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Photodesulfonylation of indoles initiated by electron transfer from triethylamine

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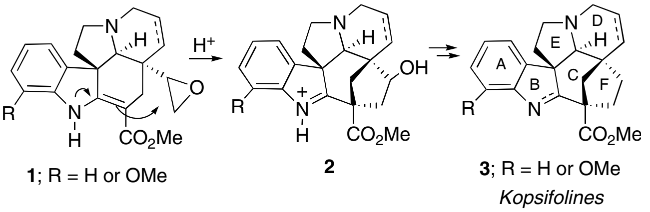
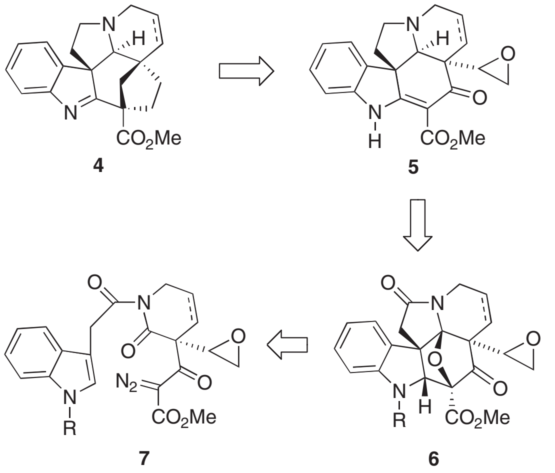
Abstract—*N*-Sulfonyl indoles can be easily deprotected by a photoinduced electron transfer reaction with triethylamine. By using an equivalent amount of *n*-Bu_3SnH in the photolysis medium, it is possible to suppress the competitive photo-Fries like rearrangement by scavenging the phenylsulfonyl radical.

The kopsifolines (**3**) represent a new group of hexacyclic monoterpenoid indoline alkaloids that were obtained from a Malayan *Kopsia* species and their structures were established on the basis of extensive NMR studies.[1] While no biological activity has yet been reported for this alkaloid family, the kopsifolines are structurally intriguing compounds, related to and possibly derived from an aspidosperma-type alkaloid precursor **1**. A possible biogenetic pathway to the kopsifolines from **1** could involve an intramolecular epoxide-ring opening followed by loss of H_2O as shown in Scheme 1.



Scheme 1.

Our approach toward the synthesis of the kopsifoline skeleton derives from a program underway in our laboratory that is designed to exploit the rhodium(II)-catalyzed cyclization/cycloaddition cascade of α-diazo carbonyl compounds for the purposes of natural product synthesis.[2,3] Our retrosynthetic analysis of **1** is shown in Scheme 2 and proceeds by a 1,3-dipolar cycloaddition of a carbonyl ylide dipole derived from diazo ketoester **7** across the indole π-bond.[4] Reductive ring opening of the resulting cycloadduct **6** followed by dehydration and N-deprotection would lead to the key precursor **5** necessary for the final F-ring closure.



Scheme 2.

We first carried out a model study using diazo amide **10** in order to test the feasibility of the key dipolar cycloaddition/ring opening sequence. Compound **10** was easily prepared by adding acid chloride **8** to diazo amide **9** in the presence of 4 Å molecular sieves at room temperature. Gratifyingly, heating a sample of **10** with $Rh_2(OAc)_4$ in benzene at 80 °C afforded cycloadduct **11** in 94% yield as a single diastereomer (Scheme 3).

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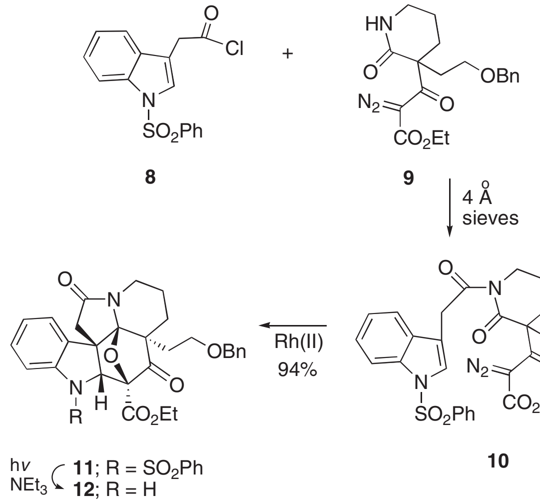


Scheme 3.

