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Elucidation of a Sequential Iminium Ion Cascade Reaction Triggered by a Silica Gel-Promoted Aza-Peterson Reaction

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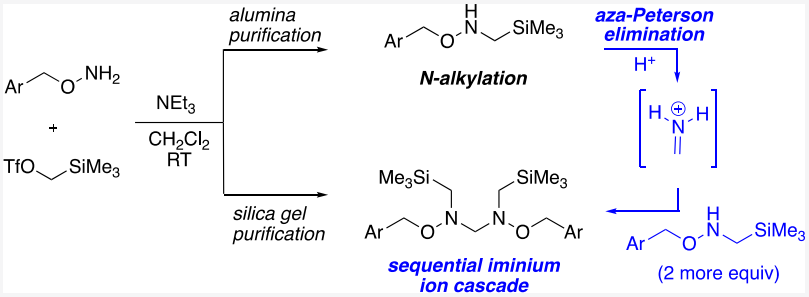

ABSTRACT: In a recent methodological study investigating the synthesis of *N*-alkoxyazomethine ylides, an unexpected aminal byproduct was generated during our attempt to isolate *O*-benzyl-*N*-((trimethylsilyl)methyl)hydroxylamine. After a strategic investigation, silica gel was discovered to be the cause of the byproduct formation. Through the mechanistic insight from control and trapping experiments, we propose the formation of a methaniminium ion via a novel aza-Peterson reaction, which ultimately triggers a sequential iminium ion cascade sequence. Herein, we discuss the elucidation of this cascade reaction mechanism and the constraints for the byproduct formation.

Research often leads to unexpected discoveries that were outside the purview of the original experimental design.[1,2] These opportunities commonly arise as one troubleshoots unknown or poor performing reactions,[3] elucidates unexpected reaction byproducts,[4] or optimizes chromatographic isolation.[5,6] Relevant to this study, chromatography proved to be the key component in uncovering an interesting cascade reaction observed during the purification of the reaction mixture of what was expected to be a simple alkylation. Our story began with a recent investigation in which we sought to explore the synthetic accessibility and reactivities of *N*-alkoxyazomethine ylides, with the objective of accessing complex heterocycles.[7] One aim of this project probed the feasibility of *N*-alkoxyazomethine ylide generation via a Katritzky-inspired benzotriazole methodology.[8,9] The installation of benzotriazole and trimethylsilyl groups was theorized to allow for the facile generation of the active ylide upon heating with a catalytic acid (Figure 1A).

Curiously, during the *N*-alkylation of *O*-benzylhydroxylamine **1a** with trimethylsilylmethyl triflate **2** to generate *O*-benzyl-*N*-((trimethylsilyl)methyl)hydroxylamine **3a**, we observed the formation of a peculiar aminal byproduct **4a** (Figure 1B).[10] The coelution of **4a** with the desired product **3a** was consistently observed when purifying by silica gel column chromatography despite mobile phase and theoretical plate modifications. Intrigued by the persistence of aminal **4a**, we launched an investigation to illuminate its origins, probe its reactivity, and identify the factors that lead to its formation. After strategic troubleshooting guided by various control experiments, we found that the column stationary phase, silica gel, caused the generation of **4a** from the desired alkylation product **3a**. Herein, we disclose our elucidation of the novel cascade reaction of *O*-aryl-*N*-methylsilyl hydroxylamines and discuss the constraints of the transformations (Scheme 1).

The structure of aminal **4a** was established using ^{1}H, ^{13}C, HSQC, and DEPT-135 NMR spectroscopy. A comparison of the ^{1}H NMR spectra of aminal **4a** to those of secondary hydroxylamine **3a** showed similar chemical shift profiles with two main differences (Figure 2). For **4a**, there is a peak at 3.66 ppm, while the N−H peak for **3a** at 5.59 ppm disappeared.[11] The comparison of ^{13}C NMR spectra showed an additional signal at 87.3 ppm for **4a**, while the other signals overlapped (Supporting Information). HSQC analysis revealed that the carbon signal at 87.3 ppm was correlated to the unique **4a** proton. In addition, DEPT-135 analysis revealed this extra carbon to be a CH_2 unit, allowing us to reassign our integrations. The combination of NMR analyses led us to

