Pergamon

Tetrahedron Letters 40 (1999) 1819–1822

TETRAHEDRON LETTERS

Synthesis of 7-Azabicyclo[2.2.1]heptanes by Anionic Cyclization

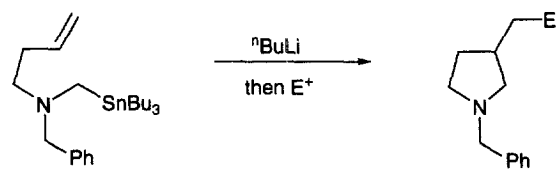
Iain Coldham,* Joan-Carles Fernàndez and David J. Snowden

School of Chemistry, University of Exeter, Stocker Road, Exeter UK EX4 4QD

Received 1 December 1998; accepted 23 December 1998

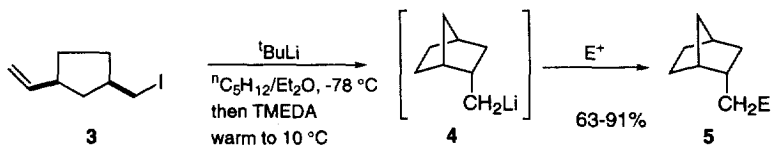
Abstract: Cyclizations of α-amino-organolithiums, derived by tin-lithium exchange, which proceed *via* a stereoselective two-electron process and totally regiospecific 5-*exo-trig* ring closure, have been extended to the preparation of the 7-azabicyclo[2.2.1]heptane ring system. Cyclization occurs from either the *cis* or the *trans* isomer of 5-allyl-2-tri-*n*-butylstannyl-*N*-benzylpyrrolidine to give only the *exo* product as a single diastereomer in isolated yields up to 83%.

Preparation of nitrogen-containing heterocyclic compounds is of significant interest in organic and medicinal chemistry. One approach which is becoming increasingly popular for the preparation of carbocyclic and heterocyclic ring systems is the use of anionic cyclizations.[1] We have reported recently that aminomethyllithium species, generated by tin-lithium exchange, *e.g.* from the stannane **1**, cyclize onto an unactivated alkene to give the intermediate 3-lithiomethylpyrrolidine which can be trapped by addition of a variety of electrophiles to afford 3-substituted pyrrolidines, *e.g.* **2**, in good yields.[2-6]



1 **2**

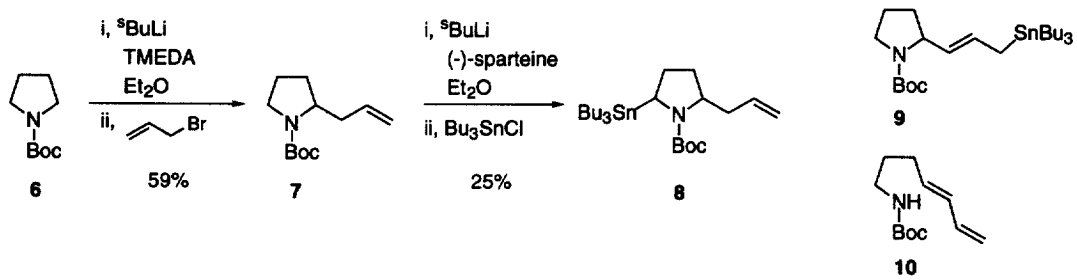
We wished to extend the versatility of this methodology by preparing more complex cyclic amines, such as 7-azabicyclo[2.2.1]heptanes, the basic ring system of which is present in a number of alkaloids, *e.g.* epibatidine.[7] Anionic cyclizations of organolithium species to give bridged bicyclic compounds are rare; an example by Bailey describes the formation of the bicyclo[2.2.1]heptane ring system **5**.[8] In this case, the iodide **3** was treated with *tert*-butyllithium to effect iodine-lithium exchange. On warming to room temperature cyclization gave the organolithium intermediate **4**, which was trapped with different electrophiles to give various functionalised bicyclic products **5** with very high stereoselectivity (*endo:exo* ≈ 50:1).