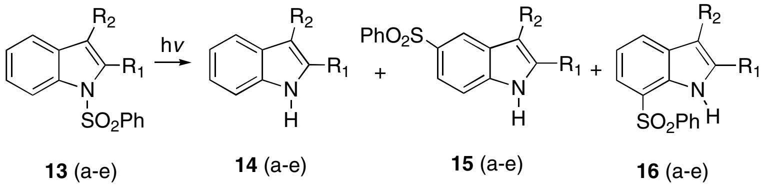
Having established a viable route to cycloadduct **11**, efforts were next centered on the reductive opening of the oxido bridge. In 1991, Cossy and co-workers reported that a photoinduced electron transfer reaction from Et_3N to 7-oxabicyclo-[2.2.1]heptan-2-ones easily generated the corresponding 3-hydroxycyclohexanone derivatives.[5] The reduction relies on the intermediacy of a ketyl radical anion[6] derived from the oxabicycloheptane under the photochemical conditions. With this result in mind, our initial attempts to carry out the reductive ring opening of **11** employed Cossy's photoreductive approach. We found, however, that the irradiation of **11** in the presence of NEt_3 (5 equiv) using CH_3CN as the solvent only furnished the desulfonylated indoline **12** in 90% yield.

The ready photodesulfonylation of indoline **11** prompted us to carry out a broader study of this deprotection reaction since substituted *N*-sulfonyl-indoles are commonly employed in organic synthesis. The powerful electron-withdrawing property of the sulfonyl group coupled with its *ortho*-directing effect has been extensively utilized for selective metalation at the C_2-position of the indole ring without having to use a large excess of metalating agent.[7] In addition, the product *N*-sulfonamides are often crystalline and stable to a variety of reaction conditions (e.g., alkaline hydrolysis and catalytic reduction). A corollary of the stability of the *N*-sulfonyl bond is the difficulty encountered in the removal of this type of protecting group. Harsh deprotection conditions are often required, which limit the synthetic usefulness of these compounds. Thus, arylsulfonamides are cleaved by sodium in liquid ammonia,[8] sodium naphthalenide, or anthracenide,[9] heating to reflux in strong acid[10] and reaction with highly nucleophilic[11] or reducing[12] reagents. These harsh conditions have led to the development of new methods for the deprotection of *N*-sulfonamides. This has included deprotection by using SmI_2,[13] $TiCl_4$/Zn,[14] Mg in methanol,[15] TBAF,[16] iodotrimethylsilane,[17] or electrolysis.[18]

While the desulfonylation of several alkyl *N*-sulfonyl amides has been achieved photochemically,[19] the related reaction using indoles has not been reported in the literature. Since the serendipitous deprotection reaction that we encountered with indoline **11** proceeded in such high yield and under very mild conditions, we set out to further explore the generality and scope of the photodesulfonylation of a series of related indoles. The photolysis of indoles **13** was carried out in the presence of 5.0 equiv of Et_3N and CH_3CN in a quartz vessel using 254 nm lamps for 1 h under a nitrogen atmosphere. Column chromatography of the crude residue followed by removal of the solvent gave the desired desulfonylated indoles **14** in 48–77% yield based on recovered starting material (Table 1, entries 1–5). Interestingly, we also observed the formation of both the *ortho*- and *para*-photo Fries like rearrangement products **15** and **16** in varying quantities (8–24%) depending on the particular system. In most cases the *para*-rearrangement product was the major isomer formed, suggesting leakage from a radical cage.

