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Preparation, Use, and Safety of *O*-Mesitylenesulfonylhydroxylamine

Javier Mendiola,*,† Juan A. Rincón,† Carlos Mateos,† José Francisco Soriano,† Óscar de Frutos,† Jeffry K. Niemeier,‡ and Edward M. Davis‡

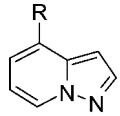
Centro de Investigación Lilly S.A., Avda. de la Industria, 30, Alcobendas-Madrid 28108, Spain, and Eli Lilly & Company LTC-South, Indianapolis, Indiana 46285-4813, U.S.A.

Abstract:

The aminating reagent *O*-mesitylsulfonylhydroxylamine (MSH) has a known potential hazard since it contains high-energy functional groups in its structure. There are references in the literature that report several incidents involving the use of pure and crystalline MSH. The preparation and safe use of this reagent at kilo scale are described herein.

1. Introduction

The resynthesis of one compound of interest involved the preparation of 4-substituted pyrazolo[1,5-*a*]pyridines (**1**). The most common route to prepare the pyrazolo[1,5-*a*]pyridine core is shown in Scheme 1, where the key step is the 1,3-dipolar cycloaddition[1] of a pyridine *N*-imine and an alkyne (Scheme 1).



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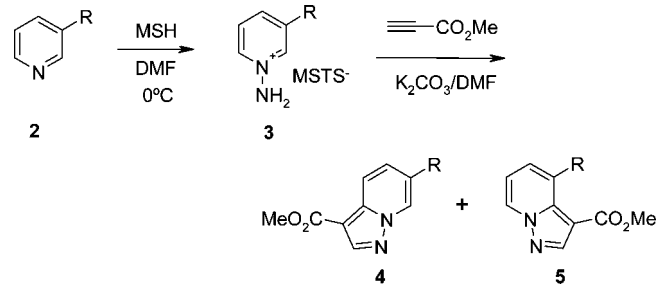
Synthesis of heteroaromatic *N*-imines like **3**, isoelectronic with *N*-oxides, requires reagents that provide NH_2^+ synthons[2] which can be generated from compounds represented as NH_2X (where X is a leaving group). These types of reagents have both electrophilic and nucleophilic properties in one molecule,[3] and they can be summarized as *O*-acyl (**6**), *O*-phosphinyl (**7**), and *O*-sulfonylhydroxylamines (**8**) (Figure 1). As a general rule, these reagents are thermally labile, and although there are no quantitative data on the thermal stability available, it can be stated that *O*-sulfonyl derivatives are more reactive and less stable than *O*-acyl and *O*-phosphinyl derivatives. *O*-Mesitylenesulfonylhydroxylamine (MSH, **9**) and hydroxylamine *O*-sulfonic acid (HOSA, **10**) are two representative examples of these *O*-sulfonyl reagents that provide NH_2^+.

Scheme 1



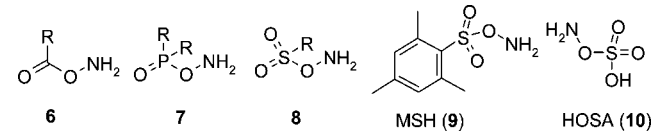


Figure 1. **Different aminating reagents.**

2. Background

For the *N*-amination of 3-substituted pyridines (**2**) we initially chose both HOSA and MSH. Due to the more thermal stability and commercial availability of HOSA several assays were performed, but in all conditions tested this reagent did not provide the desired *N*-amino 3-substituted pyridinium (**3**).

In contrast, MSH is very well-known as *N*-aminating reagent[3] for electron-deficient pyridines in organic media. In a 10 g scale pilot using this reagent, *N*-amination was quantitative, and cycloaddition afforded with moderate yield the desired pyrazolo[1,5-*a*]pyridines as major product. Given these excellent results, we considered studying the conditions to carry out this process safely on scale.

