Investigation of UV Light-Promoted Synthesis of α-Sulfonyl Amides from N -Sulfonyl Ynamides

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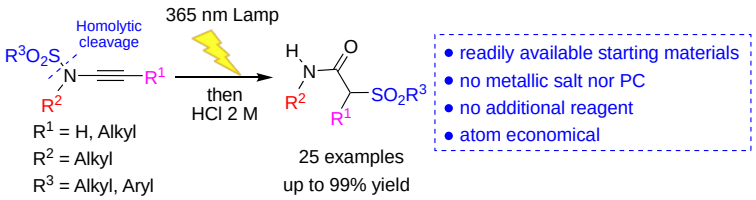
Aix Marseille Univ, CNRS, ICR, Marseille, 13013, France

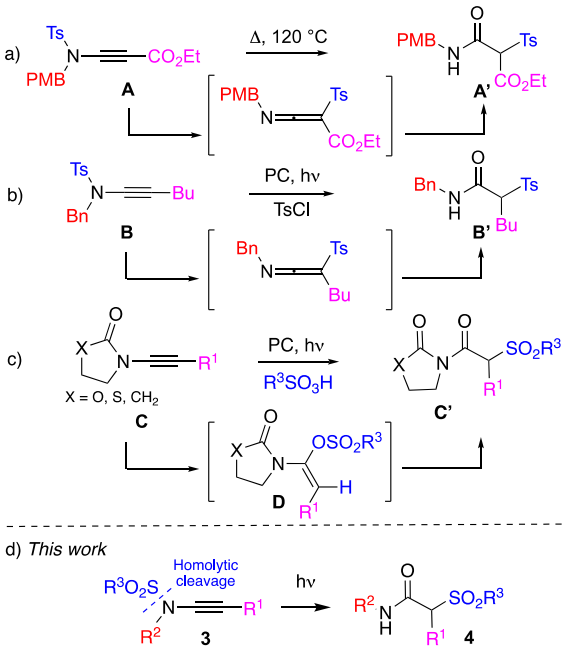


Abstract: UV Light-promoted synthesis of α-sulfonyl amides from *N*-sulfonyl ynamides without any additives is reported. The reaction proceeds through a radical chain mechanism involving the photo-induced cleavage of the nitrogen-sulfur bond, addition of electrophilic sulfonyl radical to the triple bond of the ynamide followed by beta-fragmentation of the sulfonyl group leading to a ketenimine hydrated upon work-up. This highly efficient rearrangement leads, after acidic treatment, to a wide range of α-sulfonyl amides in high yields.

Introduction. α-Sulfonyl amides are building blocks for organic synthesis and key structural motifs present in biologically active compounds.[1] Therefore, the development of efficient and rapid syntheses of these compounds is of great interest to the community of organic chemists. Current methods for the construction of the C—SO_2 bond of α-sulfonyl amides are based on a two-step strategy involving the formation of a C—S bond followed by oxidation of the sulfur atom in the presence of *m*-CPBA or H_2O_2.[2] Direct introduction of the SO_2R moiety can be achieved through sulfonylation of α-amide-carbanion intermediates[1d] or by reacting amides with sulfinates in the presence of oxidants.[3] However, these methods suffer from the use of strong bases or oxidants, and for some of them, i.e. sulfonylation of α-amide-carbanion intermediates, low to moderate yields are obtained.

Due to the presence of a nitrogen atom—bearing an electron-withdrawing substituent— directly linked to their carbon-carbon triple bond, ynamides behave as activated polarized alkynes that show unique reactivity and stability. These compounds are currently known as powerful synthetic intermediates for elegant constructions of versatile *N*-containing