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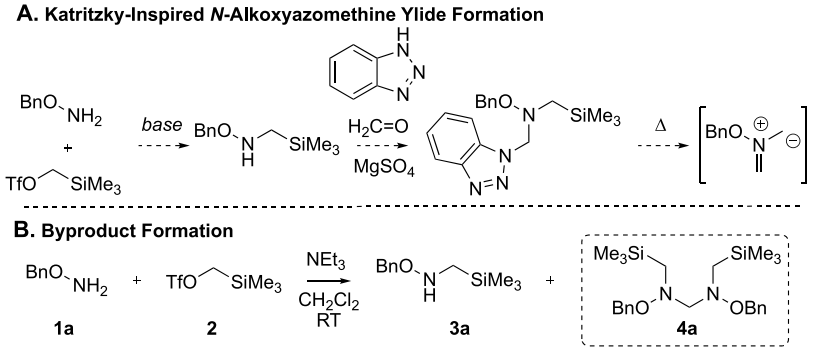
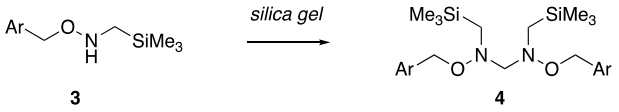


Figure 1. Katritzky-inspired ylide formation (A) and byproduct formation (B).

Scheme 1. Silica Gel-Mediated Cascade Reaction of *O*-Arylmethyl-*N*-(trimethylsilyl)methyl Hydroxylamines



determine the byproduct identity to be compound **4a** with a plane of symmetry. To attempt to corroborate this structure, HRMS analysis of **4a** was performed; however, the parent *m*/*z* peak was not observed. This is not surprising given the anticipated labile nature of the N−O bonds and the unknown stability and reactivity of the aminal. Both **3a** and **4a** are oils at ambient temperatures, preventing any X-ray crystallographic analysis.

Having established its identity, we next sought to understand the origin of aminal **4a**. We hypothesized the alkylation of *O*-benzylhydroxylamine was proceeding as planned to form product **3a**, which then underwent a further reaction to form aminal **4a**. The crude ^{1}H NMR spectra of the reaction showed no aminal formation after aqueous workup nor after solvent removal under vacuum and mild heat. Thus, we were confident that silica gel was the culprit. An additional observation that bolstered this argument was the observed increase in the isolation of **4a** with increasing column length. To test this theory, two identical reactions were run side-by-side, and the products were then purified through elongated columns with different stationary phases, one consisting of alumina and the other of silica gel (Scheme 2). The alumina-based purification gave the desired alkylation product **3a** in a 69% yield, whereas the silica gel-based purification provided aminal **4a** as the only identifiable product isolated in a 39% yield.

Intrigued by this conclusive result, we theorized that the slightly acidic environment at the surface of the silica gel was definitively the root cause.[12] It is known that in the right environment silica gel can act a weak acid, and it has been shown to mediate a variety of transformations, including acetal deprotections,[13,14] esterifications,[15,16] cyclizations,[17,18] and cycloadditions.[19,20] We subsequently ran a short series of control experiments to probe the nature of the acid required. The exposure of **3a** to trifluoroacetic acid (Brønsted acid) or $AlCl_3$ (Lewis acid), even in low concentrations, resulted in the complete degradation of **3a** and no observation of **4a**.[21] However, subjecting **3a** to acetic acid at similar concentrations gave a 57% yield of aminal **4a** after 1 h, and the full consumption of **3a** was observed within 24 h via q-NMR spectroscopy (Scheme 3). In contrast, no aminal formation and minimal degradation were detected in a stirred solution of **3a** in $CDCl_3$ (3 d at 25 °C). These observations collectively provided further evidence that an external weak Brønsted acid was required for the transformation.[22]

Understanding the need for an acid to promote the transformation, we posited a cascade reaction that proceeds mechanistically in two different stages. In the first stage, the 2° hydroxylamine nitrogen is protonated, promoting a rearrangement to reveal the exceptionally reactive methaniminium ion **5** and the transient benzyl trimethylsilyl ether **6** (Figure 3).[23] This transformation is akin to Peterson olefination, in which a *β*-hydroxysilane undergoes the elimination of Si−OH to form a C=C bond in the presence of acid or base.[24−26] In our case,

