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In Situ Preparation and Consumption of *O*-Mesitylsulfonylhydroxylamine (MSH) in Continuous Flow for the Amination of Pyridines

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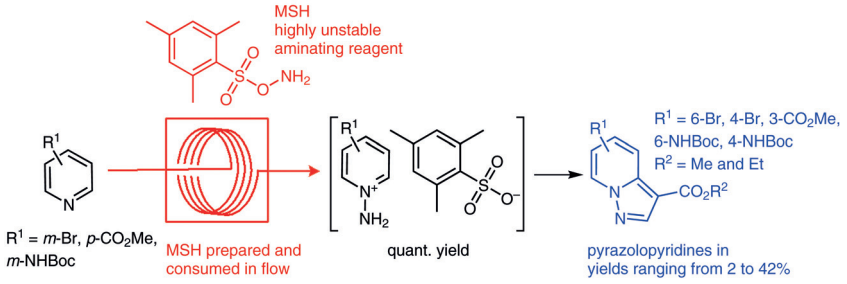

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Abstract The paper demonstrates a safe method in which highly unstable *O*-mesitylsulfonylhydroxylamine (MSH) can be prepared and consumed in continuous flow. MSH was prepared *in situ* and used for the flow amination of a range of pyridines, which were subsequently transformed into useful pyrazolopyridine building blocks.

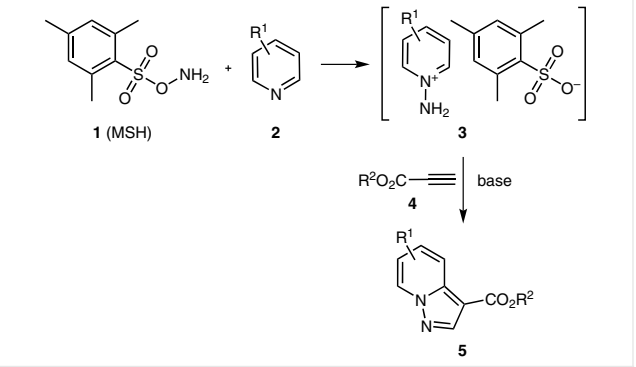
Key words safety, pyrazolopyridines, flow, *O*-mesitylsulfonylhydroxylamine, pyridine

O-Mesitylsulfonylhydroxylamine (MSH, **1**) is a highly unstable reagent, with an onset of decomposition only slightly above room temperature. The stability of **1** is dependent upon its water content; however it is strongly recommended that even damp MSH (containing 40% water) is prepared immediately prior to use and not stored.[1]

Our group was searching for a method in which MSH could be safely used, ultimately on a multi-hundred gram scale, for the amination of pyridines and their subsequent 1,3-dipolar cycloaddition to give pyrazolpyridine building blocks. Pyrazolo[1,5-*a*]pyridines are useful building blocks for medicinal chemistry and have been widely used in a number of medicinal chemistry programs.[2] Given the low thermal stability of MSH, its formation and consumption under continuous flow became an attractive target.

One of the many advantages of flow chemistry is the safe handling of hazardous reagents by minimizing their quantity at a specific time point during a chemical transformation. High-energy reagents can be prepared *in situ* and used immediately in a subsequent transformation.[3] We envisaged that the formation of only a small quantity of MSH in solution at any one time (and avoiding its isolation as a solid), using flow chemistry, would give us a safe method to prepare pyrazolopyridine building blocks for our medicinal chemistry programs.

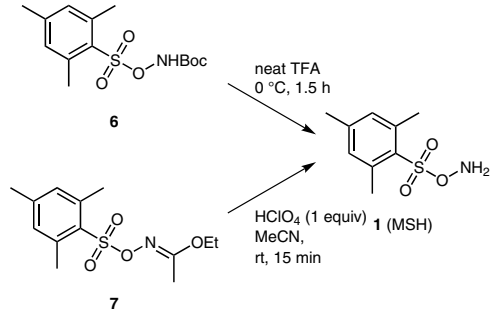
MSH (**1**) has been widely used for the *N*- or *S*-amination of heteroaromatic systems,[4] especially the amination of pyridines **2** followed by cyclization with acetylenes yielding 3-functionalized pyrazolo[1,5-*a*]pyridines **5** (Scheme 1).[5] The corresponding 2-alkyl pyrazolo[1,5-a]pyridinecarboxylates can be prepared by a two-step Knoevenagel/Hemetsberger–Knittel sequence,[6] albeit with associated hazards in handling azido-3-(pyridin-2-yl)acrylates, some of which have been overcome by adaptation to flow.[7]



