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Optimization and Gram-scale Preparation of S-Trifluoromethyl- Sulfoximines and Sulfilimino iminiums, Powerful Reagents for the Late Stage Introduction of the CF₃ Group

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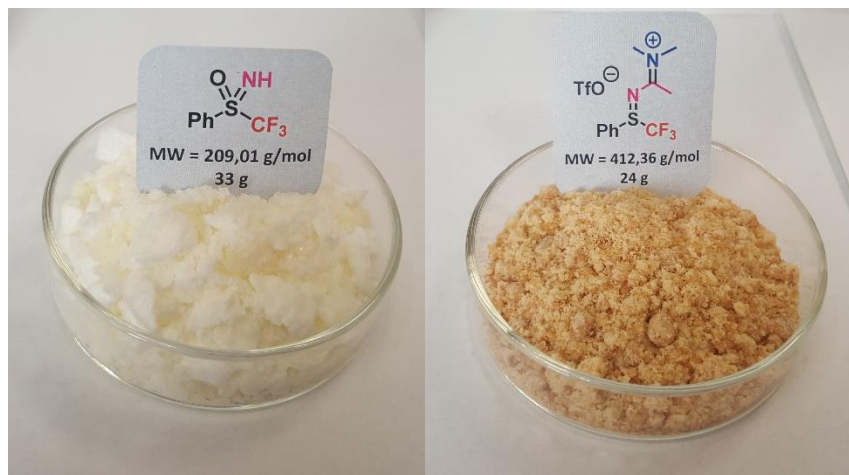
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TOC Graphic



Multigram synthesis of sulfoximine **4** and sulfilimino iminium **5**

ABSTRACT: *S*-trifluoromethyl sulfoximine and *S*-trifluoromethyl sulfilimino iminiums are important reagents for the electrophilic or radical late-stage introduction of the CF₃ group. We disclose in this article a reappraisal of our previous methodologies and their adaptation to a large scale. More than 30 g of the key sulfoximine **4** and 40 g of *S*-trifluoromethyl sulfilimino iminium **5** are prepared without purification. DSC measurements have been performed on both the crude mixture and the isolated compounds in order to insure a safe process. The cost of the synthesis is also detailed and discussed.

KEYWORDS: Trifluoromethyl, Sulfoximines, Sulfilimino iminiums, Sulfilimines, DSC measurements.

INTRODUCTION

The introduction of a fluorine atom or perfluoroalkylated moieties into an organic compound can lead to profound changes in its physical, chemical or biological properties due to the peculiar intrinsic properties of the fluorine atom.¹ Indeed, fluorine exhibits a high electronegativity (4.0 on the Pauling scale), a small atomic radius (1.47 Å) and induces a strong C-F bond (about 116 kcal/mol). This is the reason why nowadays about 20% of pharmaceuticals and 50% of agrochemical compounds contain at least one fluorine atom.² However, the number of natural organic compounds containing a fluorinated moiety is quite limited.³ This implies that access to organofluorine compounds is essentially based on the development of practical fluorination or fluoroalkylation reactions, and always requires new methodologies. The toolbox that chemists now possess contains more and more fluorinating and perfluoroalkylating reagents which are stable, selective and easy to handle. Among them, the electrophilic reagents of Umemoto and Togni (Figure 1) have probably been the most popular.⁴ In addition, a third class of compounds in this family, the fluorinated sulfoximines, should not be omitted and have received increasing attention

in the last decade.⁵ Indeed, these aza-analogs of sulfones are fluoroalkylating reagents with flexible reactivity, via nucleophilic, electrophilic or radical pathways. The Shibata reagent is the most known member of this family, but in our laboratory, we have also discovered other types of sulfoximine-based reagents as well as a very peculiar structure, a sulfilimino iminium, which has successfully been used for the efficient production of the trifluoromethyl radical.⁶

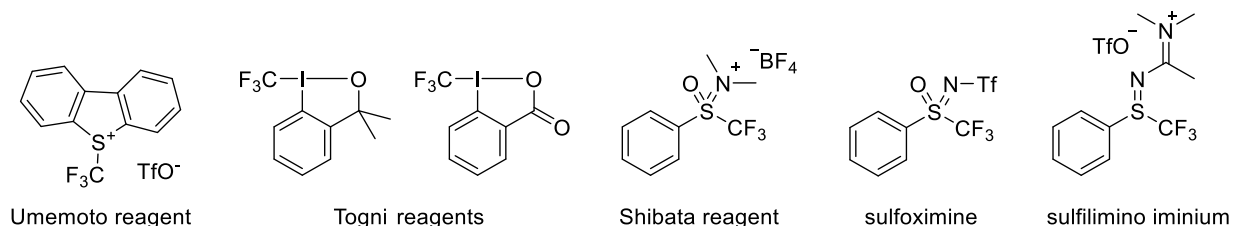


Figure 1: Electrophilic or radical perfluoroalkylating reagents

The synthesis of NH *S*-perfluoroalkylated sulfoximines was quite cumbersome, using harsh and dangerous conditions, until our group described, in 2009, a three-step methodology for the preparation of such compounds.⁷ A slight adaptation of the reaction conditions allowed access to sulfilimino iminiums.

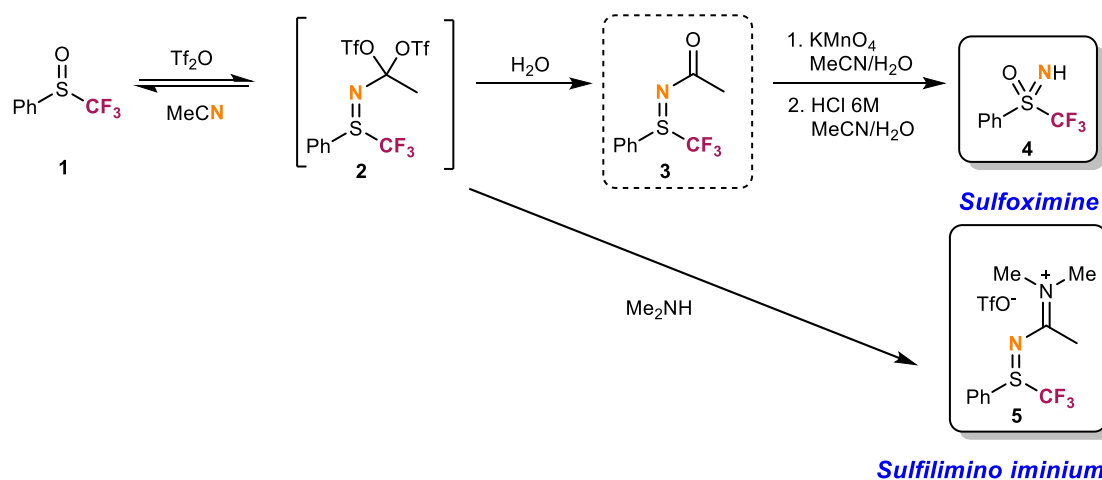
Consequently, because of the increasing use of sulfoximines as reagents, large-scale production appeared to be essential. We describe in this article a gram-scale, divergent synthesis of sulfoximine and sulfilimino iminium. Each step of our previous methodologies has been reconsidered and improved. Differential Scanning Calorimetry (DSC) measurements of both the reaction mixtures and the isolated molecules are described in order to ensure the maximum safety of the process. Total costs of the synthesis are also discussed.

