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Facile ring cleavage of basic azetidines

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ABSTRACT

Azetidines containing a basic ring nitrogen atom have been shown to undergo facile ring cleavage to afford 3-halo-1-amino propane derivatives upon exposure to alkyl bromides and acyl chlorides under certain conditions. The rate of ring cleavage appears to be determined largely by the rate at which quaternization of the azetidine nitrogen atom occurs. Alkylation of NH azetidines to afford *N*-alkyl azetidines can be carried out in synthetically useful yields if reaction times are kept short. As the free base, azetidines may undergo spontaneous oligomerization with concomitant ring cleavage.

Azetidines have come to play an important role in medicinal chemistry programs.[1] Azetidines impart lower basicity, lipophilicity, and molecular weight to target compounds than the corresponding pyrrolidine and piperidine rings, often resulting in more favorable pharmacokinetic properties. In addition, they often provide an element of novelty that can be important to securing an intellectual property position. Despite these appealing properties, the ring strain inherent in the four membered ring cannot be overlooked, and can contribute to undesired reactivity of the azetidine ring. While the ring cleavage of azetidinones (β-lactams) has been exploited for decades, the ring cleavage of all sp^3 azetidine rings has only been studied more recently. Ring cleavage by a mechanism involving the intramolecular generation of an adjacent carbenium ion center, followed by azetidine ring expansion to a pyrrolidine and trapping with a halide or other nucleophile, has been reported.[2] Similarly, the ring cleavage of tertiary azetidines by an intramolecular acid chloride has been reported.[3] Recently, the regiospecific ring cleavage of 1-alkyl-2-(trifluoromethyl)azetidines by alkyl, acyl, and hydrogen halides was reported.[4] In this Letter, we wish to report the unexpectedly facile ring cleavage of some azetidines under various intermolecular reaction conditions.

During the course of a recent medicinal chemistry program, we sought to prepare the tertiary azetidine **2** as an intermediate for further elaboration (Fig. 1). Following an established procedure for the analogous piperidine compound,[5] we attempted the preparation of **2** from the readily available[6] intermediate **1a** by alkylation with methyl bromoacetate. To our surprise, the major product of this reaction, isolated in 88% yield, was not the expected tertiary azetidine **2** but rather the trisubstituted propane derivative **3a**. The structure of **3a** was plainly evident from its mass spectrum and ^{1}H NMR. Further evidence to confirm the structure of **3a** was its conversion into the oxazolidinone **4** upon heating, a reaction characteristic of *N*-BOC amines substituted with a beta-leaving group.[7] The structure of **4** was likewise established by ^{1}H and ^{13}C NMR, mass spectroscopy, IR, and elemental analyses.

Prompted by this result, we sought to explore the scope of this reaction to determine its generality and potential synthetic utility (Table 1). Initial efforts were focused upon the use of **1a** as a substrate for this reaction, after which additional secondary and tertiary azetidines were examined.

From Table 1, it can be seen that reactive alkyl bromides, such as benzyl bromides, allyl bromide, methyl bromide,and methyl bromoacetate all afforded the products of exhaustive alkylation and ring cleavage in moderate to good yields, while the kinetically

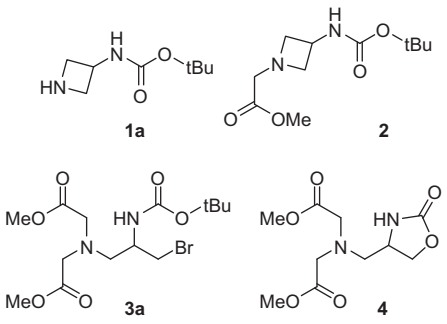

Figure 1.

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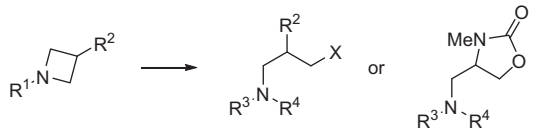
Table 1
Cleavage of azetidines **1** upon alkylation[a] Structures of starting materials **1** and products **3** and **5** are shown above



