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Critical importance of leaving group 'softness' in nucleophilic ring closure reactions of ambident anions to 1,2-diazetidines

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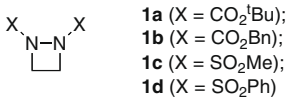
ABSTRACT

Highly strained, four-membered 1,2-diazetidine rings are produced in good yields (50–98%) in nucleophilic ring closure reactions provided 'soft' leaving groups such as iodide are used, a finding that can be rationalised in terms of the Hard Soft Acids and Bases principle.

Since the discovery of the potent biological effects of the β-lactam antibiotics,[1,2] there has been significant interest in the synthesis and properties of four-membered heterocycles.[3] However, much of this work has been hampered by the difficulty associated with the preparation of these systems, largely because of the intrinsic ring strain associated with four-membered rings.[4] An interesting case in point is the 1,2-diazetidine nucleus which has two adjacent nitrogen atoms within the four-membered ring. Although the biological effects of various 1,2-diazetidinones have been assessed because of their structural similarity to β-lactams,[5] systematic studies into the chemistry of 1,2-diazetidines have been severely impeded by the lack of general routes for their preparation. For example, simple 1,2-diazetidines such as **1a–d** bearing Boc, Cbz, Ms and SO_2Ph groups, respectively, on the nitrogen atoms have not been made (Fig. 1). In this Letter, we disclose an efficient synthesis of a range of 1,2-diazetidines including **1a–d**, by nucleophilic ring closure. We show that the nature of the leaving group is critical to facilitating four-membered ring formation, observations that can be understood qualitatively in terms of the Hard Soft Acids and Bases (HSAB) principle.[6] These findings are expected to have broader significance in relation to effecting other 'difficult' nucleophilic ring closure reactions. Moreover, these studies call into doubt earlier work[7] purporting the synthesis of 1,2-diazetidines by nucleophilic ring closure.

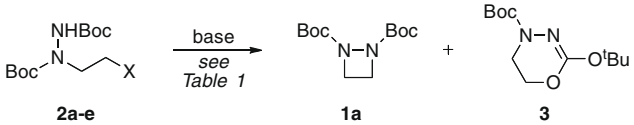
Both cycloaddition and ring closure strategies have been explored in the search for preparatively useful routes to 1,2-diazetidines.[7–11] The most direct approach centres on [2π+2π] cycloadditions of azodicarbonyl compounds with electron-rich alkenes.[8] However, competing [4π+2π] cycloadditions and ene rearrangements are often the main results in these attempts. High yielding [2σ+2σ+2π] cycloadditions of azodicarboxylate derivatives with quadricyclane have been reported, although substrate scope is very limited.[9] Of the ring closure methods, bisalkylation of 1,2-dialkylhydrazines with 1,2-dibromoethane provides 1,2-diazetidines directly, although yields are moderate at best.[10] In a related study, Miao et al. reported that the intramolecular ring closure of 1-(1-hydroxy-propan-2-yl)hydrazine-1,2-dicarboxylate derivatives provides an efficient route to enantiomerically enriched 1,2-diazetidines in high yields.[7] Most recently, Ma disclosed an efficient ring closure method based upon the reaction of 2,3-allenyl hydrazines with aryl halides under palladium catalysis.[11]

Our studies began with the examination of the ring closure of alcohol **2a** (X = OH), which was readily synthesised by treatment of commercially available 2-hydroxyethyl-hydrazine with di-*tert*-butyl dicarbonate in 94% yield. Reaction of **2a** under Mitsunobu conditions led solely to the formation of oxadiazine **3** in 64% isolated yield by way of ring closure through the carbamate oxygen to form a six-membered ring (Scheme 1 and Table 1, entry 1). Ring closure of the corresponding mesylate **2b** using Cs_2CO_3 (8 equiv) in MeCN led to the same product in essentially quantitative yield. However, formation of the required 1,2-diazetidine was encour-



1a (X = $CO_2{}^tBu$);
1b (X = CO_2Bn);
1c (X = SO_2Me);
1d (X = SO_2Ph)

Figure 1.



2a-e **1a** **3**

Scheme 1.

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Table 1
Cyclisation to 1,2-diazetidine **1a** and/or 1,3,4-oxadiazine **3**

Entry	Substrate	X	Conditions[a]	**1a**:**3**[b]	Yield[c]
1	**2a**	OH	PPh_3, DEAD, THF, 0 °C	0:100	64% (**3**)
2	**2b**	OMs	Cs_2CO_3, MeCN	3:97	96% (**3**)
3	**2c**	Cl	Cs_2CO_3, MeCN	27:73	—
4	**2d**	Br	Cs_2CO_3, MeCN	40:60	—
5	**2e**	I	Cs_2CO_3, MeCN	54:46	53% (**1a**)
6	**2e**	I	*sec*-BuLi, THF	0:100	—
7	**2e**	I	NaO^{t}Bu, THF	6:94	—
8	**2e**	I	KO^{t}Bu, THF	7:93	—
9	**2e**	I	TBD,[d] MeCN	50:50[e]	—
10	**2e**	I	DBU, MeCN	55:45	—

[a] Procedures are provided in the Supplementary data.
[b] Determined by ^{1}H NMR analysis of the crude reaction mixture. Complete consumption of starting material unless otherwise stated.
[c] Yield after silica gel chromatography.
[d] TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene.
[e] Reaction did not go to completion.