The major caveat of MSH is its well-known instability. It is described that dry samples decompose soon after storage in an amber glass bottle (the screw cap being shattered[4]). Although the instability of the compound has been mentioned,[5] there was no violent decomposition reported to the best of our knowledge at ambient temperature. It seems likely that traces of surface alkali in the soda-glass bottle catalyze both the formation of the highly reactive imidogen radical (HN**:**) from the base-labile compound, and its subsequent exothermic decomposition.

* To whom correspondence should be addressed. E-mail: mendiola_javier@lilly.com.
† Centro de Investigación, Lilly S.A.
‡ Eli Lilly & Company, LTC-South.

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(3) (a) Zeeh, B.; Metzger, H. In *Die Methoden der organischen Chemie (Houben-Weyl)*; Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1971; Vol. 10/1, p 1091. (b) Valenciano, J.; Sánchez-Pavón, E.; Cuadro, A. M.; Vaquero, J. J.; Álvarez-Builla, J. *J. Org. Chem.* **2001**, *66*, 8528–8536. (c) Fontana, A.; Benito, E. J.; Martín, M. J.; Sánchez, N.; Alajarín, R.; Vaquero, J. J.; Lambel-Guiraudet, S.; Leonce, S.; Pierré, A.; Caignard, D. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2611–2614. (d) Martínez, V.; Burgos, C.; Álvarez-Builla, J.; Fernández, G.; Domingo, A.; García-Nieto, R.; Gago, F.; Manzanares, I.; Cuevas, C.; Vaquero, J. J. *J. Med. Chem.* **2004**, *47*, 1136–1148. (e) Elsner, J.; Boeckler, F.; Davidson, K.; Sugden, D.; Gmeiner, P. *Bioorg. Med. Chem. Lett.* **2006**, *14*, 1949–1958. (f) Powell, D.; Gopalsamy, A.; Wang, Y. D.; Zhang, N.; Miranda, M.; McGinnis, J. P.; Rabindran, S. K. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1641–1645.
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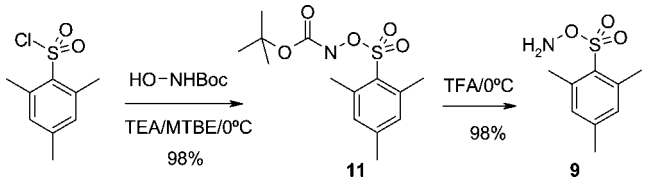
Scheme 2



However, MSH has been reported to be safely stored at 0 °C and is stable in dichloromethane solution.[6] There are also reports of violent explosions[7] when heated to 60 °C and that attempted vacuum drying of the pure crystalline compound at ambient temperature led to an instant decomposition.[8]

Having in mind this background, we concluded that additional studies on the stability of this reagent would be needed to face the synthesis of MSH. Scheme 2 shows the sequence that we followed for the preparation of MSH. This synthetic procedure has the advantage of providing MSH as a white solid that is easily purified.[9]

3. Results and Discussion

Since the Boc-protected intermediate **11** also contains the high-energy bond responsible for the instability of MSH (N−O), an ARC experiment was performed with this material. As shown in Figure 2, the onset was detected at 96.14 °C (0.1 °C/min) with a maximum temperature rate of 1.43 °C/min at 107.48 °C. The safety range of the working temperature (50 °C below the onset temperature) was compatible with the experimental procedure, so it was safe to carry out the reaction in large scale. However, it is important to note that intermediate **11** should be stored in the freezer. Although the onset temperature is high enough to stand on the benchtop, we also have experienced significant decomposition of this material after several weeks at room temperature.

