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A One-Pot Preparation of 1,3-Disubstituted Azetidines

Michael C. Hillier*,† and Cheng-yi Chen

Department of Process Research, Merck & Co., P.O. Box 2000, Rahway, New Jersey 07065

michael_hillier@merck.com

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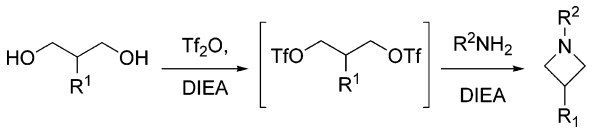
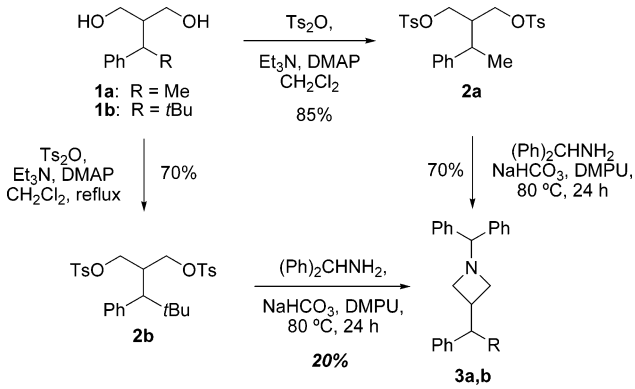


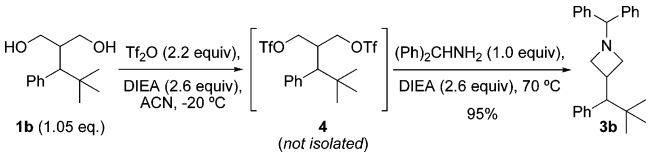
A straightforward synthesis of 1,3-disubstituted azetidines has been accomplished via the alkylation of a primary amine with the bis-triflate of a 2-substituted-1,3-propanediol species. This transformation is carried out in one reaction vessel, and elimination of the alkylating reagent is generally not a major byproduct. The scope of this methodology has been investigated using a variety 2-substituted-1,3-propanediols and amine nucleophiles.

Substituted azetidines are unique heterocycles that can be found in a number of biologically relevant compounds.[1] Many synthetic methods have been developed for the preparation of these moieties, often involving the alkylation of an amine with an activated three-carbon unit.[2] For example, unsubstituted *N*-alkyl azetidines can be assembled via intramolecular cyclization of activated amino propanols or by the double alkylation of a primary amine using 1,3-diactivated propane reagents.[3] 3-Substituted azetidines can be obtained in similar fashion from 2-substituted-1,3-propanediol derivatives and amine nucleophiles.[4] However, in some of these examples, elimination of the alkylating reagent has been observed as a major reaction byproduct.[4c,5] One solution to this problem has been to use a 2,2-disubstituted-1,3-propanediol starting material in order to block the elimination pathway.[6] Alternatively, 3-hydroxyazetidines have been prepared from an amine and epichlorohydrin, and the alcohol functionality can serve as a handle for further elaboration.[7] Despite the usefulness of these methods, no general *one-pot* method exists for the preparation of 1,3-disubstituted azetidines starting from 2-substituted-1,3-propanediols.

SCHEME 1. Azetidine Formation via Bis-Tosylate Displacement: Methyl versus *tert*-Butyl



SCHEME 2. Azetidine Formation via Bis-Triflate Activation



As part of our own program of research,[8] we became interested in the synthesis of 3-(1-phenylethyl)azetidines **3** from the corresponding diols **1** via the intermediate bis-tosylates **2** (Scheme 1). After screening a variety of bases and solvents, the activated species **2a** (1.5 equiv) was found to react slowly with aminodiphenylmethane (1 equiv) in the presence of $NaHCO_3$ (3 equiv) in DMPU at 80 °C to give **3a** (R = Me) in 70% yield after 24 h. When the same conditions were applied to the more sterically hindered substrate **2b**, the desired azetidine product **3b** (R = *t*Bu) was formed in only 20% yield, even after heating at 80 °C in a sealed vessel.[9] We postulate that the greater steric bulk of the starting material **2b** inhibits alkylation of the amine and subsequent cyclization. In light of this result, other approaches to the azetidine **3b** were examined, and a one-pot method developed by Miller and co-workers[6] using trifluoromethanesulfonic anhydride (Tf_2O) as the activator (Scheme 2) was identified. Following this procedure, the diol **1b** (1.05 equiv) was treated with Tf_2O (2.2 equiv) in the presence of

† Current address: Abbott Laboratories, North Chicago, IL 60064.