RESULTS AND DISCUSSION

The synthesis of these reagents starts from the phenyl trifluoromethyl sulfoxide **1**, which is treated with acetonitrile in the presence of triflic anhydride, leading, via a Ritter-type reaction, to

a putative bis-triflate intermediate **2** (Scheme 1). This intermediate, stable at -15°C , can further evolve by two different pathways: i) hydrolysis of the reaction gives the *N*-acetylated intermediate sulfilimine **3**, which can be smoothly oxidized by KMnO_4 and deprotected in the presence of 6M HCl to obtain the trifluoromethylated sulfoximine **4**; ii) addition of a secondary amine to intermediate **2** directly leads to the sulfilimino iminium **5**.

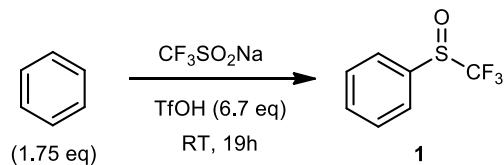
Scheme 1: Synthetic scheme of the preparation of trifluoromethyl- sulfoximines and sulfilimino iminiums



Synthesis of the phenyl trifluoromethyl sulfoxide **1**.

The phenyl trifluoromethyl sulfoxide **1** is commercially available but quite expensive (at least 78 € per gram). However, compound **1** can be easily prepared following our previously described one-pot procedure starting from sodium trifluoromethanesulfinate (Langlois reagent) and benzene.⁸ A reappraisal of our protocol is presented herein (Scheme 2). The production of compound **1** has been scaled up to 78 g without major issues and with a good yield of 73% (Table 1, entry 3) after purification by distillation.

Scheme 2: Synthesis of the sulfoxide **1**



This reaction occurs without solvent which causes two major issues: elevation of the temperature of the reaction and difficulty in stirring the reaction mixture. It is noteworthy that the addition of trifluoromethanesulfonic acid to sodium trifluoromethanesulfinate leads to a pasty mixture and to a rapid increase in temperature that can rise to 80°C. On a 10 g scale (Table 1, entry 1), magnetic stirring gives a reasonably homogeneous mixture and the exothermic phenomenon is not problematic. With larger quantities of reagents (Table 1, entries 2-3), mechanical stirring is required to obtain good dispersion and a homogeneous medium. Otherwise, the formation of aggregates proves deleterious to the yield. The triflic acid should be added portion wise (at least by thirds) to minimize temperature elevation. An additional cold-water bath is required to maintain the temperature of the reaction mixture (controlled by a thermometer) below 50°C. After 19 hours of stirring at room temperature, the reaction is poured onto ice (10 g of ice for 1 g of sodium trifluoromethanesulfinate) to control the exothermicity of the quenching.

Table 1: Multigram synthesis of phenyl trifluoromethyl sulfoxide **1**

Entry	Benzene	CF ₃ SO ₂ Na	TfOH	Sulfoxide	Yield
1	10 mL	10 g	35 mL	7.6 g	61 %
2^a	50 mL	50 g	176 mL	41.9 g	68 %
3^a	90 mL	90 g	315 mL	78.1 g	73 %

^a Use of a mechanical stirrer

The thermal stability of this compound was explored by DSC analysis (Figure 2). The phenyl trifluoromethyl sulfoxide **1** exhibits good thermal stability with decomposition from 205°C, proving the safety of the previously described reaction conditions and purification.

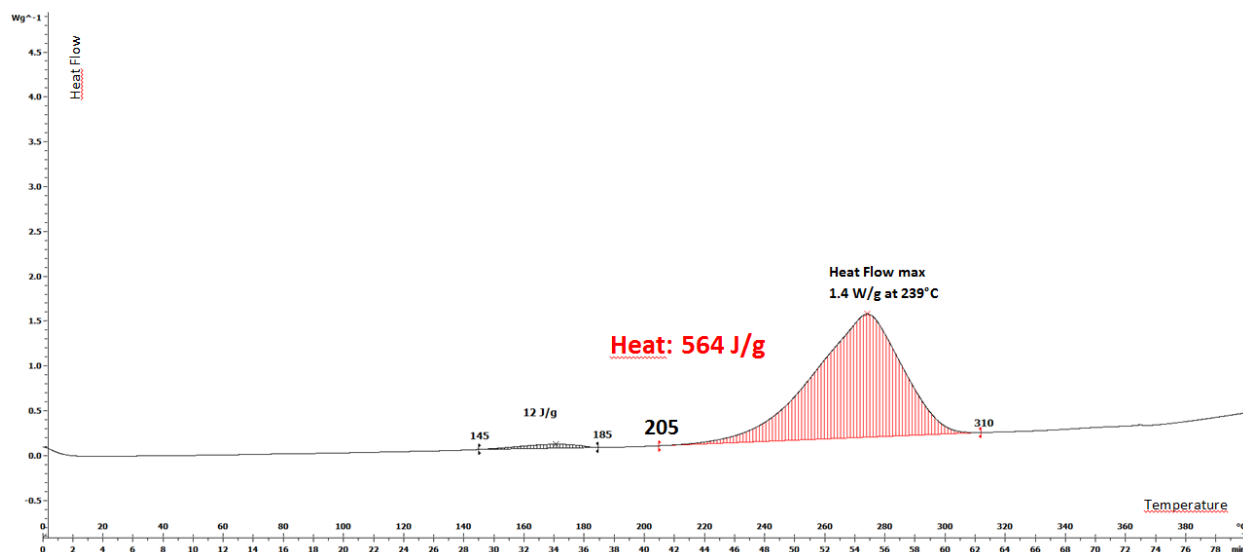


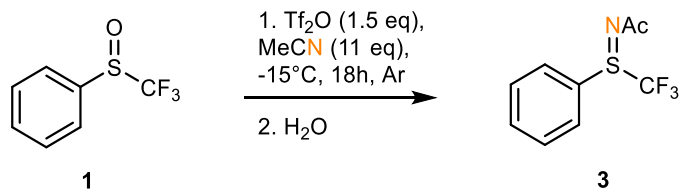
Figure 2: DSC analysis of the phenyl trifluoromethyl sulfoxide **1**

It is important to underline that purification of the sulfoxide **1** is not necessary for the next steps.

