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Synthesis of Silyl Aziridines and α-Amino Acylsilanes with Silyldibromomethyllithium

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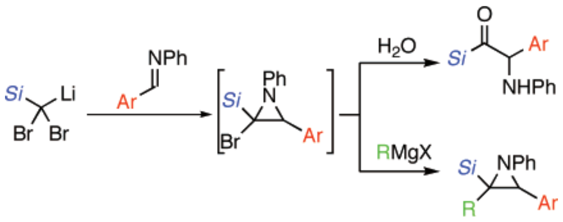
ABSTRACT



The reaction of silyldibromomethyllithium with aromatic imines provides α-amino acylsilanes via a bromo aziridine intermediate upon quenching the reaction with water. Alternatively, treatment of the bromo aziridine intermediate with various Grignard reagents or lithium aluminum hydride permits the nucleophilic displacement of the halogen to furnish substituted silyl aziridines.

Aziridines are an important class of three-membered N-heterocyclic compounds which serve as versatile intermediates in organic synthesis.[1] Their inherent ring strain activates the carbon−nitrogen bond, and they often serve as good electrophiles. Consequently, aziridine-containing natural products often exhibit strong biological activities because the aziridine motif can act as a powerful alkylating agent for DNA.[2]

Recently, Aggarwal et al. have reported that silyl aziridines can serve as useful intermediates for the synthesis of aziridine derivatives.[3] Here we wish to report a novel synthesis of silyl aziridines via a three-component coupling reaction with silyldibromomethyllithium. Additionally, this procedure allows for a facile synthesis of α-amino acylsilanes, which are known to be viable synthetic intermediates.[4]

tert-Butyldimethylsilyldibromomethyllithium (**1a**) was readily prepared by the deprotonation of dibromomethylsilane[5] with lithium diisopropylamide (LDA) in THF at −78 °C.[6] A solution of benzaldehyde imine **2a** in THF was added then dropwise to the yellow solution of **1a** at −78 °C. The reaction mixture was allowed to warm to −40 °C over 2 h, after which it was quenched with water. Extractive workup and purification provided α-amino acylsilane **3a** in 63%

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(5) (a) Dibromomethylsilanes are easily prepared according to the reported procedure. Bacquet, C.; Masure, D.; Normant, J. F. *Bull. Soc. Chim. Fr.* **1975**, 1797. (b) Yoon, K.; Son, D. Y. *J. Organomet. Chem.* **1997**, *545*, 185

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yield. The formation of the α-amino acylsilane **3** can be reasoned by the hydrolysis of bromo aziridine intermediate **5** which results from a 3-*exo-trig* cyclization of the initially formed adduct **4**.[7] Although we expected the rearrangement product **7** via a 1,3-migration of the silyl group from the carbon to the negatively charged nitrogen, no such product was detected in the reaction mixture (Scheme 1).[8]

Scheme 1

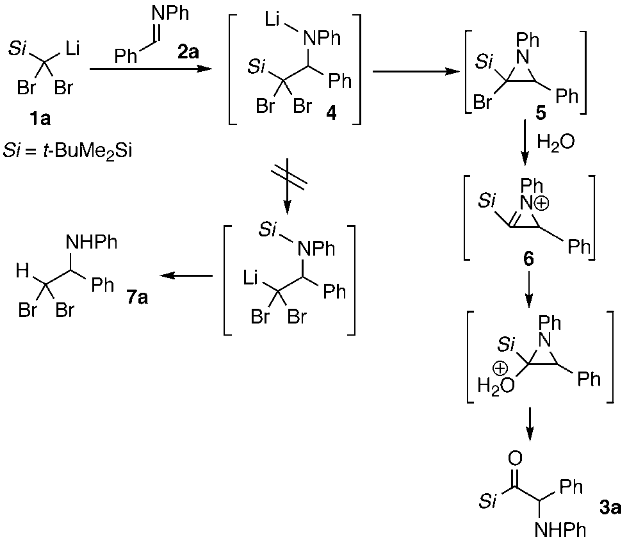
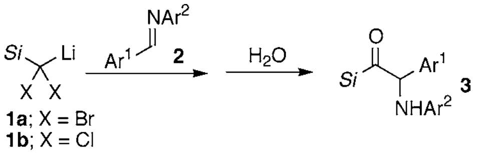


