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Intramolecular Radical Rearrangement Reactions of 2-Methyleneaziridines: Application to the Synthesis of Substituted Piperidines, Decahydroquinolines, and Octahydroindolizines

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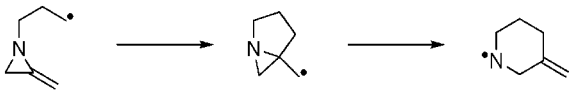
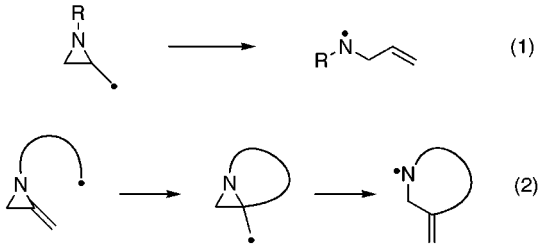
ABSTRACT



Intramolecular 5-*exo* cyclization of 3-(2-methyleneaziridin-1-yl)propyl radicals leads to the generation of a highly strained, bicyclic aziridinylcarbinyl radical that undergoes C–N bond fission to the ring-expanded aminyl radical. This methodology provides access to substituted 3-methylenepiperidines and, by combining it with an additional 5-*exo-trig* cyclization reaction, the octahydroindolizidine skeleton.

The rearrangement of the cyclopropylcarbinyl radical to the homoallyl radical has been extensively studied. By combining this rearrangement with further radical reactions, it has become a powerful method for the assembly of numerous carbocyclic ring systems.[1] By analogy, the aza variant of this reaction, involving ring opening of the aziridinylcarbinyl radical, should offer a useful method for the construction of a variety of heterocyclic skeletons. Indeed, it has been established that opening of the aziridinylcarbinyl radical is facile and usually results in the formation of the corresponding aminyl radical by preferential opening of the C−N bond (eq 1).[2] This rearrangement has been successfully used to



(1)

(2)

make several simple pyrrolidines[2b−d] and pyrrolizidines.[2i] In the search for new applications of the aziridinylcarbinyl radical rearrangement in heterocycle synthesis, we imagined that it should be possible to generate it in a conceptually new way, by cyclization of an alkyl radical in an *exo* manifold onto the double bond of a 2-methyleneaziridine. Further rearrangement of this radical would result in the generation of an aminyl radical contained within a heterocyclic ring (eq 2). By the introduction of suitable radical acceptors into the substrates, additional cyclization reactions of the resultant aminyl radical could be envisaged (vide infra).[3] This work was inspired, in part, by the work of Kilburn et al., who have successfully generated cyclopro-

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(2) (a) Stamm, H.; Assithianakis, P.; Buchholz, B.; Weib, R. *Tetrahedron Lett.* **1982**, *23*, 5021−5024. (b) Werry, J.; Stamm, H.; Lin, P.-Y.; Falkenstein, R.; Gries, S.; Irngartinger, H. *Tetrahedron* **1989**, *45*, 5015−5028. (c) Dickinson, J. M.; Murphy, J. A. *J. Chem. Soc., Chem. Commun.* **1990**, 434−436. (d) Dickinson, J. M.; Murphy, J. A. *Tetrahedron* **1992**, *48*, 1317−1326. (e) Schwan, A. L.; Refvik, M. D. *Tetrahedron Lett.* **1993**, *34*, 4901−4904. (f) DeKimpe, N.; Jolie, R.; DeSmaele, D. *J. Chem. Soc., Chem. Commun.* **1994**, 1221−1222. (g) DeKimpe, N.; DeSmaele, D.; Bogaert, P. *Synlett* **1994**, 287−288. (h) Molander, G. A.; Stengel, P. J. *Tetrahedron* **1997**, *53*, 8887−8912. (i) DeSmaele, D.; Bogaert, P.; DeKimpe, N. *Tetrahedron Lett.* **1998**, *39*, 9797−9800. (j) Marples, B. A.; Toon, R. C. *Tetrahedron Lett.* **1999**, *40*, 4873−4876.

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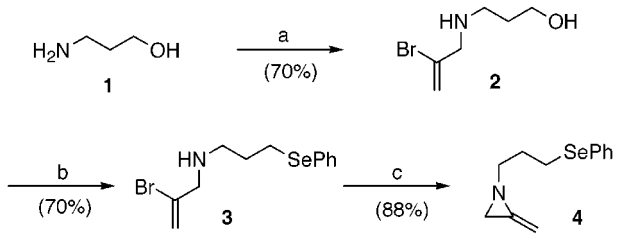
pylcarbinyl radicals by intramolecular cyclization of alkyl radicals onto methylenecyclopropanes.[4] Herein, we describe the successful implementation of radical addition−rearrangement chemistry depicted in eq 2.

