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An Application of Borane As a Protecting Group for Pyridine

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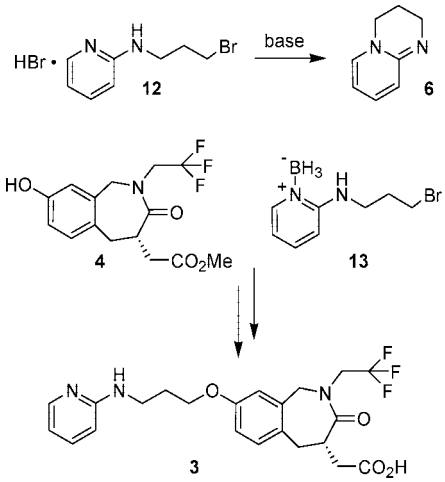
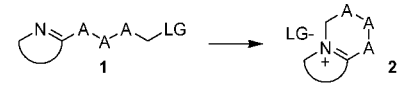


Efforts to couple **4** with **12** employing base mediation are problematic due to the formation of **6**. To circumvent this issue, **12** was converted to the pyridine borane complex (**13**). Alkylation of **4** with **13** provided **3** after removal of the borane under acidic conditions and saponification of the ester.

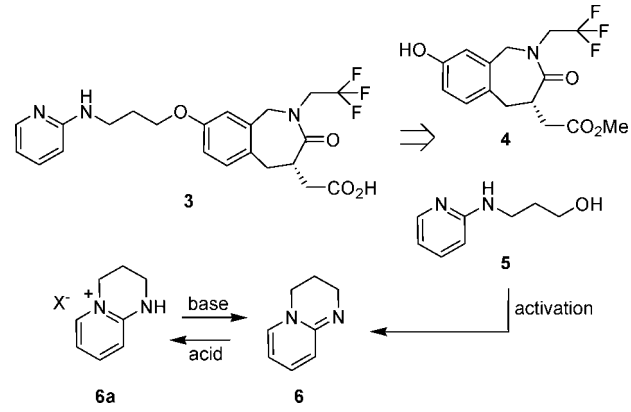
During the course of developing scalable syntheses to certain pharmaceutical targets, we identified a problem installing specific heterocyclic side chains containing a leaving group. Compounds of form **1** (Scheme 1), where a nucleophilic nitrogen is contained within an electron-rich heterocycle proximal to a leaving group, would cyclize in many cases to give **2**, which does not function as an alkylating agent.[1,2] Avoiding this issue

SCHEME 1. Cyclization of Heterocyclic Intermediates



where A = C, N, or O and LG = Leaving Group

SCHEME 2



has required protecting the hetrocyclic nitrogen as an *N*-oxide or completely excluding compounds such as **1** from the synthetic route. Many times these types of intermediates (**1**) facilitate the most direct pathway to the target compound. Because of the problems associated with removing an *N*-oxide and handling the intermediates on scale, we sought other potential solutions.

This problem was encountered during the development of a scalable synthesis to the vitronectin inhibitor **3** (Scheme 2). A straightforward disconnection of **3** reveals previously prepared **4**[3a,b] and pyridyl side chain **5**.[2b,4] However, as mentioned above, conversion of the hydroxyl group of **5** into a leaving group[5] would lead to the formation of **6**.[2b,6] To make realistic use of this route and **5**, the lone pair of the pyridine moiety would need to be occupied in some fashion to prevent cyclization.

A first generation synthesis[3a,b] of **3**, partly shown in Scheme 3, relied on this disconnection and made use of a pyridine *N*-oxide intermediate. Two alkylating agents were used with **4**: **7** under Mitsunobu conditions and **8** using sodium hydroxide.[3a,b] Unfortunately, the synthesis of both **7** and **8** required the use of commercially available but expensive 2-chloropyridine *N*-oxide. As an additional problem, this material was thermally unstable, potentially leading to safety issues.[7] Following alkylation, *N*-oxide **9** was treated with zinc dust to remove the oxide protecting group and regain the free pyridine. This step proved difficult to scale due to the density of zinc dust; variable results were often obtained due to inconsistency in stirring, which

(1) Five membered systems: (a) Birman, V. B.; Li, X.; Jiang, H.; Uffman, E. W. *Tetrahedron* **2006**, *62*, 285. (b) Copp, F. C.; Timmis, G. M. *J. Chem. Soc.* **1955**, 2021.

(2) Six membered system: (a) Klauschenz, E.; Hagan, V.; Wiesner, B.; Hagan, A.; Reck, G.; Krause, E. G. *Eur. J. Med. Chem.* **1994**, *29*, 175. (b) Mandereau, J.; Xuong, E. N.T.; Reynaud, P. *Eur. J. Med. Chem.* **1974**, *9*, 344.

