An efficient two-step synthesis of 3-amino-1-benzhydrylazetidine

Bryan Li*, Michael F. Witt, Thomas A. Brandt and David Whritenour

Chemical Research and Development, Groton Laboratories, Pfizer Global Research and Development, Groton, CT 06340, USA

A streamlined process for the synthesis of 3-amino-1-benzhydrylazetidine is described. Commercially available 1-benzhydrylazetidin-3-ol was reacted with methanesulfonyl chloride in the presence of triethylamine in acetonitrile, upon quench with water, the mesylate intermediate (**3**) was isolated by filtration. The wet filter cake was subsequently treated with ammonium hydroxide/isopropanol in a Parr reactor at ~70°C. The procedure afforded the titled compound as mono acetate salt in 72–84% yield.

Keywords: azetidine, aminolysis, mesylation, 3-amino-1-azetidine, 1-benzhydrylazetidine

3-Aminoazetidines (**1**) represent a functionality often found in compounds of therapeutic potential that are documented primarily in the patent literature.[1] To date, the most convenient method for the synthesis of 3-substituted azetidines is to start from 1-benzhydrylazetidin-3-ol (**2**)[2] which is readily prepared from benzhydrylamine and epichlorohydrin[3] and is available from several vendors at relatively low cost. Activation of the hydroxyl group in **2** was most frequently accomplished by conversion to the corresponding toluenesulfonate (39% yield) or methanesulfonate (100% yield) esters. These sulfonate esters are good substrates for substitution reactions to give the corresponding 3-alkoxide, 3-bromide, 3-cyano, and 3-carboxylic acid azetidines.[3a,4] It has been reported that the azetidine ring is sensitive to hydrolytic conditions and undergoes opening in the presence of water or a nucleophilic radical.[5] The opening of the azetidine ring has also been reported to lead to a polymerisation reaction.[6]

Recently we had a need to prepare multi-kilogram quantities of 3-amino-1-benzhydrylazetidine (**1a,** $R^1 = CHPh_2$, $R^2 = R^3 = H$). Three preparations of **1a** from **2** have been reported in the literature (Scheme 1). The Gabriel synthesis was considered inefficient for its low atom economy, and suffers from the additional disadvantages of being patented,[7] and of employing hydrazine hydrate (high thermal potential) to deprotect the phthalimide group. Another method employs azide displacement of the sulfonate followed by reduction.[8] This chemistry was not considered further due to thermal hazard issues associated with handling azides. The most attractive chemistry in the literature is the direct aminolysis of the mesylate **3**, but the procedure as described gave a poor yield (27%) of **1a**.[9]

Given the limitations of existing methods for the synthesis of 3-aminoazetidines, we undertook development a more readily scalable synthesis of **1a**. Our initial approach is a three-step sequence and is shown in Scheme 2. Following literature precedents, oxidation of azetidinol **2** provided azetidinone **5** in good yield.[10] Condensation of **5** with hydroxylamine hydrochloride provided oxime **6**,[11] which was reduced to the amine using $LiAlH_4$. This sequence routinely gave **1a** in good yields with the product conveniently isolated as the oxalic acid salt. To further streamline the process, the oxime intermediate was taken directly into the $L{:}AlH_4$ reduction without isolation.

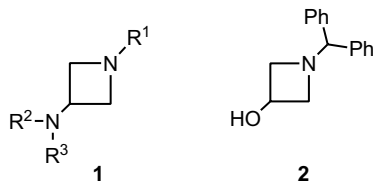
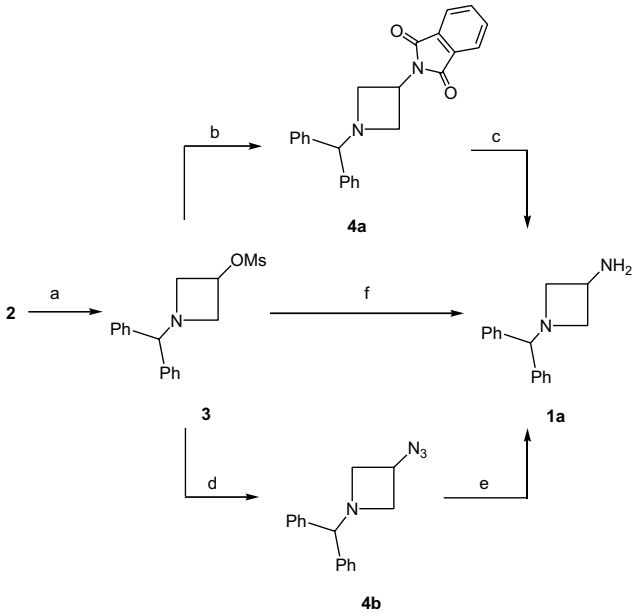


