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PII: S0040-4020(16)30100-4

DOI: 10.1016/j.tet.2016.02.038

Reference: TET 27508

To appear in: *Tetrahedron*

Received Date: 3 February 2016

Revised Date: 17 February 2016

Accepted Date: 18 February 2016

Please cite this article as: Medina JM, Jackl MK, Susick RB, Garg1 NK, Synthetic Studies Pertaining to the 2,3-Pyridyne and 4,5-Pyrimidyne, *Tetrahedron* (2016), doi: 10.1016/j.tet.2016.02.038.

Graphical Abstract

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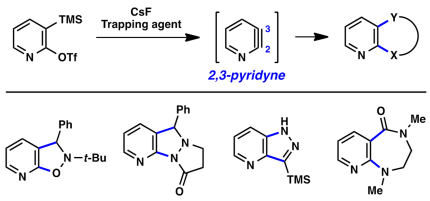

Tetrahedron
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Synthetic Studies Pertaining to the 2,3-Pyridyne and 4,5-Pyrimidyne

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
heterocycles
hetarynes
pyridine
pyridyne
pyrimidyne

ABSTRACT

We report synthetic studies pertaining to two heterocyclic aryne intermediates: the 2,3-pyridyne and the 4,5-pyrimidyne. First, a 2,3-pyridyne precursor was readily accessed from 2-pyridone using a known procedure. Subsequently, 2,3-pyridyne generation and trapping were used to access several functionalized pyridines in a regioselective manner. In addition, we report synthetic routes to two isomeric silyltriflates, which were intended to serve as precursors to the 4,5-pyrimidyne. Consecutive 4,5-pyrimidyne generation and trapping experiments were ultimately deemed unfruitful. We expect these findings will promote the use of 2,3-pyridyne and other heterocyclic arynes as building blocks for the synthesis of functionalized heterocycles.

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1. Introduction

The synthesis of heterocycles continues to be a vital area of research. Heterocycles, especially *N*-containing compounds, are commonly seen in a variety of important molecules including medicines, natural products, and agrochemicals.[1] One exciting approach to the synthesis of decorated heterocycles involves the trapping of in-situ generated heterocyclic arynes, commonly referred to as hetarynes.[2,3] This strategy was well studied several decades ago,[4] but only led to modest synthetic utility.

More recently, the chemistry of heterocyclic arynes has undergone a revival. Methodological studies pertaining to indolynes[5,6] and 3,4-pyridynes[7] have been disclosed and several silyltriflate precursors to these intermediates are now commercially available.[8] Moreover, heterocyclic arynes have been used to synthesize several natural products (e.g., **1**–**4**, Figure 1).[2,9,10] One particularly attractive subclass of heterocyclic arynes are those that possess one or more nitrogen atoms in a 6-membered ring (e.g., **5**–**7**). The successful generation and trapping of such species via cycloaddition processes would provide a powerful means to build medicinally privileged scaffolds, including compounds that may be difficult to access by other means.

