ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 11686–11688

www.rsc.org/chemcomm

COMMUNICATION

Visible light-induced 3-sulfenylation of *N*-methylindoles with arylsulfonyl chlorides†

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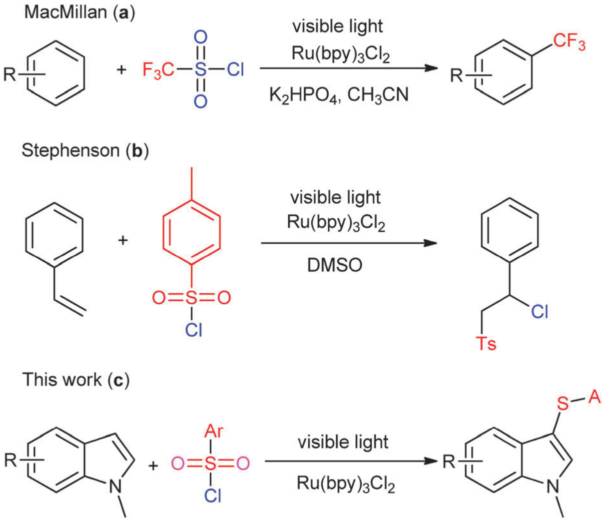
Received 21st September 2012, Accepted 19th October 2012
DOI: 10.1039/c2cc36866h

The synthesis of 1-methyl-3-(arylthio)-1*H*-indoles has been achieved by the photoredox reaction of *N*-methylindoles with readily available arylsulfonyl chlorides in moderate yields.

Early in 1912, Ciamician predicted that photochemistry utilizing sunlight could be prosperous in the not too distant future because of its natural abundance and cleanliness.[1] However, how to exploit the energy from the sun is still a great challenge in this century.[2] Recently, the visible light mediated photoredox reactions[3] with Ru (or Ir) poly-pyridine complexes[4] as photosensitizers have attracted significant interest from the research groups of MacMillan,[5] Yoon,[6] Stephenson[7] and others.[8] Among their elegant work, it is very important to investigate potential compounds initiating the photocatalysis cycle or generating highly reactive intermediates *via* whatever oxidative or reductive quenching cycle.[3a,e] Until now, the scope of reductive agents is limited, and only tertiary amines have many applications. They can give rise to iminium intermediates, which are prone to further functionalization.[9] Moreover, indole derivatives,[10] as intriguing motifs due to their fascinating bioactivities, can be deemed as enamines to some extent. They are rarely involved in initiating photoredox reactions,[7d] though their redox potentials ($E_{1/2}$ of *N*-methylindole = 0.79 V *vs.* SCE)[11] and unique electrochemical behaviors[12] show that they may serve as reductive quenchers.

On the other hand, oxidants also play an important role in such photoredox catalyses, to construct C–C or C–X bonds in the reactions of polyhalogen alkanes or halides.[5b,7a,b,g] However, to the best of our knowledge, visible light induced reactions, in which readily available sulfonyl chlorides[13] participate, are still rare. One example was reported by Nagib and MacMillan, which involves visible light induced trifluoromethylation of arenes or heteroarenes utilizing trifluoromethanesulfonyl chloride with first generation of the CF_3SO_2Cl radical anion by oxidation of $Ru(phen)_3^{2+}*$ and then release of SO_2 and chloride (Scheme 1a).[5c] Another example was discovered by Stephenson *et al.*, which involves visible light-mediated atom transfer radical addition of styrenes using *p*-toluene sulfonyl chloride with no collapse of the TsCl radical anion (Scheme 1b).[7h] Due to the interest in visible light induced reactions of available starting materials, we herein accidentally discovered the reaction of *N*-methylindoles and arylsulfonyl chlorides with not only the release of chlorides but also the extrusion of oxygens, generating 3-sulfenylated indoles[14] (Scheme 1c).



Scheme 1 Sulfonyl chlorides involved in photoredox reactions.

Our initial work was the reaction of *N*-methylindole (**1a**) with TsCl (**2a**) in the presence of 2 mol% $Ru(bpy)_3Cl_2$ in an Ar atmosphere under visible light in acetonitrile, which afforded 23% of the product 1-methyl-3-(*p*-tolylthio)-1*H*-indole (**3a**) with the complete consumption of **1a** (Table S1, entry 1, see ESI†). The structure of **3a** was confirmed by the X-ray analysis (Fig. 1). Inspired by this result, we screened some bases which may serve as deacid reagents, for removing HCl generated in the reaction.

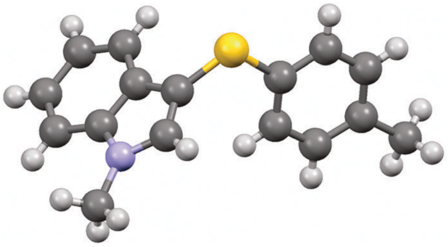


Fig. 1 The crystal structure of **3a** (C: gray; H: white; N: blue; S: yellow).