Synthesis of the intermediary sulfilimine **3**.

The second step is a Ritter-type reaction between the sulfoxide **1** and acetonitrile in the presence of trifluoromethanesulfonic anhydride. The procedure described by our group in 2009^{7a} has been adapted to a larger scale using acetonitrile as reagent and solvent, increasing its quantity from 1.5 to 11 equivalents.

Scheme 3: Synthesis of the intermediary sulfilimine **3**



It should be noticed that a low temperature (-15°C) is necessary to control the first step and to obtain an optimal formation of the intermediate sulfimine **3**. This experimental observation was supported by DSC analysis of the reaction media just after the addition of trifluoromethanesulfonic anhydride and also after full conversion of the sulfoxide **1**. The DSC analysis of the reaction medium after the dropwise addition of trifluoromethanesulfonic anhydride (Tf_2O) shows an endothermic peak at 20°C followed by an exothermic peak from 55°C , revealing the instability of the reaction medium (Figure 3). Moreover, after full conversion of sulfoxide **1**, it was shown that the medium is quite unstable with an exothermic peak starting at 15°C (Figure 4). Therefore, the temperature of the reaction should be maintained under -15°C to preserve an acceptable thermal stability. For this purpose, the reaction can be simply stored in a freezer for 18 hours, as the absence of stirring does not negatively impact the yield of the transformation.

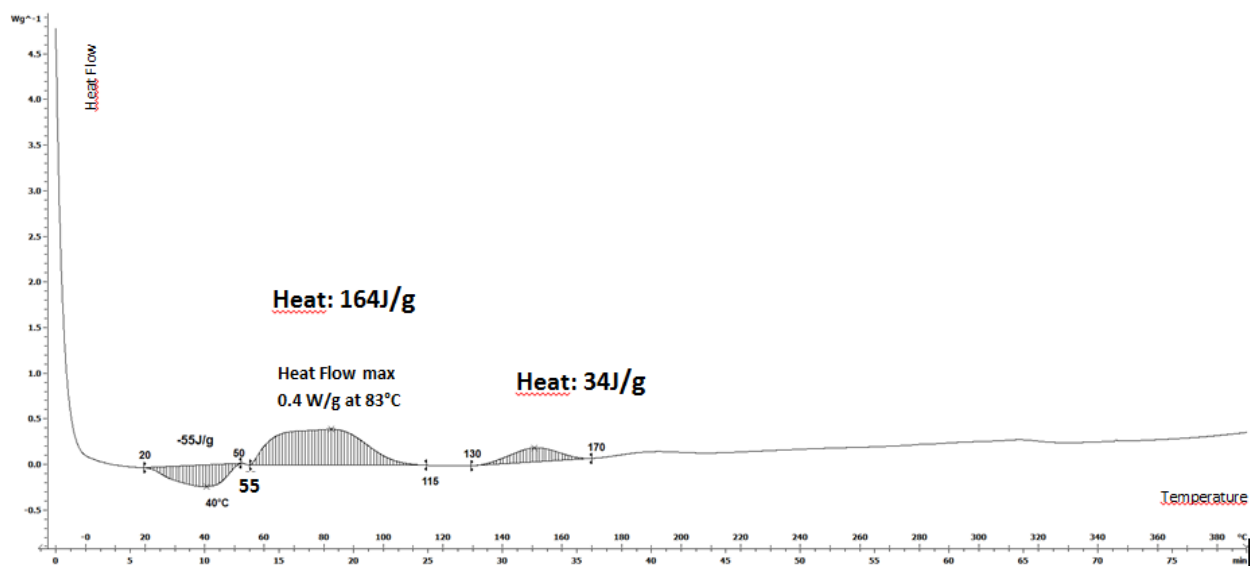


Figure 3: DSC analysis of the reaction medium after the addition of Tf_2O

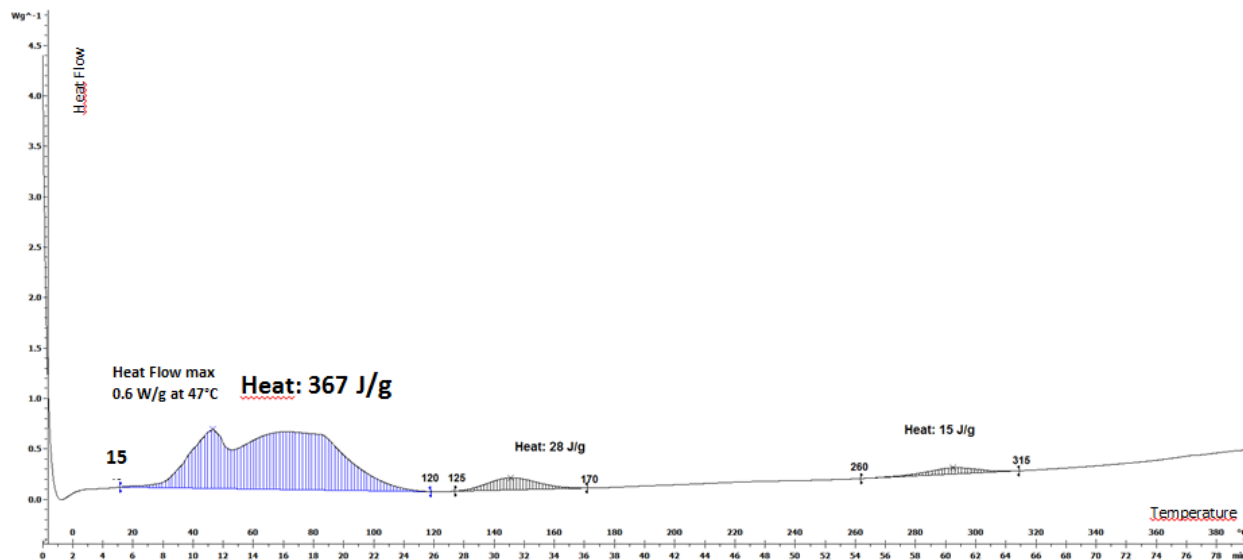


Figure 4: DSC analysis at full conversion of sulfoxide 1

It should be underlined that there is an interaction between triflic anhydride Tf_2O and acetonitrile (Figure 5), regardless of the number of equivalents, with a thermal phenomenon, which contributes to the one of the reaction (Figure 4).