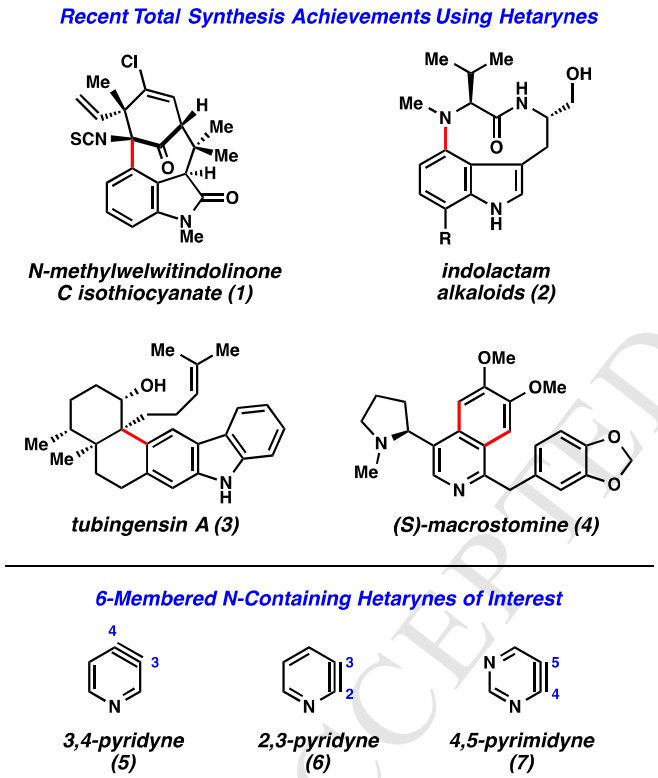


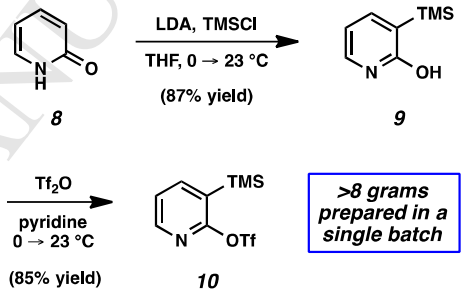
Figure 1. Natural products **1**–**4** synthesized using heterocyclic arynes and hetarynes **5**–**7**.

We have been particularly interested in the chemistry of pyridynes and pyrimidynes, each of which are classes of heterocyclic arynes with an interesting history. The 3,4-pyridyne (**5**) was first generated in 1955[11] and has subsequently been the subject of numerous investigations, including one by our own laboratory.[7] The 3,4-pyridyne and substituted versions can now be used to access polysubstituted pyridines in a controlled and predictable way by virtue of the aryne distortion model,[5,12] using robust silyltriflate precursors.[7] Similarly, the 2,3-pyridyne (**6**) has been known for several decades.[13] In more recent efforts, Walters and Shay reported the synthesis of a silyltriflate precursor to **6**.[14] In turn, a few examples where **6** can be used in Diels–Alder reactions or other annulations are available.[14,15,16,17,18,19] The least well-studied of our targets is the 4,5-pyrimidyne (**7**). Substituted derivatives have been accessed by dehydrohalogenation under strongly basic reaction conditions or by oxidation of an aminotriazole precursor.[20] Prior experiments involving 4,5-pyrimidynes have led to amination or low yields of annulated products.[20]

Given the earlier promising results involving the 2,3-pyridyne (**6**) and 4,5-pyrimidyne (**7**), we sought to further expand the utility of these intermediates for the synthesis of functionalized heterocycles. Herein, we report new trapping experiments involving pyridyne **6**, in addition to efforts toward 4,5-pyrimidyne (**7**).

2. Results and Discussion

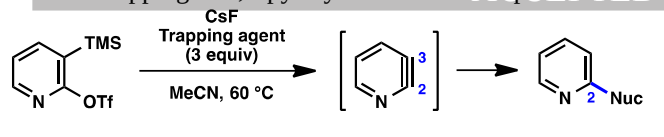
To study annulations of 2,3-pyridyne, it was first necessary to prepare a suitable silyltriflate precursor. Thus, silyltriflate **10** was synthesized using a known procedure (Scheme 1).[14] Beginning from 2-pyridone (**8**), a lithiation and silylation sequence provided silylhydroxypyridine **9**. Subsequent reaction with triflic anhydride furnished silyltriflate **10**. This high-yielding two-step sequence provides a reliable method to access **10** in multigram quantities. It should be noted that **10** is now also commercially available.[21]



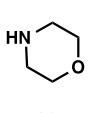
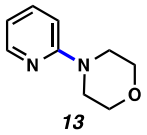
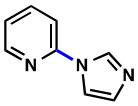
Scheme 1. Synthesis of silyltriflate **10**.

Silyltriflate **10** was examined in nucleophilic trapping experiments as shown in Table 1. Trapping with morpholine (**12**) led to the formation of **13** in 55% yield (entry 1), whereas use of imidazole (**14**) as the trapping agent delivered **15** in 63% yield (entry 2). In both cases, the 2-substituted pyridine products were obtained, with no evidence of the formation of 3-substituted adducts. This regioselectivity trend is consistent with prior observations[2c] and predictions made by the aryne distortion model.[12c]