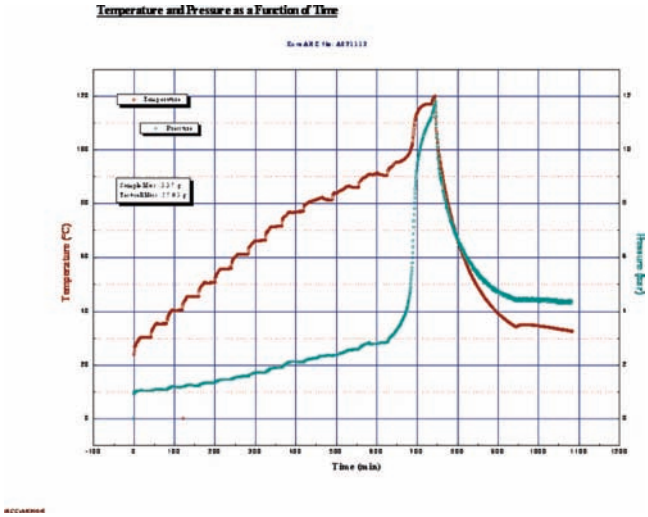


Figure 2. **Temperature and pressure vs time plots for 11 (20% in MTBE).**

The initial safety assessment of MSH (**9**) was done using ARC techniques. ARC experiments (Figure 3) of a mixture of **9** in TFA and DMF showed an exothermic process at 30 °C (starting point of the experiment). Furthermore, we decided to measure the stability of a neat sample of **9** at 30 °C over time, but decomposition was detected at the beginning of the ARC experiment. Since these experiments did not provide enough information about the real onset value and the stability of the reagent at different temperatures, we decided to perform subambient experiments. Several isothermal experiments (isothermal window ± 1 °C) were run by ageing a neat sample at different temperatures for 24 h (−10, 0, and 10 °C). The results showed no exotherms at these temperatures (Figure 4).