1a - g **3a - s** **5a - c**

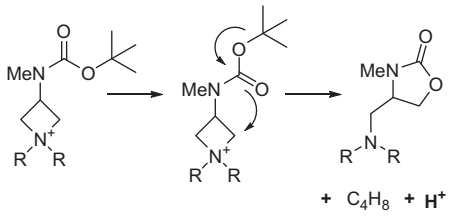
Entry	Azetidine	R^1	R^2	Alkyl halide (equiv)	Product	R^3	R^4	Yield (%)[b]
1	**1a**	H	NHBOC	$BrCH_2CO_2Me$ (2.1)	**3a**	CH_2CO_2Me	CH_2CO_2Me	88
2	**1a**	H	NHBOC	$BrCH_2C_6H_4$-4-NO_2 (2.1)	**3b**	$CH_2C_6H_4$-4-NO_2	$CH_2C_6H_4$-4-NO_2	50
3	**1a**	H	NHBOC	$BrCH_2C_6H_4$-4-CN (2.1)	**3c**	$CH_2C_6H_4$-4-CN	$CH_2C_6H_4$-4-CN	49
4	**1a**	H	NHBOC	$BrCH_2Ph$ (2.1)	**3d**	$BrCH_2Ph$	$BrCH_2Ph$	50
5	**1a**	H	NHBOC	$BrCH_3$ (5)	**3e**	CH_3	CH_3	53
6	**1a**	H	NHBOC	$BrCH_2CH_2CH_3$ (2.1)	**3f**	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	<10[c]
7	**1b**	H	NMeBOC	$BrCH_2C_6H_4$-4-CN (2.1)	**5a**	$CH_2C_6H_4$-4-CN	$CH_2C_6H_4$-4-CN	81
8	**1c**	$CH_2C_6H_4$-4-CN	NHBOC	$BrCH_2C_6H_4$-4-NO_2 (1.1)	**3g**	$CH_2C_6H_4$-4-CN	$CH_2C_6H_4$-4-NO_2	52
9	**1d**	H	$NHCO_2Me$	$BrCH_2C_6H_4$-4-CN (2.1)	**3h**	$CH_2C_6H_4$-4-CN	$CH_2C_6H_4$-4-CN	56
10	**1e**	$CH_2C_6H_4$-4-NO_2	NMeBOC	$BrCH_2CH{=}CH_2$ (1.1)	**5b**	$CH_2C_6H_4$-4-NO_2	$CH_2CH{=}CH_2$	83
11	**1e**	$CH_2C_6H_4$-4-NO_2	NMeBOC	$BrCH_2C_6H_4$-4-CN (1.1)	**5c**	$CH_2C_6H_4$-4-NO_2	$CH_2C_6H_4$-4-CN	77
12	**1e**	$CH_2C_6H_4$-4-NO_2	NMeBOC	$BrCH_2CH_2CH_3$ (1.1)	**5d**	$CH_2C_6H_4$-4-NO_2	$CH_2CH_2CH_3$	37
13	**1e**	$CH_2C_6H_4$-4-NO_2	NMeBOC	$CH_3CHBrCH_3$ (1.1)	**5e**	$CH(CH_3)_2$	$CH(CH_3)_2$	<10[c]
14	**1f**	H	OC_6H_4OMe	$BrCH_2C_6H_4$-4-CN (2.1)	**3i**	$CH_2C_6H_4$-4-CN	$CH_2C_6H_4$-4-CN	59
15	**1g**	Me	$OCHPh_2$	$BrCH_2C_6H_4$-4-CN (1.1)	**3j**	CH_3	$CH_2C_6H_4$-4-CN	50

[a] Experiments were performed using 1 mmol of **1**, the indicated alkylating agent, and 2.5 equiv of powdered K_2CO_3 in 7 mL of MeCN for 24 h at 20 °C while being monitored by LCMS.
[b] Isolated yields of purified product.
[c] The product was not isolated but was present in the reaction mixture by LCMS.

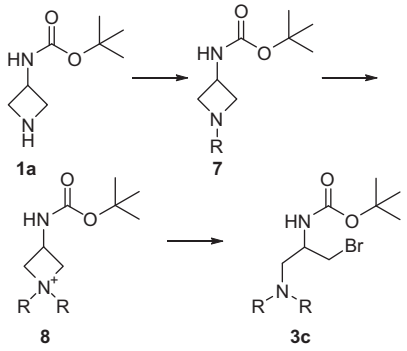
less reactive 1-bromopropane afforded a lower yield during the standard reaction time (entries 6 and 12). Similarly, 2-bromopropane failed to afford a significant amount of product (entry 13), suggesting that the overall rate of this reaction is determined largely by the rate at which alkylation of the azetidine by the alkylating agent occurs. Azetidines **1f** and **1g** likewise underwent alkylation and azetidine ring cleavage (entries 14 and 15), demonstrating that this process is not exclusive to carbamate substituted azetidines.