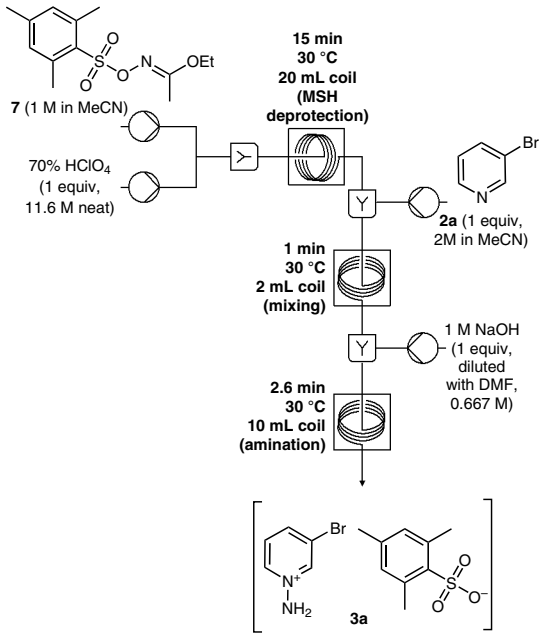
Scheme 1 General scheme for the amination of pyridines and the subsequent cycloaddition with acetylenes **4** yielding pyrazolo[1,5-*a*]pyridines **5**

The advantage of using MSH over other aminating reagents, such as *O*-2,4-dinitrophenylhydroxylamine (DPH),[8] is that MSH reacts rapidly and cleanly in the amination of many pyridines. There are two generally accepted methods for the preparation of MSH (outlined in Scheme 2): (i) deprotection of the Boc-hydroxylamine derivative **6** with TFA (Carpino's method),[9] or (ii) deprotection of the acet-

amide **7** using perchloric acid (Zinner's method).[10] Both Boc derivative **6** and acetimidate **7** are commercially available. The Boc-deprotection is performed in neat TFA and requires 1.5 hours at 0 °C. In contrast, the acetimidate deprotection with perchloric acid only requires one equivalent of acid and is complete within just 15 minutes at room temperature. Both reactions are described in the literature and require quenching into ice cold water, followed by filtration and drying under vacuum.[11] We wanted to avoid the isolation of MSH as a solid and sought to implement both, the formation of MSH and its consumption, in a flow process.



Scheme 2 Preparation of MSH using Carpino's (upper arrow) and Zinner's (lower arrow) methods



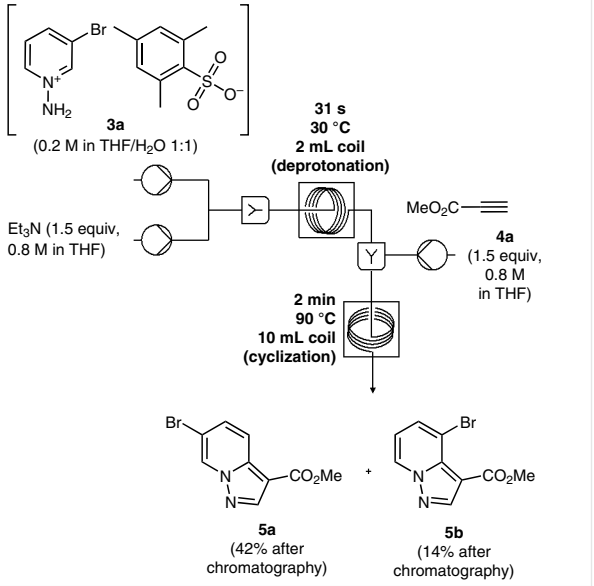
Scheme 3 Optimal set-up for the amination of 3-bromopyridine (**2a**) in flow[13]