(3) (a) Miller, W. H.; Alberts, D. P.; Bhatnager, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P. J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J. W.; Yuan, C. C.-K.; Haltiwanger, R. C.; Gowen, M.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Rieman, D. J.; Glomic, J. C.; Stroup, G. B.; Azzarano, L. M.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *J. Med. Chem.* **2000**, *43*, 22. (b) Wallace, M. D.; McGuire, M. A.; Yu, M. S.; Goldfinger, L.; Liu, L.; Dai, W.; Shilcrat, S. *Org. Process Res. Dev.* **2004**, *8*, 738.

(4) Tupin, T.; Raynaud, P.; Delaby, R. *Bull. Soc. Chim. Fr.* **1957**, 721.

(5) In our hands, Mitsunobu conditions with **5**, as in the following references, provided **6** with only trace amounts of alkylation product:(a) Leonard, K.; Pan, W.; Anaclerio, B.; Gushue, J. M.; Guo, Z.; DesJarlais, R. L.; Chaikin, M. A.; Lattanze, J.; Crysler, C.; Manthey, C. L.; Tomczuk, B. E.; Marugan, J. J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2679. (b) Marugan, J. J.; Manthey, C.; Anaclerio, B.; Lafrance, L.; Lu, T.; Markotan, T.; Leonard, K. A.; Crysler, C.; Eisennagel, S.; Dasgupta, M.; Tomczuk, B. *J. Med. Chem.* **2005**, *48*, 926. Additionally, the authors of the above paper include ^{1}H NMR data of **5** that do not match our data.

(6) It is interesting to note that treatment of **4** with **6** under acidic or basic conditions gives no trace of desired product. For **6** see ref 2b.

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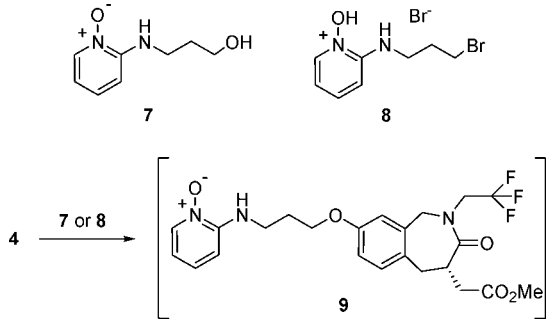
SCHEME 3. Previous *N*-Oxide Route[3a,b]



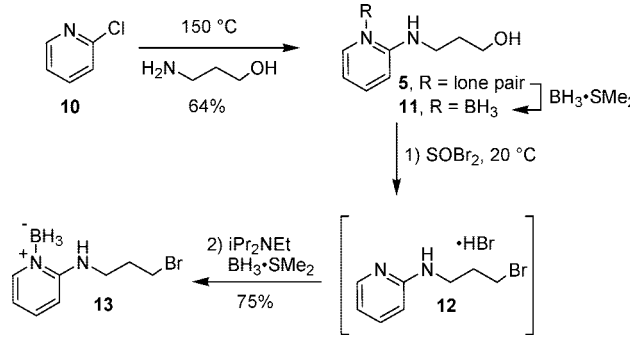
differed with reactor configuration. Hydrogenation conditions were also screened (Pt or Pd/C heterogeneous catalysts) but gave either no desired product or afforded byproducts.

This opportunity was used to develop alternative blocking groups that would avoid the three major problems with this route: (1) 2-chloropyridine *N*-oxide is expensive and supplied as an aqueous solution on scale, requiring a lengthy azeotropic distillation before use, (2) zinc dust reduction of the *N*-oxide is capricious on scale, and (3) 2-chloropyridine *N*-oxide is thermally unstable.

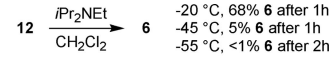
It was hypothesized that borane might be used as a protecting group instead of the *N*-oxide. Several precedents exist which illustrate the strength of the borane−heterocycle bond. For instance, oxazole−borane complexes are bench-stable and require acidic conditions or Pd treatment for removal.[8,9] These complexes are completely stable to chromatography, air, and moisture. Additionally, 4-dimethylaminopyridine (DMAP) quickly and quantitatively forms a complex with borane that exhibits stability similar to that of oxazole−borane complexes.[10] We felt that the system at hand should behave similarly to these examples and form stable borane complexes.[11] However, an example where this type of complex thwarted the nucleophilicity of a heteroaromatic system could not be found. On the basis of the relevant literature examples of a DMAP borane complex[10] and a 2-aminopyridine cyanoborane complex,[11f] the borane would be expected to reside on the pyridine nitrogen.[12]

