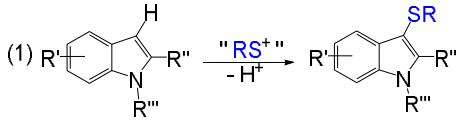
Lewis acid-activated 8-quinolinethiosulfonates: an efficient methodology for C-S(alkyl) bond formation.

Erwan Galardon*[a]

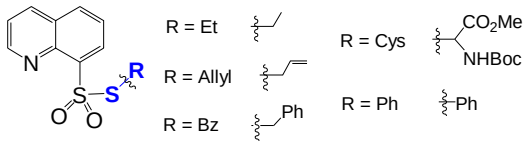
[a] UMR 8601, LCBPT, CNRS-Université de Paris, 45 rue des Sts Pères, 75006 Paris, France. Mail to erwan.galardon@parisdescartes.fr

The importance of sulfur-containing compounds in various fields, ranging from material science[1-2] to medicinal chemistry, [3] has called for the development of synthetic strategies to form carbon-sulfur (C-S) bonds. Thus, numerous approaches based on the nucleophilicity of thiols have been designed over the years, which mostly use air-sensitive noble metal catalysts.[4-9] At the opposite, the use of electrophilic sulfur reagents is also a powerful, more eco-friendly approach, in particular for the sulfenylation of C-H bonds into C-S bonds.[10-11] In this context, the sulfenylation of indoles (Equation 1) has become a benchmark reaction to develop and test new sulfenyl transfer reagents, because indoles are good nucleophiles and their occurrence in many natural products or biological active compounds makes them attractive synthetic targets.[12-14] For instance, metal-catalyzed or metal-free protocols have been proposed, in which disulfides, sulfinic acid and their salts, sulfonyl chlorides, sulfonylhydrazine, or N-thiophtalimides are used as source of electrophilic sulfur.[10,15-16] Thiosulfonates (RSO_2SR') are another class of emerging[17] reagents, which were also studied for C-S bond formation[18-20] and for indole sulfenylation.[21] However, despite the large pool of sulfenylation agents listed above, the difficult activation of the chalcogen centre essentially limits these reagents to the formation of C-S(aryl) bonds. On the other hand, the transfer of alkylsulfenyl groups requires harsher activating conditions and is so far still limited.[21-24]



To fill this gap, an original approach based on new thiosulfonates bearing a quinoline moiety (QSO_2SR, Scheme 1) is proposed to efficiently transfer *alkylsulfenyl groups to indoles* under mild conditions. Coordination of a Lewis acid to the quinoline nitrogen indeed leads to an enhanced electrophilicity of the sulfur compared to standard thiosulfonates.

Scheme 1. Sulfenylating agents QSO_2SR used in this study.



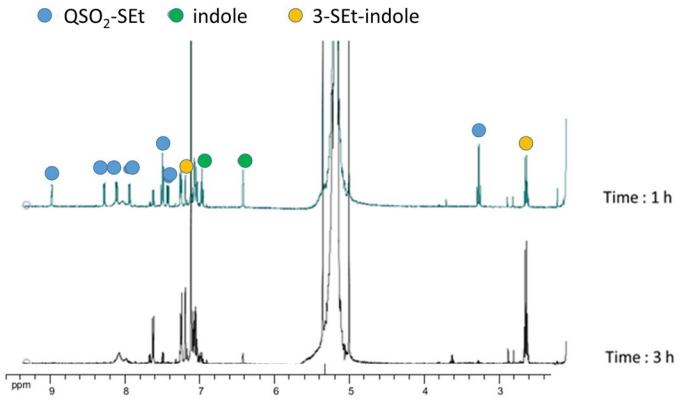
First, the reaction between equimolar amounts of QSO_2SEt, indole and various Lewis acids in dichloromethane in air was investigated by ^1H NMR at room temperature. While most of these reactions proved unsuccessful (Table 1), including the control experiment devoid of the Lewis acid, significant changes were noticed in the NMR spectra with solid $ZnCl_2$ or $ZnCl_2$ in 2-methyl-tetrahydrofuran.

Table 1. Conversions$^{\perp}$ of QSO_2SEt (determined by ^1H NMR) when reacted with stoichiometric amounts of indole and of various Lewis acids (O.2 M in dichloromethane, room temperature, 18h).