Fig. 1

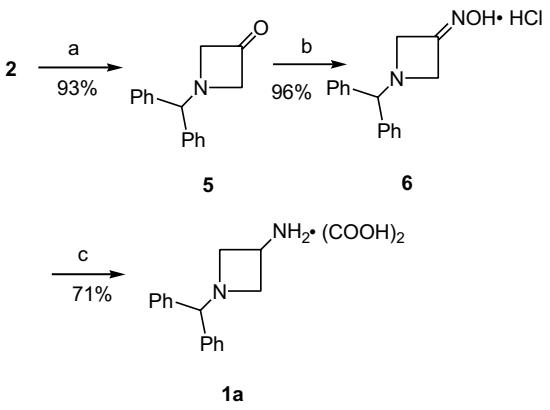
* Correspondent. E-mail: bryan.li@pfizer.com



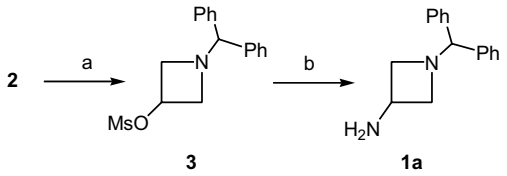
Scheme 1 a. MsCl, pyridine, –10°C, 80% b. Potassium Phthalimide, $CH_3(CH_2)_{15}P^+Bu^n{}_3Br^-$, PhMe, reflux, 67%. c. $H_2NNH_2{\bullet}H_2O$, MeOH, reflux, 96%. d. NaN_3. e. LAH. f. NH_3/MeOH, 27%.

Several hundred grams of **1a** were delivered by this route early in the program, but as material needs increased we recognised that the low temperature Swern oxidation and tedious workup of the $L{:}AlH_4$ reduction negatively impacted operational cost and efficiency if they were to be run in the pilot plant.

At this point we elected to revisit the direct aminolysis of mesylate **3** (Scheme 1, steps *a* and *f*) and initiated an optimisation of the reaction.[12] For the first step (synthesis



Scheme 2 a. Oxalyl chloride, DMSO, –78°C; b. $NH_2OH{\bullet}HCl$; c. (1) $L{:}AlH_4$, (2) oxalic acid.



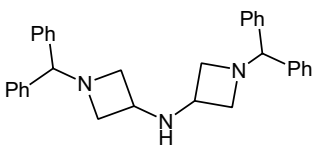
Scheme 3 a. MsCl, NEt_3, CH_3CN, –10°C, 100%; b. 28% aq. NH_3/Pr^{i}OH, 72–84%

of mesylate **3**), we first addressed reaction solvent and base, since the literature employed pyridine in both roles. By simply changing the reaction conditions to dichloromethane as the solvent and triethylamine as the base the yield was improved to *ca* 80% after a simple extractive workup. Since mesylate **3** is a crystalline solid with minimal solubility in water, the use of acetonitrile (3 vol.) as reaction solvent further streamlined the process, by enabling product isolation by simply adding water. The solid product was filtered to give quantitative yield. Subsequently, we established that the wet cake could be directly used in the subsequent aminolysis reaction without drying.

We then turned our attention to the aminolysis of the mesylate. In our hands, the literature conditions did indeed result in poor yields of **1a**.[9] Our initial modification of the procedure used the more readily handled aqueous 28% ammonium hydroxide (10 vol) and isopropanol (15 vol) at 75°C in a standard reaction flask open to the atmosphere. Under these conditions the desired product **1a** was observed as the major product, but the dimeric byproduct (**7**, Fig. 2) was also formed at high levels (>35% by HPLC). While we anticipated that some **1a** would react further with the mesylate (**3**) to give the dimer (**7**), we had hoped that the large excess of ammonia would suppress the formation of the dimer. To prevent loss of NH_3 during the course of the reaction, the process was next conducted in a Parr reactor (2 L) using 7 N ammonia in methanol for the aminolysis. On heating this reaction to 70–75°C, the pressure of the vessel rose to 40–50 psi. After 3 h, the reaction was nearly complete with a mixture of **1a:7** in a 94:6 ratio by HPLC. The product was isolated by evaporation of the volatiles and recrystallised from diisopropyl ether to give a 70% yield of **1a**. The use of a closed vessel for this process has a dual benefit of retaining the NH_3 and increasing the rate of the reaction, as the rate of S_N2 nucleophilic substitution reactions have been reported to be accelerated by applying pressure to the reaction.[13-15]