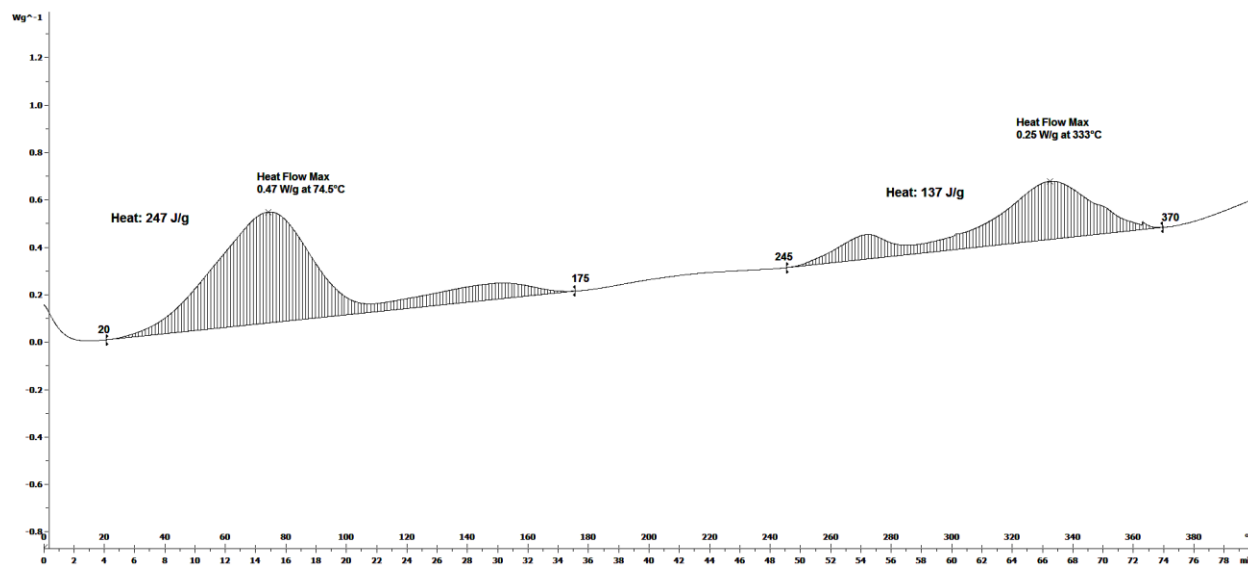


Figure 5: DSC analysis of the interaction between Tf_2O and acetonitrile ($\text{Tf}_2\text{O}/\text{MeCN} = 1/2 \text{ v/v}$)

In our initial publication,^{7a} water was directly added to the reaction mixture. On a larger scale and in order to control the exothermicity of the reaction quench, it is necessary to pour the crude mixture onto ice (10 g of ice for 1 g of sulfoxide **1**). The pure *N*-acetylated sulfilimine **3** shows a DSC profile with a decomposition starting from an onset temperature of 145°C (Figure 6), far from the process temperature.

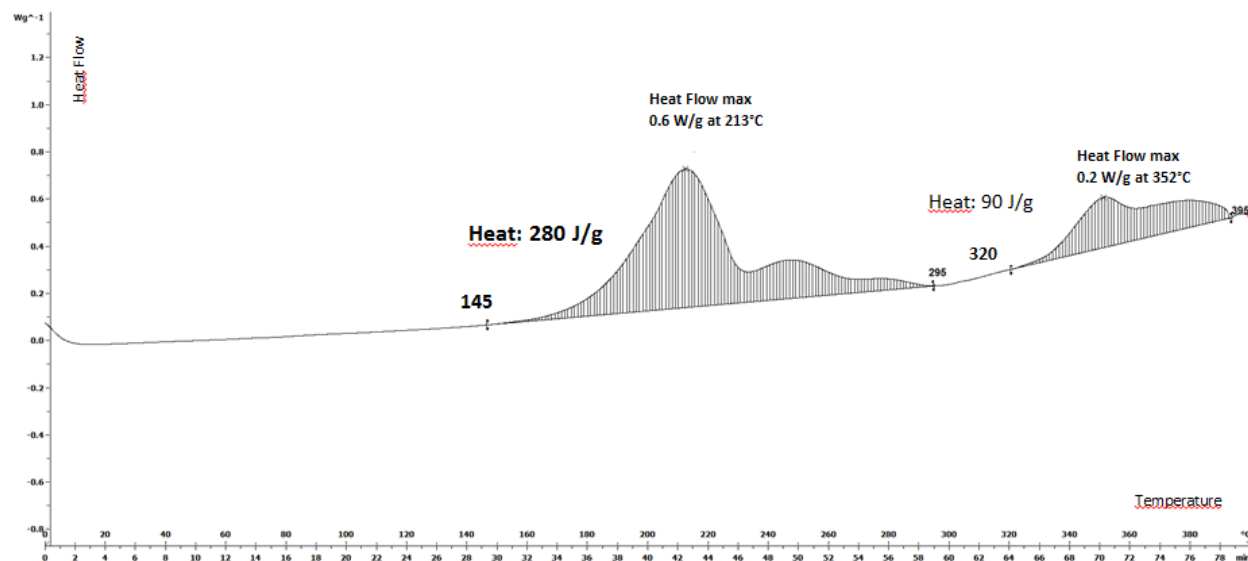
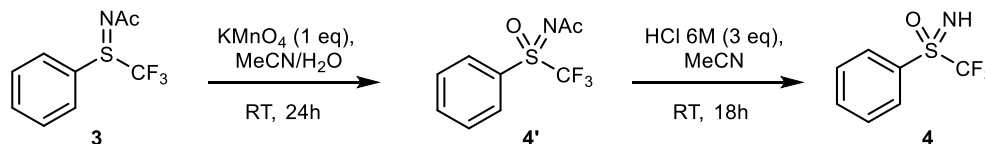


Figure 6: DSC analysis of the *N*-acetylated sulfilimine **3**

Synthesis of the trifluoromethyl sulfoximine **4**.

The sulfilimine **3** is then smoothly oxidized in the presence of potassium permanganate in dilute medium and the obtained acetylated sulfoximine **4'** is deprotected with hydrochloric acid to give the sulfoximine **4**.

Scheme 4: Synthesis of the sulfoximine **4**



On a large scale, an excellent overall yield is obtained for the production of 33 g of sulfoximine **4** (Table 2, entry 3). The scale up can be achieved without major issues. To facilitate the oxidation

step on scale-up, potassium permanganate was slowly added as a solid to the solution of intermediate sulfilimine **3** in water and acetonitrile. It is important to note that no intermediate purification is required and the final product was simply filtered through a pad of silica. Pleasingly, we noticed a substantial improvement in the yield on increasing the scale of the reaction.

