Tetrahedron Letters 54 (2013) 2502–2505

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Facile ring cleavage of basic azetidines

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ARTICLE INFO

Article history:
Received 16 February 2013
Revised 3 March 2013
Accepted 4 March 2013
Available online 13 March 2013

Keywords:
Azetidine
Heterocycle
Ring cleavage
Alkylation
Acylation

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

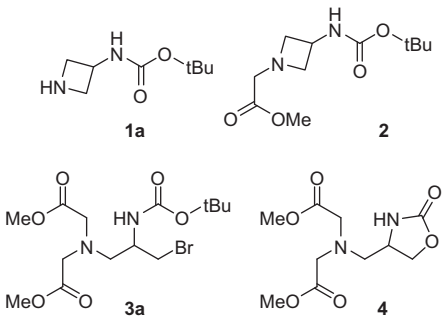

Figure 1.

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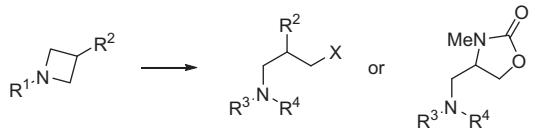
http://dx.doi.org/10.1016/j.tetlet.2013.03.012

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**

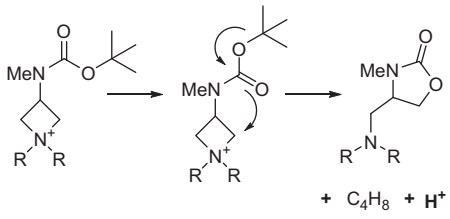
Entry	Azetidine	R^1	R^2	Alkyl halide (equiv)	Product	R^3	R^4	Yield (%)[b]
1	**1a**	H	NHBOC	$BrCH_2CO_2Me$ (2.1)	**3a**	CH_2CO_2Me	CH_2CO_2Me	88
2	**1a**	H	NHBOC	$BrCH_2C_6H_4$-4-NO_2 (2.1)	**3b**	$CH_2C_6H_4$-4-NO_2	$CH_2C_6H_4$-4-NO_2	50
3	**1a**	H	NHBOC	$BrCH_2C_6H_4$-4-CN (2.1)	**3c**	$CH_2C_6H_4$-4-CN	$CH_2C_6H_4$-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.

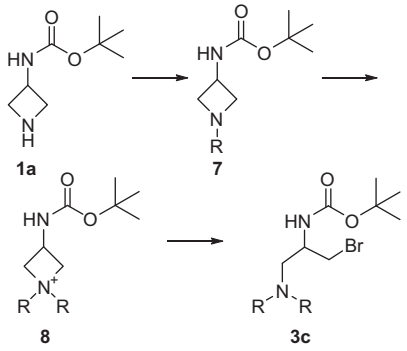
less reactive 1-bromopropane afforded a lower yield during the standard reaction time (entries 6 and 12). Similarly, 2-bromopropane failed to afford a significant amount of product (entry 13), suggesting that the overall rate of this reaction is determined largely by the rate at which alkylation of the 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