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Lithiation–substitution of *N*-Boc-2-phenylazepane

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Abstract: Preparation of 2,2-disubstituted azepanes was accomplished from *N*-*tert*-butoxy(*N*-Boc)-2-phenylazepane by treatment with butyllithium then electrophilic quench. The lithiation was followed by *in situ* ReactIR spectroscopy and the rate of rotation of the carbamate was determined by variable temperature (VT)-NMR spectroscopy and by DFT studies. Most electrophiles add alpha to the nitrogen atom but cyanoformates and chloroformates gave ortho substituted products. Cyclic carbamates were formed from an aldehyde or ketone electrophile. Kinetic resolution with sparteine was only poorly selective. Removal of the Boc group promoted cyclization to a homoindolizidine or an isoindolinone.

Key words: Alkylation; Heterocycles; Lithiation; Lithium.

Azepanes form the basis of a number of pharmaceuticals and natural products and two examples are shown in Figure 1. These include important bioactive compounds such as fenoldopam which acts on the dopamine receptor,[1] and stemona alkaloids such as stenine.[2]

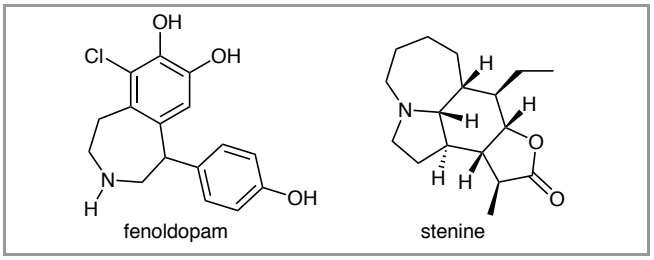
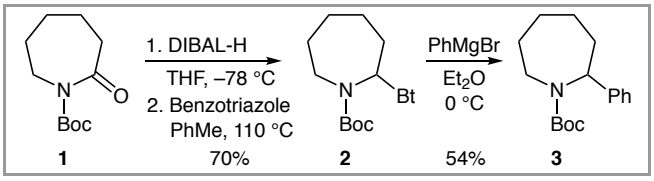


Figure 1 Examples of azepanes.

Of particular importance in medicinal chemistry are aryl-substituted saturated and partially saturated cyclic amines, so methods to access aryl-substituted azepanes are of interest. Our research group has reported the ability to prepare aryl-substituted cyclic amines by lithiation alpha to a nitrogen atom then electrophilic quench with 2-arylpiperidines,[3] tetrahydroisoquinolines,[4] and tetrahydro-β-carbolines.[5] Considering the importance of substituted azepanes in natural products and drug compounds we wanted to explore the lithiation–substitution of the 2-phenylazepane ring system and describe here our efforts with this chemistry.

The desired 2-phenylazepane framework was prepared according to a method reported in the literature (Scheme 1).[6,7] Treatment of caprolactam with Boc_2O gave the lactam **1** which was partially reduced with DIBAL-H and converted to the benzotriazole adducts **2**. Displacement of the benzotriazole group with phenylmagnesium bromide gave the desired *N*-Boc-2-phenylazepane **3**.



Scheme 1 Preparation of azepane **3** (Bt = benzotriazolyl).

To determine the optimum conditions for reaction of the azepane **3**, we followed its lithiation by using *in situ* IR spectroscopy. It was apparent that the lithiation with *n*-butyllithium was incomplete at low temperatures (*e.g.* –78 °C in THF). Complete reaction did however occur when the temperature was raised to –5 °C (Figure 2). The azepane **3** has $\nu_{C=O}$ at 1690 cm^{-1} and on addition of *n*-butyllithium this is replaced within minutes by a carbonyl stretch at 1644 cm^{-1}, corresponding to the lithiated intermediate.

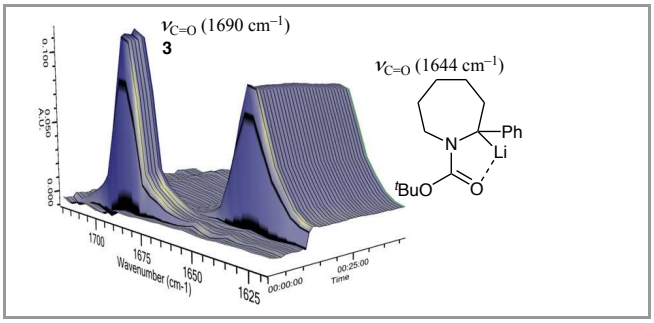


Figure 2 3D ReactIR spectrum for lithiation of **3** with *n*-BuLi in THF at –5 °C (complete lithiation occurs within minutes).