3 **4** **5**

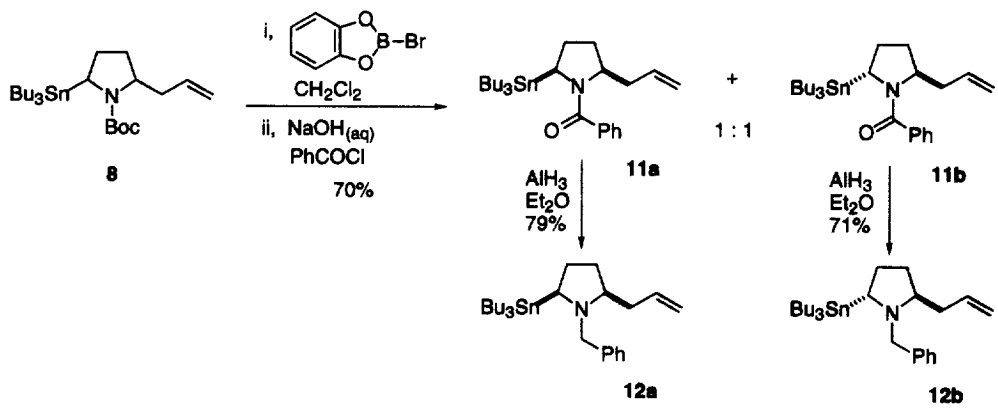
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00018-0

In order to test the feasibility of preparing the desired 7-azabicyclo[2.2.1]heptane ring system by such anionic cyclization, we investigated a method for the preparation of the stannane precursors **12**. The synthetic approach involved α-lithiation and electrophilic substitution of *N*-Boc-pyrrolidines using a procedure reported by Beak.[9] Treatment of *N*-Boc-pyrrolidine **6** with 1.2 equivalents of *sec*-butyllithium and TMEDA as external ligand in ether at -78 °C led to 2-lithio-*N*-Boc-pyrrolidine which was trapped with allylbromide (1.5 equivalents) to give the alkene **7**.

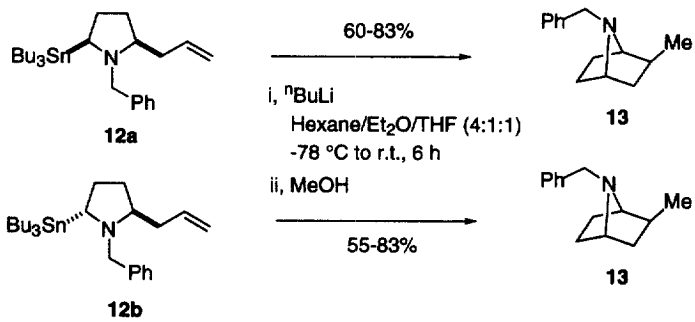


Attempts to abstract a proton from the pyrrolidine **7** using *sec*-butyllithium in Et_2O and TMEDA led only to recovered starting material and the diene **10**. However, we found that deprotonation at C-5 was successful using the ligand (-)-sparteine, rather than TMEDA. Treatment of the pyrrolidine **7** (racemic) with *sec*-butyllithium (4 equivalents) and (-)-sparteine (4 equivalents) in Et_2O at -78 °C for 6 h, followed by quenching with Bu_3SnCl (2.5 equivalents) and allowing the mixture to warm at room temperature overnight, gave an equal mixture of the two (racemic) diastereomeric (*cis* and *trans*) pyrrolidines **8** in 25% yield. Other products isolated from this reaction included the stannane **9** (15%) and the diene **10** (24%), in addition to recovered racemic starting material **7** (10%).