Also of note was the propensity with which the 3-*N*-methyl-*N*-BOC substituted azetidines **1b** and **1e** underwent cyclization to the oxazolidinone derivatives **5a–5d** (entries 7, 10–13). In these experiments, LCMS monitoring of the reaction mixtures showed the formation of **5** without the apparent intermediacy of the ring opened products **3**, suggesting that the scission of the azetidine ring was effected by intramolecular attack of the BOC group (Scheme 1). Indeed, a side–by side comparison of azetidines **1a** and **1b** under the same reaction conditions showed that accumulation of the ring–opened bromopropane product **3** was observed with **1a** but not with **1b**.

A study of the reaction using ^{1}H NMR was undertaken to further understand the alkylation and ring scission. Azetidine **1a** was treated with 4-cyanobenzyl bromide (**6**) in CD_3CN in the presence of powdered K_2CO_3 at 20 °C (Scheme 2). Aliquots of the reaction mixture were taken at intervals, filtered, and diluted with CD_3CN for immediate ^{1}H NMR analysis. The identity of the products and intermediates present in the mixture was established by comparison to the ^{1}H NMR spectra of authentic samples of **1a**, 4-cyanobenzyl bromide **6**, the tertiary azetidine **7**, and the ring cleavage product **3c**.



Scheme 1. Proposed mechanism for intramolecular cleavage of azetidinium ion by adjacent N(Me)BOC group.



Scheme 2. Species generated during reaction of **1a** with 4-cyanobenzyl bromide **6** monitored by ^{1}H NMR. R = 4-cyanobenzyl.

Table 2
^{1}H NMR study of reaction of **1a** with 2.2 equiv 4-cyanobenzyl bromide **6**[a]

Time (h)	**1a**	**6**	**7**	**8**	**3c**
0	1.0[b]	2.2[b]	0	0	0
0.25	0	1.2	1	0	0
1	0	0.8	0.7	0	0.4
2	0	0.6	0.5	0	0.5
4	0	0.5	0.3	0	0.7
21	0	0.2	0.1	0	0.9

[a] The experiment was performed using 0.7 mmol of **1a** and 1.6 mmol of **6** in 5 mL of CD_3CN containing 1.8 mmol powdered K_2CO_3 and monitored by ^{1}H NMR
[b] Molar equivalents of starting materials and products determined by integration of unique resonances and normalized to **1a** originally present. Assignments were made by comparison to ^{1}H NMR spectra of authentic samples.

From the results in Table 2, it can be noted that the initial alkylation of **1a** to afford **7** was quite rapid, having gone to completion with 15 min. The subsequent quaternization of **7** by **6** was

considerably slower. Interestingly, no accumulation of the quaternary salt **8** could be observed by ^{1}H NMR (or by UPLC–MS), suggesting that cleavage of the quaternary salt **8** to afford **3c** occurred at a significantly faster rate than the quaternization of **7**.

The ^{1}H NMR study suggested that the tertiary azetidines that were the original object of this investigation, such as **2**, could be prepared successfully by direct alkylation if the reaction time was kept short. Treatment of **1a** with methyl bromoacetate for 45 minutes afforded **2** in 68% isolated yield. Likewise, treatment of **1a** with 4-cyanobenzyl bromide for 45 min afforded **7** in 74% isolated yield, identical in all regards with a sample of **7** prepared by reductive amination of **1a** with 4-cyanobenzaldehyde.

As this study progressed, we observed that the sample of **1a** that we were using slowly underwent degradation. Originally a free flowing white solid, melting point 134–136 °C (lit. melting point 138–140 °C),[6] our sample of **1a** gradually transformed into a stiff taffy–like substance after standing at ambient room temperature in the dark for 2 years. The melting point had decreased to less than 100 °C. Trituration of this degraded material with 1-chlorobutane returned only 16% of **1a** as a white solid. Chromatography of the mother liquor afforded an additional 20% of **1a** and 35% of a colorless glass. The ^{1}H and ^{13}C NMR and high resolution mass spectrum of this substance indicated that it was a dimer of **1a**, either the diazacyclooctane structure **9** or the tertiary azetidine **10** (Fig. 2). Acylation with *p*-toluic anhydride and Et_3N in THF afforded 87% of a mono-toluamide **11** (Fig. 3), a result consistent with the tertiary azetidine **10**. The diazacyclooctane structure may therefore be eliminated from consideration, in as much as no bis-toluamide was formed.

Azetidine **1g** also underwent decomposition when stored as the free base at room temperature. Originally a mobile oil, **1g** transformed to a stiff resin within 1 week. ^{1}H NMR showed that 15% of **1g** remained in the resinous material; the remainder of the sample was composed of ring–opened oligomers of **1g**.

