Lithiated Aziridine Reagents

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Received November 9, 1992

Metalated aziridines **1** (R^1 = alkyl, aryl) have obvious potential for the stereospecific preparation of 2,3-disubstituted aziridines.[1] Several attempts to generate **1** are mentioned in the literature,[2,3] but practical results have so far been restricted to stabilized derivatives **2** (X = electron-withdrawing group).[3] There is one previous report that describes the generation of **1a** or **1b** via reductive desulfonylation of 1-phenyl-2-(phenylsulfonyl)aziridine.[2a] The *C*-lithio derivative **1a** does not survive the reaction conditions, but **1b** can be trapped by aldehydes. On the other hand, **1b** reacts with acetyl chloride to give acylation products of a ring-opened enamine (or the *N*-magnesio enamine). The mechanistic details are not yet clear.[2a] Ring opening is also encountered with the analogous *C*-lithio oxiranes, and α-elimination and electrocyclic decomposition pathways are possible.[4,5] Conditions for stabilizing and trapping these highly reactive species at −90 °C have only recently been described.[4]

In view of the above background, we were surprised to find that *C*-lithioaziridines **3a** and **3b** are accessible by tin–lithium exchange. We now describe the preparation and synthetic potential of these reagents, together with observations regarding their unusual decomposition pathway.

Scheme I summarizes the synthesis of **4** from the *N*-tritylamino alcohols **5**.[6] Swern oxidation[7a] followed by treatment of the amino aldehyde **6** with Bu_3SnLi/THF[7b] (−78 °C; slow warming to 0 °C) afforded the stannyl amino alcohols **7**. The relative stereochemistry was deduced later, after conversion to the lithio aziridines. However, the addition reaction of **6b** gave one dominant diastereomer with a 40:1 preference for **7b**. This result corresponds to a chelation-controlled addition of Bu_3SnLi to **6b**, as in analogous organolithium addition reactions of N-protected α-amino aldehyde derivatives.[8] The *C*-methyl analog **7a** was formed with similar selectivity according to NMR assay, but the exact diastereomer ratio could not be established because **7a** was less stable to chromatography. The adduct was therefore converted directly into the aziridine **4a** (74%) using Mitsunobu conditions that were effective with **7b** (79%).[9]

Treatment of **4a** or **4b** with *n*-butyllithium at −78 °C resulted in tin–lithium exchange.[10] The CH_3OCH_2O-substituted stannylaziridine was substantially more reactive toward *n*-butyllithium (for **4b**, 15 min at −78 °C; for **4a**, −60 °C followed by brief warming to −10 °C), suggesting a beneficial role for the potentially coordinating methoxymethyl (MOM) group in the tin–lithium exchange. However, no clear difference in anion reactivity was observed. Both **3a** and **3b** were trapped efficiently at −78 °C using typical electrophiles, as summarized in Table I. Quenching experiments with D_2O gave the deuterated aziridine **9d** (ca. 97% D_1), and the stereochemistry was established from the charac-

Scheme I

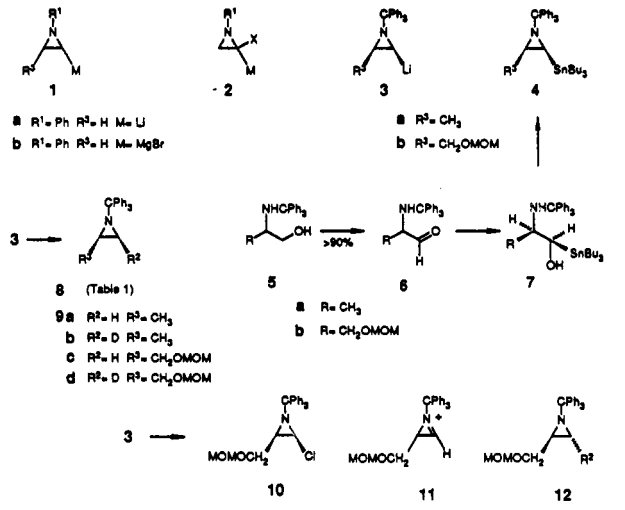

Table I. Trapping Reactions of 2-Lithioaziridines **3a** and **3b**[a]

entry	R^2	R^3	E^+	product	yield, %
1	H	Me	MeOH	**9a**	92
2	D	Me	D_2O	**9b**	85
3	PhCH(OH)	Me	PhCHO	**8a**	66 (1.9:1)[b]
4	H	CH_2OMOM	MeOH	**9c**	87
5	D	CH_2OMOM	D_2O	**9d**	84
6	CO_2Et	CH_2OMOM	EtOCOCl	**8b**	64
7	Cl	CH_2OMOM	C_2Cl_6	**10**	92
8	PhCH(OH)	CH_2OMOM	PhCHO	**8c**	81 (1.4:1)[b]

[a] All reactions were performed in THF at −78 °C. [b] Diastereomer ratio, stereochemistry not assigned.