Table 2
Selected geometric parameters and spectral data for **1a** compared to $EtO_2CNHNHCO_2Et$ (**4**)

Parameter	**1a**	**4**[d]
C6–N7	1.3915 Å	1.352 Å
C6–O6	1.2083 Å	1.209 Å
N7–N7′	1.4505 Å	1.379 Å
C6–N7–N7′–C6′	101.51°	83.92°
τ[a]	33.4°	4.3°
Pyram(N7)[b]	30.67°	n.d.
C=O stretch/cm^{-1}	1739	1712
NMR δ (C=O)[c]	160.2	158.7

[a] The amide twist angle (τ) as defined by Winkler and Dunitz,[13] and modified by Yamada.[14]
[b] The pyramidalisation of the nitrogen atoms is defined as 360 – $\sum$ where $\sum$ is the sum of the valence angles of the nitrogen atom.
[c] In $CDCl_3$.
[d] Crystallographic data from Linke and Kalker,[15] spectroscopic data from Çavdar and Saraçoglu.[16]

aged by the use of a halide as the leaving group. Using **2c** (X = Cl), a small amount of diazetidine **1a** was observed. Improved results were achieved with bromide **2d** (X = Br), and using iodide **2e** (X = I), bis-Boc diazetidine **1a** was the major product and could be isolated in appreciable quantities (53%). Moreover, the use of large, diffuse cations favoured diazetidine formation (Table 1, entries 5–10).

The structures of diazetidine **1a** (Fig. 2) and oxadiazine **3** (see Supplementary data) were deduced unambiguously by X-ray crystallography.[12] It is instructive to compare selected data for **1a** alongside diethyl hydrazinedicarboxylate (**4**) (Table 2). The crystallographically identical nitrogen atoms within **1a** are highly pyramidal, displaying significant amide twist angles (τ) and bond lengths consistent with poor overlap between the nitrogen lone pair and the C=O bond. By adopting this conformation, electron repulsion between the nitrogen lone pairs, and steric clash between the carbamate groups are minimised. Moreover, the diazetidine ring suffers less Baeyer strain than would occur if the nitrogen atoms were planar. DFT calculations (B3LYP) produce ground state structures that closely match the experimental structures of **1a** and **3** (see Supplementary data).

In the ^{1}H NMR spectrum ($CDCl_3$, 300 MHz), all the ring hydrogens of **1a** are chemically equivalent producing a single resonance at δ 4.12 (4H, s), suggesting fast pyramidal inversion on the NMR timescale. No changes to this signal occurred over a wide range of temperatures (223–373 K). The barrier to inversion in 1,2-dimethyldiazetidine is 16.4 kcal mol^{-1},[10a] indicating that the presence of electron-withdrawing Boc groups results in a greater rate of N-inversion.[17]

The optimised cyclisation conditions were applied to the synthesis of 1,2-diazetidines **1b–d** (Scheme 2). Again, conversion of iodide **5** into **1b** was accompanied by production of quantities of the corresponding 1,3,4-oxadiazine **6** (56:44 ratio before purification) by way of cyclisation through the carbamate oxygen. Interestingly, cyclisation to sulfonamides **1c** and **1d**, which can only occur through nitrogen, works much better using iodides **7b** or **8b** instead of the corresponding sulfonate esters **7a** or **8a**.

The sensitivity of these cyclisations to the nature of the leaving group can be understood in terms of the Hard Soft Acids and Bases (HSAB) principle introduced by Pearson.[6] The ambident carbamate nucleophile closes through nitrogen or oxygen producing either the four or six-membered ring, respectively. Cyclisation to six-membered rings is normally faster,[4,18] and with a substrate containing a 'hard' leaving group the reaction proceeds via oxygen giving **3** as essentially the sole product (Table 1, entries 1 and 2). Using a much 'softer' leaving group based on a polarisable C–I bond, closure through the nitrogen to produce the strained four-membered ring becomes competitive (Table 1, entry 5). Matching of the reacting centres in this way allows the kinetic preference for the formation of the six-membered ring to be overcome, and provides a synthetically useful route to 1,2-diazetidines.

