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A Photochemical Route to Benzo[*a*]carbazoles *via* Domino Elimination/Electrocyclization of 2-Aryl-3-(1-tosylalkyl)indoles

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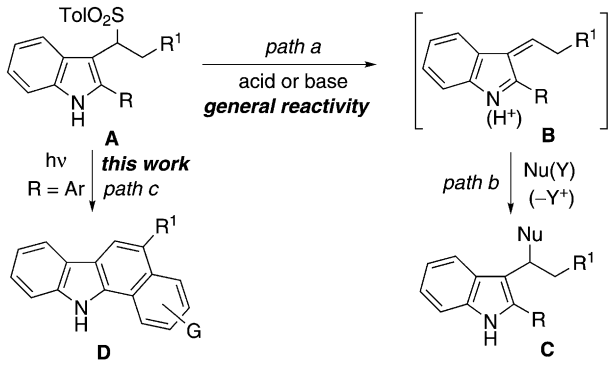
Abstract: The photochemical synthesis of benzo[*a*]carbazoles from easily synthesizable 2-aryl-3-(1-tosylalkyl)indoles is presented. Irradiation of these substrates in polar aprotic solvents (acetone or THF) gives selectively the target products in satisfactory yields. This versatile and efficient procedure promises to be a useful alternative to the multistep strategies reported in the literature.

Keywords: benzo[*a*]carbazoles; C–S bond homolytic cleavage; domino reaction; 6πe electrocyclization; photochemical activation

Functionalization of indoles at C-3 is a key synthetic process acting as a launching pad for the preparation of more complex structural entities. The Friedel–Crafts process involving Lewis acid-catalyzed electrophilic substitutions with electron-poor alkenes and carbonyl derivatives is certainly the most exploited process to attain this goal.[1] In this context, a useful starting point is offered by 3-(1-tosylalkyl)indoles **A** (Scheme 1) that were recently demonstrated to be easily available by an acid-promoted three-component coupling of an indole and an aldehyde in the presence of *p*-toluenesulfinic acid.[2]

These are promising compounds for building a side chain in indole derivatives since the arylsulfonyl group can be easily removed under basic or acid conditions (*path a*) affording a vinylogous imine **B** (or its iminium ion analogue). The thus generated electrophilic species have been found to react efficiently with various σ- and π-bond nucleophiles Nu leading to the corresponding addition products **C** (*path b*).[2,3] The reductive cleavage of the C–S bond in the presence of complex hydrides (e.g., lithium aluminum hydride) has likewise been reported.[4] Another conceivable elimination of the sulfonyl group was homolysis. We reasoned that the indolylmethyl radical formed in this case had no addition path available and thus was expected to undergo either reduction or elimination.

A heteroanalogue of stilbene would be formed in the latter case that could in turn be a useful intermediate, e.g., for addition processes (given the polarized structure) or for cyclization reactions to yield benzo[*a*]carbazoles (**D**) (Scheme 1, *path c*). These compounds are rare in nature,[5] but are of considerable interest in view of their biological activity.[5,6] Benzo[*a*]carbazoles have also found extensive applications as photographic[5a] and photorefractive[7] materials. Despite these multifaceted applications, the large-scope syntheses of these heterocycles are limited in number and the development of an efficient procedure to achieve this structural entity is desirable.[5,8] Among the possible methods to achieve the homolysis of the sulfone moiety,[9] photochemistry seemed a reasonable choice in view of the literature precedent.[10]



Scheme 1. General behaviour of 3-(1-tosylalkyl)indoles.

With this target in mind we embarked on an exploratory study of the photochemistry of a model compound, 2-phenyl-3-(1-tosylpropyl)indole (**1**). This compound shows two maxima at 226 and 298 nm, respectively, (for the latter with an ε of $1.2\times10^4\,L\,mol^{-1}\,cm^{-1}$) and was conveniently irradiated by phosphor-coated lamps (emission centered at 366 nm). HPLC monitoring of the changes occurring upon irradiation of a nitrogen-flushed 10^{-2} M solution in acetonitrile showed the formation of a single main peak and when the reaction was completed a single product was isolated. To our surprise, spectroscopic characterization demonstrated that this was benzo[*a*]-carbazole **10**. Apparently, loss of the sulfone moiety led directly to cyclization. In order to distinguish the sequence of events, UV monitoring was added.