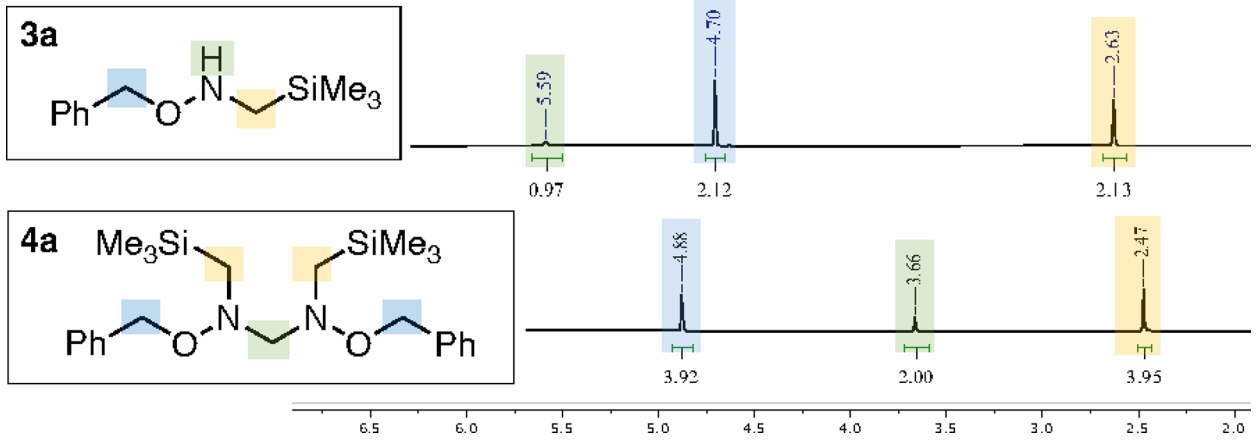


Figure 2. ^{1}H NMR spectra of alkylated hydroxylamine **3a** (top) and aminal **4a** (bottom).

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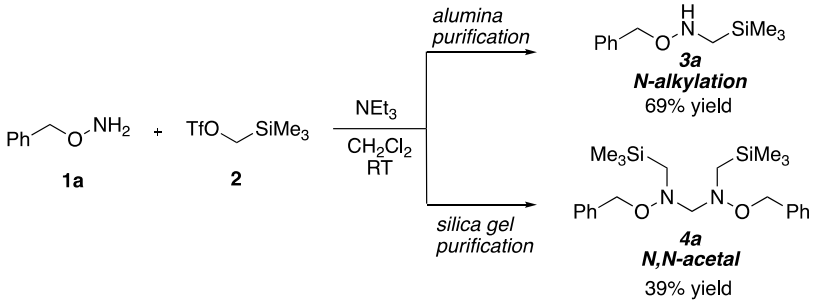
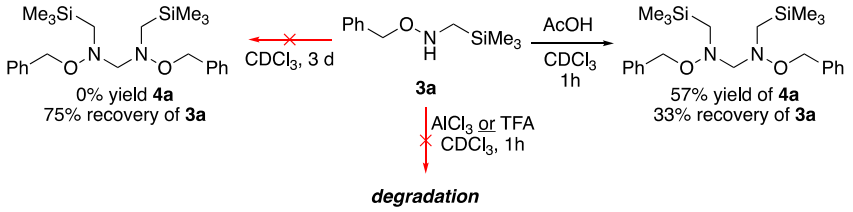
Scheme 2. Alumina vs Silica Gel Separation



Scheme 3. Reactions Probing the Necessity of Acidity for 4a Formation



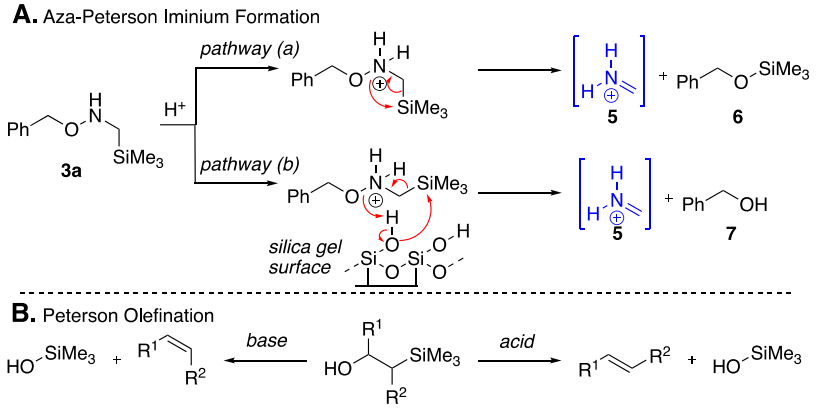


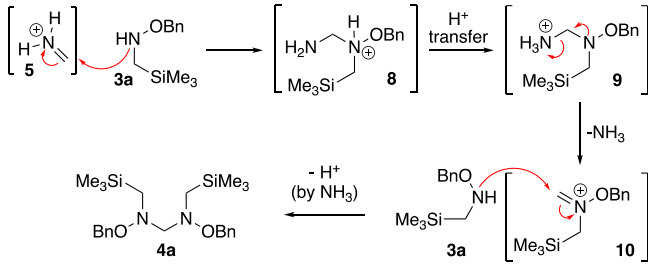
Figure 3. Aza-Peterson iminium formation from **3a** (A) vs classic Peterson olefination (B).

the *O*-benzyl-*N*-(methylsilyl)hydroxylamine presumably undergoes one of two possible pathways: (a) intramolecular silyl-oxygen migration with concurrent N−O cleavage and iminium formation or (b) silica gel-mediated E2-type elimination to form iminium **5**. To the best of our ability, we found no reported examples of Peterson-type eliminations to form iminium ions. Thus, we will further refer to this iminium ion-forming reaction as an aza-Peterson elimination.