The partial lithiation at low temperatures is due to the presence of both rotamers that are interconverting extremely slowly, with only one rotamer able to undergo reaction through a complex induced proximity effect.[8] The ratio of rotamers is approximately 1:1 from the NMR spectra and variable temperature NMR spectroscopy was used together with line shape analysis to determine the activation parameters for the rotation of the Boc group. The ^1H NMR spectra showing coalescence of signals in the region 5.50–2.00 ppm in D_6-DMSO is given in Figure 3. Analysis led to approximate values of $\Delta H^{\ddagger}$ 73 kJ/mol and $\Delta S^{\ddagger}$ 9 J/K·mol. The solvent DMSO was chosen for this study due to its ability to reach the elevated temperatures required for coalescence of these signals and the values in THF may of course be different. Nonetheless it is clear that the half-life for rotation is many hours at low temperatures such as –

78 °C but only seconds at –5 °C, thereby allowing complete lithiation at higher temperatures.

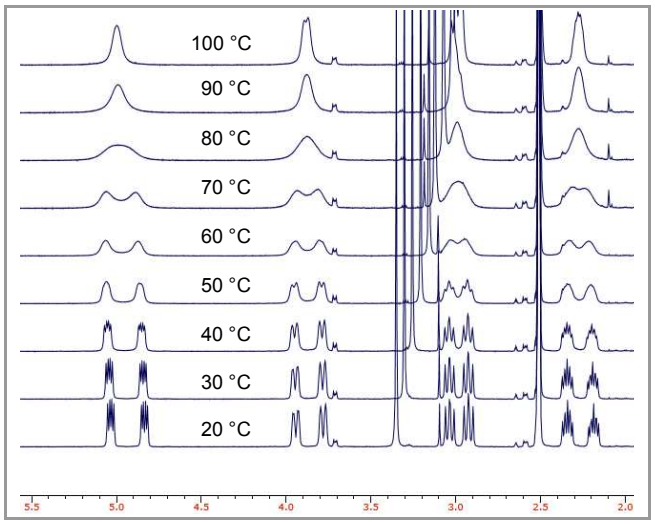


Figure 3 ^{1}H NMR spectra of azepane **3** in D_6-DMSO

The rate of rotation of the Boc group differs significantly from the corresponding 5- and 6-membered ring analogs.[3a] The pyrrolidine has a slightly lower barrier to rotation (about 64.5 kJ/mol at 46 °C) but the piperidine has a considerably lower barrier (about 50 kJ/mol at –28 °C). To probe this further, we carried out density functional calculations (using the methodology from Ref. 3a; see SI for full details) in both THF and DMSO (PCM) solvent. For both solvents we found two similar energy minima for each rotamer, indicating a more complex arrangement than in the smaller ring systems (Figure 4). Transition states were found between these structures after studying clockwise and anticlockwise rotation of the Boc group, with the lowest Gibbs energy barrier (at 298 K) in DMSO of 72.9 kJ/mol (74.1 kJ/mol in THF), which is in reasonable agreement with the Gibbs energy barrier at 298 K determined by VT-NMR spectroscopy in DMSO of 70.3 kJ/mol.

The spectroscopic and DFT studies indicated that the optimum conditions for lithiation of azepane **3** would be at temperatures of at least –10 °C as this would allow for rotation of the Boc group and therefore subsequent higher yields after electrophilic quench. We therefore allowed a lithiation period of several minutes at –5 °C in THF prior to adding an electrophile. We were pleased to find that this method allowed the formation of 2,2-disubstituted azepane products **4a**–**f** with good to excellent yields (Scheme 2).[9] In the case of the carbonyl electrophiles acetone and benzaldehyde, the products were the cyclic carbamates **4e** and **4f** where the intermediate alkoxide had cyclized on to the Boc group. In the latter case, a separable mixture of diastereomers (dr 3:1) was isolated and the stereochemistry of the major isomer (*trans* phenyl groups) was determined by single crystal X-ray analysis (Figure 5).

