Protecting-Group Migration

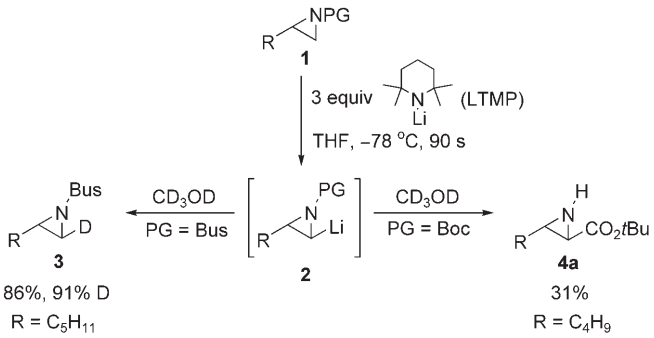
DOI: 10.1002/anie.200604920

Lithiation-Induced Migrations from Nitrogen to Carbon in Terminal Aziridines**

David M. Hodgson, Philip G. Humphreys, Zhaoqing Xu, and John G. Ward*

Aziridines are receiving increasing research interest, and a variety of methods have been recently developed for the synthesis of terminal aziridines **1** (PG = protecting group) in racemic or enantiopure form.[1,2] We have been studying the chemistry of lithiated *N*-Bus (Bus = *tert*-butylsulfonyl) terminal aziridines **2**[3] and recently reported their dimerization to give 2-ene-1,4-diamines,[4] their intramolecular cyclopropanation (where R bears an unsaturated functional group),[5] and their trapping of an external electrophile to give 2,3-disubstituted aziridines (e.g. **3**).[6] Herein, we communicate that lithiated terminal aziridines bearing a protecting group on the nitrogen atom alternative to organosulfonyl (alkoxycarbonyl, dialkoxy phosphonate) display a profoundly different reactivity mode of significant synthetic utility.

We earlier established that the Bus protecting group was the most suitable in our lithiation/electrophile-trapping reactions. Although in situ lithiation/silylation of the *N*-Boc (Boc = *tert*-butoxycarbonyl) aziridine of 1-hexene was successful, when quenching with external deuterium (CD_3OD) was attempted, the expected *trans*-deuterated *N*-Boc aziridine was not observed. Instead, a single diastereomer of N–H aziridinylester **4a** was isolated (Scheme 1), along with 50% recovered starting material with 0% D incorporation. The stereochemistry of ester **4a** was initially assigned *trans* based on the previously observed *trans*-selective lithiation by the sterically demanding LTMP with *N*-Boc and *N*-Bus aziridines,[6] and this assignment was later supported by crystallographic analysis of a related aziridinylester prepared by similar chemistry (vide infra).



Scheme 1. Reaction of terminal aziridines with lithium 2,2,6,6-tetramethylpiperidide (LTMP).

As the above transformation proceeds from readily available *N*-Boc terminal aziridines to give the synthetically useful aziridinylester motif[7] with concomitant N-deprotection, we decided to investigate the process in more detail. Although lithiation-induced N-to-C 1,2-shifts are known,[8] to the best of our knowledge only a single isolated example of this type of *N*-Boc aziridine 1,2-migration has been previously noted.[8f] In this latter work, the *N*-Boc aziridine of styrene was treated with *s*BuLi in THF at −98 °C to give a phenyl-stabilized α-lithiated aziridine, which underwent migration to give 2-phenyl-2-Boc aziridine (90%). Application of these reported conditions to aziridine **5a** gave aziridinylester **4a** in 56% yield, together with several unidentified by-products. With LTMP the yield of **4a** could be increased to 90% by leaving the reaction at −78 °C for 90 min before quenching (conditions otherwise as specified in Scheme 1). These latter conditions were then applied to a variety of terminal aziridines to assess the scope of the method (Table 1).