Table 1. Trapping of 2,3-pyridyne **6** with nucleophiles



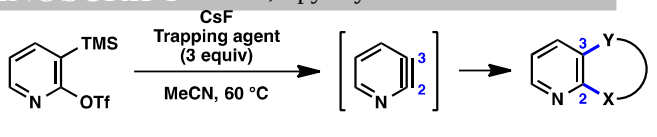
10 *6* *11*

Entry	Trapping agent	Product	Yield[a]
1	 *12*	 *13*	*55%*
2	 *14*	 *15*	*63%*

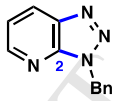
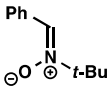
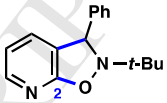
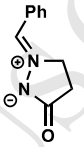
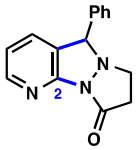
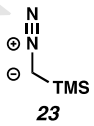
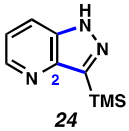
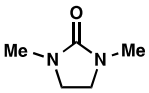
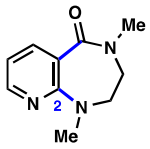
[a] Reported yields are the average of two experiments and are based on the amounts of isolated products.

We were delighted to find that silyltriflate **10** could also be employed in cycloaddition reactions (Table 2). For example, interception of pyridyne **6** by benzylazide (**17**)[22] furnished annulated product **18**, albeit only in low yield (entry 1). Alternatively, trapping with nitrone **19**[23] provided the unusual heterocycle **20** (entry 2). We also tested an azomethine imine cycloaddition[24] using **21**, which gave rise to tricycle **22** in 42% yield (entry 3). More synthetically useful yields were obtained when TMS diazomethane **23**[25] and dimethylurea **25**[16] were utilized in the trapping experiments. These reactions gave fused bicyclic pyridine derivatives **24** and **26** in 67% and 75% yield, respectively (entries 4 and 5). In all cases, only one regioisomer of annulated product was detected, indicative of preferential nucleophilic attack occurring at C2 of the 2,3-pyridyne intermediate.

Table 2. Annulations of 2,3-pyridyne **6**.



10 *6* *16*

Entry	Trapping agent	Product	Yield[a]
1	 *17*	 *18*	*20%*
2	 *19*	 *20*	*33%*
3	 *21*	 *22*	*42%*
4	 *23*	 *24*	*67%*
5	 *25*	 *26*	*75%*

[a] Reported yields are the average of two experiments and are based on the amounts of isolated products.

Despite the success of the aforementioned trapping experiments, it should be noted that silyltriflate **10** could not be employed successfully in other attempted 2,3-pyridyne trapping experiments (Figure 2). For example, the use of nitrile oxide precursor **27**, diazoester **28**, or enamide **29** in attempted annulations led only to decomposition. Similarly, efforts to utilize sydnone **30** in a Diels–Alder trapping or β-ketoester **31**[26] in a formal (2+2) cycloaddition were unsuccessful. Nonetheless, the knowledge gained from our 2,3-pyridyne studies should enable the judicious use of **10** in synthetic applications.

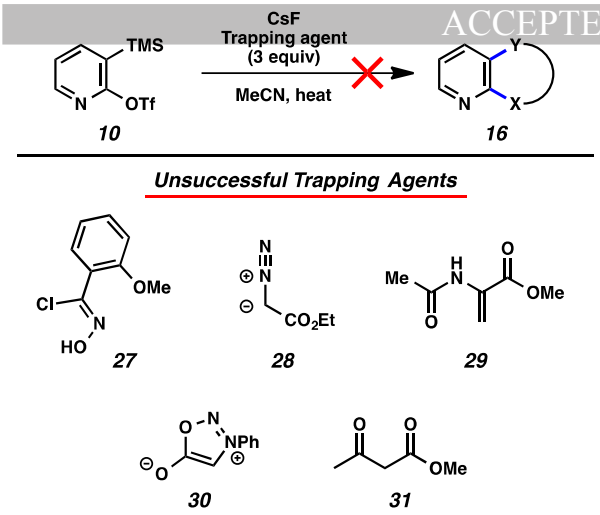
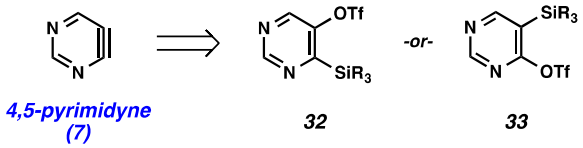