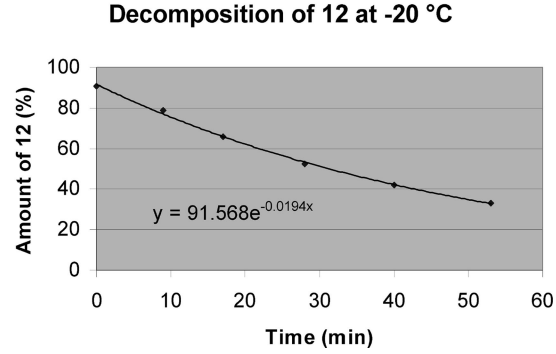
To test this strategy, a borane protected version of **7** or **8** was needed (Scheme 4). To this end, **10** was heated in 3-aminopropanol to give **5** in 64% yield after crystallization. Direct treatment of **5** with borane dimethylsulfide initially gave a complex mixture;[13] however, after aqueous workup only **5** and **11** were obtained (∼1:1 ratio). Alcohols **5** and **11** proved somewhat difficult to separate and attempts at reaction optimization did little to improve the ratio. Alternatively, **5** was treated with thionyl bromide, successfully giving **12** in situ.

SCHEME 4. Borane Alkylating Agent



SCHEME 5. Decomposition of Unprotected Pyridine





With **12** available, we studied its stability upon addition of *i*Pr$_2$NEt (Scheme 5). When **12** was treated with 2 equiv of base at −55 °C, we observed <1% decomposition after 2 h. At −45 °C, 5% loss was observed after 1 h whereas at −20 °C, 68% had cyclized after 1 h. The decomposition of **12** at −20 °C is shown graphically in Scheme 5. Additionally, the exponential decay equation that fits the data is given. This gave us a clear indication that cyclization of **12** would occur before alkylation of **4** under basic conditions since the reaction of **4** with **8** is relatively slow at room temperature. In the formation of **13** from **12**, basification of **12** must occur either in the presence of the borane source or at a temperature <−55 °C to avoid the formation of **6**.

Using this knowledge, we developed two procedures to produce electrophile **13** (Scheme 4).[12] Freebasing at temperatures between −60 and −78 °C cleanly provided **13** after treatment with borane dimethylsulfide. Alternately, the reaction could be accomplished at −20 °C without forming appreciable amounts of **6** by adding excess *i*Pr$_2$NEt to a solution of **12** and borane dimethylsulfide. It appears that the *i*Pr$_2$NEt reacted faster with **12** than the borane source and that the freebase of **12** reacted preferentially with the borane source rather than cyclizing to **6**. As we had hoped, isolated **13** was crystalline and exhibited similar stability to water and oxygen as the literature heterocycle−borane complexes.

Next, alkylation of **4** with **13** (Scheme 6) was carried out in refluxing MeCN with K_2CO_3 and a catalytic amount of tetrabutylammonium iodide.[6] The resulting crude product (**14**) after aqueous workup was first treated with 1.1 equiv of HCl (aqueous, concentrated) to remove the borane protecting group (**15**) and then with sodium hydroxide to saponify the ester. After adjusting the pH to 5−5.5, **3** crystallized out of solution in 83%

(7) Shilcrat, S. Unpublished results, HCl salt: An exotherm was observed in the range of 134.1−185.4 °C with an onset temperature of 136.1 °C and a heat of reaction of−746.7 J/g. **Freebase:** Two exotherms were observed with the first in the range of 42.7−108.1 °C with an onset of 46.6 °C and a heat of reaction of−867.6 J/g. The second exotherm was in the range of 125.9−188 °C with an onset of 146.6 °C and a heat of reaction of−6672.4 J/g.

(8) Monahan, S. D.; Vedejs, E. *J. Org. Chem.* **1996**, *61*, 5192.

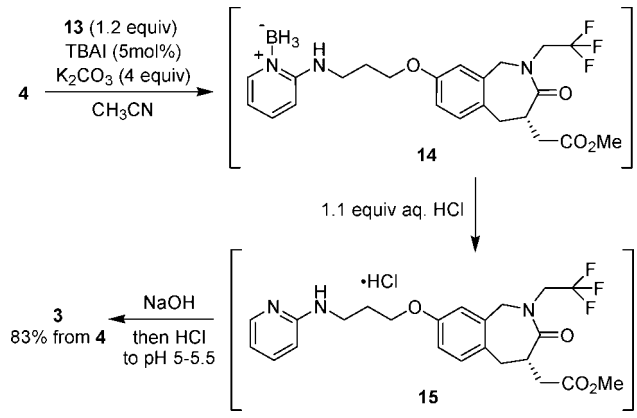
(9) Zajac, M. A.; Vedejs, E. *Org. Lett.* **2001**, *3*, 2451.