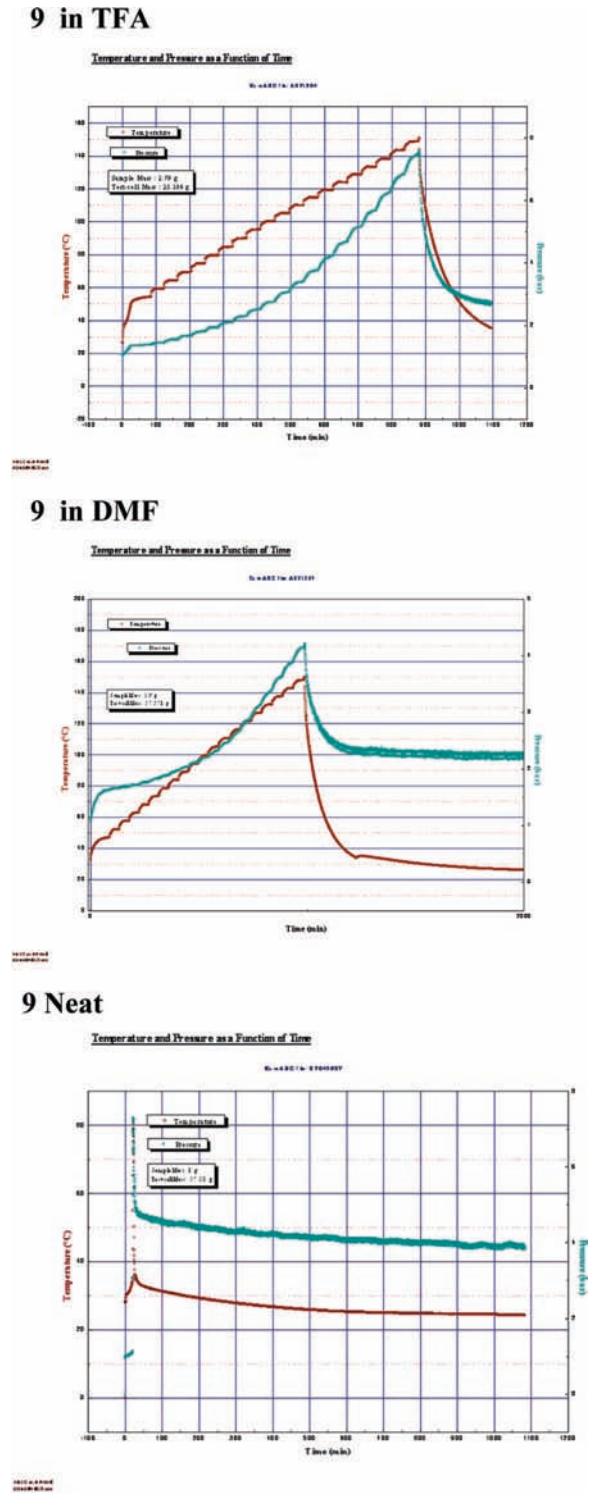


Figure 3. **Temperature and pressure vs time plots for 9 (20% in TFA or DMF) and neat.**

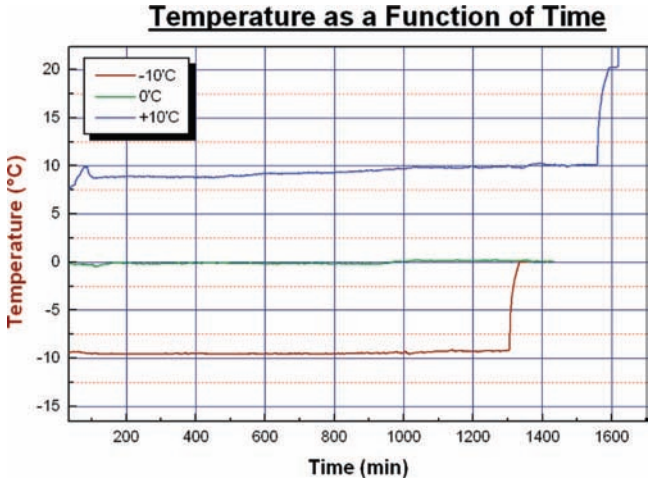


Figure 4. **Isothermal experiments at −10, 0, and 10 °C.**

Finally, a typical ARC experiment was performed starting at 10 °C and heating the sample to 250 °C using a heat step of 10 °C (Figure 5). The first onset was detected at 41.5 °C (temp rate 0.05 °C/min) with a maximum temp rate of 54.5 °C/min at 78.4 °C (Figure 6). This onset turned out to be higher than expected from our initial observations, but it was also in the borderline for the safety range of the ARC technique. The predicted TMR data (phi corrected, Figure 7) gave us tentative storage conditions for temperatures below the first onset point. These experiments helped us to make a positive decision about the scale-up and possible short-term storage of MSH.

According to literature reports and our previous experience with MSH, the safest method for the isolation of this reagent was to precipitate from water and filter without extensive drying in order to keep the material wet. Moreover, this material had to be stored in a freezer until use. Upon storage conditions, the solid slowly turned into an oil, and the purity of the material dropped. We had also observed that the maximum storage time decreased when water content was lower, and drier samples decomposed after only 24 h storage.

In order to quantify this empirical finding we designed a DSC study with samples of MSH with different water contents to obtain a qualitative relationship between percentage of water and stability. Two samples were selected: sample A with 40% of water and sample B with 15% of water. (Purity of every sample was calculated by quantitative NMR.[10]) As the following DSC graph (Figure 8) clearly indicates, there is 14−15 °C onset *T* difference between sample A and sample B. The result totally confirmed our observation that water content enhances MSH stability.

So, as it is described in the Experimental Section, we decided to carry out the isolation of MSH from water and filter the cake to eliminate the water excess (this procedure provided a water content of 30−40%) and store the material in a plastic bottle in the freezer for 1−2 h before immediate use in the 1,3-dipolar cycloaddition. We have employed this protocol for the preparation of 1.7 kg of MSH without any issue.