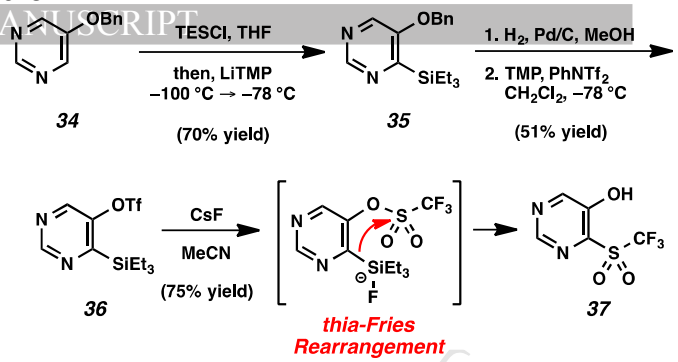
Figure 2. Unsuccessful cycloadditions using silyltriflate **10**.

As noted earlier, we were also eager to expand the limited scope of 4,5-pyrimidyne trapping experiments.[20] As such, we pursued the notion suggested in Scheme 2. Specifically, we envisioned that 4,5-pyrimidyne (**7**) could be prepared in situ from silyltriflate **32** or its constitutional isomer **33**.



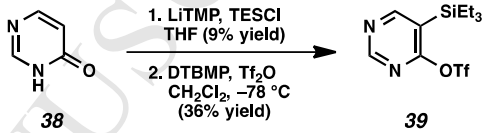
Scheme 2. Approaches to 4,5-pyrimidyne **7** from silyltriflate precursors **32** or **33**.

In our initial approach, we sought to access a silyltriflate precursor from known benzyloxypyrimidine **34**[27] (Scheme 3). As such, 5-benzyloxypyrimidine (**34**) was synthesized from the corresponding commercially available bromide using an Ullman coupling.[27] With **34** in hand, extensive efforts were put forth to effect silylation. It was ultimately found that the desired triethylsilylated product **35** could be obtained using a one-pot procedure involving mixing of **34** with TESCl, followed by low temperature lithiation, with in situ silylation.[28] From **35**, debenzylation and subsequent triflation delivered the desired silyltriflate **36**. Eager to attempt pyrimidyne generation, **36** was subjected to a battery of experiments involving variation of fluoride sources, trapping agents, and other reaction conditions. Unfortunately, no products indicative of pyrimidyne formation were observed. Instead, it was found that **36** was prone to readily undergo thia-Fries rearrangement in the presence of fluoride sources. For example, treatment of **36** with CsF in acetonitrile gave **37** as the major product.[29] Greaney and coworkers have also observed thia-Fries rearrangement in attempted aryne generation from silyltriflate precursors.[30]



Scheme 3. Synthesis of silyltriflate **36** and undesired Fries rearrangement.

With our initial efforts thwarted, we pursued the synthesis of an isomeric silyltriflate, as shown in Scheme 4. 2-Pyrimidone (**38**) was found to undergo lithiation/silylation using a protocol similar to the one described previously to access pyridyne precursor **10** (see Scheme 1). Subsequent triflation of the remaining hydroxyl group furnished silyltriflate **39**.[31]



Scheme 4. Synthesis of silyltriflate **39**.

With the desired isomeric silyltriflate **39** available in just two steps from commercially available material, we pursued pyrimidyne generation and trapping (Figure 3). Thus, **39** was exposed to fluoride sources (e.g., CsF) in the presence of trapping agents. However, in all attempts, we were unable to observe any of the desired cycloadditions adducts. Instead, only substantial non-specific decomposition or formation of 2-pyrimidone was observed.[32]

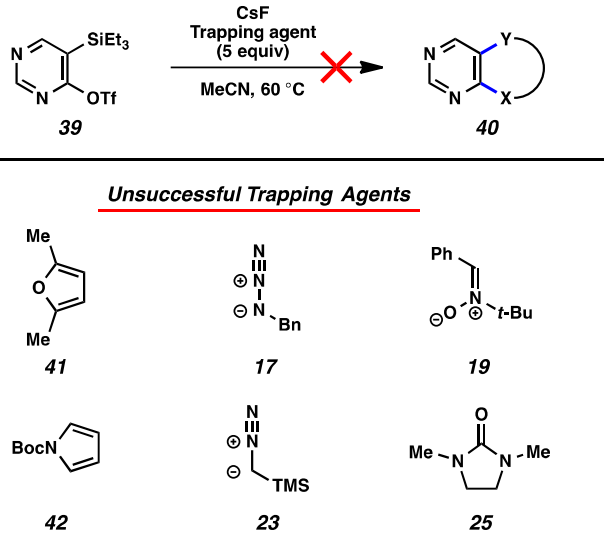


Figure 3. Unsuccessful attempts to generate and trap the 4,5-pyrimidyne from silyltriflate **39**.