molecules.[4,5] Regarding the direct synthesis of α-sulfonyl amides, only few reports involve the use of ynamides as substrates[6] (Scheme 1). Wudl[7] described in 2006 that ynamide **A** can undergo upon heating the N-to-C thermal migration of the tosyl group leading to a ketenimine intermediate that can be hydrated to give the α-tosylated amide **A'** (Scheme 1(a)). More recently, Yuan and Zhu[8] have reported a radical chain isomerization of *N*-sulfonyl ynamides in the presence of catalytic tosylchloride and an iridium-based photocatalyst to give stable ketenimines. They have shown that this process can be combined with an aza-Claisen rearrangement. During their work, closely related to our ongoing study, as an application of their study, they showed that the ketenimine resulting from the use of tosyl ynamide **B** can be transformed in α-tosyl amide **B'** via hydration (Scheme 1(b)). Finally, Yue and Feng[9] described a visible-light-promoted oxo-sulfonylation of ynamides **C** to give α-sulfonyl imides **C'** in the presence of sulfonic acids through the in-situ formation of a vinylsulfonate **D**. They proposed that this latter, activated through energy transfer process could undergoes homolytic cleavage of the O—S bond (Scheme 1(c)), that would imply subsequent sulfonyl radical addition/β-fragmentation sequence.

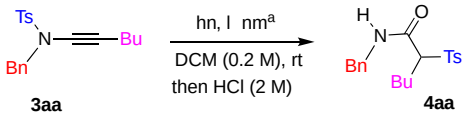


Scheme 1. Direct synthesis of α-sulfonylated amides from ynamides. (PC : Photocatalyst)

For some years now, our group has been interested in the involvement of ynamides in free-radical transformations.[10] In the course of our investigations, we found out that upon activation under irradiation at 365 nm at room temperature, in the absence of any additives, *N*-sulfonyl ynamides **3** could be converted into α-sulfonyl amides **4** in high yield through a N to C migration of the sulfonyl group[11] (Scheme 1(d)). As compared with the other methodologies, our strategy offers several advantages such as easy implementation, use of readily available starting materials, neutral conditions, diversity with respect to the sulfonyl groups that can be used, and neither expensive metals nor photocatalysts are needed. The scope

and limits of this light-promoted synthesis of a wide range of α-sulfonyl amides from *N*-sulfonyl ynamides are discussed in the following section.

Results and discussion. To find the appropriate reaction conditions, ynamide **3aa** prepared from bromohexyne **1a** and *N*-benzyl-4-methylbenzenesulfonamide **2a** according to Hsung methodology[12] was selected as model substrate and submitted to irradiation using 18 W LED lamps (Evoluchem® lamps, λ nm, light intensity: 16.7 mW/cm² at 10 cm distance) at different wavelengths in degassed dichloromethane by varying the reaction time (Table 1). For a reaction time fixed at 24 h, irradiation at 365 nm gives excellent results compared with the other wavelengths studied, i.e. 400 nm and 450nm, for which ynamide **3aa** is not fully consumed (entry 3 / entries 1,2). The reaction time can be reduced to 18 h or even 4 h[13] without loss of efficiency, leading to the desired compound in 98% yield after acidic treatment (entries 4,5). Optimized reaction conditions, i.e. irradiation at 365 nm in degassed dichloromethane followed by work-up with a 2 M aqueous solution of HCl, were used to explore the scope of the transformation .



3aa **4aa**

entry	λ (nm)	Time (h)	**4aa** Isolated yield (%)
1	450	24	40
2	400	24	Not detected
3	365	24	97
4	365	18	98
5	365	4	98

Table 1. Optimization of synthesis of α-sulfonyl amide **4aa** from *N*-sulfonyl ynamide **3aa**. [a]18 W LEDs (Evoluchem® lamps, λ nm, light intensity: 16.7 mW/cm² at 10 cm distance)