(10) Shapland, P.; Vedejs, E. *J. Org. Chem.* **2006**, *71*, 6666.

(11) For examples of nonheteroaromatic amine borane complexes see:(a) Schwartz, M. A.; Rose, B. F.; Vishnuvajjala, B. *J. Am. Chem. Soc.* **1973**, *95*, 612. (b) White, J. D.; Amedio, J. C.; Gut, S.; Jayasinghe, L. *J. Org. Chem.* **1989**, *54*, 4268. (c) Ferey, V.; Vedrenne, P.; Toupet, L.; Le Gall, T.; Mioskowski, C. *J. Org. Chem.* **1996**, *61*, 7244. (d) Carboni, B.; Monnier, L. *Tetrahedron* **1999**, *55*, 1197. (e) Blakemorene, P. R.; Kim, S. K.; Schulze, V. K.; White, J. D.; Yokochi, A. F. T. *J. Chem. Soc., Perkin Trans. I* **2001**, 1831. For an example of an α-amino pyridine borane complex see: (f) Tang, P. W.; Williams, J. M. *Carbohydr. Res.* **1985**, *136*, 259.

(12) See the Supporting Information for spectral data of **13** and **14**.

SCHEME 6. Preparation of 3



yield from **4**. This entire sequence from **10** was completed on a kilogram scale, providing 1.32 kg of **3** in two runs.[14] In conclusion, we have developed a procedure that prevents the cyclization of compound **12** using borane as a blocking group. Borane is both easy and economical to install and can be readily cleaved by using an acid workup.

Experimental Section

(3-Bromopropyl)(1-boropyridin-2-yl)amine (13). Charge **5** (600 g, 3.94 mol, 1.0 equiv) followed by methylene chloride (3.0 L). Mix the contents of the reactor thoroughly for 10 min. Cool the mixture to 0−5 °C. Add thionyl bromide (820 g, 3.94 mol, 1.0 equiv) slowly over 5−25 min to keep the internal temperature <15 °C. Warm the yellow mixture to 20−25 °C and hold for 1.5−2 h under a nitrogen atmosphere. After the reaction is complete, concentrate the solution in vacuo to 2.0−2.5 L with the jacket temperature at ca. 40 °C and add methylene chloride (3.0 L). Cool the solution to −60 to −70 °C and add diisopropylethylamine (561 g, 756 mL, 4.34 mol, 1.1 equiv) *directly* to the reaction mixture while maintaining the internal temperature below −55 °C. After addition is complete, borane dimethylsulfide complex (330 g, 412 mL, 4.34 mol, 1.1 equiv) is added *directly* to the reaction mixture over <25 min. The temperature of the mixture is kept below −50 °C during addition. Warm the solution to 10−15 °C and add a saturated aqueous solution of sodium bicarbonate (3.0 L) and water (3.0 L), mix thoroughly. Collect the organic layer and extract the aqueous layer with methylene chloride (3.0 L). Concentrate the combined organic layers in vacuo to 2.0−2.5 L. Add methanol (4.2 L) to dissolve/suspend the mixture and stir for 15 min. Concentrate the mixture to 3.0−3.5 L to remove any residual methylene chloride. Cool the mixture to 5−10 °C and isolate the resulting solid by filtration. Wash the solid twice with cold (0−5 °C) methanol (2 × 1.5 L). The wet product is dried at 20−25 °C under reduced pressure. This afforded 676 g of white solid (**13**, 75% yield) of sufficient purity for the next step. ^{1}H NMR (400 MHz, THF-d_8) δ (ppm) 8.12 (1H, d, J = 5.9 Hz), 7.67 (1H, dd, J = 7.3, 8.8 Hz), 6.82 (1H, d, J = 8.8 Hz), 6.65−6.53 (2H, m), 3.61−3.50 (4H, m), 2.60−1.75 (3H, br m), 2.19 (2H, m). ^{13}C NMR (100 MHz, THF-d_8) δ (ppm) 156.0, 147.2, 140.7, 112.0, 108.1, 41.5, 32.8, 31.3. Found (LR-ESI) 227 and 229 $[M - H]^+$, $C_8H_{13}BBrN_2$ requires 227 and 229.