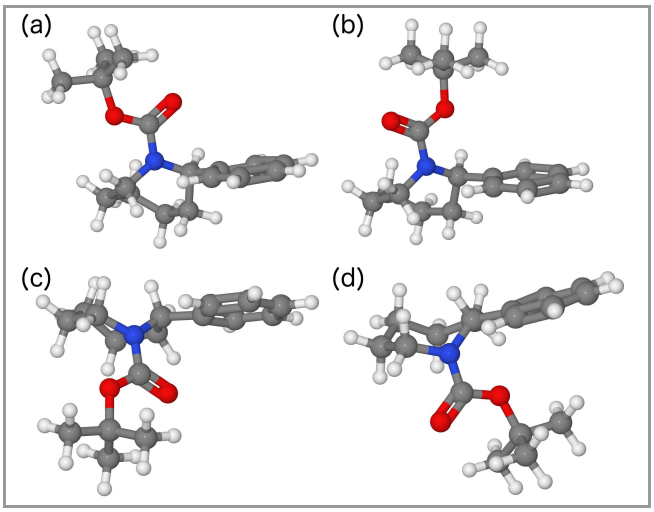
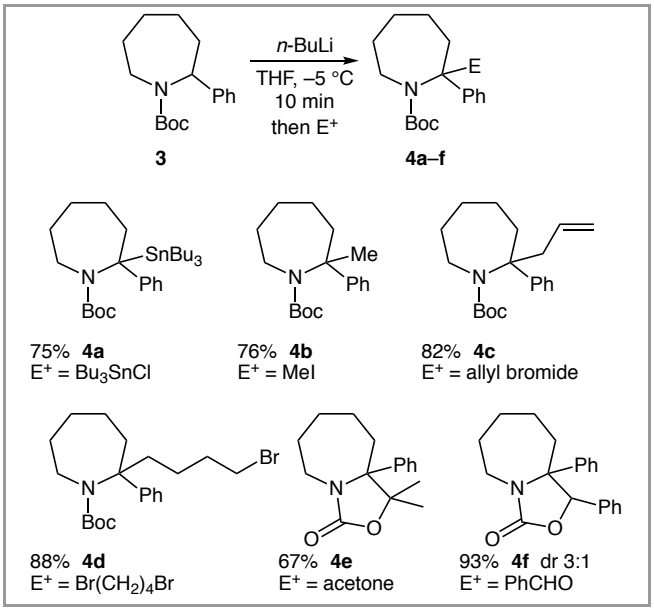


Figure 4 Minimum energy structures for the azepane **3** by DFT [6-311G(d,p) basis set with B3LYP functional in DMSO (see SI)].The relative Gibbs energies (in kJ/mol) are: (a) 0.00; (b) 0.20; (c) 2.14; (d) 2.40, meaning relative populations of 1.0:0.82:0.12:0.09.

In addition to the electrophiles shown in Scheme 2, we investigated substitution of the organolithium intermediate with alkyl cyanoformates. We were surprised to find that the *ortho* substituted products **5a**–**c** were formed exclusively in these cases (Scheme 3). The same products were also formed by using alkyl chloroformates as the electrophiles. We speculate that these products arise from a preference for reaction at the ortho position (rather than alpha to the nitrogen atom) followed by re-aromatization. The initial deprotonation alpha to the nitrogen atom should give an organolithium intermediate that will be coordinated to the carbonyl oxygen atom but which could also be η^3-coordinated due to the phenyl ring and could therefore lead to the *ortho* substituted product. We are currently investigating this reactivity aspect further.[10]



Scheme 2 Lithiation–substitution of azepane **3** to give products **4**.

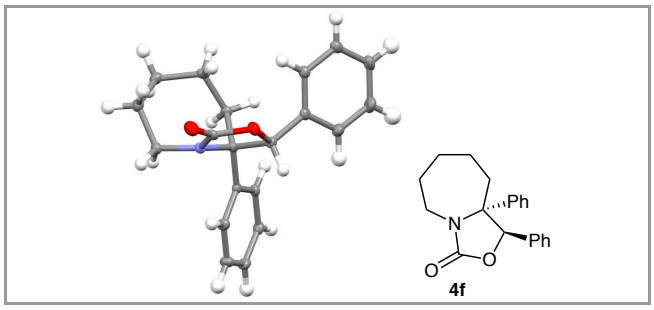
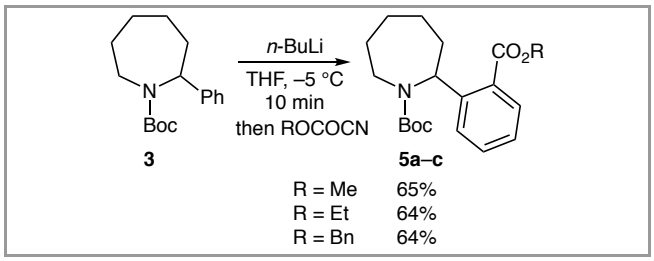