Table 1. Synthesis of α-Amino Acylsilanes[a]



entry	X	Ar^1	Ar^2	*Si*		yield (%)
1	Br	Ph	Ph	t-BuMe$_2$Si	**3a**	63
2	Br	4-Cl(C$_6$H$_4$)	Ph	t-BuMe$_2$Si	**3b**	69
3	Br	Ph	4-Cl(C$_6$H$_4$)	t-BuMe$_2$Si	**3c**	60
4	Br	Ph	2-MeO(C$_6$H$_4$)	t-BuMe$_2$Si		trace
5	Br	2-CF$_3$(C$_6$H$_4$)	Ph	t-BuMe$_2$Si	**3d**	47
6	Br	C$_6$F$_5$	Ph	t-BuMe$_2$Si		trace
7	Br	Ph	Ph	Et$_3$Si	**3e**	11
8	Br	Ph	n-Pr	t-BuMe$_2$Si		trace
9	Br	Ph	Ph	i-Pr$_3$Si	**3f**	57
10	Cl	Ph	Ph	t-BuMe$_2$Si	**3a**	68

[a] Reaction conditions: dihalomethylsilane (0.50 mmol), LDA (0.75 mmol), THF (4.5 mL), imine (0.60 mmol), −78 °C to rt.

The reaction can be utilized for the synthesis of various α-amino acylsilanes **3**, which are a rare class of functionalized acylsilanes (Table 1). Although functionalized acylsilanes have been extensively explored in organic synthesis,[9] few reports on α-amino acylsilane preparation have appeared in the literature. Unfortunately, *N*-alkyl aromatic imine did not yield the expected product (entry 8). No observable reaction occurred with aromatic oximes and hydrazones. *N*-Tosyl imine gave the adduct **4**, which did not cyclize to the bromo aziridine **5**. This is because the electron-withdrawing sulfonyl group lowers the nucleophilicity of the lithium amide. In this case, dibromo *N*-tosyl amide was obtained in 84% yield (Scheme 2). This fact could indicate the intermediacy of carbene is not involved in this reaction. The reaction of silyldichloromethyllithium **1b** provided α-amino acylsilane **3a** in 68% yield (entry 10). Again, no rearrangement products were isolated.

Scheme 2

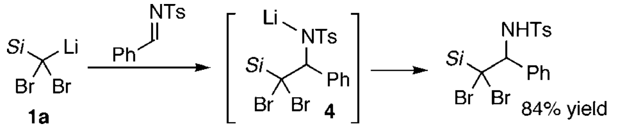
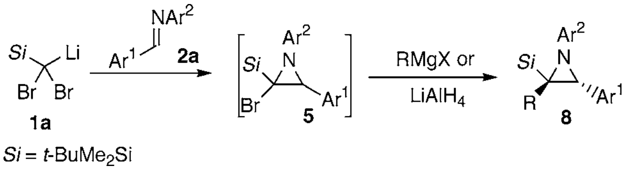


Table 2. One-Pot Synthesis of Aziridines with Grignard Reagents[a]



entry	Ar^1	Ar^2	R		yield (%)	ratio
1	Ph	Ph	Ph	**8a**	71	>99/1
2	4-Cl(C$_6$H$_4$)	Ph	Ph	**8b**	74	>99/1
3	Ph	4-Cl(C$_6$H$_4$)	Ph	**8c**	69	>99/1
4	Ph	Ph	n-Bu	**8d**	82	>99/1
5	Ph	Ph	allyl	**8e**	82	>99/1
6	Ph	Ph	H	**8f**	84	79/21

[a] Reaction conditions: dibromomethylsilane (0.50 mmol), LDA (0.75 mmol), THF (4.5 mL), imine (0.60 mmol), −78 to −40 °C, then THF solution of Grignard reagent (1.0 M, 0.75 mmol), room temperature, 30 min.

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(6) For the use of silyldihalomethyllithiums, see: (a) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1993**, *34*, 1951−1954. (b) Shinokubo, H.; Miura, K.; Oshima, K.; Utimoto, K. *Tetrahedron* **1996**, *52*, 503−514. (c) Shinokubo, H.; Oshima, K.; Utimoto, K. *Chem. Lett.* **1995**, 461−462. (d) Shinokubo, H.; Kondo, J.; Inoue, A.; Oshima, K. *Chirality* **2003**, *15*, 31. (e) Kondo, J. Ito, Y.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 106. (g) Inoue, A.; Kondo, J.; Shinokubo, H.; Oshima, K. *Chem. Eur. J.* **2002**, *8*, 1730 (h) Kondo, J.; Inoue, A.; Shinokubo, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2001**, *40*, 2085.