Table 2: Multigram synthesis of phenyl trifluoromethyl sulfoximine **4**

Entry	Sulfoxide	Tf ₂ O	MeCN	KMnO ₄	HCl 6M	Sulfoximine	Yield
1	5 g	6.5 mL	15 mL	4.07 g	8.4 mL	2.7 g	50 %
2	20 g	26 mL	60 mL	16.28 g	33.6 mL	14.3 g	66 %
3	40 g	52 mL	120 mL	32.56 g	67.2 mL	32.8 g	76 %

Both steps were analyzed by DSC. The oxidation medium exhibits an exothermic peak from 125°C, revealing a good thermal stability of the mixture (Figure 7) under the reaction conditions.

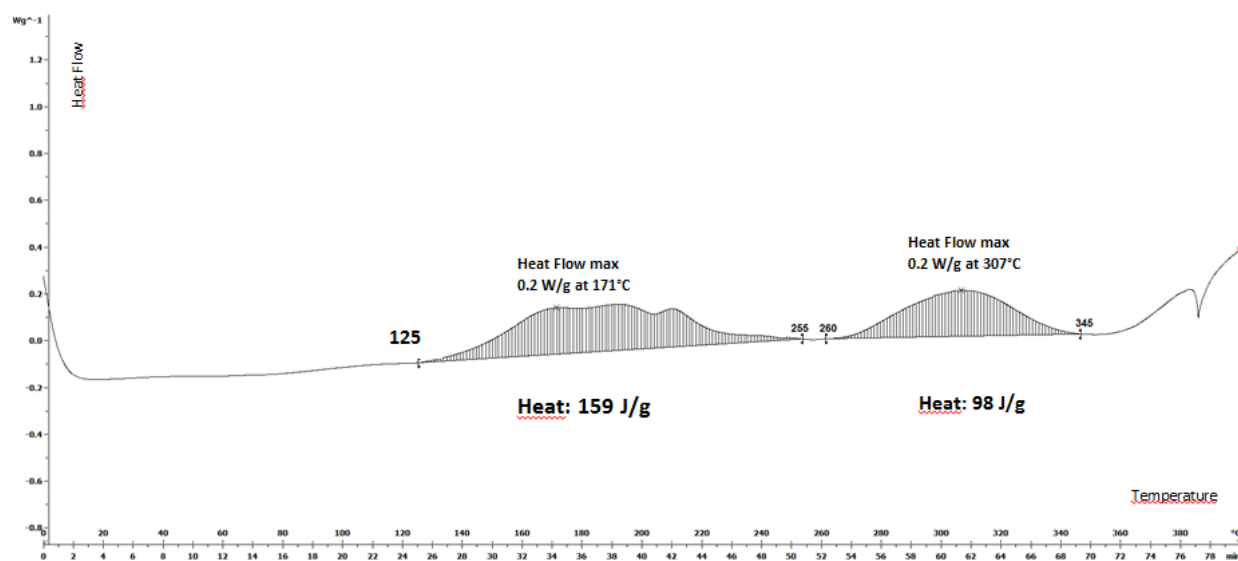


Figure 7: DSC analysis of the oxidation reaction medium

The hydrolysis of the intermediate N-protected sulfoximine **4'** medium also possesses a good thermal stability with an exothermic peak starting at 225°C (Figure 8). A slight exothermic decomposition appears from 115°C but presents no notable risk under the reaction conditions.

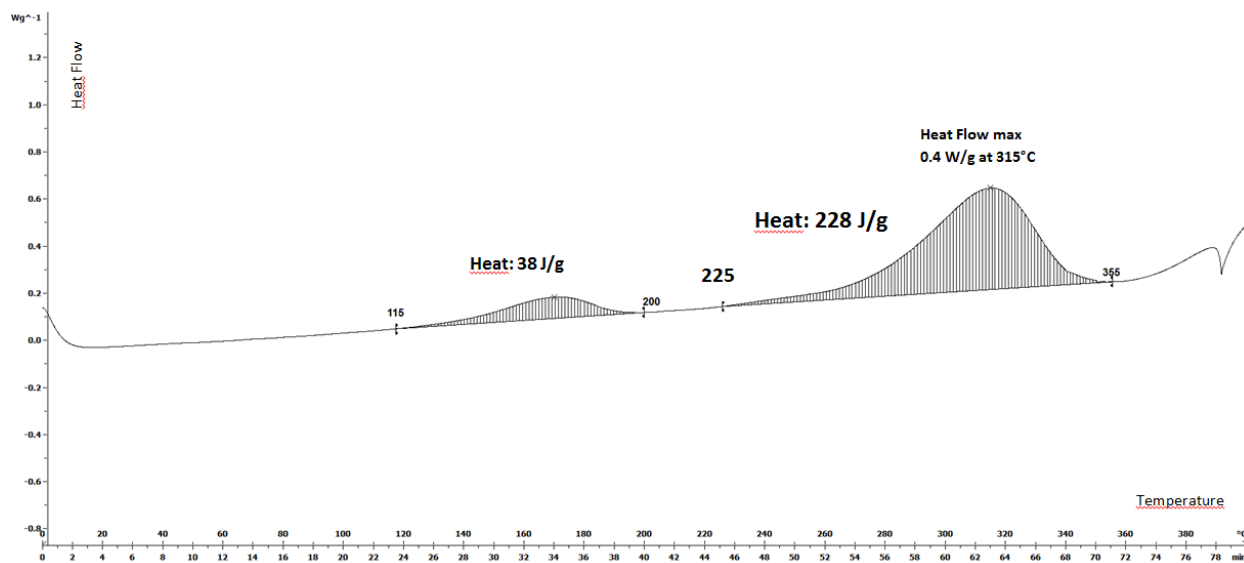


Figure 8: DSC analysis of the hydrolysis reaction medium

The DSC profile of the isolated products were also explored. It is noteworthy that both compounds **4'** and **4** exhibit an autocatalytic behavior (sharp peak) with an important exothermic peak. Indeed, the N-acetylated sulfoximine **4'** decomposes with an energy exceeding 600 J/g from 265°C (Figure 9).