Lewis acid	Conversion (%)
/	0
$NiCl_2$	10
$CoCl_2$	15
$CuCl_2$	35
$MgCl_2$	0
$ZnCl_2$ 1.9M in 2-Me-THF	95
$ZnCl_2$	95

Two features are indeed indicative of the transformation of the starting materials into the expected 3-(ethylthio)-indole as illustrated in Figure 1: i) the disappearance of the signal at 6.34 ppm, corresponding to the proton at the 3-indole position (green), and ii) the appearance of a new quadruplet at 2.65 ppm, corresponding to the new 3-S-$\underline{CH_2}$-CH_3 moiety (orange), at the expense the corresponding protons in the starting QSO_2SEt (3.29 ppm, blue)). The thiosulfonate was fully consumed after 3 hours with both zinc sources, and no trace of the possible 2-sulfenylated by-product was detected. The lack of reaction with other Lewis acid may be at least partially attributed to the poor solubility of most inorganic salts in the chlorinated solvent.

Figure 1. ^1H NMR spectrum (recorded at 500 MHz in $CDCl_3$) of the crude reaction mixture between QSO_2SEt and indole in the presence of $ZnCl_2$ in dichloromethane after 1 and 3 hours. The main peaks are labelled.



A screening of various indoles indicated that stoichiometric amounts of either $ZnCl_2$ in 2-methyl-tetrahydrofuran or solid $ZnCl_2$ efficiently convert electron-rich or electron-deficient indoles to their 3-sulfenylated derivatives at room temperature (Table 2, entries a, c, e & k). As expected, the reaction is faster with 5-methoxyindole than with 5-bromo-indole, as shown in Figures S1-S2. For instance only a 50% conversion is recorded after 3h with the latter, when the reaction is almost completed with the former.

Table 2. Conversions[⊥] of various indoles, determined as specified in the experimental section, when reacted with stoichiometric amounts of QSO_2SEt and of $ZnCl_2$ (O.2 M in dichloromethane or ethyl acetate, room temperature).

	Indole	Solvent	Conversion
a	Indole	CH_2Cl_2	95
b	Indole	EtOAc	90
c	5-methyl-indole	CH_2Cl_2	90
d	5-methyl-indole	EtOAc	85
e	5-bromo-indole	CH_2Cl_2	90
f	5-bromo-indole	EtOAc	85
g	4-bromo-indole	EtOAc	75
h	1-methyl-indole	EtOAc	85
i	2-methyl-indole	EtOAc	90
j	3-methyl-indole	EtOAc	0
k	5-methoxy-indole	CH_2Cl_2	90
l	5-methoxy-indole	EtOAc	90
m	5-hydroxy-indole	EtOAc	80
n	5-amino-indole	EtOAc	50
o	2-methyl-5-bromo-indole	EtOAc	75

To replace the toxic and environmentally harmful dichloromethane, we next tested the sulfenylation of indole with QSO_2SEt in ethanol or ethyl acetate, concentrating on the cheap Lewis acid $ZnCl_2$. Although no conversion was observed in ethanol, the reaction proceeded smoothly at room temperature in ethyl acetate, although at slower rate than in dichloromethane. Thus, a 70% conversion was observed after 18 h in ethyl acetate, while the reaction was complete after 3 h in dichloromethane. However, the conversion was very good after 42 h (Table 2, entry b). A similar behaviour was observed with 5-methoxy and 5- and 4-bromo-indoles (entries l, f & g). Interestingly, potential coordinating groups such as phenol or aniline were tolerated, and 5-hydroxy-indole or 5-amino-indole were converted to their 3-sulfenylated derivatives with reasonable yields (entries m & n). Finally, the presence of a methyl group at the 1- or 2- position did not interfere and good yields were obtained with 1-methyl and 2-methyl-indole derivatives (entries h, i & o). As expected, no conversion of the starting thiosulfonate was observed with 3-methyl indole (entry j). The reaction is not catalytic, indicating that the Lewis acid remains coordinated to the quinoline moiety after the sulfenyl

transfer, even if the reaction is carried out at 70°C. A tentative mechanism is proposed in Scheme S1.

Finally, we investigated various thiosulfonates. They were easily obtained by the reaction between 8-quinolinesufinic acid and phenylsulfenyl chloride for QSO_2SPh, or between the 8-quinolinethiosulfonate pyridinium salt and primary alkyl halides[17] (for QSO_2SEt, $QSO_2SAllyl$, QSO_2SCys or QSO_2SBz). We were however unable to obtain thiosulfonates from secondary alkyl halides, despite the previous preparation of phenylthiosulfonates using this synthetic strategy.[17,25] Although the methodology presented in this study may not be the most appropriate to introduce -S(aryl) groups, 3-(phenylthio)-indole was nevertheless cleanly formed from indole and QSO_2SPh. More interestingly, alkylthiosulfonates, including those bearing functionalized groups such as protected cysteine, were also neatly converted to the corresponding indoles, at room temperature (Table 3).

Table 3. Conversions[⊥] of various thiosulfonates, determined as specified in the experimental section, when reacted with stoichiometric amounts of indole and of $ZnCl_2$ (O.2 M in ethyl acetate, room temperature, 42 h).