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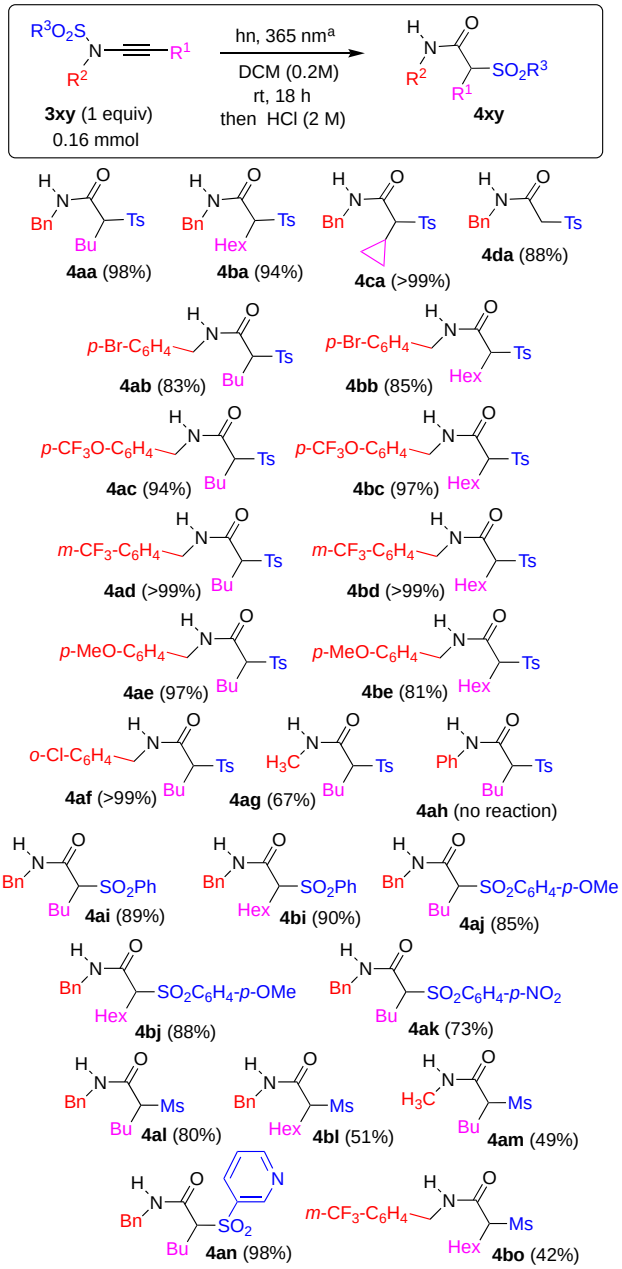
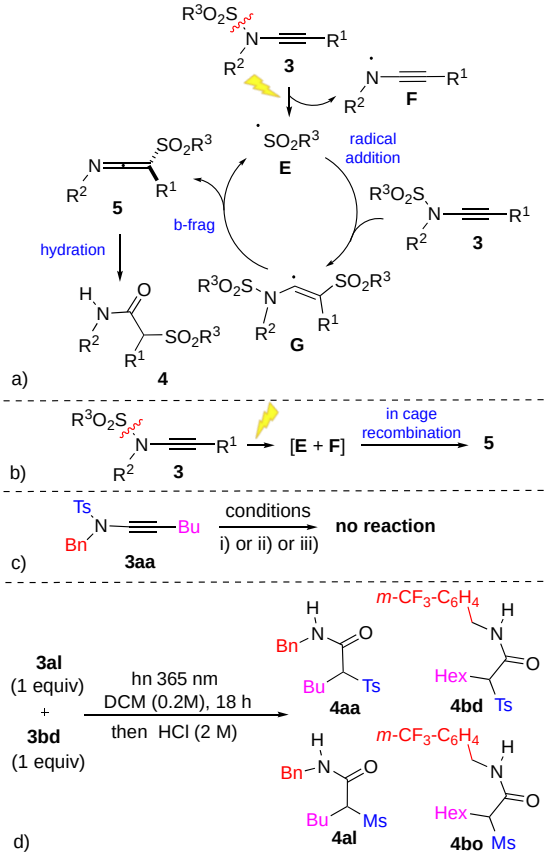


Scheme 2. Synthesis of α-sulfonyl amides. [a]18 W LEDs (Evoluchem® lamps, 365 nm, light intensity: 16.7 mW/cm² at 10 cm distance)

The results of irradiation experiments conducted with *N*-sulfonyl ynamides **3xy** are reported in Scheme 2. All ynamides were submitted to irradiation at 365 nm for 18 h at room temperature,[14] and all reactions were conducted on 0.16 mmol of substrates. Most of the tested ynamides behave as expected leading to the desired products in high yields, especially those bearing aryl- and heteroaryl sulfonyl groups. It is to be noted that *N*-mesyl ynamides were also reactive giving α-mesyl amides **4al**, **4bl**, **4am** and **4bo** in moderate to good yields. Surprisingly ynamide **3ah** derived from *N*-tosylaniline did not lead to any transformation and was totally recovered after 18 h of irradiation. This point will be discussed later on.