Complications were not observed from potential allylic deprotonation,[9] cyclopropanation,[5] or benzylic deprotonation (Table 1, entries 2 and 3). X-ray crystallographic analysis of **4c** supported the assigned *trans* stereochemistry.[10] Distal and proximal protected alcohols were tolerated (Table 1, entries 4 and 5), as was a potentially eliminable primary chloride (Table 1, entry 6). A 2,2,3-trisubstituted aziridinylester could also be accessed (Table 1, entry 7), although in this case warming to 0 °C was required for reaction to occur. Importantly for asymmetric synthesis, no degradation of *ee* was observed under the reaction conditions (Table 1, entry 8, determined by chiral HPLC analysis of the 2,4-dinitrobenzoyl derivative).[10] Attempted reaction of a 2,3-disubstituted aziridine (*N*-Boc aziridine of cyclohexene) only led to return of starting material, presumably owing to unfavorable steric interactions. When the latter reaction mixture was allowed to warm from −78 °C to 0 °C, a mixture of starting

[*] Prof. D. M. Hodgson, P. G. Humphreys, Dr. Z. Xu
Department of Chemistry
University of Oxford
Chemistry Research Laboratory
Mansfield Road, Oxford, OX1 3TA (UK)
Fax: (+44) 1865-285002
http://users.ox.ac.uk/~dmhgroup
E-mail: david.hodgson@chem.ox.ac.uk
Dr. J. G. Ward
Neurology & GI Centre of Excellence for Drug Discovery
GlaxoSmithKline
New Frontiers Science Park
Third Avenue, Harlow, Essex CM19 5AW (UK)

[**] We thank the EPSRC and GlaxoSmithKline for a CASE award (to P.G.H.), the Royal Society for an International Incoming Fellowship (to Z.X.), the EPSRC National Mass Spectrometry Service (Swansea) for mass spectra, S. P. Hughes for preliminary observations, and Prof. W. Clegg and Dr. L. Russo (University of Newcastle) for GSK-funded X-ray crystallographic analysis.

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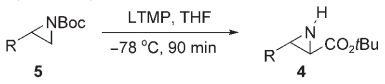
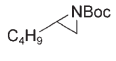
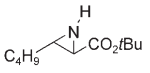
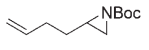
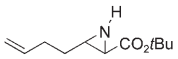
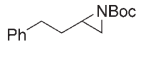
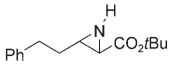
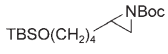
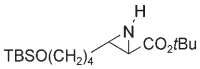
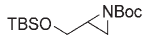
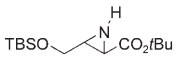
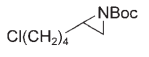
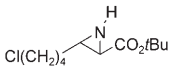
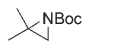
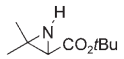
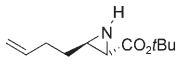
Table 1: Aziridinylester synthesis.

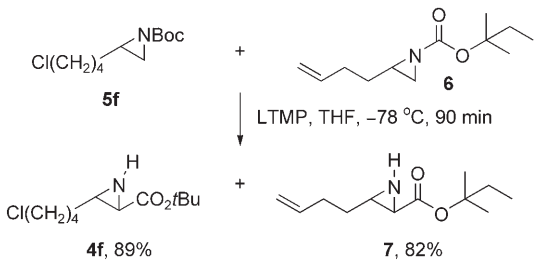


Entry	Aziridine **5**	Aziridinylester **4**		Yield [%]
1			**4a**	90
2			**4b**	86
3			**4c**	79
4[a]			**4d**	87
5[a]			**4e**	90
6			**4f**	84
7			**4g**	67[b]
8			(+)-**4b**	84

[a] TBS = *tert*-butyldimethylsilyl. [b] Reaction mixture was allowed to warm from −78 °C to 0 °C upon addition of reagents and stirred for 90 min.

material and decomposed material was obtained, whereas warming to room temperature resulted in only decomposition.

Given the propensity of related lithiated terminal aziridines to dimerize (likely as a result of aggregated species),[4] we sought to establish whether the present migration reaction was inter- or intramolecular by a crossover experiment (Scheme 2). A 1:1 mixture of aziridines **5f** and **6** was treated

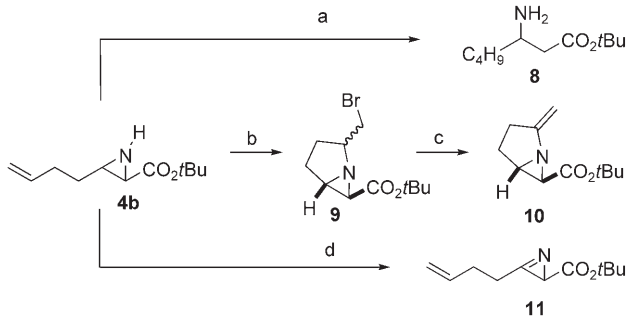


Scheme 2. Crossover experiment.

with 3 equivalents of LTMP at −78 °C for 90 min; the resulting product mixture was carefully purified and analyzed for the presence of products arising from crossover of the protecting groups. The only observed products in the crude reaction mixture were aziridinylesters **4f** and **7**, isolated in 89% and 82% yield, respectively. The lack of crossover products indicates that the reaction proceeds in an intramolecular fashion.