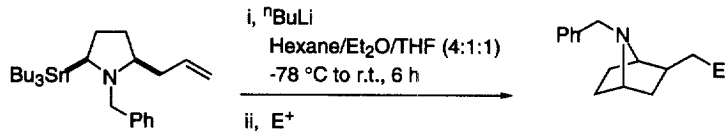
Deprotection of the *N*-Boc group was carried out using two equivalents of *B*-bromocatecholborane.[3] The resulting intermediate was not isolated, but was treated with benzoyl chloride and sodium hydroxide to give a mixture of the diastereomeric amides **11** in 70% yield. The amides **11a** and **11b** were separable by chromatography over silica gel. Reduction of the *cis*-amide **11a** and the *trans*-amide **11b** using alane gave the *cis*- and *trans*-pyrrolidines **12a** and **12b** (79% and 71% yields respectively). The stereochemistry of these amines was confirmed by n.O.e. experiments.[10]



It is generally accepted that, for a successful anionic cyclization onto an unactivated alkene, the lithium atom coordinates to the π-system.[3,11,12] As tin-lithium exchange is known to proceed with retention of configuration, it was interesting to determine whether the *trans*-pyrrolidine **12b** would undergo cyclization. Transmetallation using *n*-butyllithium (4 equivalents) was effected in hexane:Et_2O:THF (4:1:1) as the solvent system (-78°C to room temperature). Under these conditions both the *cis*-pyrrolidine **12a** and the *trans*-pyrrolidine **12b** cyclized in good yields and both led to the same *exo*-2-methyl-7-azabicyclo[2.1.1]heptane (stereochemistry confirmed by n.O.e. experiments).[13] Only the *exo* isomer **13** was isolated and it was not possible to observe (NMR spectroscopy) any *endo* isomer. This result suggests that the organolithium species derived from the *trans* isomer **12b** epimerizes to the *cis* isomer before cyclization. Very little transmetallation occurs at -78 °C and the mixture must be warmed to room temperature. Under these conditions, epimerization would be expected to be possible.[14]



Encouraged by these results, we turned our attention to the preparation of functionalized derivatives of 7-azabicyclo[2.2.1]heptanes. The addition of electrophiles gave the desired 2-substituted products **14**. Care must be taken to purify the electrophile in order to avoid the formation of the protonated 2-methyl product **13**.



E^+	E	Yield (%)
MeOD	D	75
CH_2=$CHCH_2Br$	CH_2CH=CH_2	60
DMF	CHO	34
TMSCl	TMS	55

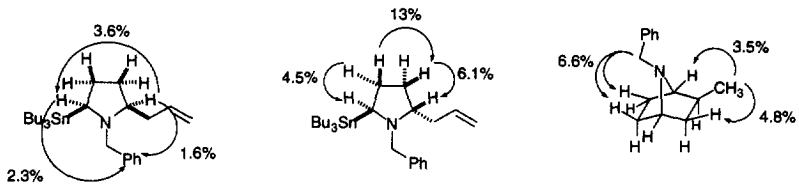
In summary, we have shown that the bridged 7-azabicyclo[2.2.1]heptane ring system can be accessed by anionic cyclization. The cyclization is stereoselective for the 2-*exo* isomer **13** or **14**, yet occurs from both the *trans* and *cis* organostannanes **12**.

Acknowledgements

We thank the EPSRC for a project studentship (to D.J.S.), the Spanish Government (Ministerio de Educación y Cultura) for a postdoctoral fellowship (to J.-C. F.), Pfizer Ltd for an unrestricted grant and Zeneca Pharmaceuticals (Strategic Research Fund). We acknowledge the use of the EPSRC mass spectrometry service at the University of Wales Swansea.