Two plausible mechanisms are proposed in scheme 3. A radical chain mechanism involving the photo-induced homolytic cleavage of the nitrogen-sulfur bond, addition of electrophilic sulfonyl radical **E** to the ynamide triple bond followed by beta-fragmentation of the sulfonyl group of **G** leading to ketenimine **5** can explain the formation of α-sulfonyl amide **4** after hydration[15] (Scheme 3(a)). Calculations of the first singlet excited state (vertical π–π* transition) at the TD/ωB97X-D/6-31+G(d,p) level of theory show that the latter spontaneously evolves via homolytic cleavage of the N-S bond when optimizing energy (see SI). Concerted 1,3-migration or in cage recombination of radicals **E** and **F** formed through the above initiation step could also be suggested at this stage (Scheme 3(b)).

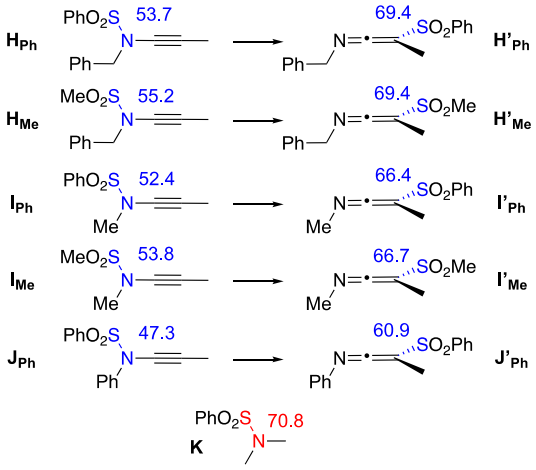


Scheme 3. Mechanistic Studies. [a]Radical chain process. [b]In cage radical recombination. [c]Blank experiments: i) DCM (0.2M), 18 h. ii) DCM (0.2M), 18 h, light protected. iii) hν 365 nm, DCM (0.2M), 18 h, TEMPO (1 equiv). [d]Cross experiments, ^{1}H NMR molar ratio of **4aa**:**4al**:**4bd**:**4bo** = 0.4:0.5:0.35:0.5.

Several experiments were carried out to prove the involvement of radicals and to determine which of the two mechanisms envisaged was involved in the process. Reactions were conducted in the presence of sun light (Scheme 3(c) conditions i)), in the dark (Scheme 3(c) conditions ii)) or in the presence of one equivalent of TEMPO under irradiation at 365 nm (Scheme 3(c) conditions iii)) using ynamide **3aa** as substrate. Throughout any of these experiments, no transformation occurred after 18 h. This confirms both the necessity to use UV light and the radical nature of the process (inhibi-

tion by TEMPO). To confirm that the chain radical mechanism was responsible for the rearrangement, a cross-over experiment involving an equimolar mixture of ynamides **3al** and **3bd** was also performed (Scheme 3(d)). If cage recombination was involved, then only products **4al** and **4bd** should be obtained. In the case of a chain process, products **4al** and **4bd** in admixture with **4aa** and **4bo** should be expected. After 18h, four α-sulfonyl amides were formed, thus supporting the radical chain process. The 0.4:0.5:0.35:0.5 molar ratio of compounds **4aa**:**4al**:**4bd**:**4bo** was determined from the ^{1}H NMR spectrum of the crude reaction mixture.