3. Conclusion

In summary, we have performed studies pertaining to two interesting heterocyclic aryne intermediates: 2,3-pyridyne and 4,5-pyrimidyne. We have shown that 2,3-pyridyne can be employed in various trapping experiments involving nucleophiles or cycloaddition partners. Several of the products obtained are unique scaffolds that would arguably be difficult to access by other means. In addition, we have developed synthetic routes to two plausible silyltriflate precursors to the 4,5-pyrimidyne, although no evidence of pyrimidyne formation was noted in attempted trapping experiments. We expect our findings will promote the use of 2,3-pyridyne and other strained heterocyclic intermediates in the synthesis of functionalized heterocycles.

4. Experimental Section

4.1 Materials and Methods. Unless stated otherwise, reactions were conducted in flame-dried glassware under an atmosphere of nitrogen using anhydrous solvents (freshly distilled or passed through activated alumina columns). All commercially obtained reagents were used as received unless otherwise specified. Cesium fluoride (CsF) was obtained from Strem Chemicals. Trifluoromethanesulfonic anhydride (Tf_2O), trimethylsilyl chloride (TMSCl), and triethylsilyl chloride (TESCl) were obtained from Oakwood Products, Inc. and distilled before use. *N*-tert-butyl-α-phenylnitrone and methyl 2-acetamidoacrylate were obtained from Alfa Aesar. Ethyl diazoacetate, (trimethylsilyl) diazomethane (1M in Et_2O), 2,5-dimethylfuran, imidazole, and *N*-Boc-pyrrole were obtained from Sigma Aldrich. Morpholine was obtained from Spectrum Chemical and distilled before use. Reaction temperatures were controlled using an IKAmag temperature modulator and, unless stated otherwise, reactions were performed at room temperature (rt, approximately 23 °C). Thin layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.25 mm) and visualized using a combination of UV light and potassium permanganate staining. Preparative thin layer chromatography (TLC) was conducted with EMD gel 60 F254 pre-coated plates (0.5 mm) and visualized using UV light. Silicycle Siliaflash P60 (particle size 0.040–0.063 mm) was used for flash column chromatography. ^{1}H NMR spectra were recorded on Bruker spectrometers (500 MHz) and are reported relative to deuterated solvent signals. Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz) and integration. ^{13}C NMR spectra were recorded on Bruker spectrometers (125 MHz) and are reported relative to deuterated solvent signals. Data for ^{13}C NMR spectra are reported in terms of chemical shift and, when necessary, multiplicity, and coupling constant (Hz). IR spectra were obtained using a Perkin-Elmer 100 spectrometer or a Perkin-Elmer UATR two spectrometer, and are reported in terms of frequency absorption (cm^{-1}). High-resolution mass spectra were obtained on Waters LCT Premier with ACQUITY LC and Thermo Scientific™ Exactive Mass Spectrometers with DART ID-CUBE.

4.2 Representative experimental procedure for 2,3-pyridyne trapping. Adduct 13 (Table 1, entry 1). To a stirred solution of silyltriflate **10**[14] (51.1 mg, 0.172 mmol, 1.0 equiv) and morpholine (48.0 μL, 0.516 mmol, 3.0 equiv) in MeCN (7.0 mL) was added CsF (128 mg, 0.840 mmol, 5.0 equiv). The reaction vessel was sealed and placed in a preheated aluminum heating block maintained at 60 °C for 2 h. After cooling to 23 °C, the reaction mixture was filtered over silica gel (EtOAc eluent, 12 mL). Evaporation under reduced pressure and further purification by preparative thin layer chromatography (2:1 hexanes:EtOAc) afforded **13** as a colorless oil (55% yield, average of two experiments). **13**: R_f 0.48 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.19 (ddd, *J* = 4.9, 2.0, 0.8, 1H), 7.49 (ddd, *J* = 9.0, 7.2, 2.0, 1H), 6.65 (ddd, *J* = 7.2, 4.9, 0.8, 1H), 6.62 (d, *J* = 8.7, 1H), 3.82 (t, *J* = 5.0, 4H), 3.49 (t, *J* = 5.0, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.7, 148.1, 137.6, 113.9, 107.0, 66.9, 45.7; IR (film): 1593, 1481, 1437, 1376, 1312, 1243 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_9H_{12}N_2O$, 165.1022; found 165.1024.