The course of the photolysis of a 4×10^{-5} M solution of **1** (Optical Bench, $\lambda_{irr}>280$ nm) showed the gradual decrease of the absorption maxima at 226 and 298 nm concomitant with the rise of new absorption bands located at 254, 283, 308 and a shoulder at 360 nm (see Figure 1 for details). The end spectrum was practically coincident with that of **10**, whereas the non-univocal profile at different wavelengths (see Inset) demonstrated that further intermediates were involved. The reaction was examined in various solvents (Table 1). Product **10** was formed in methanol and isopropyl alcohol with a yield similar to that in MeCN, but was not observed in *t*-BuOH. Addition of water to acetonitrile strongly depressed the yield. The best results were obtained in acetone and THF, where it reached and slightly exceeded 50% (entries 6 and 7). Furthermore, ionic chromatography analysis of the photolyzed solution in acetone showed that, along with the formation of **10**, *p*-toluenesulfinic acid was generated in a comparable yield (60%).

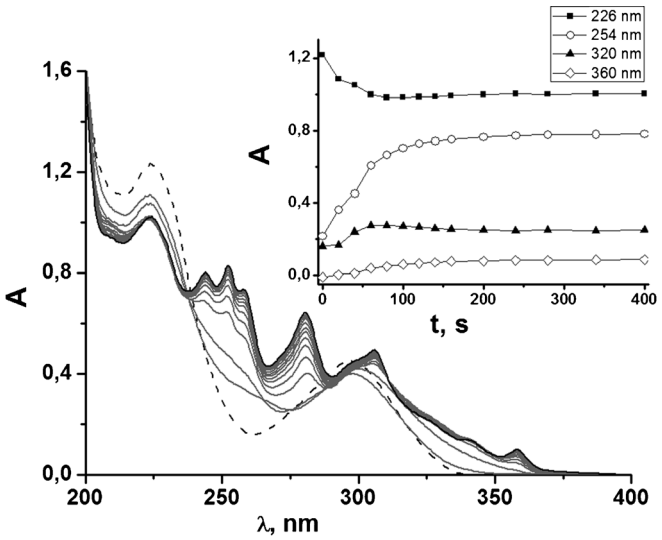
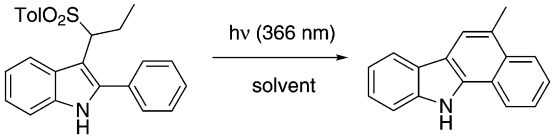


Figure 1. UV-monitoring of a 4×10^{-5} M solution of **1** in MeCN ($\lambda_{irr}>280$ nm) from 0 (black dotted line) to 400 s (black continuous line). Inset: absorbance profiles recorded at 226, 254, 320 and 360 nm.

Table 1. Irradiation of 2-phenyl-3-(1-tosylpropyl)indole (**1**) in neat solvents.[a]



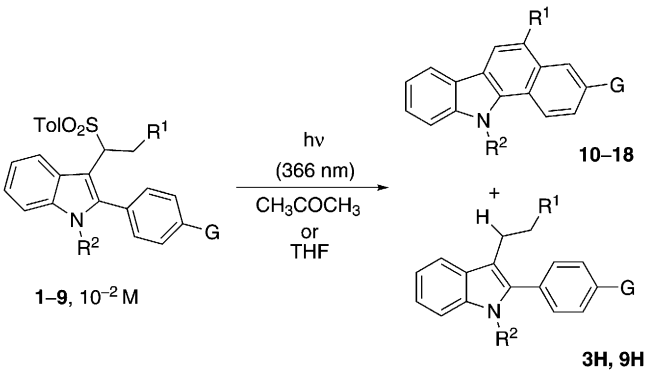
Entry	Solvent	**10**[b] Yield [%]
1	MeCN	35
2	MeOH	22
3	*i*-PrOH	40
4	*t*-BuOH	0
5	MeCN/H_2O 5/1	8[c]
6	THF	54
7	acetone	49 (0)[d]

[a] *Conditions:* A nitrogen-equilibrated solution of **1** (10^{-2} M) in the chosen solvent, irradiated at 366 nm (10 lamps) for 18 h.
[b] A complete conversion of **1** was observed, except where indicated.
[c] 40% conversion of **1**, yield based on the consumption of the indole.
[d] Oxygen-saturated solution.

