ORGANIC LETTERS

2010
Vol. 12, No. 21
5044−5047

Diastereoselective Preparation of Azetidines and Pyrrolidines

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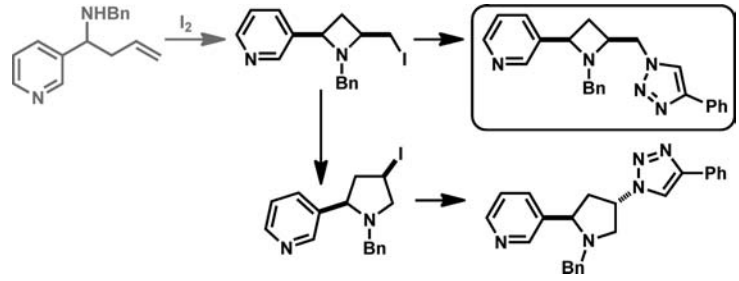
Received September 15, 2010

ABSTRACT



Iodine-mediated cyclization of homoallyl amines at room temperature delivered *cis*-2,4-azetidine through a 4-*exo* trig cyclization. Isomerization of iodo-azetidines to *cis*-pyrrolidines could be achieved by heating, with complete stereocontrol. The relative stereochemistry of the iodo-azetidines and pyrrolidines was confirmed by NMR spectroscopy and X-ray crystallography. Further functionalization was achieved through nucleophilic displacement of iodine to deliver substituted azetidines and pyrrolidines. 1,2,3-Triazole-appended azetidines and pyrrolidines were also prepared.

Amido oxidation level nitrogen containing 4-membered rings (β-lactams) are a common pharmaceutical motif, and a range of versatile methods are available for their synthesis.[1] Amine oxidation level 4-membered rings (azetidines) are important structures, they have been used as ligands[2] and as synthetic building blocks[3] and can be found in a range of natural products.[4] The antibacterial activity,[5] binding to acetylcholine receptors,[6] and the psychotropic potency[7] of azetidine derivatives have been studied and contrasted with those of their 5-membered pyrrolidine congeners, revealing them to be an intriguing class of compounds.

Azetidines[8] can be prepared by cyclization of 1,3-diols with amines.[9] The OH functionality of 1,3-amino alcohols can be converted into leaving groups which are then intramolecularly displaced by amine to furnish azetidines.[10] Intramolecular epoxide[5] and aziridine ring-opening,[11] double

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10.1021/ol102215e
Published on Web 09/29/2010

halide displacement from 1,3-dihalides by amines,[2a,f] sulfuric acid treatment of homoallyl amines,[12] and selenium mediated reactions of homoallyl amines have delivered both 4-*exo* and 5-*endo* azetidines and pyrrolidines, respectively.[13] Upon treatment of homoallyl amines with NBS Corey was also able to produce a bicyclic 4-*exo* azetidine.[14] Bromonium-mediated 4-*endo* cyclizations have also been achieved.[15−17]

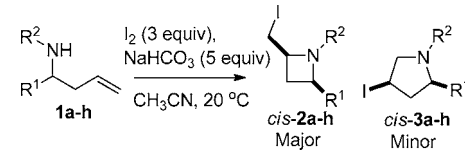
The homoallyl amine motif is readily accessible through allylation of imines, yet their cyclization protocols are plagued with problems. Mixtures of 2,4-azetidines (overall 4-*exo*) and 2,4-pyrrolidines (overall 5-*endo*, Baldwin disfavored) are commonplace, decomposition can be problematic, and stereochemical integrity is not always high. These issues can be addressed when the homoallylic carbon is a quaternary center, but even then robust protocols for the diastereoselective 4-*exo* trig cyclization of homoallylic amines to furnish 3-unsubstituted azetidines has remained somewhat elusive.[18] Park and co-workers cyclized homoallyl amines (with a bulky amine substituent) to deliver pyrrolidines.[19] Outurqin and co-workers have shown that treatment of homoallylic amines with PhSeX (X = Br, Cl, or I) results in ring closure to give SePh-appended 4-membered azetidines and 5-membered pyrrolidines.[13b,c] When X = I low yields of an azetidine product could be obtained.[13c]