Adduct 15 (Table 1, entry 2). Purification by preparative thin layer chromatography (6:3:1 EtOAc:PhH:MeOH) afforded **15** (63% yield, average of two experiments) as a light orange oil. **15**: R_f 0.62 (9:1 EtOAc:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.49 (ddd, *J* = 4.9, 1.8, 0.9, 1H), 8.35 (s, 1H), 7.83 (dt, *J* = 7.5, 1.8, 1H), 7.65 (s, 1H), 7.36 (d, *J* = 8.2, 1H), 7.24 (ddd, *J* = 7.5, 4.9, 0.8, 1H), 7.20 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.4, 149.3, 139.1, 135.1, 130.9, 122.1, 116.3, 112.5; IR (film): 1598, 1578, 1487, 1444, 772, 738 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_8H_7N_3$, 146.0713; found 146.0714.

Adduct 18 (Table 2, entry 1). Purification by preparative thin layer chromatography (3:1 hexanes:EtOAc) afforded **18** (20% yield, average of two experiments) as a light yellow oil. **18**: R_f 0.35 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (dd, *J* = 4.5, 1.4, 1H), 8.37 (dd, *J* = 8.2, 1.4, 1H), 7.46 (d, *J* = 7.2, 2H), 7.36–7.28 (m, 4H), 5.92 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 145.8, 137.2, 135.2, 129.0, 128.7, 128.5, 128.4, 120.0, 50.6; IR (film): 3032, 2927, 2852, 1591, 1216 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{12}H_{11}N_4$, 211.0978; found 211.0974.

Adduct 20 (Table 2, entry 2). Purification by preparative thin layer chromatography (3:1 hexanes:EtOAc) afforded **20** (33% yield, average of two experiments) as an amorphous white solid. **20**: R_f 0.52 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 5.0, 1H), 7.42 (d, *J* = 7.2, 2H), 7.35 (t, *J* = 7.2, 2H), 7.28 (tt, *J* = 7.2, 1.2, 1H), 7.19 (dt, *J* = 7.3, 1.3, 1H), 6.74 (dd, *J* = 7.3, 5.0, 1H), 5.62 (s, 1H), 1.20 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.1, 147.9, 143.0, 132.8, 128.9, 127.9, 127.4, 123.0, 116.8, 66.3, 61.4, 25.5; IR (film): 1604, 1420, 1282, 1270, 775, 739 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{16}H_{18}N_2O$, 255.1492; found 255.1492.

Adduct 22 (Table 2, entry 3). Purification by preparative thin layer chromatography (95:5 EtOAc:MeOH) afforded **22** (42% yield, average of two experiments) as a colorless amorphous solid. **22**: R_f 0.48 (95:5 EtOAc:MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (dt, *J* = 5.1, 1.1, 1H), 7.44–7.38 (m, 5H), 7.18 (dt, *J* = 7.5, 1.3, 1H), 6.94 (dd, *J* = 7.5, 5.1, 1H), 5.16 (s, 1H), 3.64–3.60 (m, 1H), 3.19–3.06 (m, 2H), 2.89–2.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 148.8, 148.5, 137.6, 132.5, 129.2, 129.1, 128.8, 128.4, 119.7, 73.5, 52.5, 36.9; IR (film): 1708, 1597, 1460, 1430, 1388, 1308 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_{15}H_{13}N_3O$, 252.1131; found 252.1126.

Adduct 24 (Table 2, entry 4). Purification by preparative thin layer chromatography (2:1 PhH:MeCN) afforded **24** (67% yield, average of two experiments) as a white amorphous solid. **24**: R_f 0.41 (2:1 PhH:MeCN) ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.77 (s, 1H), 7.54 (dd, *J* = 6.4, 2.1, 1H), 7.34 (dd, *J* = 6.4, 2.1, 1H), 6.23 (t, *J* = 6.4, 1H), 0.27 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 167.9, 147.5, 135.7, 131.8, 106.7, –1.7; IR (film): 2953, 2362, 1630, 1537, 1244, 1050 cm^{-1}; HRMS-ESI (*m/z*) $[M + H]^+$ calcd for $C_9H_{13}N_3Si$, 192.0952; found 192.0951.