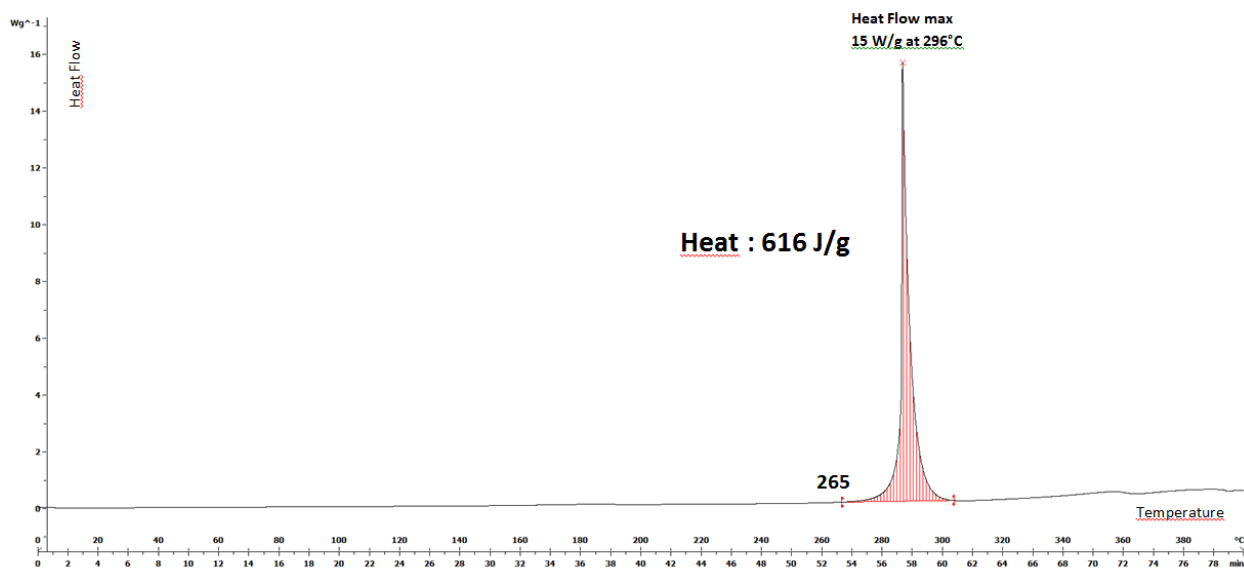


Figure 9: DSC analysis of the intermediate 4'

Similarly, the sulfoximine **4** decomposes with an exceptionally strong exothermic peak with an energy exceeding 896 J/g from 270°C (Figure 10) after an endothermic peak at 48°C corresponding to the melting point of the compound.

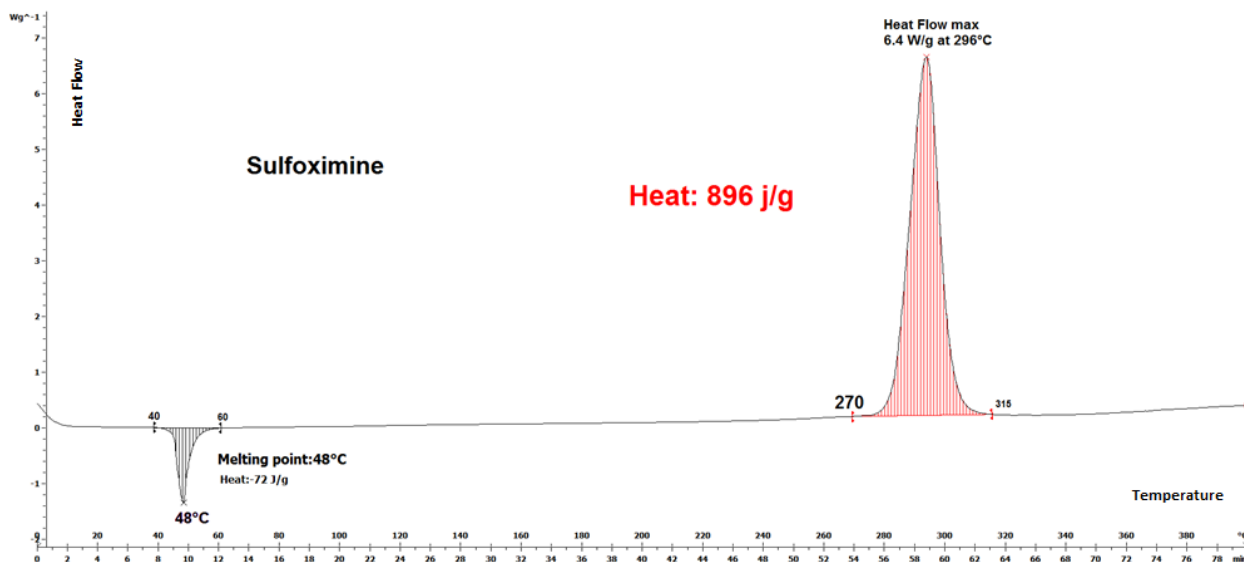
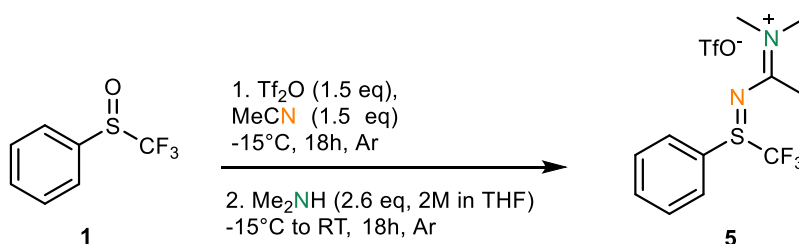


Figure 10: DSC analysis of the sulfoximine **4**

Synthesis of the phenyl trifluoromethyl sulfilimino iminium **5.**

In the same way as the synthesis of the sulfoximine **4**, the synthesis of the sulfilimino iminium **5** starts from the trifluoromethyl sulfoxide **1**, and the first step is a Ritter-type reaction between the sulfoxide **1** and acetonitrile in the presence of triflic anhydride. The major difference is the quench reagent. This time, the addition of dimethylamine delivers the desired sulfilimino iminium **5** (Scheme 5).

Scheme 5: Synthesis of the sulfilimino iminium **5**



In our previous protocol,^{7b} the dimethylamine was added in pure form. The use of a commercial solution of dimethylamine in THF (2M) is more convenient and was added dropwise at -15°C (Table 3, entry 1). At the end of the addition, the temperature of the reaction was allowed to rise slowly to room temperature. During the scale-up of the reaction conditions, we realized that the introduction of 4 equivalents of dimethylamine led to a very dilute reaction medium, and we assumed that fewer equivalents could afford the desired product with a similar yield. When 2.6 equivalents of dimethylamine in THF are introduced, the desired sulfilimino iminium **5** is obtained with a good yield of 76 % (Table 3, entry 2), similar to the yield with 4 equivalents (Table 3, entry 1).