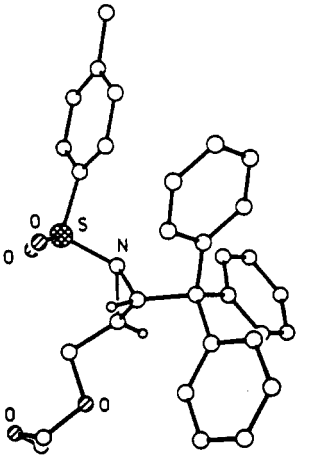

Figure 1. X-ray structure of crystalline **15**.

(1) Vedejs, E.; Sano, H. *Tetrahedron Lett.* **1992**, *31*, 3261.
(2) (a) Satoh, T.; Sato, T.; Oohara, T.; Yamakawa, K. *J. Org. Chem.* **1989**, *54*, 3973. (b) Atkinson, R. S.; Kelly, B. J. *Tetrahedron Lett.* **1989**, *30*, 2703.
(3) (a) Pohland, A. E.; McMaster, M. C.; Badger, R. C.; Cromwell, N. H. *J. Am. Chem. Soc.* **1965**, *87*, 2510. Tarburton, P.; Chung, A.; Badger, R. C.; Cromwell, N. H. *J. Heterocycl. Chem.* **1976**, *13*, 295. Tarburton, P.; Wall, D. K.; Cromwell, N. H. *J. Heterocycl. Chem.* **1976**, *13*, 411. (b) Gaillot, J.-M.; Gelas-Mialhe, Y.; Vissière, R. *Can. J. Chem.* **1979**, *57*, 1958. (c) Seebach, D.; Häner, R. *Chem. Lett.* **1987**, 49. Häner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676.
(4) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615.
(5) Crandall, J. K. *Org. React. (N.Y.)* **1983**, *29*, 345. Dubuffet, T.; Sauvetre, R.; Normant, J. F. *Tetrahedron Lett.* **1988**, *29*, 5923. Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042. Ashwell, M.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1989**, 835. Eisch, J. J.; Galle, J. E. *Org. Chem.* **1990**, *55*, 4835 and references therein. Ashwell, M.; Clegg, W.; Jackson, R. F. W. *J. Chem. Soc., Perkin Trans. 1* **1991**, 897.
(6) van Leusen, A. M.; Hoogenboom, B. E.; Siderius, H. *Tetrahedron Lett.* **1972**, *13*, 2369.
(7) (a) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480. (b) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481. (c) Kuyl-Yeheskiely, E.; Lodder, M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1992**, *33*, 3013.
(8) (a) Herold, P. *Helv. Chim. Acta* **1988**, *71*, 354. (b) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531. (d) Polt, R.; Peterson, M. A.; DeYoung, L. *J. Org. Chem.* **1992**, *57*, 5469.
(9) Mitsunobu, O. *Synthesis* **1981**, 1. Pfister, J. R. *Synthesis* **1984**, 969. Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(10) (a) Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027. Quintard, J.-P.; Elissondo, B.; Jousseaume, B. *Synthesis* **1984**, 495. Verlhac, J.-P.; Quintard, J.-P. *Tetrahedron Lett.* **1986**, *27*, 2361. (b) Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209. (c) Pearson, W. H.; Lindbeck, A. C. *J. Org. Chem.* **1989**, *54*, 5651. MacLeod, D.; Quayle, P.; Davies, G. M. *Tetrahedron Lett.* **1990**, *31*, 4927. Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. (d) Elissondo, B.; Verlhac, J.-P.; Quintard, J.-P. *J. Organomet. Chem.* **1988**, *339*, 267. (e) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.; Ito, S. *Tetrahedron Lett.* **1991**, *32*, 1975.