References and Notes

1. For recent exemples of anionic cyclizations onto alkenes, see Bailey, W.F.; Longstaff, S.C. *J. Org. Chem.*, **1998**, *63*, 432; Bailey, W.F.; Carson, M.W. *J. Org. Chem.*, **1998**, *63*, 361; Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commum.*, **1998**, 297; Katritzky, A.R.; Qi, M. *Tetrahedron*, **1998**, *54*, 2647; Lorthiois, E.; Marek, I.; Normant, J.F. *J. Org. Chem.*, **1998**, *63*, 2442; Oestreich, M.; Frölich, R.; Hoppe, D. *Tetrahedron Lett.*, **1998**, *39*, 1745; Nakamura, E.; Sakata, G.; Kubota, K. *Tetrahedron Lett.*, **1998**, *39*, 2157; Woltering, M.J., Frölich, R.; Wibbeling, B.; Hoppe, D. *Synlett*, **1998**, 797; Barluenga, J.; Sanz, R.; Granados, A.; Fañanás, F.J. *J. Am. Chem. Soc.*, **1998**, *120*, 4865; Nishiyama, H.; Sakata, N.; Sugimoto, H.; Motoyama, Y.; Wakita, H.; Nagase, H. *Synlett*, **1998**, 930.
2. Coldham, I.; Hufton, R. *Tetrahedron Lett.*, **1995**, *36*, 2157.
3. Coldham, I.; Hufton, R.; Snowden, D.J. *J. Am. Chem. Soc.*, **1996**, *118*, 5322.
4. Coldham, I.; Hufton, R. *Tetrahedron*, **1996**, *52*, 12541.
5. Coldham, I.; Hufton, R.; Rathmell, R.E. *Tetrahedron Lett.*, **1997**, *38*, 7617.
6. Coldham, I.; Lang-Anderson, M.M.S.; Rathmell, R.E.; Snowden, D.J. *Tetrahedron Lett.*, **1997**, *38*, 7621.
7. Chen, Z.; Trudell, M.L. *Chem. Rev.*, **1996**, *96*, 1179.
8. a) Bailey, W.F.; Khanolkar, A.D.; Gavaskar, K.V.; *J. Am. Chem. Soc.*, **1992**, *114*, 8053; b) Bailey, W.F.; Gavaskar, K.V.; *Tetrahedron*, **1994**, *50*, 5957; c) Bailey, W.F.; Khanolkar, A.D. *J. Org. Chem.*, **1990**, *55*, 6058.
9. a) Beak, P.; Kerrick, S.T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.*, **1994**, *116*, 3231. b) Beak, P.; Lee, W.K. *J. Org. Chem.*, **1993**, *58*, 1109.
10. Representative n.O.e. data are shown below:



12a **12b** **13**

11. Rölle, T.; Hoffmann, R.W. *J. Chem. Soc., Perkin Trans. 2*, **1995**, 1953.
12. Bailey, W.F.; Khanolkar, A.D.; Gavaskar, K.; Ovaska, T.V.; Rossi, K.; Thiel, Y.; Wiberf, K.B. *J. Am. Chem. Soc.*, **1991**, *113*, 5720.
13. All compounds were characterised by infrared, ^{1}H and ^{13}C NMR and accurate mass spectroscopic data; ^{1}H NMR (400 MHz, $CDCl_3$) for the amine **13**: 7.44-7.24 (5H, m, Ph), 3.63 (1H, d, *J* 14, $CH^{A}H^{B}Ph$), 3.48 (1H, d, *J* 14, $CH^{A}H^{B}Ph$), 3.28-3.23 (1H, bm, NCH at C-1), 2.86-2.81 (1H, bm, NCH at C-4), 1.90-1.83 (2H, m, $NCHCH^{exo}H^{endo}CH^{exo}H^{endo}$), 1.64-1.55 (1H, m, $NCHCHCH_3$), 1.49 (1H, dd, *J* 11 and 8.5, $NCHCH^{exo}H^{endo}$), 1.35-1.28 (2H, m, $NCHCH^{exo}H^{endo}CH^{exo}H^{endo}$), 1.28-1.20 (1H, m, $NCHCH^{exo}H^{endo}$), 1.02 (3H, d, *J* 7, CH_3); representative n.O.e. data are shown above in ref. 10.
14. Amano, S.; Fujiwara, K.; Murai, A. *Chem. Lett.*, **1998**, 409.