In the second stage of the reaction, we propose that the reactive iminium is immediately trapped by a second molecule of 2° hydroxylamine **3a** to form intermediate **8** (Scheme 4). Intermediate **8** undergoes proton transfer to form **9**, which eliminates NH_3 to generate a new iminium ion **10**. Iminium **10** is then trapped by a third molecule of the 2° hydroxylamine **3a**. Finally, the proton loss affords the aminal **4a**. Thus, the overall sequence of reactions can be classified as a sequential iminium ion cascade triggered by silica gel-mediated aza-Peterson iminium ion formation, and requires 3 equiv of 2° hydroxylamine to provide the aminal. To date, this is the first reported example of such a cascade reactivity involving *O*-substituted-*N*-silylmethyl hydroxylamines.

If we assume that the aza-Peterson iminium formation occurs through intramolecular silyl transfer followed by elimination, the cascade reaction is also expected to yield 1

Scheme 4. Second Stage of the Cascade Formation of Aminal 4a



equiv of the corresponding benzyl silyl ether **6** (Figure 3).[23] In the presence of a high excess of silica gel, the deprotection of the TMS silyl ether to benzyl alcohol is expected. Anticipating challenges with the isolation of the benzyl alcohol, we elected to use an analogous derivative for a proof of concept that would afford a more easily isolatable alcohol. *O*-(2-Naphthylmethyl)-*N*-(silylmethyl)hydroxylamine **3b** was synthesized using a known protocol to access naphthyl hydroxylamine **1b**.[27] Naphthyl derivative **3b** was subjected to treatment with silica gel, and the anticipated aminal **4b** from the aza-Peterson-triggered iminium ion cascade reaction was formed

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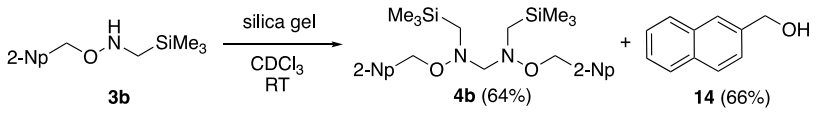
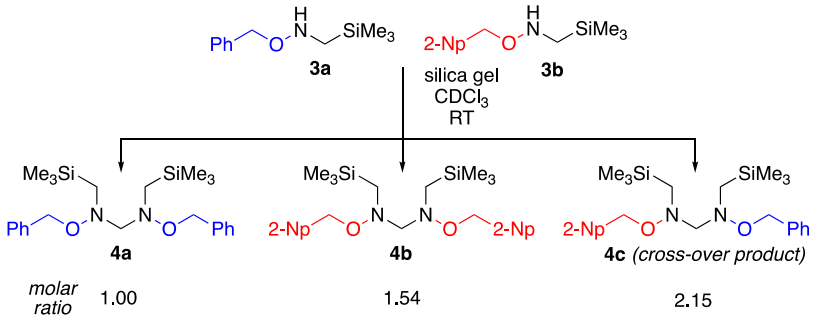
Scheme 5. Reactivity of 2-Naphthylmethyl Derivative 3b



Scheme 6. Cascade Crossover Experiment



and isolated in a 64% yield (Scheme 5). Gratifyingly, the anticipated 2-naphthylmethanol **14** was also isolated in a 66% yield and matched a commercial sample by ^{1}H NMR, GC-MS, and melting point data.

After confirming the conversion of **3b** to **4b**, we sought another way to provide evidence of methaniminium **5** formation. We predicted that the direct observation of **5** would be near impossible, as it is likely too reactive to be directly observed by NMR spectroscopy. Attempts to trap the imine with traditional nucleophilic sources were unsuccessful,[28] so we elected to run a crossover experiment by mixing the *O*-benzyl and *O*-naphthylmethyl hydroxylamines, **3a** and **3b**, respectively, in the presence of silica gel (Scheme 6). In this experiment, if methaniminium ion was generated, each of the homocoupled aminals **4a** and **4b** would be expected to form, as well as the mixed aminal **4c**. A 1:1 mixture of **3a** and **3b** in a silica gel slurry was stirred for 1 h, and the resulting crude reaction ^{1}H NMR spectra show evidence of **4a**, **4b**, and heterocoupled aminal **4c** formation in a 1.00:1.54:2.15 molar ratio.