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 902004 (**3a**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc36866h

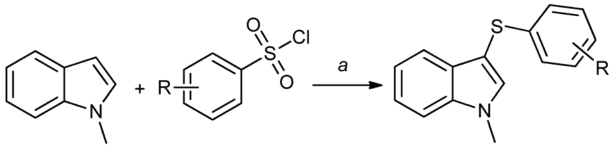
However, the reactions rarely took place no matter which organic or inorganic bases were added (Table S1, entries 2–6, ESI†). So we turned to adjust the ratio of **1a**/**2a**, and surprisingly found that 3 equiv. of **1a** benefited the yield dramatically albeit a slightly higher yield with more **1a** (Table S1, entries 7–9, ESI†).

Temperature had a little effect on the reactions (Table S1, entries 10 and 11, ESI†). Moreover, the counteranion of photocatalyst, PF_6^-, seemed to be beneficial to the yield (Table S1, entry 12, ESI†). Further optimization of the reaction was focused on the media. Other polar solvents such as DMF, DMSO and NMP gave rise to no products, as did mixed solvent or solvent with 4 Å molecular sieves (Table S1, entries 13–17, ESI†). Last, control experiments showed that a photocatalyst and visible light were essential.

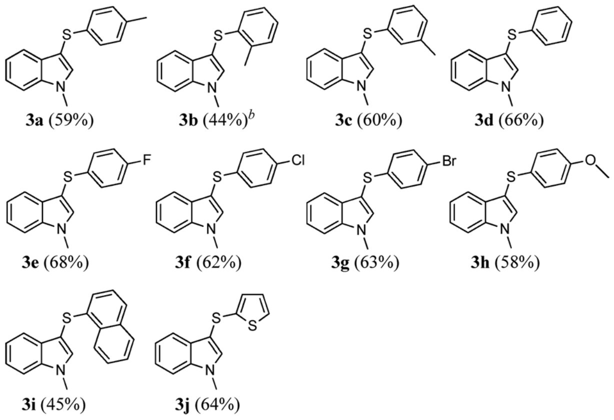
With the optimized reaction conditions in hand, we then explored the scope of arylsulfonyl chlorides (Table 1). *o*-, *m*- or *p*-Toluene sulfonyl chlorides and benzene sulfonyl chloride could be utilized to give the corresponding products **3** in moderate yields (Table 1, **3a–d**). Steric hindrance of *o*-methyl made the reaction sluggish, with longer reaction time and lower yield (Table 1, **3b**). Sulfenylating reagents **2** bearing both electron-donating (Table 1, **3h**) as well as electron-withdrawing groups (Table 1, **3e–g**) generated products in almost the same yields. 1-Naphthyl sulfonyl chloride could afford the product in just 45% yield because of the steric hindrance effect (Table 1, **3i**). This reaction was available for heteroaryl sulfonyl chloride too (Table 1, **3j**).

By varying the substituents on indoles **1**, we further investigated the scope of indoles (Table 2). *N*-methyl indoles bearing groups on C-5 with either electron-donating or withdrawing groups could react with **2h** to provide sulfenylated products respectively (Table 2, **4a–c**). Substitutions on various positions of the *N*-methylindole are also tolerated (Table 2, **4d–e**). However, the reaction of Br or Cl-substituted *N*-methyl indole was a little complex, and the reason is unknown. Besides *N*-methyl indoles, other *N*-substituted groups were also involved (Table 2, **4f–h**). *N*-benzyl indole worked well (Table 2, entry **4f**), but *N*-Boc indole didn't react at all (Table 2, entry **4h**), which may be explained by its high redox potential ($E_{1/2}$ of *N*-Boc indole = 1.6 V *vs.* SCE) and weak nucleophilic ability, since no **4h** was detected in the reaction of 3 mmol **1a**, 3 mmol *N*-Boc indole and 1 mmol TsCl under standard conditions. To our delight, when 4 equiv. of free (N–H) indole reacted with TsCl, the corresponding product was obtained in 33% yield (Table 2, entry **4g**).

Table 1 Scope of arylsulfonyl chlorides



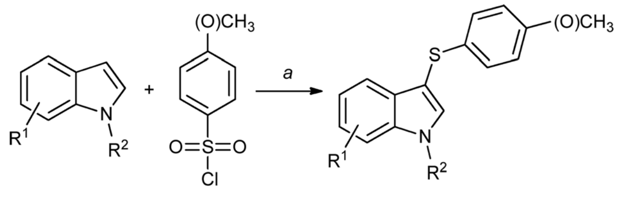
1a **2** **3**



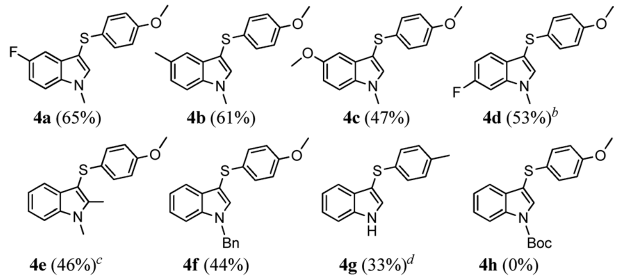
3a (59%) **3b** (44%)[b] **3c** (60%) **3d** (66%)
3e (68%) **3f** (62%) **3g** (63%) **3h** (58%)
3i (45%) **3j** (64%)

[a] Unless otherwise specified, all reactions were carried out with **1a** (3 mmol), **2** (1 mmol), photocatalyst (2 mol%) in CH_3CN, under 23 W fluorescent light at 40 °C under the atmosphere of Ar for 12 h, and the yield is isolated yield. [b] 24 h.