In designing suitable precursors, we elected to use the phenylselenide group as the precursor to the alkyl radical because it is simple to introduce and is an excellent radical source.[5] Furthermore, we anticipated that the PhSe group would be compatible with the relatively harsh conditions required for the construction of the methyleneaziridine ring (vide infra). Our synthetic approach to radical precursor **4** is illustrated in Scheme 1. 3-Amino-propan-1-ol **1** was

Scheme 1[a]



[a] (a) 2,3-Dibromopropene, K_2CO_3, THF, reflux; (b) NPSP, Bu_3P, THF, 0 °C; (c) $NaNH_2$ (15 equiv), NH_3, 25 min.

alkylated with 2,3-dibromopropene to give alcohol **2**, which was converted into selenide **3** using *N*-phenylselenophthalimide (NPSP) and tri-*n*-butylphosphine. Final ring closure to methyleneaziridine **4** was achieved using sodium amide in liquid ammonia according to the method originally described by Pollard and Parcell.[6] This cyclization was sufficiently clean that **4** could be fully characterized and used in the subsequent radical chemistry without further purification beyond a simple aqueous workup. Other 2-methyleneaziridines used in this study (**8**, **10**, **12**, **14**) were made from the appropriate amino alcohols and again were used without purification.

(3) For a review on the use of aminyl radicals in synthesis, see: Fallis, A. G.; Brinza, I. M. *Tetrahedron* **1997**, *53*, 17543−17594.

(4) (a) Destabel, C.; Kilburn, J. D. *J. Chem. Soc., Chem. Commun.* **1992**, 596−598. (b) Pike, K. G.; Destabel, C.; Anson, M.; Kilburn, J. D. *Tetrahedron Lett.* **1998**, 39, 5877−5880. (c) Penfold, D. J.; Pike, K.; Genge, A.; Anson, M.; Kitteringham, J.; Kilburn, J. D. *Tetrahedron Lett.* **2000**, *41*, 10347−10351 and references therein.

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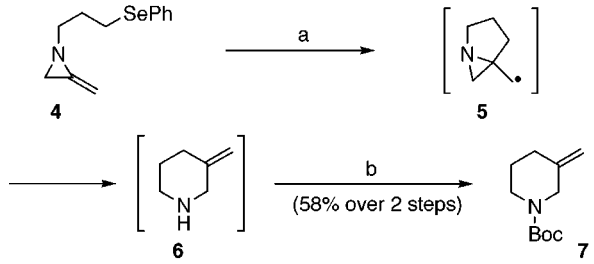
(6) (a) Pollard, C. B.; Parcell, R. F. *J. Am. Chem. Soc.* **1951**, *73*, 2925−2927. (b) Bottini, A. T.; Roberts, J. D. *J. Am. Chem. Soc.* **1957**, *79*, 1462−1464. (c) Ince, J.; Ross, T. M.; Shipman, M.; Slawin A. M. Z.; Ennis, D. S. *Tetrahedron* **1996**, *52*, 7037−7044.

(7) **Typical Procedure.** To a stirred, degassed, refluxing solution of **4** (100 mg, 0.397 mmol) in benzene (21 mL) was added AIBN (27 mg, 0.164 mmol) and tri-*n*-butytin hydride (147 μL, 0.56 mmol) in benzene (5 mL) over 5 h by syringe pump. After the addition was complete, the mixture was refluxed for 1 h and then allowed to cool to room temperature. Di-*tert*-butyl dicarbonate (173 mg, 0.79 mmol) and Et_3N (110 μL, 0.79 mmol) were added, and the mixture was stirred overnight. The solvent was removed in vacuo, and the residue was chromatographed on silica gel (5% EtOAc/95% petroleum spirit) to give **7** (45 mg, 58%) as a colorless oil: ν_{max} 1685 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 4.81 (1H, s), 4.74 (1H, s), 3.86 (2H, s), 3.43 (2H, m), 2.25 (2H, m), 1.61 (2H, m), 1.45 (9H, s); ^{13}C NMR (75 MHz, $CDCl_3$) 154.8, 143.0, 109.7, 79.4, 50.5, 44.1, 32.7, 28.4, 26.7; found (MH^+) 198.1493; $C_{11}H_{20}NO_2$ requires 198.1494.