The method by which the MSH deprotection and consumption was adapted to flow, using 3-bromopyridine (**2a**) as a model reaction, is detailed in Scheme 3. After multiple batch trials, in which the concentration of reagents and solvents were sequentially changed to check that every compound involved remained in solution, we arrived at the optimized set-up shown (Scheme 3).[12]

A solvent screen revealed that MSH shows reasonable stability over several hours in acetonitrile. Acetimidate **7** (used as a 1 M solution in acetonitrile) was mixed with one equivalent of 70% perchloric acid in the first Y-piece. The MSH formation subsequently occurred in the first reaction coil within 15 minutes at 30 °C. We observed that the thus-formed MSH solution, which still contained one equivalent of perchloric acid, did not react with 3-bromopyridine (**2a**). For this reason, the second coil shown acted as a mixing coil. One equivalent of sodium hydroxide solution was provided by the fourth pump, and in the third reactor, the perchloric acid was quenched and the neutralized MSH reacted rapidly with the pyridine to form the aminated salt **3a**. DMF was added to the incoming sodium hydroxide solution provided by the fourth pump, not only to ensure that the aminated salt **3a** remained in solution, but also to facilitate any subsequent cyclization steps. It should be noted that the rate-limiting step in the whole sequence remained the deprotection step, with all other subsequent steps being inferred by the initial flow rates of the acetimidate **7** and perchloric acid. The power trace for the third reactor (in which the amination occurred) showed that less power was required to heat to 30 °C, indicating an exothermic reaction.

We have been able to show that 1,3-dipolar cycloaddition reactions between the 1-amino-3-bromopyridinium salt **3a** and methyl propiolate (**4a**) can also be adapted to flow (Scheme 4). In the first Y-piece the aminated pyridinium salt **3a** [prepared by mixing 3-bromopyridine (**2a**) and damp solid MSH (**1**)] was mixed with triethylamine, and the deprotonation occurred in the first reactor. In the second Y-piece, methyl propiolate (**4a**) was added, and the cyclization step reached completion in the second reactor coil at 90 °C within just 2 minutes.[14] Pyrazolopyridines **5a** and **5b** were isolated in 42% and 14% yield, respectively (compared to 17% yield of **5a** and 27% yield of **5b** using a batch method).

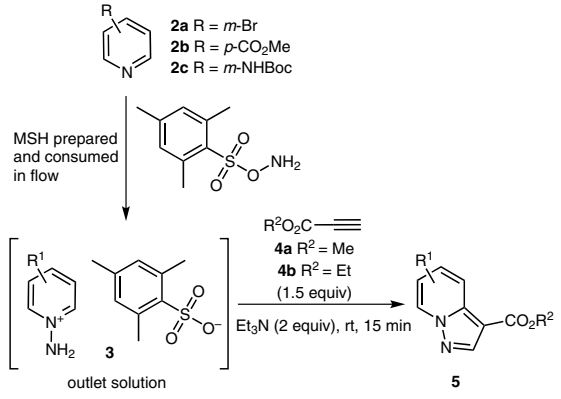
Differential scanning calorimetry (DSC) of the aminated salts **3** showed that the latter undergo decomposition at a considerably higher temperature than MSH [decomposition above 200 °C vs. an exothermic decomposition with an onset at 50 °C for solid MSH (**1**)]. In order to reduce the complexity, and also to reduce the number of pumps required, we did not regard the last deprotonation/cyclization steps as essential to be adapted to flow, because by this point the safety risk of handling explosive MSH has been circumvented. The output solution of aminated pyridine salt **3a** (from Scheme 3) was therefore treated directly with triethyl-



Scheme 4 Flow chemistry deprotonation and cyclization steps to yield pyrazolopyridines **5a** and **5b**

amine and ethyl propiolate (**4b**) in the outlet flask to yield pyrazolopyridines **5c** and **5d** in 29% combined yield (Table 1, entries 1 and 2).