Encouraged by these positive results, we studied the effect of adding different additives in order to capture the initially produced sulfonyl radical and thereby enhance the yield of the desulfonylated indole. The use of *tert*-butyl mercaptan as a radical scavenger showed

Table 1. Photodesulfonylation of indoles

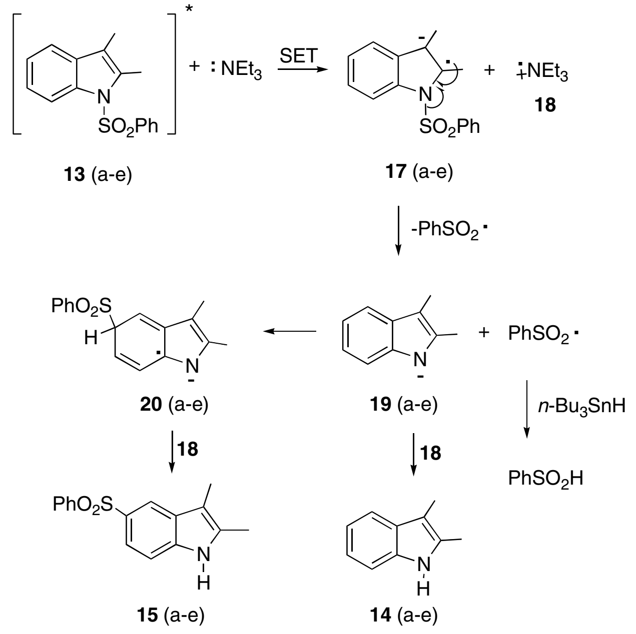


Entry	R_1	R_2	Product + yield (%)		
			14	**15**	**16**
13a	H	H	48	11	8
13b	Me	Me	55	11	11
13c	CH_2CH_2OTBS	H	57	19	5
13d	CO_2Me	H	77	4	4
13e	COMe	CH_2OH	60	—	—

no improvement in the overall yield of the desulfonylated indole **14**. However, in the presence of 1.0 equiv of *n*-Bu_3SnH, the photoreaction of **13d** afforded indole **14d** in 96% yield (based on recovered starting material) with no signs of the rearranged aryl sulfones **15d** and **16d**. The more highly activated tin hydride (weaker Sn–H bond) allows for capture of the sulfonyl radical thereby suppressing attack at the *ortho*- and *para*-positions.

More than likely, the photodesulfonylation reaction can be attributed to a photoinduced electron transfer as outlined in Scheme 4. Amines are well known to undergo such a transfer with electronically excited carbonyl groups.[20] The reaction is initiated by single electron transfer from NEt_3 to the electronically excited indole with formation of the radical cation of triethylamine (**18**) and the radical anion of the indole (**17**). Formation of **17** weakens the *N*-SO_2Ph bond and facilitates bond cleavage.[21] Proton transfer from the radical cation of NEt_3 (**18**) would lead to the observed desulfonylated indole **14**. In competition with this process, the phenylsulfonyl radical can undergo addition to the aromatic framework of the indole anion **19** producing radical anion **20** as a transient species. A subsequent electron transfer from **20** to **18** would afford the rearranged indole **15** (and/or **16**). In the presence of *n*-Bu_3SnH, the phenylsulfonyl radical undergoes bimolecular hydrogen atom transfer and is no longer available to add to the aromatic ring.[22]

In summary, *N*-sulfonyl indoles can be easily deprotected by a photoinduced electron transfer reaction with triethylamine. By using an equivalent amount of *n*-Bu_3SnH in the photolysis medium, it is possible to suppress the competing photo-Fries like rearrangement by scavenging the phenylsulfonyl radical. It is anticipated that the mild and chemoselective nature of this deprotection reaction should lead to its application in synthesis.



Scheme 4.

Further studies directed toward the synthesis of the kopsifoline alkaloid family are currently underway and will be described in a forthcoming publication.

Acknowledgments

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22. In the case of indoles **13a–c**, which are devoid of an electron-withdrawing substituent at the 2-position of the ring, no significant effect on the yield of the desulfonylated indole **14** was noticed when *n*-Bu_3SnH was added to the reaction mixture. We assume that with these systems the initially formed indolyl anion (i.e., **19a–c**) is simply more reactive and therefore undergoes reaction with the phenylsulfonyl radical at a faster rate than bimolecular hydrogen transfer with *n*-Bu_3SnH.