Although cleavage–recombination mechanisms have been proposed for lithiation-induced N-to-C 1,2-shifts, typically those reactions required higher (> −78 °C) temperatures and migration is the rate-limiting step.[8b] As the current reaction is complete within 90 min at −78 °C and the rate-limiting step is lithiation,[10] the process may proceed from a lithiated aziridine by intramolecular attack at the carbamoyl carbonyl.[8f,11]

tert-Butyl-protected N–H aziridinylesters accessed by this methodology can undergo a variety of synthetically useful subsequent transformations (see Scheme 3). Regioselective

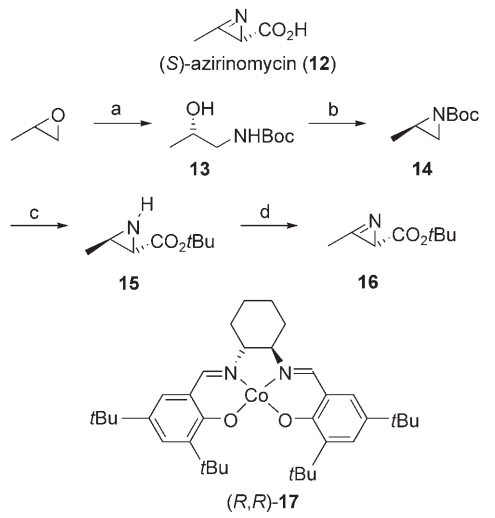


Scheme 3. Aziridinylester transformations: a) Raney Ni, H_2, EtOH, RT, 12 h, 99%; b) *N*-bromosuccinimide, CH_2Cl_2, RT, 20 h, 95%; c) DBU, toluene, 110 °C, 10 h, 92%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to RT, 5 h, 92%. DMSO = dimethyl sulfoxide.

hydrogenolysis[12] of aziridinylester **4b** gave protected β-amino acid **8** in quantitative yield. β-Amino acids are of interest owing to their stability against proteolytic degradation in vivo which can make them suitable for incorporation in drug candidates.[13] Oxidative cycloamination of the tethered olefin of **4b** with *N*-bromosuccinimide[14] gave azabicycle **9**. Subsequent elimination using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave enamine **10** in an excellent overall yield. Such bicyclic enamines undergo regioselective ring opening to give substituted pyrrolidines.[14] Regioselective Swern oxidation of aziridinylester **4b** occurred in a completely regioselective manner to give azirine **11**.[15] Azirines are useful heterocycles in synthesis, not only as imino dienophiles but also as conventional electrophiles in the synthesis of more substituted aziridines.[16]

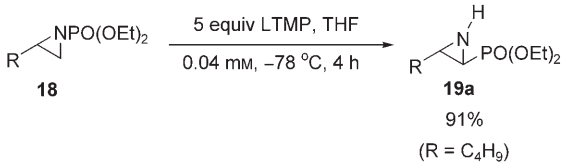
To further demonstrate the utility of this methodology, a concise asymmetric synthesis of a stable ester of the unstable antibiotic natural product azirinomycin (**12**)[17] was examined (Scheme 4). Aminolytic kinetic resolution of racemic propylene oxide using the method of Bartoli and co-workers gave amino alcohol **13** in excellent yield and enantiopurity (> 99% *ee*).[2d,10] Subsequent one-flask tosylation of the alcohol and ring closure proceeded smoothly to give *R*-aziridine **14**. Treatment with LTMP under the optimized migration conditions gave aziridinylester **15**, which then underwent regioselective Swern oxidation to give the *tert*-butyl ester of natural (*S*)-azirinomycin **16**.

