried out using 1,4-dicarbonyl derivatives on indoles is effective for the preparation of 1,4-dialkylcarbazoles.[7] Unfortunately, this approach is only useful for the synthesis of symmetrical carbazole derivatives because of the unavoidable lack in regioselectivity in the double electrophilic substitution.[8] In order to circumvent this drawback, the carbon-carbon bond connection at the indole ring would be done in two distinct steps, with final aromatization of the resulting partially unsaturated carbacycle. Thus a suitable indole system with a reactive electrophilic 'benzylic' position, e.g., **1**, could react with a stabilized carbanion **2** leading to the first carbon-carbon bond connection (Scheme 1).



Scheme 1. General strategy for the synthesis of carbazoles.

The resulting intermediate **3** undergoes a Friedel–Crafts (F-C) reaction by which the tricyclic skeleton **4** is formed. Aromatization of the latter cycle occurs upon elimination of the activating electron-withdrawing group (EWG) leading to the carbazole compound **5**.[9] The depicted synthetic strategy requires a three-step process that, however, could be shortened if the ring closure and the aromatization steps are joined in a tandem operation. Among carbanion stabilizing groups, the nitro group occupies a prominent position since its formidable electron-withdrawing power

allows the generation of the corresponding nitronate anions under mild conditions.[10] Furthermore, nitroalkanes are deeply involved in several synthetic approaches aimed at the synthesis of benzene derivatives, with the easy elimination of nitrous acid being one of the key steps in the aromatization process.[11] Reactive indolyl intermediates of type **1** are readily available starting from stable precursors having a good leaving group at the 'benzylic' position.[12] Recently, we have introduced a new class of indole derivatives, namely 3-(1-arylsulfonylalkyl)indoles **6**, that have been demonstrated to be efficient precursors of alkylideneindolenines **7**, or their parent iminium ions, for the synthesis of 3-substituted indoles **8** by reaction with suitable nucleophiles (Scheme 2).[13]

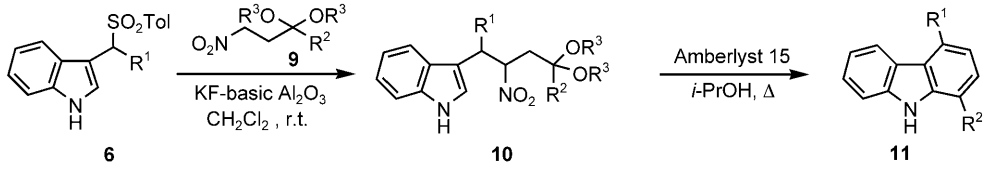


Scheme 2. Synthetic approach to 3-substituted indoles using sulfonylindoles.

Particularly, these sulfonyl derivatives may react with nitroalkanes, in the presence of a basic promoter, leading to the corresponding 3-(2-nitroalkyl)indoles.[14] Although a large variety of functionalized nitroalkanes successfully react with sulfonylindoles **6**, β-nitro ketones **2** (EWG = NO_2, R^2 = Me, Et) gave disappointing results in the same reaction under different solvent/base combinations. The failure is probably ascribable to a preliminary retro-Michael reaction suffered by β-nitro ketones under basic conditions which leads to a decomposition of the nitro derivative.[15] This unwanted side process could be avoided by a suitable protection of the carbonyl group that prevents the retro-Michael process. As a matter of fact, conversion of β-nitro ketones into the corresponding nitro acetals **9**[16] and their reaction with sulfonylindoles **6** in the presence of KF-basic alumina generate adducts **10** in good yield (Table 1, entries 3, 5, 8, 10, 13).

The subsequent transformation of 3-(2-nitroalkyl)indoles **10** into carbazoles **11** would entail three different transformations, namely acetal cleavage, Friedel–Crafts cyclization and final aromatization by elimination of nitrous acid. In principle, all these synthetic operations could be performed under acidic

Table 1. Synthesis of carbazoles **11** by reaction of sulfonylindoles **6** with nitro acetals **9**, followed by tandem cleavage-cyclization and aromatization of the intermediate adducts **10**.