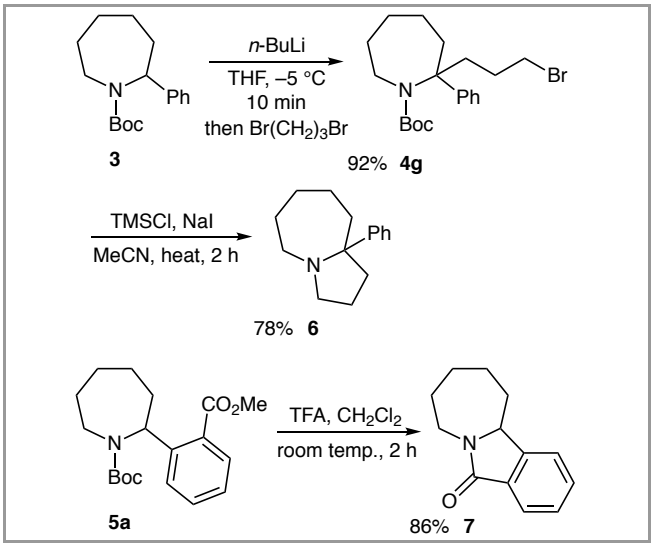
Figure 5 Crystal structure of the major isomer of product **4f**.



Scheme 3 Lithiation–substitution of azepane **3** to give products **5**.

The azepane **3** is chiral but racemic and it is possible that a kinetic resolution could be achieved by conducting the lithiation in the presence of a chiral ligand such as sparteine.[3b,11] However we were disappointed to find that poor enantiomer ratios were obtained on treating azepane **3** with BuLi/(+)-sparteine in PhMe at various temperatures and times after electrophilic quench. For example, treatment of azepane **3** with 1.5 equiv. (+)-sparteine in PhMe at –5 °C followed by addition of 1.2 equiv. *n*-BuLi then, after 3 h, addition of tri-*n*-butyltin chloride, gave recovered **3** (40%, er 59:41), together with the product **4a** (40%, er not determined). It appears that the azepane **3** is less amenable to the kinetic resolution than the corresponding piperidine, presumably due to greater flexibility of the larger ring size.[3b]

Finally, treating the azepane **3** with *n*-butyllithium in THF at –5 °C followed by addition of 1,3-dibromopropane gave the azepane **4g** (Scheme 4). Initial attempts to remove the Boc group with trifluoroacetic acid (TFA) gave a mixture of products that lacked the Boc group but contained alkene protons in the ^{1}H NMR spectrum, possibly arising from ready E1 elimination through a tertiary benzylic cation. We therefore treated the carbamate **4g** with TMSI, generated from TMSCl and NaI to remove the Boc group and promote in situ cyclization to give the desired bicyclic product **6** (Scheme 4). In addition, we treated the azepane **5a** with TFA, which did not suffer from the same problem, possibly due to the lack of full substitution adjacent to the nitrogen atom, and we were able to isolate the desired lactam (isoindolinone) product **7** (Scheme 4).



Scheme 4 Preparation of bicyclic products **6** and **7**.

In conclusion, a range of 2,2-disubstituted azepanes have been prepared by lithiation–substitution reactions. Relatively high temperatures (–5 °C) are required for effective lithiation to allow for the slow rate of rotation of the Boc group, as verified by VT-NMR spectroscopy and DFT studies. A selection of substituted products can be prepared with different carbon-based electrophiles although cyanoformate electrophiles provide aryl-substituted products and the reason for the change in regiochemistry requires further investigation. The increase in the conformational freedom of the larger ring in comparison with the piperidine presumably accounts for the reduced selectivity in the kinetic resolution with sparteine as the chiral ligand. The products are amenable to further transformation, such as removal of the Boc group and cyclization to give bicyclic ring systems.

Experimental details and spectroscopic data, including NMR spectra and X-ray crystal structure, together with DFT data, are provided in the Supporting Information.

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

Primary Data for this article are available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083 and can be cited using the following DOI: (number will be inserted prior to online publication).

Acknowledgment

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References and Notes

(1) See, for example, (a) Murphy, M. B.; Murray, C.; Shorten, G. D. *New Engl. J. Med.* **2001**, *345*, 1548. (b) Stote, R. M.; Dubb, J. W.; Familiar, R. G.; Erb, B. B.; Alexander, F. *Clin. Pharmacol. Ther.* **1983**, *34*, 309.