Nitrogen flushing was required, since indole **1** reacted only sluggishly and no carbazole was formed in an oxygen-saturated solution. The above data give some indication about the conditions under which a benzo[*a*]carbazole may be obtained and, on this basis, the exploration was extended to further substituted indole derivatives (**2**–**9**). As reported in Table 2, irradiation of **2** afforded the corresponding benzo[*a*]carbazole (**11**) in both acetone and THF (55 and 65% yields, respectively) after 16 h of irradiation. Similar satisfactory results have been obtained in the case of **3** where the formation of 5-hexylbenzo[*a*]carbazole (**12**, 57% yield) was accompanied by a small amount of the desulfonylated indole **3H** (2% in acetone).

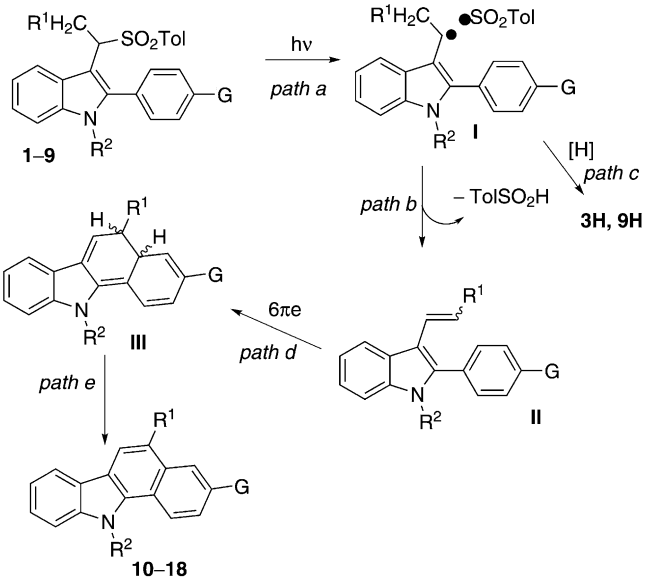
As for indole **4**, the corresponding 5-benzyl derivative **13** was isolated in acetone (56%) and, although with lower efficiency, in THF. Furthermore, a longer irradiation time (30 h) was required to achieve a complete consumption of **4**. Benzo[*a*]carbazoles have likewise been obtained starting from substrates that contain a substituent at the 4-position of the phenyl ring. Thus, 3,5-dialkyl derivatives **14** and **15** have been isolated in good yields after 24 h irradiation of the precursors **5** and **6**. Likewise, the 4-methoxyphenyl-substituted indole (**7**) was found to generate, under irradiation, the corresponding 3-methoxybenzo[*a*]carbazole (**16**) both in acetone and THF with satisfactory yields (62 and 55% yields, respectively) and the tri-

Table 2. Synthesis of benzo[a]carbazole **10–18**.[a]



Indole	R^1	R^2	G	t_{irr} [h]	Product,[b,c] (Yield [%])
1	CH_3	H	H	16	**10**, 49 (*54*)
2	C_4H_9	H	H	16	**11**, 55 (*65*)
3	C_6H_{13}	H	H	16	**12**, 57 (*53*)
					3H, 2 (*<1*)
4	$CH_2C_6H_5$	H	H	30	**13**, 56 (*37*)
5	C_2H_5	H	CH_3	24	**14**, 46 (*45*)
6	C_6H_{13}	H	CH_3	24	**15**, 54 (*69*)
7	C_2H_5	H	OCH_3	24	**16**, 62 (*55*)
8	C_3H_{10}	H	CF_3	30	**17**, 61 (*75*)
9	C_7H_{15}	CH_3	H	30	**18**, 54 (*35*)
					9H, 4 (*<1*)

[a] *Conditions:* **1–9** (10^{-2} M) in acetone or THF, λ_{irr} = 366 nm (10 lamps), 18 h.
[b] Irradiation carried out in acetone (isolated yield).
[c] In parentheses the reaction carried out in THF; yield determined by HPLC analysis.