4. Conclusions

In conclusion, we have evaluated the stability of a high energy reagent and concluded that the use of a wet batch increased its stability and provide us the possibility to use it safely in 1.7 kg scale. Material should be used either in solution

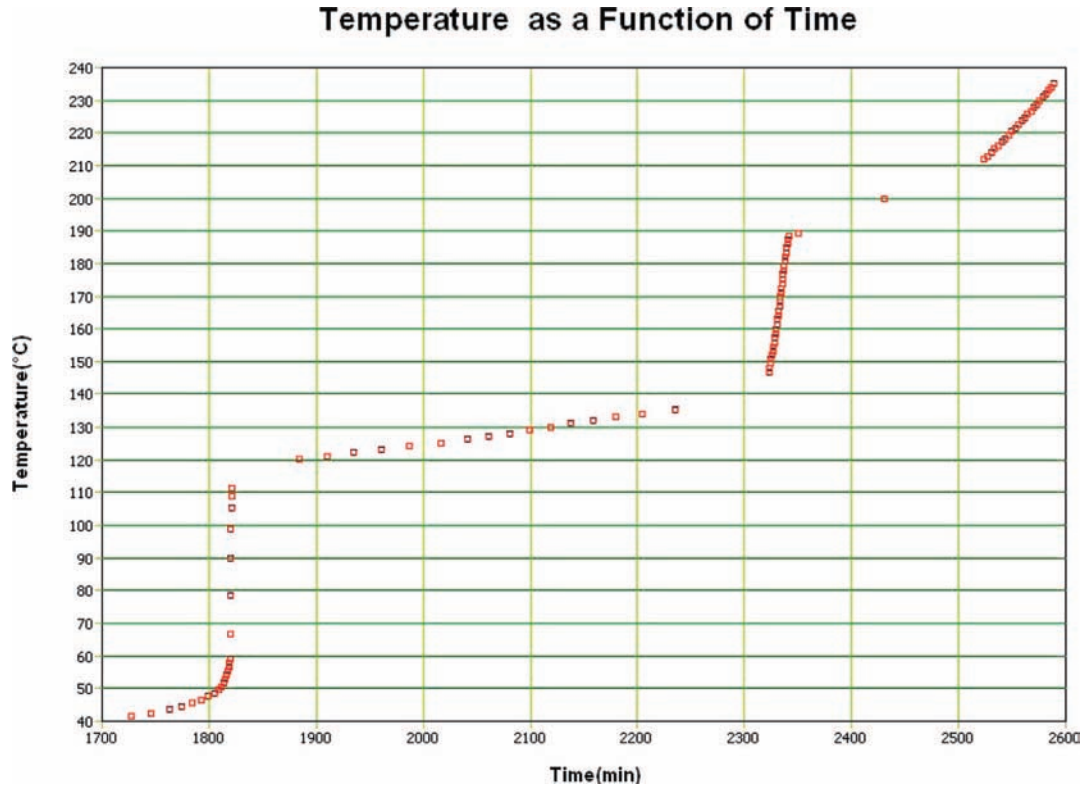


Figure 5. **Temperature vs time plot for 9 (neat).**

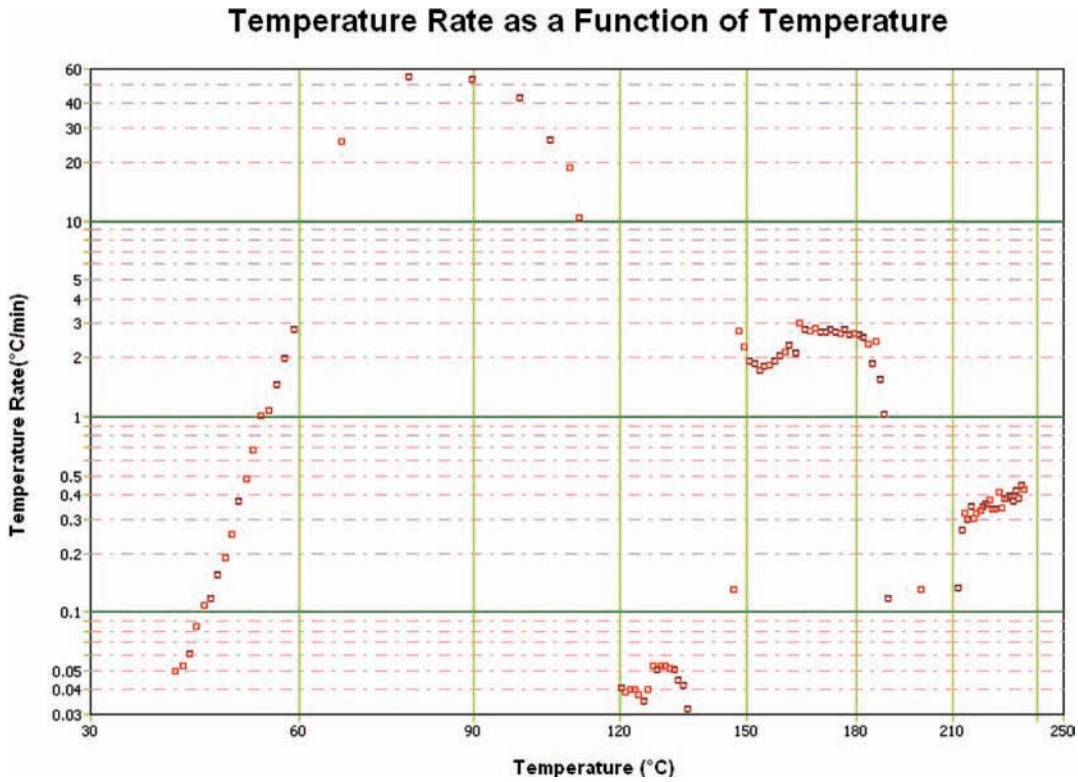


Figure 6. **Temperature rate vs temperature plot for 9 (neat).**

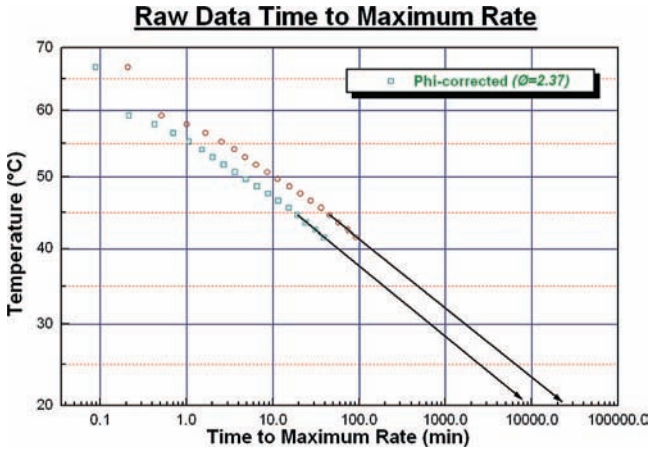


Figure 7. **Predicted TMR data for 9 (neat).**

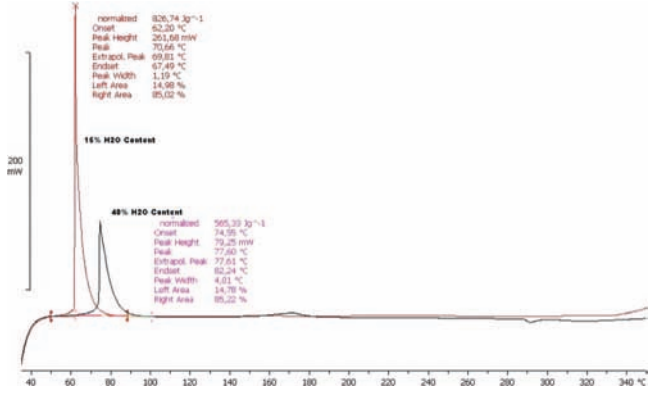


Figure 8. **DSC plots for 9 with 15% and 40% of water.**

or as wet crystalline solid and the neat molten liquid form should be avoided, as it would evolve heat on crystallization. For this reagent, long storage should be avoided and the material should be generated when needed.[11] Due to the demonstrated hazard potential of the reagent and the difficulty to manage larger amounts of compound quickly to avoid storage, we do not recomend the preparation of the reagent in larger than kg scale. If no substitute is found for the reagent, it must be considered to perform the corresponding transformation in several batches up to 1.7 kg scale.