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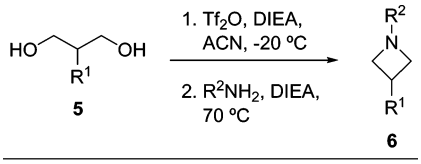
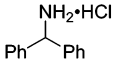
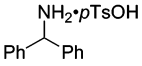
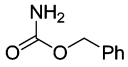
TABLE 1. Generality of the Azetidine Formation



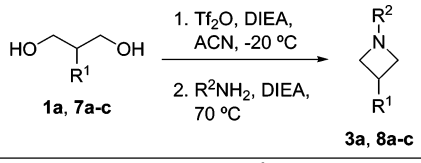
5 **6**

entry	R^1	R^2NH_2	yield (%)
1	H		64 (**6a**)
2	Me		64 (**6b**)
3	Ph		92 (**6c**)
4	OBn		92 (**6d**)
5	*t*Bu		86 (**6e**)
6	*t*Bu		39 (**6e**)
7	*t*Bu		84 (**6e**)
8	*t*Bu		32 (**6f**)
9	Ph		58 (**6g**)
10	Ph		nr
11	Ph		decomp.

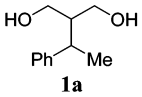
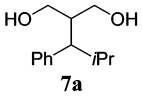
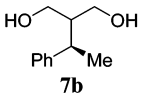
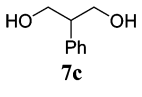
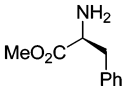
diisopropylethylamine (DIEA, 2.6 equiv) at −20 °C in acetonitrile (ACN) and aged for 10−30 min.[10] The intermediate bis-triflate **4** was not isolated but was treated with excess DIEA (2.6 equiv) and the amine nucleophile (1.0 equiv), followed by heating to 70 °C. After 1 h at this temperature, the azetidine **3b** was obtained in 95% yield with no elimination byproducts being detected.[11] Clearly, use of the bis-triflate species **4** greatly increases the rate of amine alkylation and azetidine formation compared to that obtained with the bis-tosylate **2b**. Another advantage of this method is that the alkylating reagent **4** is formed and utilized in one vessel, thereby obviating the need to prepare this intermediate in a separate step. Encouraged by the dramatic improvement observed using these conditions, the scope of this reaction was examined with other substrates.

The condensation of commercially available 2-substituted-1,3-propanediols **5** and various amines was carried out according to the procedure outlined above (Table 1). In a number of cases, the azetidine products **6** were obtained in good to excellent yield (64−92%) using a slight excess of the diol.[12] The steric bulk

TABLE 2. Azetidine Formation with Complex Substrates



1a, **7a-c** **3a**, **8a-c**

entry	diol	R^2NH_2	yield, %
1	 **1a**		85 (**3a**)
2	 **7a**		92 (**8a**)
3	 **7b**		90 (**8b**)
4	 **7c**		73 (**8c**)

of the starting diol **5** (R^1 = *t*Bu, entry 5) did not impact conversion to product, and elimination was not observed as a major byproduct even with the more acidic 2-phenyl-1,3-propanediol (R^1 = Ph, entry 3). The nature of the amine nucleophile was found to have a significant impact on the outcome of this transformation. For example, when the HCl salt of aminodiphenylmethane was employed, the azetidine product **6e** was produced in 39% yield (entry 6) compared to 86% yield obtained with the free base (entry 5). On the other hand, the tosylate salt worked well, and the azetidine **6e** was formed in 84% yield. Aniline, a generally less nucleophilic amine, reacted with the bis-triflate of 2-phenyl-1,3-propanediol, but the product **6f** was obtained in low yield (32%, entry 8). Benzyl carbamate (entry 10) did not react under these conditions, resulting in decomposition of the activated 1,3-diol. On the other hand, *tert*-butylamine did react with the bis-triflate species, but the desired azetidine product did not form and multiple unidentified byproducts were obtained (entry 11).

Other conditions were briefly screened in an attempt to improve the efficiency of the azetidine formation via the bis-triflate. When excess amine nucleophile was employed, a 5% higher yield of product was achieved, but this led to difficulties during purification.[13] Other bases were also examined with varying degrees of success. For example, the use of Na_2CO_3 led to the formation of product, but in 10−15% lower yield due to incomplete triflate formation.[14] Reactive bases, such as pyridine or *N*-methylimidazole, resulted in consumption of the activated diol, but no desired azetidine products were formed.