Table 3: Multigram synthesis of sulfilimino iminium **5**

Entry	Sulfoxide	Tf ₂ O	MeCN	Me ₂ NH in THF	Compound	Yield
1	2.0 g	2.6 mL	5.8 mL	20.6 mL/ 4 eq	3.0 g	71 %
2	15.0 g	19.5 mL	43.6 mL	100.0 mL/ 2.6 eq	24.3 g	76 %
3	30.0 g	39.1 mL	87.1 mL	200.9 mL/ 2.6 eq	40.5 g	64 %

The production of sulfilimino iminium **5** has been scaled up to 40 g with a good yield of 64 % (Table 3, entry 3). From a practical point of view, the purification of compound **5** by chromatography on silica is quite cumbersome, using a lot of solvent and time. Changing the purification method quickly became essential during the scale-up of the synthesis. Sulfilimino iminium **5** is insoluble in diethyl ether. Therefore, compound **5** can be placed on a pad of Celite[®] (10 g of Celite[®] per gram of sulfoxide), impurities are removed by washing the Celite[®] with diethyl ether and the desired product is then recovered by washing the celite[®] with dichloromethane. If some impurities remain, the obtained solid can be washed again with diethyl ether. It is important to mention that the use of a newly opened bottle of high quality trifluoromethanesulfonic anhydride is crucial for the success of the reaction.

The thermal stability of sulfilimino iminium **5** has also been explored by DSC analysis (Figure 11). After an endothermic phenomenon corresponding to the melting of **5** around 64°C, an exothermic peak is observed from 120°C with an energy at 412 J/g revealing its good thermal stability under the process temperature.

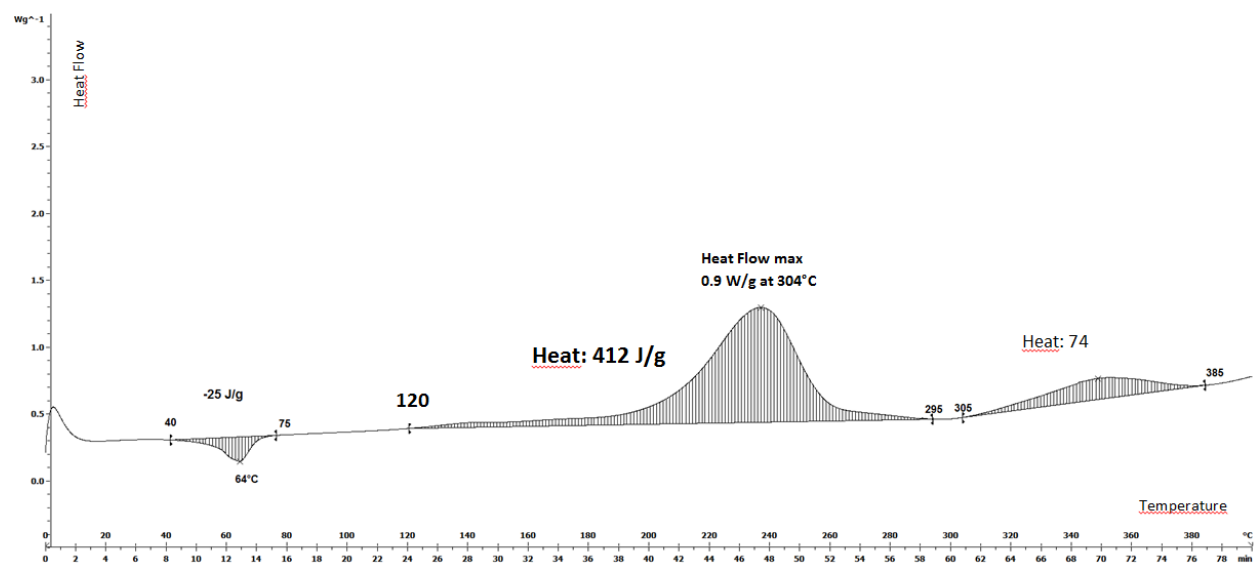


Figure 11: DSC analysis of sulfilimino iminium **4**

Financial estimation for reagent production.

We have been able to produce 78 g of sulfoxide **1**, 33 g of sulfoximine **4** and 40.5 g of sulfilimino iminium **5**. We decided to determine the cost of the production of such batches. To estimate the cost, the reagents, the solvents used for reactions and extraction, and the solvents, Celite[®] or silica used for purifications have been taken into account (Tables 4, 5 and 6) but the cost of manpower has been overlooked.

Table 4: Financial estimation for the synthesis of sulfoxide **1**

Reagent	Chemicals cost ^a	Quantity	Cost (€)
Benzene	20.79 € / 500 mL	50 mL	2.08
CF₃SO₂Na	£ 83.00 / 100 g	50 g	47.00 ^b
TfOH	193.98 € / 1 kg = 590 mL	176 mL	57.87
Dichloromethane (Extraction)	8.10 € / 5 L	300 mL	0.49
Total cost for the production of 42 g of sulfoxide 1			107.43
Total cost for the production of 1 g of sulfoxide 1			2.56 (2.91 \$) ^b

^a Negotiated prices with chemical suppliers. ^b Exchange rate on 01/21/19, 13:15 UTC.

Table 5: Financial estimation for the production of sulfoximine **4**

Reagent	Chemicals cost ^a	Quantity	Cost (€)
Sulfoxide 1	2.56 € / 1 g	40 g	102.4
Tf₂O	£ 270.0 / 1 kg = 596 mL	52 mL	26.61 ^b
Acetonitrile	13.70 € / 2.5 L	119 + 344 mL	2.54
KMnO₄	59.90 € / 500 g	32.55 g	3.90
HCl 37 %	5.57 € / 2,5 L	33.6 mL	0.07
Dichloromethane (Extraction)	8.10 € / 5 L	1 L	1.62
Silica (Purification)	11.80 € / 1 kg	200 g	2.36
Petroleum ether (Purification)	8.35 € / 5 L	2.1 L	3.51
Ethyl acetate (Purification)	10.0 € / 5 L	0.4 L	0.8
Total cost for the production of 33 g of sulfoximine 4			142.93
Total cost for the production of 1 g of sulfoximine 4			4.33 (4.91 \$) ^b

^a Negotiated prices with chemical suppliers. ^b Exchange rate on 01/21/19, 13:15 UTC.

Table 6: Financial estimation for the production of sulfilimino iminium **5**

Reagent	Chemicals cost ^a	Quantity	Cost (€)
Sulfoxide 1	2.56 € / 1 g	30 g	76.8
Tf₂O	£ 270.0 / 1 kg = 596 mL	39.1 mL	20.05 ^b
Acetonitrile	13.70 € / 2.5 L	87.1 mL	0.48
Me₂NH in THF (2M)	74.00 € / 500 mL	200.9 mL	29.7
Dichloromethane (Extraction)	8.10 € / 5 L	360 mL	0.58
Celite[®] (Purification)	399.00 € / 25 kg	300 g	4.79
Diethyl ether (Purification)	21.40 € / 5 L	0.6 L	2.57

Dichloromethane (Purification)	8.10 € / 5 L	0.6 L	0.97
Total cost for the production of 40.5 g of sulfilimino iminium 5			135.94
Total cost for the production of 1 g of sulfilimino iminium 5			3.36 (3.81 \$) ^b

^a Negotiated prices with chemical suppliers. ^b Exchange rate on 01/21/19, 13:15 UTC.