Herein a highly diastereoselective, 4-*exo* trig, iodo-cyclization of homoallyl amines to furnish 2,4-*cis*-azetidines, in up to quantitative conversion is reported. Functionalization of the obtained azetidines is exemplified and thermal isomerization to the *apparent* 5-*endo* product akin to the ring expansion protocol of Couty et al.[20] is also demonstrated,

Homoallyl amines, **1a**−**h**, were prepared as racemates by a standard literature protocol.[21] To probe the potential for direct funtionalized azetidine synthesis compound **1a** was initially investigated. We envisaged 4-*exo* halide-mediated cyclization ought to deliver azetidines. Since iodine has already been shown to deliver pyrrolidines in a 5-*exo* fashion,[22] and this sterically encumbered halide could perhaps offer high stereodefinition, it was selected as the cyclization promoter.

Compound **1a** was treated with molecular iodine under a variety of conditions, and while consumption of starting material could be monitored by TLC, in most cases only very small amounts of mixtures of *cis*-**2a** and *cis*-**3a**, where **3** was the major product, were obtained following column chromatography (silica). However, when a 3-fold excess of iodine was used at room temperature in acetonitrile accompanied by a 5-fold excess of $NaHCO_3$ azetidine *cis*-**2a** could be obtained, albeit in 45% isolated yield, but most of the starting amine (**1a**) had been consumed (Table 1).

Table 1. 2,4-*cis*-Azetidine Formation by Iodocyclization of Homoallylamines



	R^1	R^2	Conv,[a] %	**2**:**3**[b]	(**2** + **3**) yield,[c] %	**2** yield,[d] %
a	Ph	Bn	>99	>99:1	96	45[e]
b	Ph	PMB[g]	>99	>99:1	85	41[e]
c	Ph	PTB[h]	>99	>99:1	93	45[e]
d	3-Py	Bn	>99	5:1	91	42[f]
e	4-Py	Bn	>99	6:1	95	51[f]
f	4-NO_2-phenyl	Bn	>99	3:1	90	46[f]
g	2-Br-phenyl	Bn	>99	3:1	83	42[f]
h	*t*-Bu	Bn	>99	>99:1	87	41[e]

[a] Conversion to **2** + **3** based on consumption of **1** by ^{1}H NMR spectroscopy. [b] *cis*-(**2**:**3**) ratio obtained by inspection of the ^{1}H NMR spectrum post aqueous workup. [c] Yield (**2** + **3**) post aqueous workup. [d] Yield obtained after flash chromatography. [e] The **2**:**3** ratio was eroded after column chromatography to ∼20:1 due to isomerization of **2** to **3**. [f] The **2**:**3** ratio was ∼20:1 after column chromatography. [g] PMB = *p*-methoxybenzyl. [h] PTB = *p*-tolylbenzyl.

To address the apparent mass loss we examined the crude reaction mixture in more detail, and to our delight discovered, after workup, the corresponding azetidine *cis*-**2a** was the major constituent. A number of trials confirmed that chromatography (on silica) results in a dramatic loss of material.

With satisfactory reaction conditions in hand the homoallyl amines **1b** to **1h** were also cyclized, with iodine, to the corresponding azetidines *cis*-**2b** to *cis*-**2h**. Purification by column chromatography, in our hands, gave only around 45% isolated yield in all cases. Analysis of the crude materials' proton NMR spectra revealed some pyrrolidine had formed in the case of **d** to **g** but azetidines *cis*-**2** were always the major product.[23] The cyclization of the 2-pyridyl analogue was also attempted but failed to give the desired product(s).[24] The X-ray crystal structure of **2b** (Figure 1a) along with

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(23) For proton NMR spectra comparing post work-up and post column chromatography on obtained **2d** see the Supporting Information.