Aziridinylphosphonates **19** are important sources of diversely substituted aminophosphonates, and the latter find significant utility as amino acid surrogates in biologically active peptides.[1,18] We considered whether the phosphonate N-to-C migration[19] might be possible with *N*-phosphonate



Scheme 4. Synthesis of (*S*)-azirinomycin ester **16**: a) 2 mol% (*R*,*R*)-**17**, 4 mol% 4-nitrobenzoic acid, *tert*-butylcarbamate, *t*BuOMe, RT, 24 h, 99%; b) TsCl, KOH, THF, RT, 24 h, 62%; c) LTMP, THF, −78 °C, 90 min, 70%; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C to RT, 12 h, 72%. Ts = toluene-4-sulfonyl.

aziridines to give stereocontrolled access to aziridinylphosphonates, in an analogous manner to that reported above.[20] Application of our earlier conditions for *N*-Boc migration to *N*-phosphonate aziridine **18** (R = C_4H_9,[21] Scheme 5) gave the



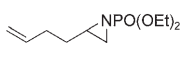
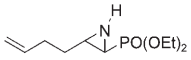
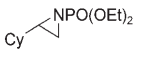
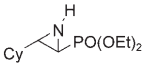
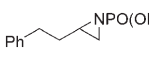
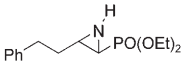
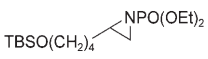
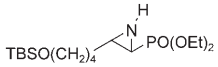
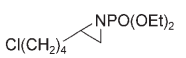
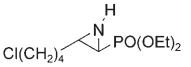
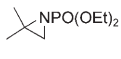
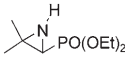
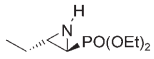
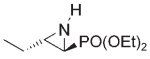
Scheme 5. Phosphonate N-to-C migration.

desired aziridinylphosphonate **19a** in 52% yield, and solely as the *trans* diastereomer,[10] along with 42% recovered starting material. It was subsequently found that increasing the number of equivalents of LTMP to 5, a more dilute reaction mixture, and an extended reaction time gave aziridinylphosphonate **19a** in 91% yield (Scheme 5).

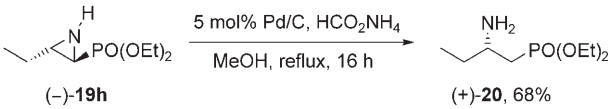
These latter conditions were then applied to a variety of *N*-phosphonate aziridines (Table 2), and a similar selectivity profile to that seen earlier in the *N*-Boc series was observed. β-Aminophosphonates and the corresponding phosphonic acids have attracted considerable interest as replacements for natural amino acids in various targets of medicinal interest.[13,18] Hydrogenolytive ring opening of aziridinylester (−)-**19h** was accomplished under transfer-hydrogenation conditions[22] to give β-aminophosphonate (+)-**20** in 68% yield and over 99% *ee*[10] (Scheme 6).

In summary, [1,2] anionic rearrangement in *N*-Boc and *N*-phosphonate terminal aziridines provides a stereocontrolled access to synthetically valuable aziridinylesters and aziridinylphosphonates under experimentally straightforward conditions. The utility of this chemistry has been demonstrated in

Table 2: Aziridinylphosphonate synthesis.[a]

Entry	Aziridine **18**	Aziridinylphosphonate **19**		Yield [%]
1			**19b**	79
2[b]			**19c**	79
3			**19d**	87
4			**19e**	95
5[c]			**19f**	87
6			**19g**	58
7[d]			(−)-**19h**	89

[a] Reaction time: 2 h at −78 °C unless indicated otherwise. [b] Cy = cyclohexyl. [c] Reaction time: 1 h. [d] Reaction time: 4 h.



Scheme 6. β-Aminophosphonate synthesis.

the synthesis of a β-amino ester and phosphonate, and a synthesis of (*S*)-azirinomycin *tert*-butyl ester in four steps from racemic propylene oxide.

Experimental Section

Representative procedure for migration of *N*-Boc aziridine: *n*BuLi (1.6 M in hexanes, 0.94 mL, 1.50 mmol) was added dropwise to a stirred solution of 2,2,6,6-tetramethylpiperidine (0.25 mL, 1.50 mmol) in THF (3.8 mL) at −78 °C under argon. This mixture was allowed to warm to room temperature for 30 min, then the resulting solution was recooled to −78 °C and a solution of aziridine (0.50 mmol) in THF (1.5 mL) was added dropwise over 1 min. The reaction mixture was stirred for 90 min at −78 °C, then saturated aqueous NH_4Cl (2 mL) was added and the flask was warmed to room temperature. The aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried ($MgSO_4$) and then concentrated under reduced pressure. Purification of the residue by column chromatography (petroleum ether/Et_2O, SiO_2) gave the aziridinylester.

Received: December 5, 2006
Published online: February 15, 2007

Keywords: amino acids · aziridines · lithiation · rearrangement · synthetic methods

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