Globally, the cost per gram of these reagents is highly reasonable.

CONCLUSION

The production of sulfoxide **1**, sulfoximine **4** and sulfilimino iminium **5** has been optimized and performed on a multi-gram scale. DSC analyses, performed on only a few milligrams of substance, allowed us to investigate the thermal stabilities of the intermediates and final species. It is noteworthy that we are confident that these quantities do not represent an upper limit, and that larger quantities could be obtained in good yields with such optimized conditions. Moreover, the overall costs of these reagents are highly reasonable. These efficient conditions clearly pave the way to easy syntheses of such reagents in any laboratory for further applications, and should contribute to the popularization of their use.

EXPERIMENTAL SECTION

Synthesis of the ((trifluoromethyl)sulfinyl)benzene **1**

A dry 1 L, three-necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer was charged with sodium trifluoromethanesulfinate (90 g, 0.58 mol) and dried under vacuum for 24 hours prior to use. The flask is placed in a cold-water bath and trifluoromethanesulfonic acid (315 mL, 3.56 mol) is added, under argon, in three portions with vigorous stirring (around 100 mL each), in order to keep the temperature under 50°C. After the addition, the reaction is stirred for 20-30 minutes until the temperature decreases to room temperature. Then, benzene (90 mL, 1.01 mol) is added in one portion and the solution is stirred at room temperature for 19 h under an inert atmosphere. The reaction is quenched by pouring the

reaction medium on ice (900 g), extracted with dichloromethane (3 x 100 mL), and washed with a saturated solution of NaHCO₃ (3 x 60 mL). The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. The product is purified by distillation under reduced pressure (78 - 80°C at 15 mmHg) to afford **1** (78.1 g, 73%, colorless oil).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 7.76 (d, *J* = 7.4 Hz, 2H), 7.70 – 7.49 (m, 3H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 135.6 (q, *J* = 1.72 Hz), 133.6, 129.61, 125.9, 124.7 (q, *J* = 335 Hz, CF₃). ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -75.0 (s, 3F).

Imino(phenyl)(trifluoromethyl)-λ⁶-sulfanone 4

In a dry 500 mL two-necked round-bottomed flask equipped with a dropping-funnel and a thermometer, a solution of phenyl trifluoromethyl sulfoxide **1** (40 g, 206.0 mmol) in dry acetonitrile (120 mL, 2.28 mol) is cooled to -15°C under argon. Tf₂O (52 mL, 309.1 mmol) is introduced into the dropping-funnel and added dropwise to the solution, keeping the temperature around -15°C. The solution is then left at -15°C for 18 h under argon in a freezer. The reaction is quenched by pouring the reaction media on ice (400 g), extracted with dichloromethane (3 x 80 mL), and washed with a saturated solution of NaHCO₃ (3 x 40 mL). The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure.

To a solution of this crude product in acetonitrile (160 mL) and water (40 mL) is added KMnO₄ (32.56 g, 206.0 mmol) portion wise. The reaction is stirred at room temperature for 18 hours, diluted with H₂O (150 mL) and a saturated solution of Na₂S₂O₄ is added until complete discoloration of the solution. The product is extracted with dichloromethane (3 x 70 mL), and the organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure.

The crude product is dissolved in acetonitrile (184 mL) and HCl 6M (67.2 mL) is added. The reaction is stirred at room temperature for 18h. Then, water (100 mL) is added and the organic

phase is extracted with dichloromethane (3 x 50 mL), washed with a solution of saturated NaHCO₃ (3 x 20 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The product is filtered on silica (200 g) using petroleum ether/ethyl acetate 8/2 as eluent to afford the desired sulfoximine **4** (32.8 g, 76 %, white solid).

¹H NMR (300 MHz, CDCl₃) δ (ppm): 8.15 (d, *J* = 7.5 Hz, 2H), 7.84 – 7.72 (m, 1H), 7.63 (dd, *J* = 8.5, 7.1 Hz, 2H), 3.53 (s, br s, 1H). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 135.6, 131.6, 130.7, 129.6, 121.0 (q, *J* = 333 Hz, CF₃). ¹⁹F NMR (282 MHz, CDCl₃) δ (ppm): -70.3 (s, 3F).

(Z)-N-methyl-N-(1-((phenyl(trifluoromethyl)-λ⁴-sulfanylidene)amino)ethylidene)methaniminium **5**

In a dry 500 mL two-necked round-bottomed flask equipped with a dropping-funnel and a thermometer, under argon, a solution of phenyl trifluoromethyl sulfoxide **1** (30 g, 154.5 mmol) in dry acetonitrile (87.1 mL, 1.67 mol) is cooled to -15°C. Tf₂O (39.1 mL, 232.4 mmol) is added dropwise, keeping the temperature around -15°C. The solution is then left at -15°C for 18 h under argon in a freezer. A solution of Me₂NH (2M in THF, 200.9 mL, 401.8 mmol) is added dropwise to the reaction, keeping the temperature at around -15°C, under an inert atmosphere. Then, the reaction mixture is allowed to warm to room temperature slowly. The reaction is stirred at room temperature for 18h, under an inert atmosphere. The reaction is quenched by addition of 100 mL of water and the product is extracted with dichloromethane (3 x 120 mL). The organic phase is dried over MgSO₄, filtered and concentrated under reduced pressure. The crude residue is placed on Celite[®] (300 g) and the solid is washed three times with diethyl ether to remove impurities. Then, the deposit is washed three times with dichloromethane to recover the desired product **5** (40.5 g, 64 %, brownish solid).

^1H NMR (300 MHz, CDCl_3) δ (ppm): 8.07 (d, $J = 7.9$ Hz, 2H), 7.89 – 7.75 (m, 1H), 7.70 (dd, $J = 8.3, 6.8$ Hz, 2H), 3.39 (s, 3H), 3.35 (s, 3H), 2.67 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 174.2, 135.9, 130.8, 129.2, 124.7, 123.3 (q, $J = 127$ Hz, CF_3), 120.7 (q, $J = 320$, CF_3), 41.7, 40.0, 19.5. ^{19}F NMR (282 MHz, CDCl_3) δ (ppm): -67.4 (s, 3F), -79.0 (s, 3F, OTf).

Experimental conditions for DSC: DSC analysis were performed in a gold-plated closed crucible high pressure 40 μL Mettler, under air, applying a heating rate of 5 K/min in the range 0 K to 400 K/min.

Supporting Information

NMR Spectra of the compounds **1**, **4** and **5** are provided.

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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