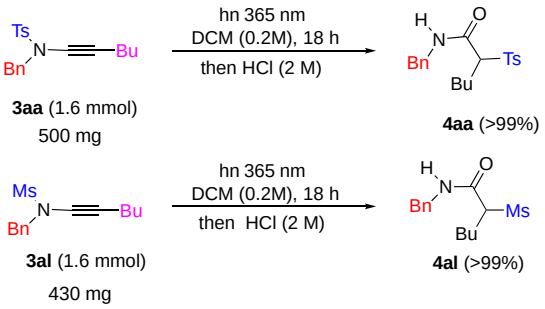
Since the proposed mechanism involves the homolytic cleavage of the N—S bond, theoretical investigations were conducted in order to estimate N—S bond dissociation energy in ynamides **H**, **I**, and **J** chosen as models for *N*-aryl- and *N*-alkyl-sulfonyl ynamides (Scheme 4). Additional calculation of the C—S BDE in ketenimines showed the exothermicity of the process. It is to be noted that the presence of the triple bond lowers the N—S BDE by approximately 18 kcal/mol as compared to *N, N*-dimethyl-*N*-phenylsulfonyl amine **K**.



Scheme 4. Molecular Modelling: N—S and C—S bond dissociation enthalpies calculated in kcal/mol at the M06-2X/6-311++G(3df,3pd)//M06-2X/6-31+G(d,p) level for model ynamides and ketenimines.

The behaviour of **3ah** recovered unchanged after 18 h of irradiation is surprising.[16] Both the similarity of UV absorption spectra and the lowering of the N—S bond BDE (Scheme 4, ynamide **J**) with respect to the others ynamides would lead to the conclusion that rearrangement should be very easy in that particular case. Reaction pathways, i.e., addition followed by β-fragmentation, calculated at the M06-2X/6-311++G(3df,3pd)//M06-2X/6-31+G(d,p) level for model ynamides $\mathbf{H_{Ph}}$ and $\mathbf{J_{Ph}}$. confirmed the expected similar reactivity. Even the possibility of a competitive photo-Fries rearrangement[17] was simulated for $\mathbf{J_{Ph}}$; it might be a plausible alternative path (see SI). Finally, we tried to carry out N to C migration of sulfonyl group of **3ah** under thermic activation. While the reaction conducted in decaline at 120 °C on ynamide **3aa** led after acidic treatment to α-sulfonyl amide **4aa** in 96 %yield, a complex mixture was obtained when reacting **3ah** under the same ex-

perimental conditions. The desired compound **4ah** was detected as traces in the crude mixture on the ^{1}H NMR spectrum. Thus the presence of a phenyl group at nitrogen remains the unexplained limitation of the scope of the reaction.



Scheme 5. Scale up

Finally, this protocol was scaled up to 1.6 mmol of ynamides **3aa** and **3al**. (Scheme 5). α-Sulfonyl amides **4aa** and **4al** were isolated in quantitative yields, showing the synthetic utility of the process.

Conclusion. In summary, a light-promoted synthesis of α-sulfonylated amides from *N*-sulfonyl ynamides has been developed. A wide range of α-sulfonyl amides were prepared through a radical chain process initiated by homolytic cleavage of the N—S bond under irradiation at 365 nm. This photochemical rearrangement features high atom economy, large substrate scope, mild / neutral reaction conditions, and high efficiency.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its supporting information.

Supporting Information

Experimental procedures, Computational details, and NMR spectra (PDF file). The Supporting Information is available free of charge on the ACS Publications website.

AUTHOR INFORMATION

Corresponding Author

* Aix Marseille Univ, CNRS, ICR, Marseille, 13013, France. laurence.feray@univ-amu.fr, ORCID : 0000-0001-8931-9621

* Aix Marseille Univ, CNRS, ICR, Marseille, 13013, France. michele.bertrand@univ-amu.fr

Notes

The manuscript was written through contributions of all authors. / All authors have given approval to the final version of the manuscript. The authors declare no competing financial interest.

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(13) 4 h reaction time is needed to consume all the substrate.

(14) Tosylated derivatives react much faster than mesylated substrates that necessitate 18 h for reaction completion. All experiments were conducted over 18 h reaction time for the sake of homogeneity.

(15) Ketenimine derived from ynamide **3aa** has been clearly identified through ^{1}H NMR proton realized on the crude reaction mixture before work-up with HCl (2 M).

(16) A longer irradiation time (48 h) and a change in wavelength (400 or 450 nm) do not change the result.

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