The most structurally distinct peaks for **4a** and **4b** are the aminal methylene protons and carbons (Figure 4A and B),

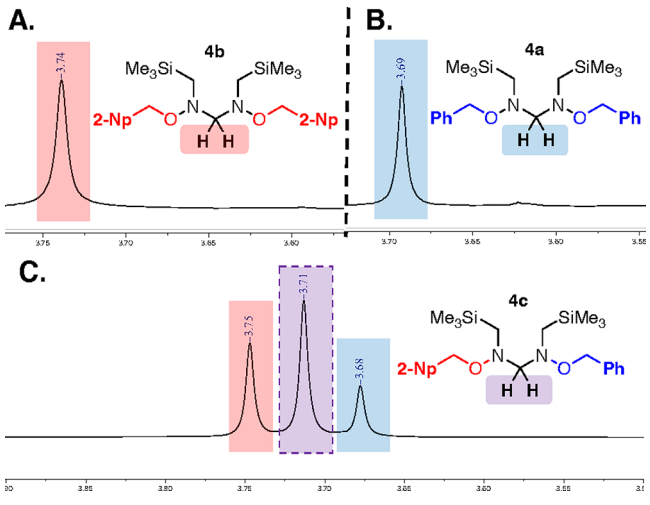


Figure 4. ^{1}H NMR spectra of aminals **4a** (A), **4b** (B), and the crossover reaction mixture for **4c** (C).

whereas in the crude mixture of the crossover experiment a new aminal proton peak appears neatly between the two analogous peaks of **4a** and **4b** (Figure 4C). Attempts at isolating **4c** from the mixture of **4a** and **4b** were unsuccessful,[29] but HSQC analysis of the crude mixture shows the expected peak correlations in regions consistent with both **4a** and **4b**. As additional peak confirmation, known quantities of **4a** and **4b** were added to the crude crossover reaction mixture and appropriately correlated with their assigned peaks (Figure 4C, blue and red peaks, respectively).

Confident that our proposed mechanism for the formation of aminals **4** was logically sound, we were still puzzled by the moderate isolated yields of **4a** observed even when **3a** was fully consumed. An NMR time study found a decreased yield of **4a** with an increased reaction time (3 h or more) on silica gel, suggesting that **4a** itself was susceptible to slow degradation. To probe this notion, a solution of **4a** was left on silica gel overnight, and complete degradation was seen the following day. This made it evident that, like **3a**, **4a** was susceptible to silica gel-promoted reactivity but at a much slower rate. It is conceivable that **4a** could undergo aza-Peterson elimination reactions as a degradation pathway.

Even with reaction times under 3 h, the yields of aminals stayed generally between 40 and 66% without recovering starting material. Crude ^{1}H NMR mixtures showed evidence of other reaction byproducts between 3.0 and 6.0 ppm, and we suspected that these were born from methaniminium **5** polymerizing or reacting through other unidentified pathways. After consulting the literature for known reactivities of methaniminium, particularly valuable insight was gained from a reported NMR study of the reaction of formaldehyde with ammonia to produce hexamethylenetetramine (HMT, **19**, Scheme 7).[30] In that study, Nielsen and co-workers proposed that HMT formation begins when methanimine **5′** is produced from ammonia and formaldehyde. After the nucleophilic attack of another ammonia molecule to give methylene diamine **15**, two additional molecules of **5′** are sequentially attacked by diamine **15** to give triazinane **17** after the loss of ammonia. Further repetition of this aminal formation process eventually produces HMT (**19**).[31] A computational analysis by Zeffiro and co-authors of this proposed mechanism found that the overall process from methanimine **5′** to intermediate **17** has a ΔG value of −17.2 kcal mol^{-1},[32] with the transformation from