Heavily functionalized 2-substituted-1,3-propanediols were found to participate in this condensation reaction (Table 2). For example, the 2-(1-phenylethyl)-1,3-propanediol substrates **1a** and **7a** underwent triflate formation and reaction with aminodiphenylmethane to give the corresponding products **3a** and **8a** in 85 and 92% yield, respectively. The use of a chiral amine, (*S*)-α-methylbenzylamine (98% ee), and the chiral diol **7b** (94% ee) gave product **8b**, which could be isolated as a single

(8) Baker, R. K.; Bao, J.; Miao, S.; Rupprecht, K. M. WO 2005/000809 A1, 2005.

(9) The remainder of the reaction mass balance was unreacted bis-tosylate **2b**, mono-tosylate, and *N*-tosyl aminodiphenylmethane.

(10) Formation of the bis-triflate could be monitored by thin-layer chromatography or by HPLC.

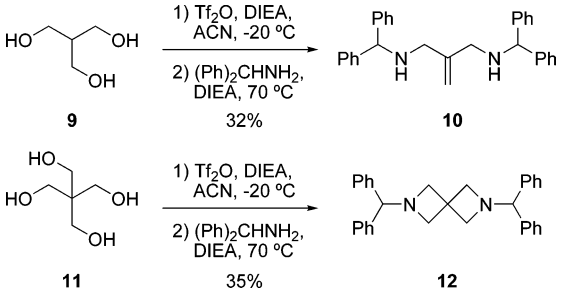
(11) No byproducts due to elimination of the bis-triflate were observed by ^1H NMR.

(12) The reaction yield is based on the amine as the limiting reagent.

(13) On large scale, the removal of excess amine nucleophile is difficult using nonchromatographic methods.

(14) Observed by HPLC analysis of the reaction mixture.

SCHEME 3. Azetidine Formation with Polyols



diastereomer in 90% yield after purification. The reaction of (*S*)-phenylalanine methyl ester (99% ee) with the bis-triflate of 2-phenyl-1,3-propanediol **7c** gave product **8c** in good yield (73%) and *with no detectable racemization.*[15]

Polyol substrates were found to undergo activation and subsequent reaction with varying results (Scheme 3). For example, the triol **9** was converted to the triflate followed by reaction with aminodiphenylmethane to give the dimeric product **10** in 32% yield. Apparently, with this substrate, triflate displacement and elimination is favored over cyclization to give azetidine products. The reaction of pentaerythritol **11** gave the spirocyclic azetidine dimer **12** in 35% yield when excess Tf_2O (4.2 equiv), DIEA (10 equiv), and the amine (3.8 equiv) were employed.[16]

In conclusion, we have demonstrated the one-pot formation of 1,3-disubstituted azetidines via the reaction of amine nucleophiles with in situ prepared bis-triflates of 2-substituted-1,3-propanediols. This method has broad substrate scope, works well with a variety of functionalized chiral or achiral diol substrates, and does not require preparation of the alkylating species as a separate step. In general, sterically bulky diols react smoothly under these conditions, and elimination of the alkylating reagent is not a major reaction pathway. On the other hand, sterically hindered and electron-poor amines are not good coupling partners, but chiral amines work well with no racemization.

(15) As determined by comparison to a racemic standard according to chiral SFC analysis.

(16) A number of other unidentified products were obtained in this reaction.

Experimental Section

General Azetidine Formation Procedure. To a solution of the diol (5 mmol) in dry ACN (10 mL) at −20 °C was slowly added trifluoromethanesulfonic anhydride (10.5 mmol) over 10−20 min followed by diisopropylethylamine (DIEA, 12.5 mmol) over 10−20 min. Both reagents were added at such a rate as to maintain the internal reaction temperature below −10 °C, and the resulting reaction mixture was aged for 10−30 min at −20 to −10 °C. Additional DIEA (12.5 mmol) was then added over 5 min followed by the amine (4.75 mmol) over 5 min, and the reaction was heated to 70 °C for 1−2 h. Solvent was removed in vacuo, and the resulting crude reaction mixture was purified via silica gel chromatography to give the azetidine products in the yields indicated.

Acknowledgment. The authors thank Dr. Ross A. Miller for useful discussions.

Supporting Information Available: Experimental details for the synthesis of 2-substituted-1,3-propanediols **1a**,**b** and **7a**,**b** and the bis-tosylates **2a**,**b**, full characterization data for all compounds, and ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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