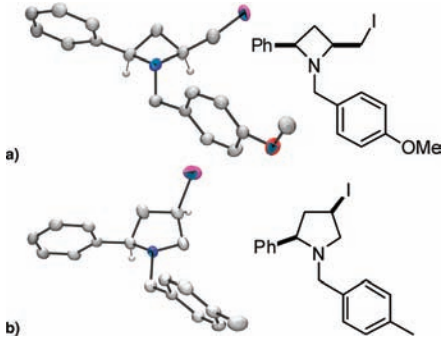
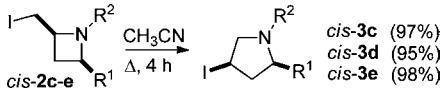


Figure 1. X-ray crystal structures with ellipsoids drawn at the 50% probability level of (a) *cis*-**2b**[25] and (b) *cis*-**3c**. Most of the hydrogen atoms have been omitted for clarity and *cis*-stereochemistry is confirmed in both cases.

inspection of NOE data and comparison among the NMR spectra obtained confirmed *cis* stereochemistry for the azetidines.

It was rapidly discovered that storage of iodo-azetidines *cis*-**2** (even at 4 °C) resulted in the formation of some of the corresponding pyrrolidines *cis*-**3**. Thermal ring-expansion, in accordance with the findings of Couty et al.,[20] was confirmed: heating *cis*-**2c**−**e** in acetonitrile at reflux for 4 h gave *cis*-**3c**−**e** in 97%, 95%, and 98% overall yield, respectively (Scheme 1). The relative stereochemistry of *cis*-

Scheme 1. Thermal Isomerization of Azetidines **2c**−**e** to Pyrrolidines **3c**−**e**

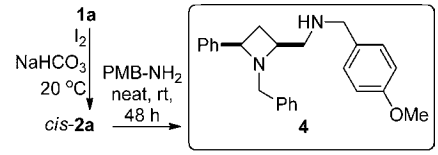


3c was corroborated by NOE studies and confirmed by X-ray crystal structure analysis (Figure 1b).

This isomerization can account for not only our initial trouble of product distribution between azetidine and pyrrolidine but also the apparent mixtures of products obtained by others discussed earlier.

Since azetidines **2** were not robustly stable and initially obtained reaction products, post-workup, contained mostly the desired *cis*-azetidines (Table 1), it was speculated that replacement of iodide might arrest decomposition or isomerization and post-derivatization purification might provide higher overall yield, especially in the cases where mixtures of **2** and **3** are initially obtained. To test this hypothesis the iodo-cyclization of **1a** was repeated; after aqueous workup the obtained material was dissolved in neat *p*-methoxybenzylamine, and stirring at room temperature for 48 h gave the corresponding amino azetidine in 78% yield (Scheme 2). Thus, demonstrating derivatization of material obtained

Scheme 2. Two-Step Protocol for the Conversion of Homo Allylamines **1a** into Substituted Azetidine **4**

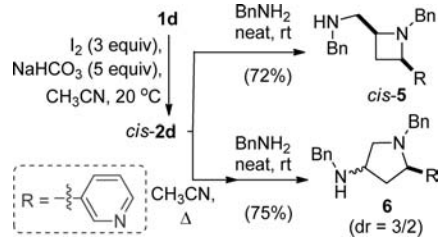


(78%, two steps)
(PMB = *p*-methoxybenzyl)

from the cyclization reactions may be performed without purification, to give higher yields than would be possible otherwise.

Next **1d** was exposed to an analogous two-step cyclization−derivatization sequence. Derivatives of **2d** (and **3d**) are especially attractive owing to the 3-pyridyl motif, allowing access to a potentially useful class of azetidine (and pyrrolidine), nicotine analogues, and derivatives. The pharmacological activity of such analogues is an area of persistent interest.[7,10a,26] In the case of the cyclization of **1d** it had already been shown a 5:1 mixture of **2d**:**3d** in high conversion was obtained, yet only 42% of **2d** could be isolated by column chromatography (Table 1). Pleasingly, purification post-derivatization gave the corresponding amino azetidine **5** as a single diastereoisomer in 72% overall isolated yield (Scheme 3, upper).