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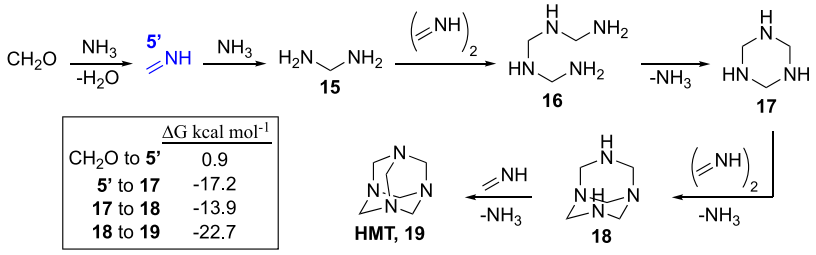
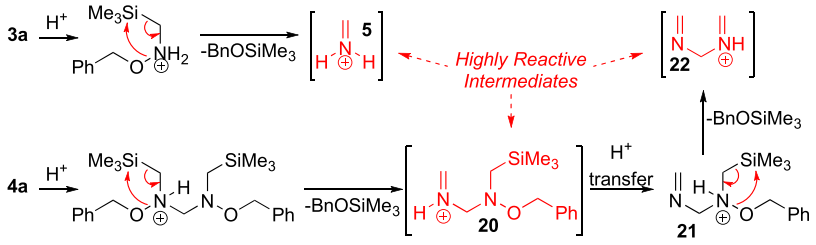
Scheme 7. Nielsen's Proposed Formation of HMT (19) from 5′ and the Supporting Computational Analysis



Scheme 8. Potential Iminium Aza-Peterson Elimination Products



17 to 19 being exothermic as well (−36.6 kcal mol^{-1} over five steps).[33] Zeffiro and co-authors ultimately concluded that Nielsen's proposed argument for HMT formation from 5′ was energetically supported.

This computational work validates our proposal that methaniminium 5 can react with itself to potentially produce a handful of amino-carbon intermediates and products. Attempts at isolating our suspected amino-carbon byproducts were unsuccessful, and subsequent 2D NMR studies on the crude mixtures gave little additional insight. As an alternative method of identification, a commercial sample of HMT was added to our reaction mixtures to observe the peak correlation. This NMR study confirmed that HMT itself was not a component of our crude reaction mixtures despite the similarity of its NMR profile to our observed byproducts.[34] This similarity leaves us suspicious that we are forming either 17 or 18, one of the Nielsen group's observed precursors to HMT.[35] Without the ability to isolate these reaction mixture byproducts or observe them by HRMS,[36] it is difficult to conclusively prove their identity and assess their quantity. As an added complication, once 4a is formed it is also likely susceptible to aza-Peterson elimination (Scheme 8), albeit more slowly. This could in theory produce additional iminium intermediates like 20 and 22 to potentially react with 5, 3a, or one of the many other intermediates in the reaction mixture. Any of these reactions, in competition with the 4a formation pathway, would experimentally result in a reduced yields of 4a while still having a high consumption of 3a, which is consistent with our observed reaction outcomes.

In conclusion, the identification of an unexpected reaction byproduct led to the elucidation of a novel sequential iminium ion cascade sequence that forms aminals from *O*-(arylmethyl)-*N*-(trimethylsilyl)methyl hydroxylamines. The ensuing investigation of solid-phase media, in the pursuit of uncovering the reaction origin and mechanism, serves as a humbling reminder of silica gel's potential to play a noninnocent role in reaction outcomes. Furthermore, the observed reaction pathway represents a new reactivity for 2° hydroxylamines and highlights the potential of these hydroxylamines to serve as an iminium precursor for the development of novel cascade processes.

EXPERIMENTAL SECTION

General Information. Chromatographic purification was performed as flash chromatography with either Silicycle silica gel (40−65 μm) or Dynamic Adsorbents Inc. neutral alumina gel (50−200 μm) and solvents indicated as the eluent with a 0.1−0.5 bar pressure. For flash chromatography, technical-grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on Sorbent Technologies Alumina N UV_{254} (250 μm) TLC glass plates or Silicycle SiliaPlate TLC silica gel F254 (250 μm) TLC glass plates. Analytical plate media always matched the media of solid-phase purification. Visualization was accomplished with UV light. Proton, carbon, and silicon nuclear magnetic resonance spectra (^{1}H NMR; ^{13}C NMR, 1D and 2D experiments; and ^{29}Si NMR, respectively) were recorded on a Varian Mercury Vx 300 MHz spectrometer or a Bruker 500 MHz spectrometer with solvent resonances (^{1}H NMR, $CDCl_3$ at 7.26 ppm; ^{13}C NMR, $CDCl_3$ at 77.0 ppm) or Me_4Si (^{29}Si NMR, 0 ppm) as the internal standard. MestReNova (ver. 14.0) was used to analyze NMR spectra. ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet, and br = broad), coupling constants (Hz), and integration. Both ^{13}C NMR and ^{29}Si data were recorded as proton-decoupled spectra. Infrared (IR) spectra were obtained on a Thermo Nicolet iS10 FTIR spectrometer and analyzed using OMNIC software. Mass spectra were obtained with a MicroMass Autospec M instrument. The accurate mass analyses were run in the ESI mode at a mass resolution of 10 000 using PFK (perfluorokerosene) as an internal calibrant. Compounds 1a, 2, 11, 12, 15a, 15b, and 17 were purchased from commercial sources and used without further purification.