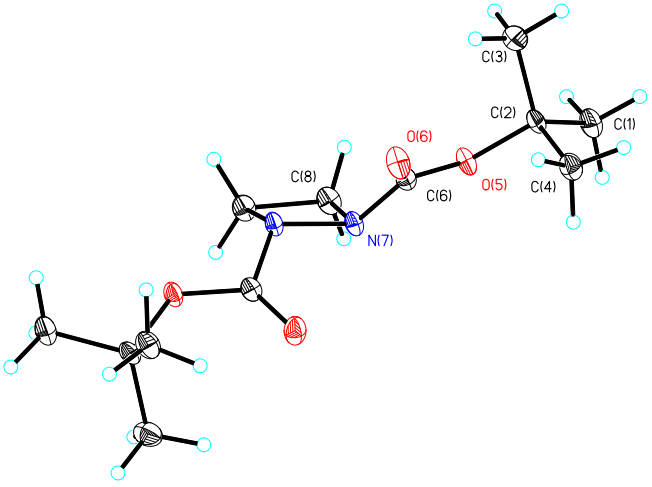
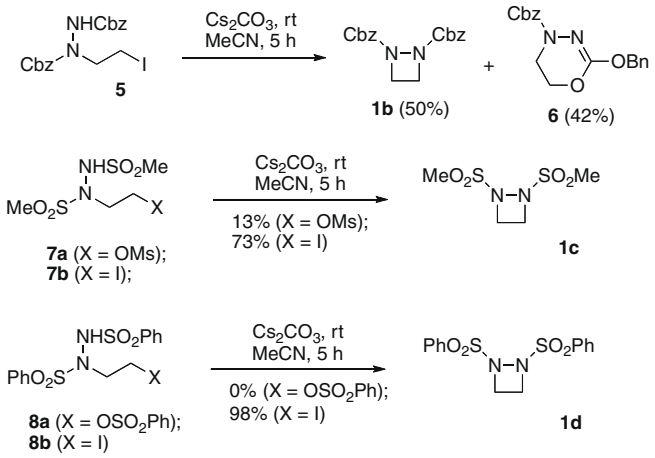
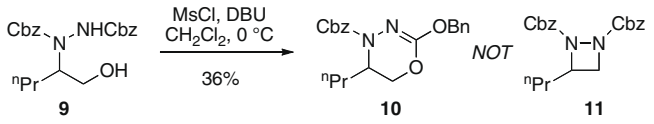


Figure 2. ORTEP representation of the X-ray structure of **1a** with thermal ellipsoids drawn at 50% probability.



Scheme 2.



Scheme 3.

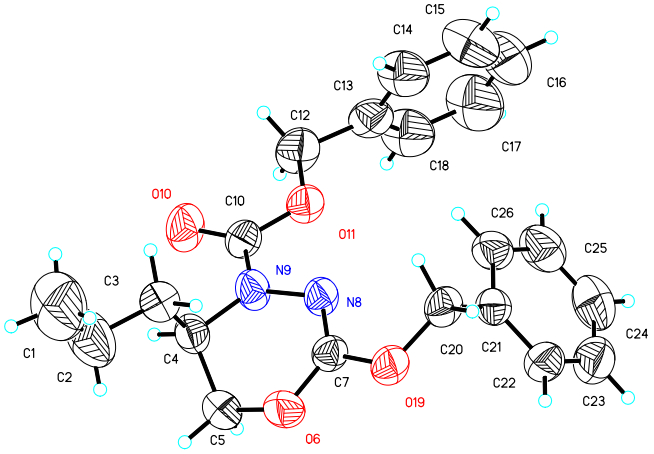


Figure 3. ORTEP representation of the X-ray structure of **10** with thermal ellipsoids drawn at 50% probability.

These findings contradict those of Miao et al. who reported that treatment of 2-hydroxyethylhydrazine **9**, bearing a pendant propyl group, with MsCl and an excess DBU provided 1,2-diazetidine **11** in 95% yield.[7] Based on our data, use of a 'hard' mesylate leaving group would be expected to furnish oxadiazine **10** by ring closure through oxygen (cf. Table 1, entry 2). In an effort to understand these differences, we reinvestigated the cyclisation of **9**. In our hands, this alcohol failed to produce any detectable amounts of 1,2-diazetidine **11** upon subjection to the published conditions (Scheme 3). Instead, 1,3,4-oxadiazine **10** was isolated in a modest 36% yield. X-ray crystallographic analysis confirmed unambiguously the identity of this material (Fig. 3).[12] As expected, cyclisation of the corresponding iodide produced diazetidine **11**, along with oxadiazine **10** (41:59 ratio) in good overall yield. Although we have not re-examined the other examples reported by Miao, we suggest that 1,3,4-oxadiazine formation most likely occurred in all reported cases and that no 1,2-diazetidines were produced.

To conclude, we have determined that the nature of the leaving group undergoing nucleophilic displacement has a significant impact on the cyclisation manifold in the context of 1,2-diazetidine synthesis. By judicious choice of this leaving group, it is possible to direct closure to favour either the four or six-membered ring. In addition to providing a preparatively useful route to simple 1,2-diazetidines and also to 1,3,4-oxadiazines, these observations demonstrate how changes in the nature of the leaving group can have a significant effect on cyclisation rates, and can be used to encourage 'difficult' ring closures.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.11.024.

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