Adduct 26 (Table 2, entry 5). Purification by preparative thin layer chromatography (95:5 EtOAc:MeOH) afforded **26** (75% yield, average of two experiments) as a colorless oil. **26**: R_f 0.45 (95:5 EtOAc:MeOH) ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.29 (dd, *J* = 4.9, 2.0, 1H), 8.01 (dd, *J* = 7.6, 2.0, 1H), 6.76 (dd, *J* = 7.6, 4.9,

1H), 3.61–3.57 (m, 2H), 3.57–3.52 (m, 2H), 3.18 (s, 3H), 3.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.2, 155.7, 150.9, 140.7, 119.4, 114.6, 56.3, 48.1, 38.9, 35.6; IR (film): 1633, 1504, 1408, 1385, 1247, 1208 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{10}H_{13}N_3O$, 192.1131; found 192.1131.

Pyrimidine 35 (Scheme 3). To a stirred solution of freshly distilled tetramethylpiperidine (1.97 g, 14.0 mmol, 1.4 equiv) in THF (50 mL) at 0 °C was added *n*-BuLi in hexanes (2.3 M, 5.65 mL, 13.0 mmol, 1.3 equiv). The resulting solution was allowed to stir at 0 °C for 30 min. A separate flask was charged with 5-benzyloxypyrimidine **34** (2.00 g, 10.0 mmol, 1.0 equiv), TESCl (4.53 g, 30.0 mmol, 3.0 equiv), and THF (50 mL). The resulting solution was cooled to –100 °C and the LiTMP solution was added dropwise via cannula over 20 min. The resulting solution was warned to –78 °C and allowed to stir for 3.5 h. The solution was then allowed to warm to 0 °C and quenched with saturated NH_4Cl (25 mL). The volatiles were removed under reduced pressure and EtOAc (75 mL) was added. The organic phase was separated and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was further purified by column chromatography (5:1 hexanes:EtOAc) to yield pyrimidine **35** (2.09 g, 70% yield) as a colorless oil. **35**: R_f 0.41 (3:1 hexanes:EtOAc) ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.95 (s, 1H), 8.24 (s, 1H), 7.42–7.34 (m, 5H), 5.12 (s, 2H), 0.95–0.91 (m, 9H), 0.91–0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.5, 158.4, 151.7, 137.6, 135.7, 128.9, 128.6, 127.7, 70.6, 7.5, 3.0; IR (film): 2953, 2874, 1558, 1456, 1397, 1284 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{17}H_{25}N_2OSi$, 301.1731; found 301.1729.

Silyltriflate 36 (Scheme 3). To a stirred solution of pyrimidine **35** (1.00 g, 3.33 mmol, 1.0 equiv) in dry MeOH (20 mL) was added 10% Pd/C (350 mg, 0.330 mmol, 0.1 equiv). The resulting mixture was placed under an atmosphere of H_2 (balloon) and was allowed to stir at 23 °C for 2 h. The mixture was filtered over celite (MeOH eluent). Evaporation of the solvent under reduced pressure afforded the crude alcohol intermediate, which was used in the subsequent step without further purification.

The alcohol intermediate (510 mg, 2.43 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (7 mL) and freshly distilled tetramethylpiperidine (282 mg, 9.72 mmol, 4.0 equiv) was added dropwise over 10 min. The resulting solution was cooled to –78 °C and a solution of $PhNTf_2$ (714 mg, 2.92 mmol, 1.2 equiv) in CH_2Cl_2 (7 mL) was added dropwise over 15 min. The resulting solution was stirred at –78 °C for 2 h and was then quenched with saturated $NaHCO_3$ (10 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was further purified by column chromatography (30:1 hexanes:EtOAc) to yield silyltriflate **36** as a colorless oil (581 mg, 51% yield, 2 steps). **36**: R_f 0.70 (3:1 hexanes:EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.26 (s, 1H), 8.64 (s, 1H), 0.97 (br s, 15H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 156.7, 152.4, 147.0, 118.5 (q, J = 318.2, CF_3), 7.3, 3.0; IR (film): 2960, 2880, 1565, 1428, 1386, 1211 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{11}H_{18}F_3N_2O_3SSi$, 343.0754; found 343.0748.