General Procedure for the Preparation of *O*-Aryl-*N*-((trimethylsilyl)methyl)hydroxylamine Derivatives (3). *O*-Arylhydroxylamine (1) (8.12 mmol, 2.0 equiv) was dissolved in CH_2Cl_2 (81 mL). To this was added triethylamine (1.13 mL, 8.12 mmol, 2.0 equiv), followed by (trimethylsilyl)methyl trifluoromethanesulfonate 2 (0.813 mL, 4.06 mmol, 1.0 equiv) and stirred at 25 °C for 16 h. The crude reaction mixture was concentrated and purified via alumina chromatography.

O-Benzyl-N-((trimethylsilyl)methyl)hydroxylamine (3a). From *O*-benzylhydroxylamine (1a); clear oil, 0.585 g, 2.79 mmol, 69% yield (1% EtOAc/hexanes, R_f = 0.53): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.29 (m, 5H), 5.59 (s, 1H), 4.70 (s, 2H), 2.63 (s, 2H), 0.05 (s, 9H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 138.1, 128.5, 128.3, 127.7, 75.1, 43.7, −2.3; ^{29}Si {^{1}H} NMR (99 MHz, $CDCl_3$) δ −1.91; IR

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(cm^{-1}) 2954 (m), 1248 (s), 1026 (br), 840 (s); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{11}H_{19}NOSi$ 210.1309, found 210.1306.

*O-(Naphthalen-2-ylmethyl)-N-((trimethylsilyl)methyl)-hydroxylamine (**3b**).* From *O*-naphthalen-2-ylmethyl hydroxylamine (**1b**); clear oil, 0.864 g, 3.33 mmol, 82% yield (1% EtOAc/hexanes, R_f = 0.24): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92−7.78 (m, 4H), 7.60−7.43 (m, 3H), 4.89 (s, 2H), 2.68 (s, 2H), 0.07 (s, 9H); ^{13}C {^{1}H} NMR (126 MHz, $CDCl_3$) δ 135.7, 133.3, 133.0, 128.02, 127.96, 127.7, 127.3, 126.6, 126.0, 125.9, 75.2, 43.8, −2.3; IR (cm^{-1}) 3055 (w), 2953 (m), 1248 (s), 1037 (w); HRMS (ESI/QTOF) m/z $[M + H]^+$ calcd for $C_{15}H_{21}NOSi$ 260.1465, found 260.1457.

General Procedure for the Preparation of *N,N′*-Methylenebis(*O*-arylmethyl-*N*-((trimethylsilyl)methyl)-hydroxylamine) Derivatives (4). *O*-Arylmethyl-*N*-((trimethylsilyl)methyl)hydroxylamine (**3**, 100 mg) was loaded onto a preparative TLC plate with minimal CH_2Cl_2 and left to dry for 20 min. The plate was eluted with 5% EtOAc/hexanes twice, and the topmost band was removed and extracted with CH_2Cl_2. The solvent was removed *in vacuo* to reveal the product as an oil.

*N,N′-Methylenebis(O-benzyl-N-((trimethylsilyl)methyl)-hydroxylamine) (**4a**).* From *O*-benzyl-*N*-((trimethylsilyl)methyl)-hydroxylamine (**3a**); clear oil, 25.6 mg, 0.062 mmol, 39% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.28 (m, 10H), 4.88 (s, 4H), 3.66 (s, 2H), 2.47 (s, 4H), 0.08 (s, 18H); ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$) δ 137.8, 128.8, 128.2, 127.6, 87.3, 75.3, 49.4, −1.4; ^{29}Si {1H} NMR (99 MHz, $CDCl_3$) δ −1.52; IR (cm^{-1}) 3032 (w), 2954 (s), 2900 (m), 1249 (s), 1037 (w), 859 (s); HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{23}H_{38}O_2N_2Si_2$ 430.2472, found 222.1307 and 210.1307 (m/z parent ion not found).