Pyridine 14. Charge **4** (600 g, 1.81 mol, 1.0 equiv), potassium carbonate (1.0 kg, 7.24 mol, 4.0 equiv), tetrabutylammonium iodide (33.4 g, 90.6 mmol, 0.05 equiv), **13** (498 g, 2.17 mol, 1.2 equiv), and acetonitrile (3.0 L) at 18−23 °C to the reactor. Stir the mixture vigorously and heat to 49−52 °C under a nitrogen atmosphere. After the reaction is complete (typical hold is 16−24 h), cool the mixture to 18−23 °C and concentrate to 2.0−2.5 L. Add TBME (6.0 L) and mix thoroughly. Add water (6.0 L) and mix thoroughly. Collect the TBME layer and back extract the water layer with TBME (6.0 L). Wash the pooled TBME with water (3.0 L) and concentrate the TBME layer to 2.0−2.5 L. Add methanol (6.0 L) and concentrate to 2.0−2.5 L. This solution is then used directly in the next step. For reference purposes, an analytically pure sample was obtained by concentrating a portion of this solution to near dryness and subjecting the residue to silca gel column chromatography eluting with 0 to 100% EtOAc/hexanes. ^{1}H NMR (400 MHz, toluene-d_8) δ (ppm) 8.04 (1H, d, J = 5.7 Hz), 7.07 (1H, dd, J = 7.7, 8.7 Hz), 6.78−6.70 (2H, m), 6.67−6.60 (2H, m), 6.15 (1H, d, J = 8.7 Hz), 6.09 (1H, dd, J = 5.7, 7.7 Hz), 4.90 (1H, d, J = 16.8 Hz), 4.05−3.90 (1H, m), 3.80−3.60 (4H, m), 3.52 (1H, m), 3.44 (3H, s), 3.06−2.98 (2H, m), 2.89 (1H, dd, J = 8.8, 16.8 Hz), 3.00−2.50 (5H, m), 2.17 (1H, dd, J = 4.9, 16.8 Hz), 1.73 (2H, m). ^{13}C NMR (100 MHz, toluene-d_8) δ (ppm) 174.7, 172.3, 157.0, 155.2, 146.5, 139.8, 135.1, 131.9, 128.7, 125.1 (q, J = 280.7 Hz), 115.4, 114.2, 111.4, 107.2, 65.8, 53.0, 51.3, 47.4 (q, J = 33.2 Hz), 40.2, 37.0, 36.7, 34.7, 28.8. Found (LR-ESI) 478 $[M - H]^+$, $C_{23}H_{28}BF_3N_3O_4$ requires 478.

Pyridine 3. Dilute the methanol solution of **14** (100% assumed yield on the previous stage) up to 6.0 L with methanol. Cool to 0−5 °C and add concentrated aqueous hydrochloric acid (181 mL, 2.17 mol, 1.2 equiv, 12 M solution) while maintaining the temperature at <15 °C. Warm the mixture to 20−25 °C and hold for up to 3 h. After the reaction is complete, cool to 0−5 °C and add 3 M NaOH (4.23 L, 7.0 equiv) while maintaining the temperature at <15 °C. Warm the mixture to 20−25 °C and hold for up to 3 h. After the reaction is complete, add enough concentrated hydrochloric acid (~4.8 equiv) to bring the pH to 6.1−6.5 while maintaining the temperature at <25 °C. Hold for 16−24 h at 18−25 °C, during which time **3** precipitates out of solution. Isolate **3** by filtration and wash with water (2 × 4.3 L). Dry the solid product in a vacuum oven at 50−60 °C for up to 12 h. This afforded 683 g of **3** as an off-white solid (83% yield from **4**). All spectral data matched the previously reported data.[3a,b]

Acknowledgment. The author thanks Alan Freyer for taking NMR spectra of **5**, **13**, and **14**. Assistance from the Analytical Sciences group at GlaxoSmithKline has been appreciated.

Supporting Information Available: Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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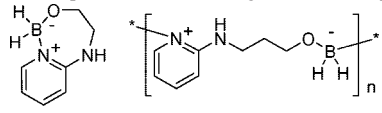
(13) It seems that the rate of reaction of borane at the pyridine nitrogen to give **11** is about as fast as the reaction with the hydroxyl function of **5**. If the reaction occurs at the hydroxy site, either or both of the following two compounds could be present and would give **5** after aqueous workup:



(14) The best cost comparison that can be made between the previous route (Scheme 3) and the new borane route is in the price difference of the starting materials on a kilogram scale. Both routes use **4**, thionyl bromide, and 3-aminopropanol, which can be left out of consideration. The 2007 pricing for 2-chloropyridine *N*-oxide is about $400/mol whereas the price of 2-chloropyridine is about $5/mol and that of borane dimethylsulfide is about $21/mol.