5. Experimental section

Analytical Conditions. ^{1}H NMR spectra were acquired on a Brucker Avance DPX 300 MHz spectrometer. HPLC/MS was used for the determination of reaction conversion on a series 1100 liquid chromatography/mass selective detector LC/MSD (Agilent, Waldbronn, Germany) driven by ChemStation software (Rev. A10.02, Agilent Technologies).

***N*-Boc-*O*-mesitylenesulfonylhydroxylamine (Boc-MSH, 11).** 2-Mesitylenesulfonyl chloride (1200 g, 1.00 equiv; 5.43 mol; 1.20 kg) and *tert*-butyl *N*-hydroxycarbamate (1 equiv; 1.00 equiv; 5.43 mol; 738.02 g) were dissolved in *m*-methyl *tert*-butyl ether (12.5 L). The mixture was purged with nitrogen and cooled to 0 °C. Triethylamine (772.27 mL, 560.67 g, 5.54 mol) was added dropwise with stirring at 1 °C (time of addition: 1 h 30 min, final temperature: 10 °C). The mixture was stirred

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for 2 h after addition. The reaction was monitored by TLC (*n*-hexane (ethyl acetate 7:3). After 2 h, internal temperature was 4 °C. Et_3NHCl was filtered at the pump and washed with MTBE (4 L). Liquid phase was concentrated *in vacuo* at 20 °C and 150 mmHg until ∼1 L of MTBE was left. *n*-Hexane (6 L) was added at 20 °C and 760 mmHg. After 5 min stirring a white solidappeared, and it was filtered and washed with *n*-hexane (2 L). The liquid phase was concentrated, and more *n*-hexane was added (2 L). The solid was filtered and combined with the first one to give carbamic acid (**11**), *N*-Boc-*O*-mesitylenesulfonylhydroxylamine (1705.85 g, 99.57% yield) as a white solid.

***O*-Mesitylenesulfonylhydroxylamine (MSH, 9).** Trifluoroacetic acid (5 L) was cooled to 2 °C. Carbamic acid, *N*-Boc-*O*-mesitylenesulfonylhydroxylamine (**11**) (1695 g, 5.37 mol) was added portionwise over 1 h. Reaction was stirred at 2 °C for 90 min and monitored by TLC (*n*-hexane/ethyl acetate 8:2). After 90 min, TLC showed completed conversion. Crushed ice was added (∼2 L) followed by water (4 L), increasing the internal temperature to 2 °C. A white solid appeared while the internal temperature increased to 8 °C. Additional ice/cold water was added (6 L). After 15 min, the solid was filtered, washed with water (20 L) until the pH ≈ 7, and dried of excess water for 15 min. *O*-Mesitylenesulfonylhydroxylamine (MSH, **9**) (1747 g, 151,00% yield) was isolated as a white solid. This material contained 33% of water, and the material was stored in plastic bottles in the freezer for 2 h.

Safety Evaluation of MSH (9) and MSH-Boc (11) Derivatives. ARC experiments were recorded in accelerating rate calorimeter equipment purchased from Thermal Hazard Technologies. Experiments were run by weighing an appropriate sample (3−5 g) of the compound to be tested using 1/4 Hastelloy bombs (temp rate 5 °C/min).

Differential scanning calorimetry of MSH samples was performed using a Mettler DSC 823e (Mettler-Toledo Instrument AG, Switzerland). It was calibrated using an indium pellet. For the analysis, 3−8 mg of solid samples and sealed 40 μL high-pressure gold-plated steel crucibles were employed. An empty crucible of the same type was used as reference. DSC runs were performed within the temperature range of 35 to 350 °C at a 10 °C/min rate.

Supporting Information Available

^1H NMR spectra for **9** and **11**. Plots for ARC experiments of **9** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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