(7) For the synthesis of aziridines via the addition of lithium carbenoids to imines, see: (a) Deyrup, J. A.; Greenwald, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 4538. (b) Deyrup, J. A.; Greenwald, R. B. *Tetrahedron Lett.* **1965**, *6*, 321. (c) Reutrakul, V.; Prapansiri, V.; Panyachotipun, C. *Tetrahedron Lett.* **1984**, *25*, 1949. (d) Chulabhorn, M.; Reutrakul, V.; Prapansiri, V.; Panyachotipun, C. *Chem. Lett.* **1984**, *6*, 969. (e) Cantrill, A. A.; Hall, L. D.; Jarvis, A. N.; Osborn, H. M. I.; Raphy, J.; Sweeney, J. B. *Chem. Commun.* **1996**, 2631. (f) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T. N.; Reddy, G. V.; Zhang, Y. L. *J. Org. Chem.* **1999**, *64*, 7559.

(8) 1,3-Rearrangement of a silyl group has been observed in the reaction of silyldichloromethyllithium with aromatic nitriles; see: Yagi, K.; Tsuritani, T.; Takami, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2004**, *126*, 8618.

(9) (a) Page, P. C. B.; Klair, S. S.; Rosenthal, S. *Chem. Soc. Rev.* **1990**, *19*, 147−195. (b) Ricci, A.; Degl'Innocent, A. *Synthesis* **1989**, 647−666. (c) Cirillo, P. F.; Panek, J. S. *Org. Prep. Proc. Int.* **1992**, *24*, 555−582.

The bromo aziridine intermediate **5**, which has a reactive carbon−bromine bond activated by the nitrogen atom, underwent efficient nucleophilic displacement with Grignard reagents. The results are summarized in Table 2. The reaction was conducted in one pot and provided substituted aziridines in good yields with excellent stereoselectivity. Hydride transfer to **5** can be accomplished with lithium aluminum hydride but with a decreased selectivity.

The stereochemistry of the products was established unambiguously from an X-ray crystallographic analysis of **8a** (Figure 1). The stereoselectivity depends on the bulkiness of the nucleophiles (carbon nucleophile vs hydride). The substitution process in these bromo aziridines is an S_N1-type process involving the cyclic iminium species **6**.[8a] The observed stereoselectivity can be rationalized by looking at the addition of nucleophiles to **6** from the less hindered side (Scheme 3).

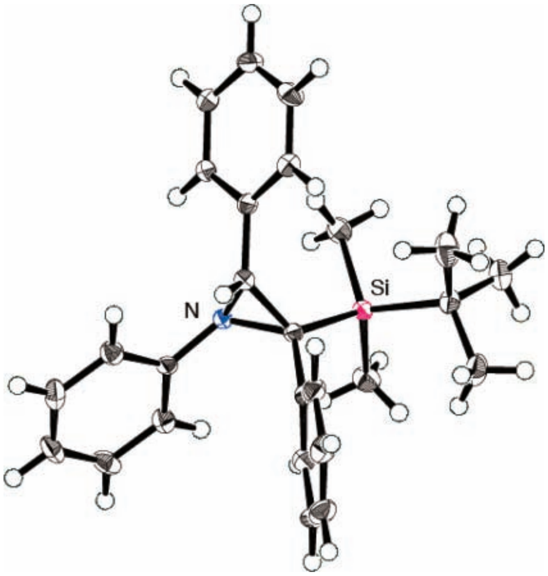
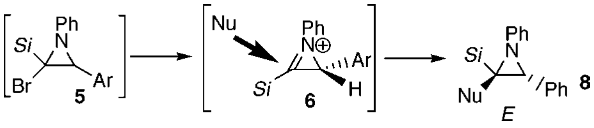


Figure 1. ORTEP drawing of **8a**.

Scheme 3



In conclusion, we have developed the reaction of silyldibromomethyllithium with aromatic imines to provide α-amino acylsilanes. The reaction proceeds via a bromo aziridine intermediate, which can be efficiently alkylated upon treatment with Grignard reagents, providing trisubstituted silylated aziridines in good yields with high stereoselectivity.

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Supporting Information Available: Experimental procedures, compound data, and X-ray crystallographic data for **8a** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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