R^3 = -$(CH_2)_2$- and -$CH_2C(CH_3)_2CH_2$-

Entry	Indole **6**	R^1	Nitro Acetal **9**	R^2	**10**	Time [h]	Yield[a] [%]	**11**	Time [h]	Yield[b] [%]
1	**6a**	Me	**9b**	Me	**10a**	3.0	–	**11a**	1.5	55
2	**6a**	Me	**9d**	$Ph(CH_2)_2$	**10b**	7.0	–	**11b**	2.0	54
3	**6b**	Et	**9b**	Me	**10c**	3.5	89	**11c**	1.5	64[c]
4	**6b**	Et	**9b**	Me	**10c**	3.5	–	**11c**	1.5	61
5	**6b**	Et	**9a**	H	**10d**	3.5	83	**11d**	1.5	68[c]
6	**6b**	Et	**9a**	H	**10d**	3.5	–	**11d**	1.5	62
7	**6b**	Et	**9d**	$Ph(CH_2)_2$	**10e**	9.0	–	**11e**	2.0	56
8	**6c**	*c*-C_6H_{11}	**9c**	Et	**10f**	16	78	**11f**	1.5	65[c]
9	**6c**	*c*-C_6H_{11}	**9c**	Et	**10f**	16	–	**11f**	1.5	62
10	**6d**	4-Me-C_6H_4	**9c**	Et	**10g**	5.0	90	**11g**	2.5	56[c]
11	**6d**	4-Me-C_6H_4	**9c**	Et	**10g**	5.0	–	**11g**	2.5	53
12	**6d**	4-Me-C_6H_4	**9e**	4-MeO-C_6H_4	**10h**	5.0	–	**11h**	4.5	44
13	**6d**	4-Me-C_6H_4	**9f**	Me	**10i**	7.0	84	**11i**	2.0	58[c]
14	**6d**	4-Me-C_6H_4	**9f**	Me	**10i**	7.0	–	**11i**	2.0	55
15	**6e**	CH_2=$CH(CH_2)_3$	**9c**	Et	**10j**	9.0	–	**11j**	6.0	47
16	**6f**	4-MeO-C_6H_4	**9f**	Me	**10k**	9.0	–	**11k**	1.5	68

[a] Yield of pure, isolated products.
[b] Yield of pure, isolated products from substrates **6**.
[c] Yield of pure, isolated products from intermediates **10**.

conditions so that different promoters have been tested to efficiently obtain conversion of compounds **10** into carbazoles **11**. Solid acid systems are known to be efficient promoters in many synthetic processes including cleavage of various carbonyl protecting groups.[17] Furthermore, working under heterogeneous conditions allows an easy recovery of the solid acid and a considerable speeding up in the subsequent work-up operations. The best conditions for this process have been found in the utilization of Amberlyst 15 as proton source in isopropyl alcohol at reflux as evidenced by the satisfactory results displayed in Table 1. Although the intermediate adducts **10** can be isolated, we have observed that crude products **10**, obtained by simple filtration of the solid basic promoter and solvent evaporation, are suitable for the next cyclization step. This simplified procedure has a beneficial effect on the overall waste reduction and allows us to record a better chemical yield over the two-step process involving purification of intermediate compounds **10** (Table 1, compare entries 3/4, 5/6, 8/9, 10/11, 13/14). In a couple of examples we changed the nature of the acetal protection from 1,3-dioxolanyl to 5,5-dimethyl-1,3-dioxanyl without evidencing any substantial advantage (Table 1, entries 13, 14, 16).

