Tetrahedron Letters 50 (2009) 6590–6592

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Microwave-assisted synthesis of azetidines in aqueous media

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ARTICLE INFO

Article history:
Received 9 August 2009
Revised 2 September 2009
Accepted 11 September 2009
Available online 15 September 2009

Keywords:
Azetidines
Microwaves
Cyclization
Cyclic sulfates
Green chemistry

ABSTRACT

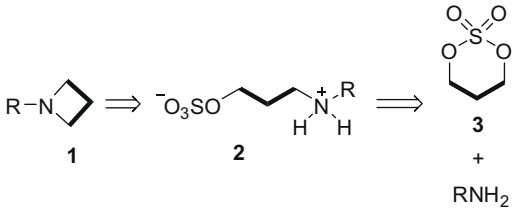
Simple azetidines are synthesized in good to excellent yields and high purity via cyclization of 3-(ammonio)propyl sulfates derived from primary amines and the cyclic sulfate of 1,3-propanediol. A feature of this methodology includes the accelerated synthesis of azetidines in water under the influence of microwave-assisted heating.

Azetidines (**1**) are heterocycles of enormous interest owing to their wide and varied applications. Azetidines and azetidine-containing structures are well known not only for their biological activities,[1] but also for their usefulness as monomers and cross-linkers in the polymer industry[2] and as valuable synthetic intermediates in their own right.[3] Traditional methods of accessing azetidines include the cyclization of suitably activated γ-amino alcohols,[4,5] γ-amino halides[5a,6] and ω- and β-haloimines.[7] Whilst some of these methods result in problematic elimination, dimerization or fragmentation,[5g] other methods[8] tend to be less applicable for general use. We report here an alternative and efficient methodology for accessing simple azetidines through cyclization of 3-(*N*-alkylamino)propyl sulfates (**2**) furnished from the reaction of primary amines with the cyclic sulfate of 1,3-propanediol (**3**) (Scheme 1).

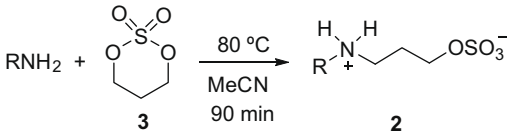
The use of **3** as the source of the azetidine backbone is advantageous as the zwitterionic 3-(N-substituted ammonio)propyl sulfates would avoid problems associated with dialkylation and oligomerization commonly encountered in azetidine synthesis employing 1,3-dihalopropanes or bis-activated diols as alkylating agents. In addition, the use of **3** provides an expedient method of accessing activated 3-amino alcohols in a single step without requiring the handling of air/moisture-sensitive reagents.

Whilst the base-mediated thermal cyclization of 3-(N-substituted ammonio)propyl sulfates is low yielding,[5a] microwave-assisted synthesis of *N*-phenylazetidine from aniline and 1,3-dichloropropane has been reported to proceed in good yield.[9] We were therefore intrigued to investigate whether the superior heating offered by modern microwave reactors could be exploited to improve the yields in our proposed synthesis.

A range of 3-(N-substituted ammonio)propyl sulfates (**2a–i**) were synthesized in excellent yields following reaction of a variety of primary amines with **3** in acetonitrile (Scheme 2). An attractive feature of the preparation is the fact that the zwitterionic ammonium sulfates precipitate from the reaction mixture allowing most of the products to be obtained analytically pure following filtration of the crude reaction mixture (Table 1).



Scheme 1. Synthetic strategy for the synthesis of simple azetidines.



Scheme 2. Synthesis of 3-(N-substituted ammonio)propyl sulfates 2.

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doi:10.1016/j.tetlet.2009.09.063

Table 1
Isolated yields of **2a–i**

Entry	R	Product	Yield (%)
1	Bn	**2a**	91
2	*n*-C_6H_{13}	**2b**	77
3	*n*-$C_{12}H_{25}$	**2c**	88
4	*i*-Pr	**2d**	72
5	*t*-Bu	**2e**	89
6	Cyclopentyl	**2f**	83
7	Cyclohexyl	**2g**	86
8	Ph	**2h**	80[a]
9	Allyl	**2i**	84

[a] Estimated 90–95% purity by ^{1}H NMR spectroscopy.

Sulfate **2a** was then used as a model system to establish optimal conditions for the cyclization reaction (Table 2). Heating at 120 °C for 15 min resulted in only trace amounts of **1a** being detected (entry 1) and increasing the temperature to 150 °C improved this conversion to 10% (entry 2), however, extending the reaction time led to decomposition of the products. Addition of 0.2% water had no effect on the product distribution (entry 3) and a gradual increase in the amount of water to 50% (entry 4) had an improvement in the recovery of mass balance, but also resulted in the increased formation of by-products.