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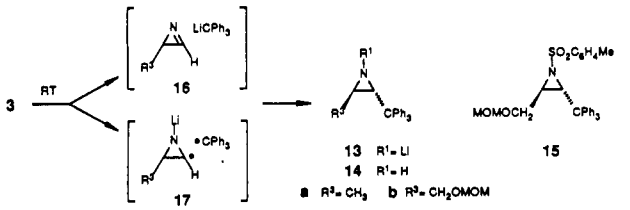
teristic $J_{2,3}$ = 6.1 Hz.[11,12] Similar coupling constants of ca. 6 Hz were eventually found in a number of the other trapping products **8**, all of which are assigned cis stereochemistry on the basis of the NMR data. Thus, **3** is configurationally stable due to the aziridine effect.[3c,10c] Finally, to establish synthetic utility, the ester **8b** (entry 6, Table I) was detritylated to give the corresponding N-H aziridine (80% yield) using formic acid in methanol at room temperature.[7c]

When **3b** was quenched with hexachloroethane, the 2-chloroaziridine **10** was obtained in good yield. Only a few isolated reports mention 2-chloroaziridines,[13] but they are relatively stable compared to other α-chloroamines. Thus, **10** survived rapid chromatography over silica gel. However, prolonged contact with the adsorbent (TLC, PLC) resulted in ring cleavage and formation of **6b**, probably via hydrolysis of the azirenium intermediate **11**. The same intermediate could also be trapped with Grignard reagents to give 2,3-disubstituted aziridines. Heating in THF was necessary to convert the chloroaziridine to **12**, and the trans diastereomers predominated (R^2 = Ph, 6.5:1 trans:cis, 64% isolated; R^2 = 1-naphthyl, 10:1 trans:cis, 71% isolated). These are the results expected from trapping of **11** from the less hindered face, and increased selectivity is observed with the more hindered naphthyl Grignard reagent.[14]

Based on the behavior of *C*-lithiooxiranes,[4,5] we had expected that thermal decomposition of **3** might lead to mixtures resulting from α-elimination or electrocyclic ring opening.[4,5] However, these reactions have not been detected. Instead, warming the pale orange **3a** or **3b** in THF above −10 °C produced a red color, and quenching at room temperature afforded a single major product in each case.[15] Since the product is an isomer of **9a** according to exact mass and contains the characteristic NMR signals of a *trans*-2,3-disubstituted aziridine ($J_{2,3}$ = ca. 3 Hz), it can only be **14**, the product of N-to-C trityl migration. This structure has been confirmed after tosylation of **14b** to afford **15**. The X-ray structure of this crystalline substance is shown in Figure 1.

We have been unable to find previous examples of anionic Stevens rearrangement involving trityl groups. There is one reported case of an anionic N-to-C migration of a benzyl group in the literature,[10b] as well as several other more distantly related nitrogen Stevens rearrangements.[16] There are also some indications that triarylmethyl can behave as an anionic leaving group.[17] This precedent suggests the hypothetical sequence from **3** to **16**, followed by recombination to give **13**. However, **16** is not intercepted by external butyllithium even if a 10-fold excess of the reagent is used for tin-lithium exchange. A caged radical-radical anion pair mechanism via **17** appears more likely from **3** to **13**.

Tin-lithium exchange succeeds with secondary α-aminoalkyllithium reagents $R_2NCH(R')Li$ if R′ can stabilize the C-Li bond by dipole[10c] or conjugation effects,[10d] but metal exchange usually fails when R′ = alkyl.[10e] The *C*-lithiated aziridines **3** are the first known exceptions to this rule, probably due to enhanced



s character in the exocyclic bonds. However, the enforced syn arrangement of C-Li and lone-pair orbitals may also be important and could be among the reasons why **3** is resistant to electrocyclic ring opening. Work is in progress to determine the role, if any, of nitrogen stereochemistry in the aziridine.

The methodology summarized above provides access to *cis*- or *trans*-2,3-disubstituted aziridines. We plan to evaluate enantiomerically pure *C*-lithioaziridines for applications in total synthesis.

Acknowledgment. This work was supported by the National Institutes of Health (CA17918). The authors also thank D. Powell for the X-ray structure of **15**.

Supplementary Material Available: Representative procedures and preparation of key intermediates (8 pages). Ordering information is given on any current masthead page.

(11) **9b**: colorless prisms from methanol, mp 114-116 °C; 200-MHz NMR ($CDCl_3$) δ 7.56-7.46 (6 H, m) 7.30-7.14 (9 H, m) 1.31 (3 H, d, *J* = 4.9 Hz) 1.26-1.15 (1 H, m) 1.04 (1 H, d, *J* = 5.9 Hz). **9d**: oil; 270-MHz NMR ($CDCl_3$) δ 7.52-7.47 (6 H, m) 7.30-7.16 (9 H, m) 4.62 (2 H, s) 3.90 (1 H, dd, *J* = 5.1, 10.4 Hz) 3.56 (1 H, dd, *J* = 6.1, 10.4 Hz) 3.34 (3 H, s) 1.52 (1 H, dt, *J* = 5.2, 6.1 Hz) 1.17 (1 H, d, *J* = 6.1 Hz).