Table 1 Yields of Pyrazolopyridines via Flow Amination and Batch Cyclization

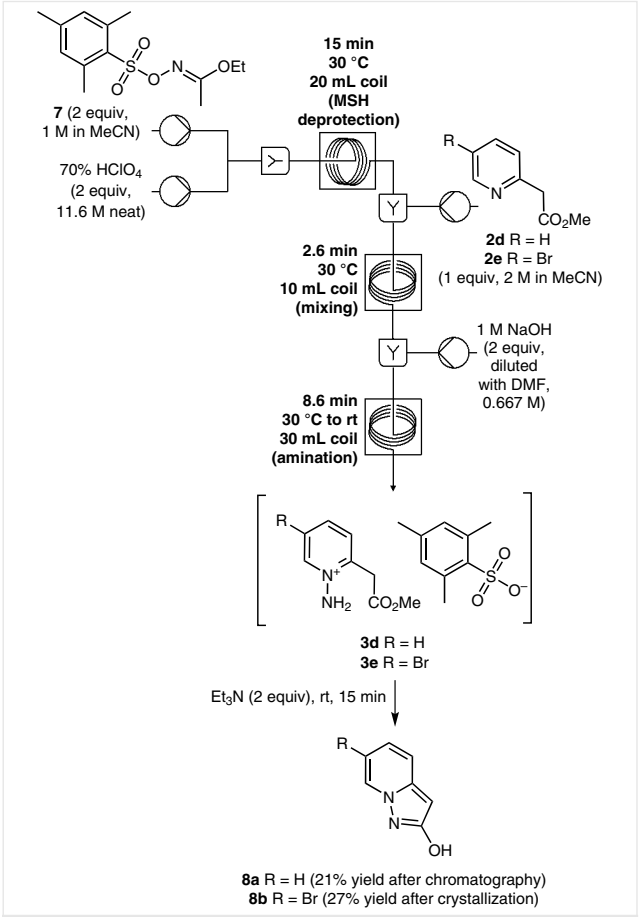


Entry	Product	R^1	R^2	Yield (%)
1	**5c**	6-Br	Et	11
2	**5d**	4-Br	Et	18
3	**5e**	3-CO_2Me	Me	24
4	**5f**	6-NHBoc	Et	2
5	**5g**	4-NHBoc	Et	23

Three substituted pyridines (**2a**, **2b** and **2c**) were treated under our optimized conditions shown in Scheme 3 to yield pyrazolopyridines **5c–g** shown in Table 1. Although the yields are modest, they are not far away from those observed in the literature (20–40% yield).[2a] The productivity of pyrazolopyridine **5e** (Table 1, isolated by direct filtration of the reaction mixture quenched into water) was 4.2 grams per hour using the flow methodology, which demonstrates that useful quantities of difficult-to-obtain scaffolds can be prepared in a safe and efficient manner, on a gram scale using a lab flow machine.

Pyrazolopyridines **5a–d** (Scheme 4 and Table 1, entries 1 and 2) are useful heterocyclic intermediates in which the bromo-handle provides the possibility of diversification via, for example, palladium-catalyzed coupling reactions.[2b] The amino-substituted pyrazolopyridines **5f** and **5g** (Table 1, entries 4 and 5) provide a branching point for amide couplings, reductive aminations or conversion into halides via Sandmeyer chemistry.

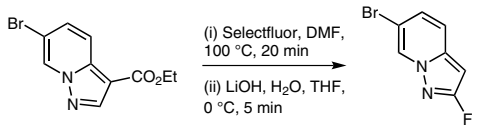
Our flow methodology to prepare MSH *in situ* has also been used to aminate methyl 2-(pyridin-2-yl)acetate (**2d**) and methyl 2-(5-bromopyridin-2-yl)acetate (**2e**) under continuous flow conditions. Both undergo an intramolecu-



Scheme 5 Amination of methyl 2-(pyridin-2-yl)acetate (**2d**) and methyl 2-(5-bromopyridin-2-yl)acetate (**2e**) with subsequent intramolecular ring closure

lar cyclization to give pyrazolopyridin-2-ol (**8a**) and 6-bromopyrazolopyridin-2-ol (**8b**) in 21% and 27% yield, respectively, after purification. In contrast to previous examples for pyrazolopyridine formation by intermolecular cyclization, an excess of MSH (**1**) was shown to give higher yields of product in the intramolecular case. For this reason, two equivalents of acetimidate **7**, perchloric acid and sodium hydroxide solution were used for the transformations shown in Scheme 5. We also observed that the amination of pyridines **2d** and **2e** was much slower than that of pyridines **2a–c**, and a longer reaction coil (30 mL) was required in the third reactor. Without the longer third coil, decomposition of MSH occurred in the back-pressure regulator before it had a chance to aminate the pyridine.