Table 2 Scope of indoles



1 **2h** **4**

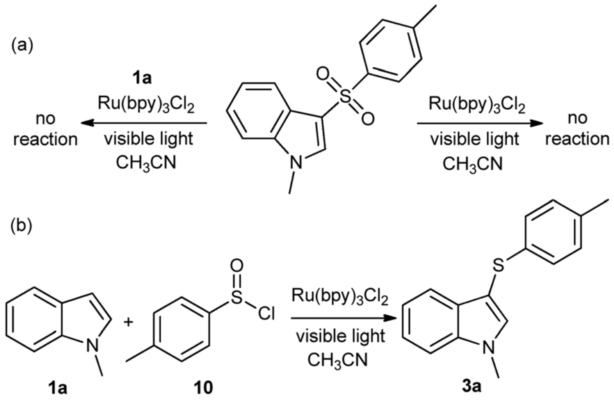


4a (65%) **4b** (61%) **4c** (47%) **4d** (53%)[b]
4e (46%)[c] **4f** (44%) **4g** (33%)[d] **4h** (0%)

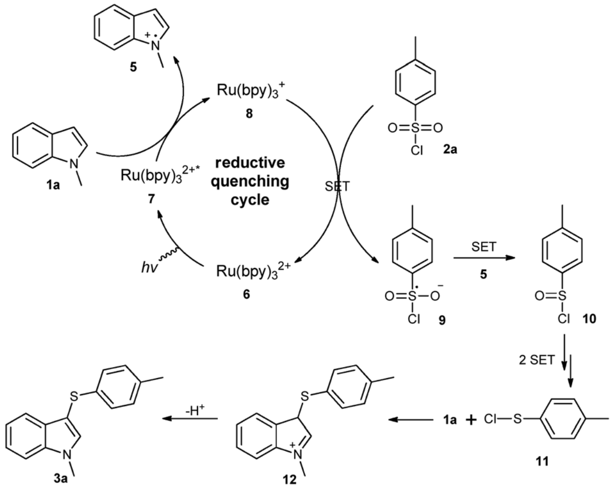
[a] Unless otherwise specified, all reactions were carried out with **1** (3 mmol), **2h** (1 mmol), photocatalyst (2 mol%) in CH_3CN, under 23 w fluorescent light at 40 °C under the atmosphere of Ar for 12 h, and the yield is isolated yield. [b] 24 h. [c] 48 h. [d] 4 equiv. of free (N–H) indole were used.

Although the Friedel–Crafts reaction of indoles with sulfonyl chlorides in the presence of Lewis acid was well developed, the sulfonylated product or related intermediates were not involved in the reaction under discussion. This was confirmed by the reaction of 1-methyl-3-tosyl-1*H*-indole under standard conditions with or without **1a** (Scheme 2a). The sulfenylation exclusively occurred at C3 rather than C2 of *N*-methylindole, indicating that no routine of radical addition to indoles occurred[15] but nucleophilic attack of electron-rich *N*-methylindoles did. As sulfenyl chlorides are reactive sulfenylating agents especially for indoles,[16] we deduced that *p*-tolyl hypochlorothioite **11** was produced in this reductive system somewhat similar to what You[16a] reported *via* multiple steps SET. Although a detailed process of reduction of TsCl to *p*-tolyl hypochlorothioite was not clear, partially reductive intermediate 4-methylbenzene-1-sulfinic chloride (**10**) may be generated. So the reaction of **10** with **1a** was carried out, yielding **3a** in 64% yield (Scheme 2b). Moreover, addition products with other byproducts have been detected *via* GC-MS.[17]

While the mechanism of this photoredox reaction was not very clear, the hypothetical process may include: (i) **1a** reductively quenching **7** to generate highly reductive **8**, (ii) **2a** being reduced to **9** by getting an electron from **8**, (iii) three other steps of SET



Scheme 2 Control experiments.



Scheme 3 Proposed mechanism.

generating key intermediate **11**,[18] and (iv) **11** attacking **1a** to produce **12**, which was finally transformed into the major product **3a** (Scheme 3).

In conclusion, we have developed a method to synthesize 1-methyl-3-(arylthio)-1*H*-indoles by the photoredox reactions of *N*-methylindoles with readily available arylsulfonyl chlorides in moderate yields. Further study on the photoredox of arylsulfonyl chlorides is ongoing.

Financial support from the Major State Basic Research Development Program of China (2011CB808602) is acknowledged.

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17 For GC-MS scheme and other byproducts, see ESI†.
18 The detailed process is not clear now. And reductive agents providing electrons may not only be **1a** but also **5** or other oligomers, for the system consist of only 3 equiv. of **1a**.