Scheme 3. Conversion of Amine **1d** to the Corresponding Amino-Azetidine **5** and Pyrrolidine **6**



To demonstrate the versatility of iodoazetidines **2** a second reaction sequence starting from homoallyl amine **1d** was conceived. A 4 h preheating step was performed, as such isomerization to the corresponding pyrrolidine (**3d**) and

(24) (a) Pyridinium iodide formation was postulated. Cf.: (b) Chen, W.; Elfeky, S. A.; Nonne, Y.; Male, L.; Ahmed, K.; Amiable, C.; Axe, P.; Yamada, S.; James, T. D.; Bull, S. D.; Fossey, J. S. *Chem. Commun.* DOI: 10.1039/c0cc01420f. Published Online: July 5, 2010. (c) Richter, I.; Minari, J.; Axe, P.; Lowe, J. P.; James, T. D.; Sakurai, K.; Bull, S. D.; Fossey, J. S. *Chem. Commun.* **2008**, 1082.

(25) The X-ray crystal structure of **2b** consists of two crystallographically independent molecules, the geometry of which are very similar to one another and of which only one has been shown.

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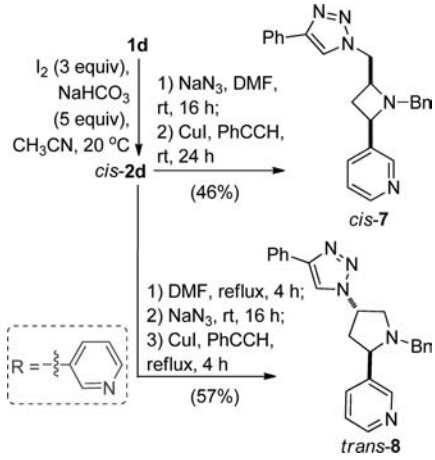
subsequent iodide displacement was anticipated (Scheme 3, lower). Following solvent removal in vacuo exposure to neat benzylamine afforded a 3:2 mixture of diastereomeric pyrrolidines **6** in 75% isolated yield.[27]

A similar protocol employing **1d** with more nucleophilic azide was next performed. A room temperature reaction was compared with a reaction that included a preheating step. In one pot, the obtained azides were transformed into the corresponding 1,2,3-triazoles utilizing conditions similar to those employed elsewhere (Scheme 4).[28]

Scheme 4. Conversion of Azetidine **2d** to the Corresponding Triazole-Appended azetidine **7** and Pyrrolidine **8**



Addition of sodium azide to the pseudo in situ generated **2d** at room temperature in DMF, followed by addition of copper(I) iodide and phenyl acetylene gave azetidine triazole derivative *cis*-**6** in 46% isolated yield, whereas the same reaction performed with a 4 h preheating step gave the corresponding pyrrolidine triazole. The anionic nucleophile N_3^- had displaced iodide with inversion delivering only *trans*-pyrrolidine **8** in 57% isolated yield, via *cis*-**2d** (Scheme 4); the relative stereochemistry was confirmed by NOE experiments (see the Supporting Information).

To confirm the thermal stability of azetidines samples of *cis*-**5** and *cis*-**7** were each heated in refluxing DMSO for 4 h. Solvent removal in vacuo gave materials with unchanged proton NMR spectra, confirming the robustness of the azetidine motif in the absence of iodide.

Electrophile-mediated 4-*exo* trig azetidine formation furnishes azetidines with a reactive leaving group-appended methylene functionality in the 4-position, resulting in a tendency for isomerization to the more stable pyrrolidine congener. However, performing iodo-cyclization reactions at room temperature delivered *cis*-2,4-azetidines. If desired, full conversion to *trans*-pyrrolidines could be achieved with complete stereocontrol by heating. Displacement of iodide with nitrogen nucleophiles gave thermally stable azetidines; the analogous pyrrolidines were also prepared demonstrating the versatility of this iodo-cyclization protocol. We are currently perusing single enantiomer azetidines and pyrrolidines for the generation of libraries with applications in synthesis and catalysis.

Acknowledgment. The University of Birmingham is thanked for funding and studentship (A.F.). ERDF AWM II is thanked for support. Dr Neil Spencer (UoB NMR Facility) is thanked for invaluable help with NMR spectroscopy. The EPSRC National Crystallography Service is thanked for collection of X-ray diffraction data.

Supporting Information Available: Experimental procedures, analysis, and X-ray crystallographic data including CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The *trans*:*cis* ratio for **6** was 1:1 when the benzylamine addition step was carried out in DMF (71% yield).

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