Fluorinated heterocyclic cores are privileged structures in medicinal chemistry;[15] however, little is known about the preparation of 2-fluoropyrazolopyridines in the literature. We have therefore demonstrated that pyrazolopyridine-3-carboxylate **5c** prepared in flow can be fluorinated using Selectfluor at 100 °C, followed by saponification and decarboxylation to yield 2-fluoropyrazolopyridine **9** (Scheme 6) in high yield.



5c **9** (91% yield)

Scheme 6 Fluorination and decarboxylation of pyrazolopyridine-3-carboxylate **5c**

In conclusion, we demonstrated a safe method in which MSH (**1**) can be prepared and consumed in continuous flow and showed how this method can be applied to the synthesis of pyrazolopyridine building blocks.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1588799.

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(11) When MSH (**1**) was isolated as a damp solid and analyzed by ion chromatography, no anions were observed, indicating the formation of free MSH and not a salt.

(12) It should be noted that, when damp solid MSH was dissolved in acetonitrile and pumped through the Vapourtec Knauer pump heads, decomposition occurred presumably due to the mechanical action of the pistons. Both the batch and the flow deprotection of **7** required 15 minutes. Warming of the first reaction coil above 30 °C resulted in the decomposition of MSH. Combining the inlet solutions of pyridine **2a** and sodium hydroxide was not tolerated and also resulted in decomposition.

(13) **1-Aminopyridin-1-ium 2,4,6-trimethylbenzenesulfonate Salts 3, General Flow Procedure**
All reactions were performed using a commercially available Vapourtec R-series set-up equipped with four pumps. (*E*)-Ethyl *N*-(mesitylsulfonyl)oxyacetimidate (**7**) was dissolved in MeCN (1 M) and filtered. Perchloric acid (neat, 11.6 M) was mixed with the first inlet via a Y-piece with flow rates of 1.228 mL/min and 0.106 mL/min, respectively. Pyridine **2** was dissolved in MeCN (2M), filtered and introduced into a second Y-piece at a flow rate of 0.614 mL/min. Sodium hydroxide (1 M, aq.) was diluted with DMF to a concentration of 0.667 M and introduced in a third Y-piece at a flow rate of 1.840 mL/min. The stoichiometric ratio of all four inlets was 1:1:1:1. The system solvent was MeCN for the first three inlets and H_2O/DMF (2:1) for the fourth inlet. The PFA (polyfluoroalkoxy alkane polymer) reactor coils, with volumes of 20 mL, 2 mL and 10 mL, respectively, were all set to a temperature of 30 °C. The reaction mixture

from the first two inlet streams had a residency time of 15 min in the first reactor, of 1.02 min in the second and of 2.64 min in the third.

1-Amino-3-bromopyridin-1-ium 2,4,6-Trimethylbenzenesulfonate (3a)

The reaction was performed by adapting the general flow procedure to the reaction of 3-bromopyridine (**2a**) with MSH. The outlet solution (25 mL, collected over 3.6 min) was concentrated in vacuo to give an orange solid (3.6 min collection time, >99%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.18 (s, 9 H, 3 × CH_3), 6.77 (s, 2 H, NH_2), 7.93 (dd, *J* = 4, 8 Hz, 1 H, ArH), 7.95 (s, 2 H, ArH), 8.49 (d, *J* = 8 Hz, 1 H, ArH), 8.81 (d, *J* = 8 Hz, 1 H, ArH), 9.17 (s, 1 H, ArH). ^{13}C NMR (101 MHz, d_6-DMSO): δ = 20.3, 22.7, 121.4, 128.6, 129.9, 135.8, 136.4, 138.6, 141.4, 142.5, 166.0. HRMS (FAB): *m/z* calcd for $C_5H_6BrN_2^+$: 172.97144; found: 172.97105; *m/z* calcd for $C_9H_{11}O_3S^-$: 199.04289; found: 199.04277. DSC showed small exotherm with 61 J/g onset 249 °C and larger exotherm with 573 J/g onset 299 °C.

(14) It should also be noted that combining any of the three inlet solutions, in order to simplify the set-up, led to decomposition and poor yield.

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