Since 7 N NH_3/MeOH is not readily available on scale, we next employed 28% aqueous NH_4OH. Again we opted to run the same reaction (10 vol of 28% NH_4OH and 15 vol of isopropanol) in the Parr Reactor and observed the dimer was reduced to approx. 4%. For workup, the reaction mixture was concentrated under reduced pressure to remove the isopropanol and the residue extracted into isopropyl ether. As the free base is difficult to isolate as a solid, the acetate salt was precipitated directly from the organic extracts on addition of 1 equiv of acetic acid. This protocol gave 72–84% yield of **1a** on multi-hundred gram scale in the lab.

The methanolic ammonia and the ammonium hydroxide aminolysis reactions were comparable in yields. In both reactions, azetidine ring opening products were not observed. The workup and isolation using methanolic ammonia was more straightforward, but 7 N methanolic ammonia is tedious to prepare on scale and its commercial availability is limited. Using aqueous ammonium hydroxide method has advantages since 28 wt% ammonium hydroxide is readily available and of low cost, and there are no handling issues. Using this protocol, multi-kilograms of 3-amino-1-benzhydrylazetidine monoacetate was prepared in high quality. In addition, both the production cost and the waste streams generated in the manufacturing were reduced significantly.



7

Fig. 2

Experimental

1-Benzhydrylazetidin-3-yl methanesulfonate: To a 51 3-neck round bottom flask was charged 632 g (2.64 mol) of 1-benzhydrylazetidin-3-ol, acetonitrile (1.9 l) and triethylamine (601 g, 1.5 equiv). The mixture was cooled in ice-acetone bath (-5°C). Methanesulfonyl chloride (436 g, 1.20 equiv) was added via a drop funnel while keeping the reaction temperature at < 5°C. HPLC showed reaction completion after 15 min. Water (6.3 l) was added, and the reaction mixture was stirred for 2 h at room temperature, and filtered. The filter cake was rinsed with water (2 × 1 l), and pulled dried under vacuum, and directly subjected to the amination reaction in the next step. An analytical sample was dried under vacuum at 45°C, its spectroscopic data were identical to those reported.[3a]

1-Benzhydrylazetidin-3-amine monoacetate: The mesylate wet cake (838 g dry weight expected, 2.64 mol) was dissolved in isopropanol at 50°C. The solution was charged to a 2 gallon Parr reactor, followed by the addition of 28 wt% ammonium hydroxide under vacuum. The Parr reactor was sealed, and heated to 71°C for 3 h (38–40 psi pressure observed). The reaction was assayed by HPLC, and showed reaction completion. The reaction mixture was cooled to room temperature, discharged from the Parr reactor, and concentrated under vacuum. The product was extracted with diisopropyl ether (8.4 l). The organic extract was concentrated to ~ 4 l under atmospheric pressure, and 159 g (1 equiv) of acetic acid was added, the mixture was stirred for 2 h, and the product (mono acetate salt) was collected by filtration. The solids were dried at 40°C under vacuum to give 662 g of product as monoacetate salt (84% yield), m.p. 149.6–152.9°C ^{1}H NMR (CD_3OD, 400 MHz) 7.42–7.04 (m, 10 H), 4.44 (s, 1H), 3.78–3.62 (m, 1H), 3.43–2.36 (m, 2H), 3.03–2.99 (m, 2H), 1.93 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz) 176.2, 141.4, 128.3, 127.3, 127.2, 77.5, 58.3, 41.2, 22.2

We thank Drs Martin A. Berliner and John A. Ragan for their valuable inputs in preparation of the manuscript.