Scheme 2. Photochemistry of 2-phenyl-3-(1-tosylalkyl)indoles (**1–9**) in polar solvents.

fluoromethylphenyl derivative **8** gave a somewhat better yield (75% in THF, Table 2). Finally, we found that the alkylation of the indole nitrogen did not affect the reaction, and 11-methylbenzo[*a*]carbazole **18** was obtained in a satisfactory yield (54% in acetone), again accompanied by some desulfonylated **9H**.

As for the mechanism, the above indoles are characterized by a broad fluorescence with a discrete Stokes shift (λ_{em} at 360 and 460 nm, respectively, for compound **1**) that is little affected in air- *vs.* nitrogen-equilibrated solution. Oxygen-quenching of the photochemical reaction thus suggests that this proceeds from the triplet state. The positive identification of *p*-toluenesulfinic acid along with the literature precedent for some benzyl sulfones,[10b] supports that homolytic cleavage of the C–S bond with the generation of a benzyl/sulfonyl radical pair occurs (Scheme 2, *path a*) and is followed by β-hydrogen abstraction from **I** by the sulfonyl radical. The reduction of **I** (*path c*) to give desulfonylated **3H** and **9H** observed as minor products in two cases is likewise well explained by the homolytic cleavage and the role of radical intermediates. The main product is however alkenylindole (**II**, *E*/*Z* isomer, *path b*). This is not isolated and undergoes 6πe electrocyclization, apparently a process too fast for allowing accumulation of sufficient materia for isolation. This probably corresponds to the intermediate indicated by UV monitoring (see inset in Figure 1). Sparse evidence for cyclization of compounds containing the 3-styrylindole moiety under both photochemical[11] and thermal conditions[12] has been reported in the literature. In particular, the photochemical rearrangement of 3*H*-indole-spirocyclopropanes followed by photocyclization of the obtained 2-phenyl-3-styrylindole has been found to afford, among other products, a mixture of the corresponding benzo[*a*]carbazole (about 30% yield) and 6,11-dihydrobenzo[*a*]carbazole.[11a] In the present case, the reaction appears to involve an efficient photochemical reaction that gives dihydrocarbazole **III** *(path d)*. Chemoselective aromatization of systems like **III** (presumably preceded by a [1,5]-hydride shift)[11a] has been reported in the literature both in the presence[11c] and in the absence of oxygen[11b]and is supposed to occur in the formation of the final benzocarbazoles **10–18** (*path e)*.

In conclusion, we have found a general synthesis of benzo[*a*]carbazoles that proceeds as a one-pot process involving both photochemical (initial C–S bond homolysis, and 6πe electrocyclization) as well as thermal steps. Along with the above-mentioned facile access to sulfonylmethyl derivatives of 2-arylindoles, the present method represents an annelation procedure with large scope (in particular electron-donating or withdrawing substituents do not affect the reaction) that gives novel access to this family of heterocycles.

Experimental Section

Typical Procedure for the Synthesis of 10–18

A nitrogen-equilibrated solution of the chosen compound (**1**–**9**, 0.4 mmol, 10^{-2} M) in acetone or THF (40 mL) was irradiated in a multilamp reactor equipped with 10 phosphor coated lamps (emission centered at 366 nm) until the complete consumption of the substrates. Work-up of the reaction and purification of the obtained products involved concentration under vacuum and chromatographic separation using Millipore (60 Å, 35–70 μm) silica gel and cyclohexane/chloroform mixture as eluant.

Supporting Information

See the Supporting Information for experimental details, characterization of products and copies of ^{1}H and ^{13}C NMR spectra of compounds **10**–**18** and **3H**, **9H.**

Acknowledgements

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