*N,N′-Methylenebis(O-(naphthalen-2-ylmethyl)-N-((trimethylsilyl)methyl)hydroxylamine) (**4b**).* From *O*-(naphthalen-2-ylmethyl)-*N*-((trimethylsilyl)methyl)hydroxylamine (**3b**); clear oil, 65.7 mg, 0.124 mmol, 64% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84−7.77 (m, 8H), 7.51 (dd, J = 8.2, 1.7 Hz, 2H), 7.47−7.44 (m, 4H), 5.07 (s, 4H), 3.74 (s, 2H), 2.54 (s, 4H), 0.10 (s, 18H); ^{13}C {1H} NMR (126 MHz, $CDCl_3$) δ 135.4, 133.3, 133.0, 127.9, 127.9, 127.7, 127.4, 126.8, 125.2, 125.8, 87.2, 75.3, 49.4, −1.3; IR (cm^{-1}) 3056 (w), 2953 (m), 2900 (m), 1249 (s), 1046 (w); HRMS (ESI) m/z $[M + Na]^+$ calcd for $C_{31}H_{42}O_2N_2Si_2Na$ 553.2677, found 553.2663.

*2-(Naphthalen-2-ylmethoxy)isoindoline-1,3-dione (**13**).* To a flask containing *N,N*-dimethylformamide (45 mL) was added *N*-hydroxyphthalimide (**12**) (3.69 g, 22.6 mmol) and triethylamine (3.15 mL, 22.6 mmol). The deep red solution was stirred at 25 °C for 10 min. 2-(Bromomethyl)naphthalene (**11**) (5.00 g, 22.6 mmol) was added slowly, and mixture was left for 12 h. The resulting suspension was chilled to 0 °C and filtered, washing repeatedly with water. The solid was vacuum-dried to give clean 2-(naphthalen-2-ylmethoxy)-isoindoline-1,3-dione (5.48 g, 18.07 mmol, 80% yield) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98−7.95 (m, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 7.2 Hz, 2H), 7.82 (dd, J = 5.4, 3.1 Hz, 2H), 7.77−7.72 (m, 3H), 7.52 (s, 2H), 5.41 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 163.6, 134.5, 133.7, 133.0, 131.2, 129.4, 128.9, 128.5, 128.2, 127.8, 127.1, 126.7, 126.3, 123.5, 80.0; HRMS(ESI/QTOF) m/z $[M + H]^+$ calcd for $C_{19}H_{13}NO_3$ 304.0895, found 304.0961.[27]

*O-(Naphthalen-2-ylmethyl)hydroxylamine (**1b**).* To a flask with ethanol (12 mL) was added 2-(naphthalen-2-ylmethoxy)isoindoline-1,3-dione (1.09 g, 3.59 mmol). To this hydrazine monohydrate (1.05 mL, 21.56 mmol) was added and stirred at 25 °C for 1 h. The suspension was filtered, and the crude filtrate was concentrated. The crude mixture was purified via silica gel chromatography (30% EtOAc/hexanes, R_f = 0.30) to provide *O*-(naphthalen-2-ylmethyl)-hydroxylamine (0.54 g, 3.12 mmol, 87% yield) as a white solid (mp 56−59 °C): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95−7.80 (m, 4H), 7.59−7.44 (m, 3H), 5.46 (s, 2H), 4.88 (s, 2H); ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$) δ 134.9, 133.3, 133.2, 128.3, 128.0, 127.7, 127.4, 126.2, 126.1, 78.1; IR (cm^{-1}) 3287 (s), 3054 (w), 1582 (m); HRMS (ESI/QTOF) m/z $[M + H]^+$ calcd for $C_{11}H_{11}NO$ 174.0913, found 174.0910.[27]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02102.

^{1}H NMR spectra for known compounds and NMR (^{1}H, ^{13}C, HSQC, and DEPT, where applicable) spectra for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(11) The N−H peak at 5.59 ppm was observed only at certain concentrations and was not a diagnostic peak for the product identity.
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(22) The loss of **3a** is likely due to slow N−O bond cleavage. Samples of **3a** that were kept neat over a period of several weeks were not subject to this observed slow degradation.
(23) Reaction monitoring of the conversion of **3a** to **4a** in the presence of acetic acid by ^{29}Si NMR shows the presence of new silyl derivatives, but their identities could not be readily characterized or confirmed as standards for direct comparison were inaccessible (^{29}Si spectra can be found in the Supporting Information).
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(34) The ^{1}H NMR chemical shift of HMT did match an unknown reaction peak (4.72 ppm in $CDCl_3$); however, its ^{13}C NMR chemical shift was distinctly different from any reaction byproduct.
(35) Unfortunately, the only reported NMR data for key intermediates **16** and **17** were from Nielsen's NMR study where materials were reported in D_2O. This prevented the direct comparison of these intermediates to our crude reaction mixture by the chemical shift.
(36) These hypothetical intermediates are below the limit of detection for our available HRMS instrument.

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