Received 21 November 2005; accepted 28 January 2006
Paper 05/3657

References

1 K. Yager, S. Chu, and K. Appelt, X. Li, *U.S. Pat. Appl. Publ.* 2005**,** US 2005054697. *Chem. Abstr.,* 2005, **142**, 316830; (b) S. Rajinder, A. Ankush, H. Li, S. Bhamidipati, D. Carroll, C. Sylvain, J. Clough and H. Keim, *PCT Int. Appl.,* 2005, WO 2005016893. *Chem. Abstr.,* 2005*,* **142**, 254587; (c) D.J. Bartkovitz, X-J. Chu, Q. Ding, N. Jiang, A,J. Lovey, J.A. Moliterni, J.G. Mullin, B.T. Vu and P.M. Wovkulich, U.S. *Pat. Appl. Publ*. 2004, *US 2004162303*. *Chem. Abstr.,* 2004, **141**: 207221; (d) S.C.M. Fell, H.K. Rami, M. Thompson and D.R. Witty, *PCT Int. Appl*. 2004, *WO 2004078744*. *Chem. Abstr.,* 2004, **141**,260562; (e) G.J. MacDonald, H.K. Rami and M. Thompson, *PCT Int. Appl*. 2004, *WO 2004078101*. *Chem. Abstr.,* 2004, **141**, 260560; (f) M. Nazare, M. Essrich, D.W. Will, H. Matter, K. Ritter, M. Urmann, A. Bauer, H. Schreuder, J. Czech, M. Lorenz, V. Laux and V. Wehner, *Bioorg. Med. Chem. Lett.,* 2004, **14,** 4197; (g) F.E. Janssens, F.M. Sommen, B.C.A.G. De Boeck and J.E. Leenaerts, *PCT Int. Appl*. 2004, *WO 2004056800. Chem. Abstr.,* 2004*,* **141**,106497; (h) D.A. Burnett, M.A. Caplen, M.F. Czarniecki, M.S. Domalski, G.D. Ho, D. Tulshian and W-L. Wu, *PCT Int. Appl*. 2003, *WO 2003043980. Chem. Abstr.,* 2003, **139**, 6758; (i) M. Asselin, J.W. Ellingboe and R.E. Mewshaw, *PCT Int. Appl*. 2001, *WO 2001034598*. *Chem. Abstr.,* 2001, **134**, 366798; (j) D. Alker, T.V. Magee, G.N. Maw and D.S. Middleton, *PCT Int. Appl*. 1999, *WO 9901451*. *Chem. Abstr.,* 1999, **130**, 125092; (k) A. Jimenez and S. Vega, *J. Heterocycl. Chem*., 1986, **23**, 1506.

2 Commercially available from Oakwood Chemicals and Fluorochem Chemical companies.

3 (a) A. Anderson, Jr. and R. Lok, *J. Org. Chem*., 1972, **37**, 3953; (b) S.S. Chatterjee and D.J. Triggle, *Chem. Commun*., 1968, **33**, 3046; (c) V.R. Gaertner, *Tetrahedron Lett*., 1966, 4691.
4 J. Frigola, J. Pares, J. Corbera, D. Vano and, R. Merce, *J. Med. Chem*., 1993, **36**, 801.
5 C. Mannich and G. Paumgarter, *Chem. Ber*., 1937, **70**, 210.
6 C.F. Gibbs and C.S. Harvel, *J. Am. Chem. Soc*.,1935, **57**, 1137.
7 D. Nisato and M. Frigerio, *Fr. Demande* 1985, *FR 2560194*. *Chem. Abstr.,* 1986, **105**, 533737.
8 T. Okada, K. Ezumi, M. Yamakawa, H. Sato and T. Tsuji, *Chem. Pharm. Bull*., 1993, **41**,126.
9 M. Arimoto, T. Hayano, T. Soga, T. Yoshioka, H. Tagawa and M. Furukawa, *J. Antibiotics* 1986, **39**, 1243.
10 A.P. Kozikowski and A.H. Fauq, *Synlett*, 1991, **11,** 783.
11 A.R. Katritzky, D.J. Cundy and J. Chen, *J. Heterocycl. Chem*., 1994, **31**, 271.
12 M.E. Jung and Y.M. Choi, *J. Org. Chem*., 1991, **56**, 6729.
13 (a) K.R. Brower and J.S. Chen, *J. Am. Chem. Soc*., 1965, **87**, 3396; (b) K.E. Weale, *Discuss. Faraday Soc*., 1955, **20**, 83.
14 K.I. Lee and Y. Okamoto, *J. Org. Chem*., 1976, **41**, 1552.
15 M.G. Evans and M. Polanyi, *Trans. Faraday Soc*., 1935, **31**, 875.