Gratifyingly, radical rearrangement of 2-methyleneaziridine **4** to 3-methylenepiperidine **6** could be accomplished using standard tin hydride conditions (Scheme 2). Optimiza-

Scheme 2[a]

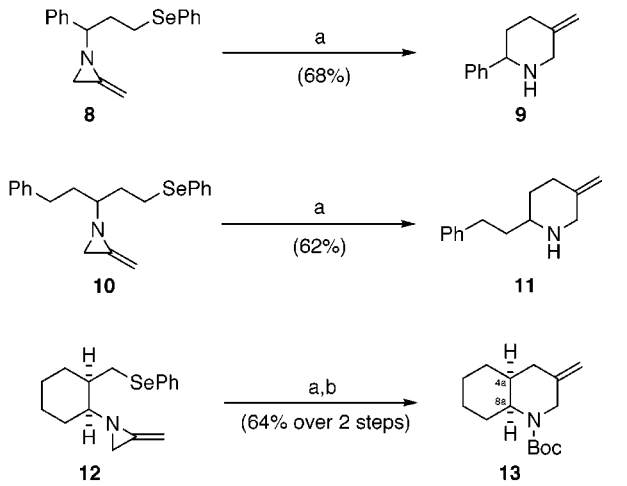


[a] (a) Bu_3SnH, AIBN, benzene, slow addition, reflux; (b) Boc_2O, Et_3N.

tion studies established that these reactions were best performed by slow addition of tri-*n*-butyltin hydride and AIBN via syringe pump over 5 h to a dilute solution (final concentration, 0.015 M) of **4** in benzene.[7] In this manner, 3-methylenepiperidine **7** could be isolated in 58% overall yield after in situ Boc protection of **6** to reduce volatility and water solubility. We speculate that this reaction proceeds via aziridinylcarbinyl radical **5**, formed by 5-*exo*-*trig* cyclization of the initially formed alkyl radical, which then undergoes C−N bond cleavage to relieve the ring strain associated with the 1-azabicyclo[3.1.0]hexane ring system. The regioselectivity of the bond fission of **5** parallels findings made using simple monocyclic systems (cf. eq 1).[2]

We have used this radical rearrangement sequence to make several monocyclic and bicyclic systems (Scheme 3). Methyleneaziridines **8** and **10** were readily rearranged to 6-aryl and 6-alkyl piperidines **9** and **11**, respectively, using the same method. Furthermore, methyleneaziridine **12** rearranged to

Scheme 3[a]

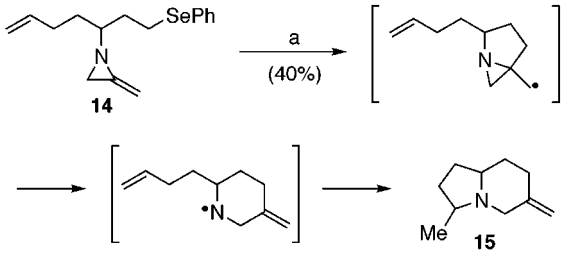


[a] (a) Bu_3SnH, AIBN, benzene, slow addition, reflux; (b) Boc_2O, Et_3N.

the decahydroquinoline skeleton, which was conveniently isolated after in situ *N*-Boc protection. The ring junction stereochemistry within **13** was assigned as *cis* on the basis of strong NOE enhancements observed between H-4a and H-8a {H-8a (5.8%) from H-4a; and of H-4a (9.2%) from H-8a}.

We have examined whether the aminyl radical generated by this 5-*exo* cyclization−aziridinylcarbinyl rearrangement will participate in additional radical cyclization reactions.[3] To this end, we made methyleneaziridine **14** possessing an alkene suitably positioned for an additional 5-*exo*-*trig* cyclization. Treatment of **14** with tri-*n*-butyltin hydride and AIBN as described previously resulted in the isolation of octahydroindolizine **15** in 40% yield as a single diastereomer after careful chromatography on neutral alumina (Scheme 4). More careful analysis reveals that both diastereoisomers (dr 4:1) were actually produced in the reaction. This diastereomeric ratio was obtained by integration of the two resolved methyl doublets {δ 1.02 (major) and 1.15 (minor)} in the ^{1}H NMR spectrum ($CDCl_3$) prior to chromatography. We believe the modest isolated yield of octahydroindolizine **15** is largely a reflection of its polarity and volatility and not the efficiency of this reaction sequence. Unfortunately, we have been unable to unambiguously establish the relative stereochemistry within **15**.[8] Further work to use these radical rearrangement reactions for the synthesis of other heterocyclic systems is ongoing, and this work will be disclosed in due course.

Scheme 4[a]



[a] (a) Bu_3SnH, AIBN, benzene, slow addition, reflux.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for compounds **4**, **7**, **9**, **11**, **13**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) ^{1}H NMR experiments (NOE and NOESY) failed to provide any useful information concerning the relative stereochemistry within **15**. Attempts to grow single crystals for X-ray diffraction studies have thus far been unsuccessful.

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