Acylation of the dimer **10** with *p*-toluoyl chloride and Et_3N in THF did not afford **11**, but instead afforded 58% of **12**,[8] resulting from the reaction of **10** with additional *p*-toluoyl chloride and ring cleavage by chloride ion.

Likewise, acylation of the azetidine **13** with *p*-toluoyl chloride and Et_3N in THF afforded 96% of the amide **14** within 10 min at ambient temperature (Fig. 4). These results demonstrate yet again the exceptional susceptibility of the azetedinium ion to ring cleavage by halide ions.

Having shown that the azetidine ring was readily cleaved by exposure to alkyl halides and acyl halides under conditions during which formation of an azetidinium ion was likely, we sought to determine whether exposure to hydrogen halides would result in a similar general ring cleavage reaction. The cleavage of azetidines by hydrogen halides is known,[9] and can cause difficulty during the removal of a BOC group,[10] but the generality of this side reaction is not known. Surprisingly, the azetidine **1f** resisted ring cleavage in a ^{1}H NMR experiment upon exposure to D_2O solutions containing either 6 M DCl or 8 M DBr, even at 80 °C for up to 4 h. Similarly, **1f** and *N*-BOC **1f** afforded no significant amounts of ring cleavage product upon exposure to 4 M HCl in dioxane solution.

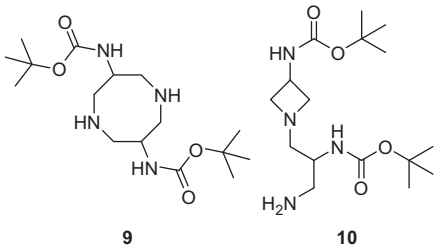


Figure 2. Structures of possible products of spontaneous dimerization of **1a** .

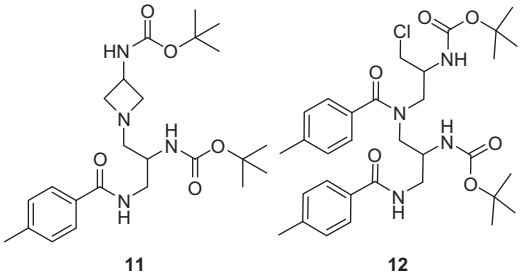


Figure 3. Structures of products resulting from treatment of **10** with *p*-toluic anhydride and *p*-toluoyl chloride, respectively.

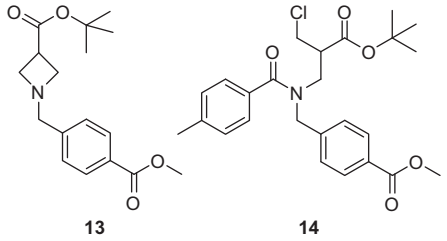


Figure 4. Acylation and concomitant ring cleavage of a tertiary azetidine.

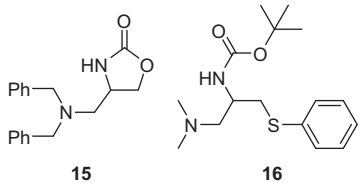


Figure 5. Medicinal chemistry intermediates prepared from **1a** by azetidine alkylation and ring cleavage.

The ring cleavage of azetidines may be used to prepare tri-substituted propane derivatives that otherwise might require lengthier syntheses.[11] For example, we prepared *rac*-**15**[12] (Fig. 5) in 96% isolated yield in a single step from **1a** by heating for 16 h with excess benzyl bromide and K_2CO_3 in MeCN.

Likewise, *rac*-**16**[13] was prepared in 65% yield in two-steps starting from **1a**: (a) alkylation with methyl bromide, followed by (b) treatment with sodium thiophenoxide.

In conclusion, we have found that azetidines with a basic ring nitrogen atom may be easily cleaved upon exposure to alkyl and acyl halides. N-Unsubstituted azetidines may be successfully alkylated or acylated with appropriate selection of reaction conditions. Azetidines, as the free base, may undergo oligomerization involving ring cleavage and the formation of dimeric and possibly other products. The reactivity that we describe should inform the organic chemistry community that azetidines should not be viewed simply as lower molecular weight, less polar analogs of pyrrolidines and piperidines. Indeed, azetidines may bring an undesirable reactivity profile to synthetic targets. In these regards, azetidines may be viewed similarly to aziridines.[14] Finally, the ring opening of appropriately substituted azetidines may offer a synthetic approach for the preparation of tri-substituted propane derivatives.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.03.012.

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