Thiosulfonate	Conversion (%)
QSO_2SEt	90
$QSO_2SAllyl$	90
QSO_2SCys	75
QSO_2SBz	75
QSO_2SPh	90

In conclusion, an efficient method to introduce an alkylsulfenyl moiety at the 3- position of indoles using affordable and environmentally benign solvents and activator is proposed. The extension of this methodology to other activated C-H bonds is currently under study.

Conflicts of interest

There are no conflicts to declare.

Notes and references

[⊥] Conversions are rounded to the nearest 5%.

EG thanks I. Martin for her help, and Pr. H. Dhimane (UMR8601) for useful discussions.

1 H. Mutlu, E. B. Ceper, X. Li, J. Yang, W. Dong, M. M. Ozmen, P. Theato, *Macromol. Rapid Commun.,* 2019, 40 e1800650.
2 M. J. H. Worthington, R. L. Kucera, J. M. Chalker, *Green Chem.,* 2017, 19 2748.
3 M. H. Feng, B. Q. Tang, S. H. Liang, X. F. Jiang, *Curr .Top. Med. Chem.,* 2016, 16 1200.
4 P. Bichler, J. A. Love, *Top. Organomet. Chem.,* 2010, 31 39.

5 P. Chauhan, S. Mahajan, D. Enders, *Chem. Rev.,* 2014*,* 114 8807.
6 T. Kondo, T. A. Mitsudo Ta, *Chem. Rev.,* 2000*,* 100 3205.
7 X. D. Li, Y. T. Gao, Y. J. Sun, X. Y. Jin, D. Wang, L. Liu, L. Cheng, *Org. Lett.,* 2019*,* 21 6643.
8 K. Tanimoto, R. Ohkado, H. Iida, *J. Org. Chem.,* 2019*,* 54 14980.
9 Q.-H. Teng, Y. Yao, W.-X. Wei, H.-T. Tang, J.-R. Li, Y.-M. Pan, *Green Chem.,* 2019*,* 21 6241.
10 D. Q. Dong, S. H. Hao, D. S. Yang, L. X. Li, Z. L. Wang, *Eur. J. Org. Chem.,* 2017*,* 6576.
11 C. Shen, P. F. Zhang, Q. Sun, S. Q. Bai, T. S. A. Hor, X. G. Liu, *Chem. Soc. Rev.,* 2015*,* 44 291.
12 N. K. Kaushik, N. Kaushik, P. Attri, N. Kumar, C. H. Kim, A. K. Verma, E. H. Choi, *Molecules,* 2013*,* 18 6620.
13 K. N. Pham, A. Lewis-Ballester, S. R. Yeh, *J. Am. Chem. Soc.,* 2019*,*
14 T. V. Sravanthi, S. L. Manju, *Eur. J. Pharm. Sci.,* 2016*,* 91 1.
15 D. Equbal, R. Singh, Saima, A. G. Lavekar, A. K. Sinha, *J.Org. Chem.,* 2019*,* 84 2660.
16 A. Hosseinian, S. Arshadi, S. Sarhandi, A. Monfared, E. Vessally, *J.Sulfur Chem.,* 2019*,* 40 289.
17 P. Mampuys, C. R. McElroy, J. H. Clark, R. V. A. Orru, B. U. W. Maes, *Adv. Synth. Catal.,* 2020*,* 362 3.
18 C. Ravi, A. Joshi, S. Adimurthy, *Eur. J. Org. Chem.,* 2017*,* 2017 3646.
19 T. T. Song, H. Y. Li, F. Wei, C. H. Tung, Z. H. Xu, *Tetrahedron Lett.,* 2019*,* 60 916.
20 R. J. Reddy, A. H. Kumari, J. J. Kumar, J. B. Nanubolu, *Adv. Synth. Catal.,* 2019*,* 361 1587.
21 J. B. Azeredo, M. Godoi, G. M. Martins, C. C. Silveira, A. L. Braga, *J. Org. Chem.,* 2014*,* 79 4125.
22 Y. Z. He, J. Jiang, W. H. Bao, W. Deng, J. N. Xiang, *Tetrahedron Lett.,* 2017*,* 58 4583.
23 R. Rahaman, P. Barman, *Eur. J. Org. Chem.,* 2017*,* 6327.
24 F. H. Xiao, H. Xie, S. W. Liu, G. J. Deng, *Adv. Synth. Cat.,* 2014*,* 356 364.
25 D. P. Gamblin, P. Garnier, S. J. Ward, N. J. Oldham, A. J. Fairbanks, B. G. Davis, *Org. Biomol. Chem.,* 2003*,* 1 3642.