(2) See, for example, Chen, J.; Xie, Y.; Chen, J.; Zhang, H. *Tetrahedron* **2015**, *71*, 3747 and references therein.

(3) (a) Sheikh, N. S.; Leonori, D.; Barker, G.; Firth, J. D.; Campos, K. R.; Meijer, A. J. H. M.; O'Brien, P.; Coldham, I. *J. Am. Chem. Soc.* **2012**, *134*, 5300. (b) Cochrane, E. J.; Leonori, D.; Hassall, L. A.; Coldham, I. *Chem. Comm.* **2014**, *50*, 9910.

(4) (a) Li, X.; Leonori, D.; Sheikh, N. S.; Coldham, I. *Chem. Eur. J.* **2013**, *19*, 7724. (b) Li, X.; Coldham, I. *J. Am. Chem. Soc.* **2014**, *136*, 5551. (c) Talk, R. A.; Duperray, A.; Li, X.; Coldham, I. *Org. Biomol. Chem.* **2016**, *14*, 4908.

(5) Cochrane, E. J.; Hassall, L. A.; Coldham, I. *J. Org. Chem.* **2015**, *80*, 5964.

(6) Madan, S.; Milano, P.; Eddings, D. B.; Gawley, R. E. *J. Org. Chem.* **2005**, *70*, 3066.

(7) For alternative syntheses of compound **3**, see (a) Chen, F.; Ding, Z.; Qin, J.; Wang, T.; He, Y.; Fan, Q.-H. *Org. Lett.* **2011**, *13*, 4348. (b) Coldham, I.; Leonori, D. *Org. Lett*. **2008**, *10*, 3923.

(8) (a) Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1995**, *60*, 7092. (b) Bertini Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315.

(9) Typical conditions: *n*-BuLi (0.19 mL, 0.45 mmol, 2.4 M in hexanes) was added to the azepane **3** (100 mg, 0.36 mmol) in dry THF (2 mL) at –5 °C under nitrogen. After 10 min, the electrophile (1.09 mmol) was added and the mixture was allowed to warm to room temperature. After 18 h, MeOH (1 mL) was added. The solvent was evaporated and the residue was purified by column chromatography, eluting with petrol–EtOAc, see Supporting Information.

(10) For competitive *alpha* and *ortho* lithiation of *N*-alkylarylaziridines and other small ring heterocycles, see (a) Affortunato, F.; Florio, S.; Luisi, R.; Musio, B. *J. Org. Chem.* **2008**, *73*, 9214. (b) Capriati, V.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2014**, 5397.

(11) For kinetic resolutions with BuLi/sparteine, see ref 3b and (a) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561. (b) Kessar, S. V.; Singh, P.; Singh, K. N.; Venugopalan, P.; Kaur, A.; Bharatam, P. V.; Sharma, A. K. *J. Am. Chem. Soc.* **2007**, *129*, 4506. (c) Becker, J.; Fröhlich, R.; Salorinne, K.; Hoppe, D. *Eur. J. Org. Chem.* **2007**, 3337. (d) Granander, J.; Secci, F.; O'Brien, P.; Kelly, B. *Tetrahedron: Asymmetry* **2009**, *20*, 2432. (e) Doulcet, J.; Stephenson, G. R. *Chem. Eur. J.* **2015**, *21*, 18677.

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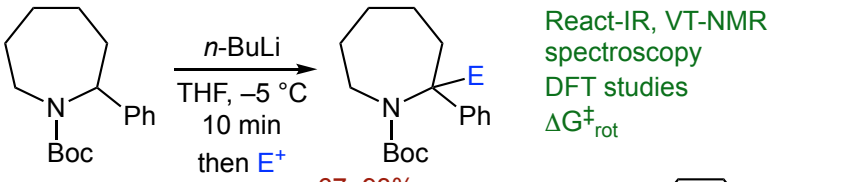

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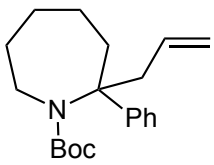
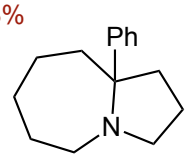
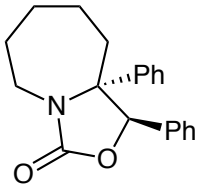


E^+ = allyl bromide



$E^+ = Br(CH_2)_3Br$
then TMSCl, NaI



E^+ = PhCHO