Alcohol 37 (Scheme 3). To a stirred solution of silyltriflate **36** (130 mg, 0.380 mmol, 1.0 equiv) in MeCN (3.8 mL) was added CsF (173 mg, 1.14 mmol, 3.0 equiv). The reaction vessel was sealed and placed in a preheated aluminum heating block maintained at 60 °C for 2 h. After cooling to 23 °C, the reaction mixture was filtered over celite (MeOH eluent, 12 mL). Evaporation under reduced pressure and further purification by preparative thin layer chromatography (10:1:0.1 CH_2Cl_2:MeOH:Et_3N) afforded **37** as a colorless oil (75% yield). **37**: R_f 0.76 (MeCN); ^{1}H NMR (500 MHz, MeOD): δ 8.28 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (125 MHz, MeOD): δ 165.6, 161.0, 142.0, 137.6, 122.5 (q, J = 327.9, CF_3); IR (film): 3349, 1643, 1575, 1510, 1445, 1341 cm^{-1}; HRMS-ESI (*m/z*) [M – H]$^-$ calcd for $C_5H_2F_3N_2O_3S$, 226.9733; found 226.9750.

Silyltriflate 39 (Scheme 4). To a stirred solution of freshly distilled tetramethylpiperidine (1.02 g, 7.20 mmol, 1.4 equiv) in THF (10 mL) at 0 °C was added *n*-BuLi in hexanes (2.3 M, 2.94 mL, 6.80 mmol, 1.3 equiv). The resulting solution was stirred at 0 °C for 30 min. A separate flask was charged with 2-pyrimidone **38** (500 mg, 5.20 mmol, 1.0 equiv), TESCl (1.97 g, 13.0 mmol, 2.5 equiv), and THF (16 mL). The resulting solution was cooled to 0 °C and the LiTMP solution was added dropwise via cannula over 20 min. The resulting solution was warmed to 23 °C and allowed to stir for 24 h. The solution was then quenched with saturated NH_4Cl (10 mL). The volatiles were removed under reduced pressure and EtOAc (30 mL) was added. The organic phase was separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was further purified by column chromatography (1:2 to 1:4 hexanes:EtOAc) to yield an alcohol intermediate (100 mg, 9% yield (unoptimized)) as a colorless oil.

The alcohol intermediate (90.0 mg, 0.430 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (2 mL) and DTBMP (96.0 mg, 0.470 mmol, 1.1 equiv) was added. The resulting solution was cooled to –78 °C and Tf_2O (133 mg, 0.470 mmol, 1.1 equiv) was added dropwise over 5 min. The resulting solution was allowed to stir at –78 °C for 2 h and was then quenched with saturated $NaHCO_3$ (1 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 3 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The resulting oil was further purified by column chromatography (40:1 hexanes : EtOAc) to yield silyltriflate **39** as a colorless oil (55 mg, 36% yield). **39**: R_f 0.52 (5:1 hexanes : EtOAc) ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.14 (d, J = 1.2, 1H), 7.29 (d, J = 1.2, 1H), 0.99 (t, J = 7.2, 9H), 0.92–0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 184.2, 162.2, 158.2, 118.6 (q, J = 320.6, CF_3), 117.0, 7.2, 2.6; IR (film): 2959, 2880, 1579, 1511, 1428, 1211 cm^{-1}; HRMS-ESI (*m/z*) [M + H]$^+$ calcd for $C_{11}H_{18}F_3N_2O_3SSi$, 343.0754; found 343.0755.

Acknowledgments

The authors are grateful to the NIH-NIGMS (R01 GM090007 for N.K.G.), the A. P. Sloan Foundation, the Dreyfus Foundation, the University of California, Los Angeles, the UCLA Cota Robles Fellowship Program (J.M.M.), the UCLA Gold Shield Alumnae, and the Oskar–Jeger Scholarship Program (M.J.) for financial support. These studies were supported by shared instrumentation grants from the NSF (CHE-1048804) and the NIH NCRR (S10RR025631).

Supplementary Material

Supplementary data associated with this article, including materials and methods and NMR spectra, can be found in the online version.

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[32] At present, it is unclear why the silyltriflate approach to the 4,5-pyrimidyne is unsuccessful.