In summary, unsymmetrical 1,4-disubstituted carbazoles can be easily prepared by a two-step procedure starting from sulfonylindoles. The first reaction consists in the nucleophilic addition of acetal protected β-nitro ketones to alkylideneindolenine intermediates generated from sulfonylindoles under basic conditions. The following transformation includes three consecutive synthetic operations involving acetal cleavage, Friedel–Crafts cyclization and final aromatization by elimination of nitrous acid. Every single step is carried out under heterogeneous conditions so that work-up operations are minimized and isolation is required only to obtain the target carbazole.

Experimental Section

General Procedure for the Preparation of Carbazoles 11

To a stirred solution of sulfonylindole **6** (1.0 mmol) and nitroalkane **9** (1.0 mmol) in dichloromethane (4 mL), potassium fluoride on basic alumina (2.0 g) was added at room temperature. After stirring for the appropriate time (see Table 1), the mixture was filtered over a short pad of celite and washed with EtOAc (15 mL). Removal of the solvent at reduced pressure, gave crude nitroalkyl indole **10** that was dissolved in *i*-PrOH (4 mL) and heated at reflux. To the boiling mixture Amberlyst 15 (1 g), was then added and heating was continued for the appropriate time (see Table 1). After cooling, the solid promoter was filtered off and washed with EtOAc (3×8 mL). The crude product obtained after removal of the solvent at reduced pressure was purified by flash chromatography (hexanes/toluene 90:10).

4-Methyl-1-phenethyl-9*H*-carbazole (11b): Yield: 54%; yellow solid, mp 116–119 °C. IR (nujol): ν = 1250, 1588, 3030, 3420 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 2.88 (s, 3H), 3.08 (t, 2H, *J* = 6.8 Hz), 3.21 (t, 2H, *J* = 6.8 Hz), 6.98 (d, 1H, *J* = 7.3 Hz), 7.16 (d, 1H, *J* = 7.3 Hz), 7.20–7.34 (m, 6H), 7.38–7.41 (m, 2H), 7.83 (bs, 1H), 8.18 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.7, 33.6, 36.4, 110.6, 119.3, 121.0, 121.3, 122.6, 124.4, 125.1, 125.4, 126.3, 126.6, 127.7, 128.7, 131.3, 138.6, 139.7, 142.1; GC-MS (70 eV): *m/z* = 285 ([M^+], 40), 195 (26), 194 (100), 167 (6), 91 (8), 65 (3); anal. calcd. for $C_{21}H_{19}N$ (285.38): C 88.38, H 6.71, N 4.91; found: C 88.50, H 6.78 N, 4.98.

4-Cyclohexyl-1-ethyl-9*H*-carbazole (11f): Yield: 65% (from pure **10f**), 62% (from crude **10f**); white solid, mp 71–73 °C. IR (nujol): ν = 1228, 1580, 1619, 3055, 3409 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ = 1.34–1.47 (m, 1H), 1.42 (t, 3H, *J* = 7.7 Hz), 1.54–1.72 (m, 4H), 1.84–1.93 (m, 1H), 1.95–2.03 (m, 2H), 2.16–2.26 (m, 2H), 2.92 (q, 2H, *J* = 7.7 Hz), 3.46–3.56 (m, 1H), 7.10 (d, 1H, *J* = 7.7 Hz), 7.23–7.30 (m, 2H), 7.39–7.45 (m, 1H), 7.49 (dt, 1H, *J* = 0.9, 8.1 Hz), 8.06 (bs, 1H), 8.13 (d, 1H, *J* = 7.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.9, 24.1, 26.8, 27.5, 33.4, 41.0, 110.7, 116.0, 119.6, 120.6, 123.0, 123.3, 123.8, 124.6, 125.1, 138.4, 139.6, 141.5; GC-MS (70 eV): *m/z* = 277 ([M^+], 100), 262 (11), 248 (10), 234 (14), 208 (30), 206 (24), 205 (28), 204 (31), 191 (23), 180 (36); anal. calcd. for $C_{20}H_{23}N$ (277.40): C 86.59, H 8.36, N 5.05; found: C 86.21, H 8.45, N 5.02.

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