When a completely aqueous system was utilized, **1a** was isolated cleanly and in excellent yield (entry 5) following work-up. Subsequent experiments focused on establishing the minimum temperature required for successful conversion of **2a** into **1a** (entries 6–9). It can clearly be seen that reactions conducted at 100 °C and below resulted in inferior yields or no reaction at all. Similar low yields were noted for the reaction carried out in boiling water (entry 10) using conventional heating. In contrast, reactions carried out at 120 and 150 °C for 15 min gave moderate to good yields of **1a**, although the yield dropped when the reaction time was reduced to 5 min. The use of LiOH as a base showed some improvement in the isolated yield of **1a** under conventional heating, but the difference between KOH and LiOH under microwave conditions was found to be negligible.

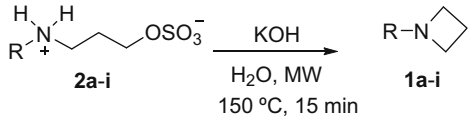
Gratifyingly, azetidines **1b–i** were obtained reproducibly in good to excellent yields and in high purity when sulfates **2b–h** were reacted under the optimized conditions (Scheme 3, Table 3).

In the case of **2i** it was evident that, in addition to the formation of minor quantities of **1i**, oligomerization had occurred to afford **4** with evidence of $n = 1$, 2 and 3 detected by ES-MS. This may arise from direct nucleophilic displacement of the sulfate by deprotonated **2i** followed by hydrolysis of the terminal sulfate moiety. Alternatively, ring-opening oligomerization of the initially formed *N*-allyl azetidine could occur, initiated by nucleophilic attack by hydroxide on the azetidine ring. Variation of the reaction temperature and time did not prevent oligomerization and this anomalous result was not investigated further.

Table 2
Selected optimization studies for the cyclization of **2a** to **1a**

Entry	Conditions[a]	**2a**:**1a**	Yield (**1a**)
1	120 °C, MeCN, 15 min	1:trace	0
2	150 °C, MeCN, 15 min	9:1	<5%[b]
3	150 °C, MeCN (+0.2% H_2O)	9:1	<5%[b]
4	150 °C, 1:1 MeCN/H_2O, 15 min	n.d.	<10%[b]
5	150 °C, H_2O, 15 min	0:1	74%
6	120 °C, H_2O, 15 min	0:1	50%
7	100 °C, H_2O, 15 min	0:1	8%
8	60 °C, H_2O, 15 min	NR	0
9	rt, H_2O, 15 min	NR	0
10	100 °C, H_2O, reflux, 15 min[c,d]	NR	0
11	150 °C, H_2O, 5 min	0:1	41%
12	100 °C, H_2O, reflux, 15 min[d,e]	0:1	9%
13	150 °C, H_2O, 15 min[e]	0:1	71%

[a] All reactions were performed with KOH (2 equiv) under microwave heating unless otherwise indicated.
[b] Estimated by ^{1}H NMR spectroscopy/mass recovery.
[c] Impurities detected.
[d] Conventional heating.
[e] LiOH (2 equiv).

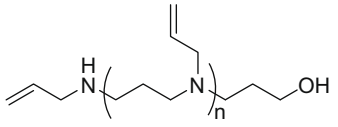


Scheme 3. Preparation of azetidines **1a–i**.

Table 3
Isolated yields of azetidines **1a–i**

Entry	R	Product	Yield
1	Bn	**1a**	74
2	*n*-C_6H_{13}	**1b**	73
3	*n*-$C_{12}H_{25}$	**1c**	79
4	*i*-Pr	**1d**	55
5	*t*-Bu	**1e**	57
6	Cyclopentyl	**1f**	84
7	Cyclohexyl	**1g**	79
8	Ph	**1h**	67[a]
9	Allyl	**1i**	Trace[b]

[a] 74% mass balance, 90% purity (^{1}H NMR).
[b] 20% of mass balance recovered as the oligomer.



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Whilst the influence of microwave energy on the cyclization step was not specifically investigated as part of this study, the similar results obtained in experiments at 100 °C under conventional and microwave heating seem to rule out such an effect. This is particularly evident when considering the heating data, with reactions at 100 and 120 °C having almost identical exposure to microwave energy in the first 5 min of the reaction. We believe that the high efficiency of microwave heating, the ability to reach temperatures well above the boiling point of the solvent and the associated increase in internal pressure all contribute favourably to the efficient cyclization of **2** to azetidines.

In summary we have demonstrated an efficient microwave-assisted approach to the synthesis of azetidines starting from **3** and demonstrated its effective application with a range of structurally diverse primary amines. Both the synthesis of the zwitterionic ammonium sulfates **2** and the azetidines proceed in good to excellent yield and produce products of high purity through simple work-up.

Acknowledgement

This research was supported by the Science and Engineering Research Council of A*STAR (Agency for Science, Technology and Research), Singapore.

Supplementary data

Full experimental details, including microwave heating profiles and spectroscopic data for all compounds. ^{1}H and ^{13}C NMR spectra for compounds **1a–g** and **2a–i** are provided. Supplementary data

associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.063.

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