(12) Booth, H. In *Progress in Nuclear Magnetic Resonance Spectroscopy*; Emsley, J. W., Feeney, J., Sutcliffe, L. H., Eds.; Pergamon Press: Oxford, 1969; Vol. 5, p 186.

(13) (a) Deyrup, J. A.; Greenwald, R. B. *Tetrahedron Lett.* **1965**, *6*, 321. Deyrup, J. A.; Greenwald, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4538. (b) Nicoletti, R.; Forcellese, M. L. *Tetrahedron Lett.* **1965**, *6*, 153. (c) Fowler, F. W.; Hassner, A. *J. Am. Chem. Soc.* **1968**, *90*, 2875. Hassner, A.; Burke, S. S.; I., J. C. *J. Am. Chem. Soc.* **1975**, *97*, 4692. See also ref 3b.

(14) For previous examples of chloroaziridine reactions with Grignard reagents, see ref 13c.

(15) For characterization of **14a** and **14b**, see supplementary material.

(16) Cockburn, W. F.; Johnstone, R. A. W.; Stevens, T. S. *J. Chem. Soc.* **1960**, 3340. Johnstone, R. A. W.; Stevens, T. S. *J. Chem. Soc.* **1966**, 3346. Anderson, A. G.; Wills, M. T. *J. Org. Chem.* **1967**, *32*, 3241. Durst, T.; LeBelle, M. J. *Can. J. Chem.* **1972**, *50*, 3196. Durst, T.; Van Den Elzen, R.; LeBelle, M. J. *J. Am. Chem. Soc.* **1972**, *94*, 9261. Eisch, J. J.; Dua, S. K.; Kovacs, C. A. *J. Org. Chem.* **1987**, *52*, 4437. Broka, C. A.; Shen, T. *J. Am. Chem. Soc.* **1989**, *111*, 2981.

(17) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236.

Total Synthesis of the Marine Polypropionate (+)-Muamvatin. A Configurational Model for Siphonariid Metabolites

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Received December 1, 1992

Muamvatin,[1] isolated from the Fijian pulmonate mollusc *Siphonaria normalis*, is a novel marine polypropionate containing an unusual 2,4,6-trioxaadamantane ring system. Extensive NMR studies by Ireland et al.[1] allowed the partial structural assignment **1**, where the side-chain stereochemistry (C_{10}, C_{11})[2] could not be fully defined. We now report the first total synthesis of (+)-muamvatin, making use of efficient, substrate-based, aldol stereocontrol. This synthesis allows the complete assignment of the stereochemistry and leads to a general configurational model for this class of siphonariid metabolites.[3,4] We find that the trioxaadamantane ring system is readily produced by silica gel-promoted rearrangement, such that the muamvatin structure may well be an artifact of the isolation process.

Molecular modeling[5] of the four possible diastereomers of **1** allowed a prediction of the C_{10} relative stereochemistry (but not C_{11}).[6] Hence, we chose to first synthesize the aldehyde **2** with

(1) Roll, D. M.; Biskupiak, J. E.; Mayne, C. L.; Ireland, C. M. *J. Am. Chem. Soc.* **1986**, *108*, 6680.

(2) We use a different numbering system for muamvatin from that used by Ireland et al.,[1] based on the likely polypropionate chain biosynthesis (Scheme III).

(3) (a) Denticulatins: Hochlowski, J. E.; Faulkner, D. J.; Matsumoto, G. K.; Clardy, J. *J. Am. Chem. Soc.* **1983**, *105*, 7413. (b) Siphonarins: Hochlowski, J. E.; Coll, J. C.; Faulkner, D. J.; Biskupiak, J. E.; Ireland, C. M.; Qi-tai, Z.; Cun-heng, H.; Clardy, J. *J. Am. Chem. Soc.* **1984**, *106*, 6748. (c) Baconipyrones: Manker, D. C.; Faulkner, D. J.; Stout, T. J.; Clardy, J. *J. Org. Chem.* **1989**, *54*, 5371.

(4) (a) Manker, D. C.; Garson, M. J.; Faulkner, D. J. *J. Chem. Soc., Chem. Commun.* **1988**, 1061. (b) Garson, M. J.; Small, C. J.; Skelton, B. W.; Thinapong, P.; White, A. H. *J. Chem. Soc., Perkin Trans. 1* **1990**, 805.

(5) We used the MM2 force field in MacroModel, v 3.1. Mohamedi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

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