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A novel synthesis of cyclic α-amino aldehydes, amino alcohols, and α-amino acid methyl esters from cyclic ketones through sulfinylaziridines

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Abstract—Treatment of 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from cyclic ketones and chloromethyl *p*-tolyl sulfoxide in three steps in good yields, with *N*-lithio arylamines gave sulfinylaziridines in high yields. On treatment with *N*-lithio aniline or *N*-lithio *p*-chloroaniline, the sulfinylaziridines gave α-amino aldehydes in high yields. The α-amino aldehydes were converted to amino alcohols and α-amino acid methyl esters in moderate to good yields. This procedure offers an efficient method for synthesis of cyclic α-quaternary α-amino aldehydes, amino alcohols, and α-amino acid derivatives from cyclic ketones.

Amino acids are the fundamental building blocks of peptides and proteins and play essential roles in living organisms.[1] Because of the physiological importance of α-amino acids, innumerable studies for their chemistry and synthesis have been published.[2] Recently, quaternary α-amino acids[3] and β-amino acids[4] have received considerable attention. Especially, the cyclic α-quaternary α-amino acids are conformationally constrained, they are used in controlling peptide secondary structures and in drug design and development.[5] The synthesis and chemistries of cyclic α-quaternary α-amino acids have attracted great attention these days.[6] On the other hand, α-amino aldehydes and amino alcohols are also quite important and interesting compounds in organic chemistry.[7]

We have reported some new synthetic methods starting from 1-chlorovinyl *p*-tolyl sulfoxides **2**,[8] which were synthesized easily from aldehydes and ketones **1**, and chloromethyl *p*-tolyl sulfoxide. In continuation of our study concerning the use of 1-chlorovinyl *p*-tolyl sulfoxides in the development of new synthetic methods, herein we report our recent results for a novel synthesis of cyclic α-quaternary α-amino aldehydes **4** and α-amino acid methyl esters **5** from the 1-chlorovinyl *p*-tolyl sulfoxide **2** via the sulfinylaziridines **3** (Scheme 1).

First, 1-chlorovinyl *p*-tolyl sulfoxide **6**[9] was treated with 1.2 equiv of *N*-lithio aniline in THF at 0 °C for 30 min. Quite clean reaction took place and sulfinylaziridine **7c** [10] was obtained in 92% yield (Scheme 2). It is interesting to note that the product **7c** is a single isomer though it has two stereogenic centers. On the other hand, when this reaction was conducted with excess *N*-lithio aniline at room temperature, α-amino aldehyde **8c**[11] was obtained in 90% yield.

A plausible mechanism of this very interesting reaction is as follows (Scheme 3). Conjugate addition of *N*-lithio aniline to the 1-chlorovinyl *p*-tolyl sulfoxide **6** gave the adduct **9**, which affords α-sulfinyl carbenoid **10** with elimination of LiCl. N–H insertion reaction, then, took place to give the sulfinylaziridine **7c**. Another plausible path for the formation of **7c** is thought to be the substitution of the chloride by nitrogen via **11**.

The mechanism for the formation of the α-amino aldehyde **8c** by treatment of **6** with excess *N*-lithio aniline was confirmed to be as follows. The sulfinylaziridine **7c** is attacked by the anilide to give ring-opened adduct **12**. The sulfinyl group in **12** is eliminated via **13** to give imine **14**, which is hydrolyzed in the work-up process to give the α-amino aldehyde **8c**. In fact, treatment of the sulfinylaziridine **7c** with excess *N*-lithio aniline at room

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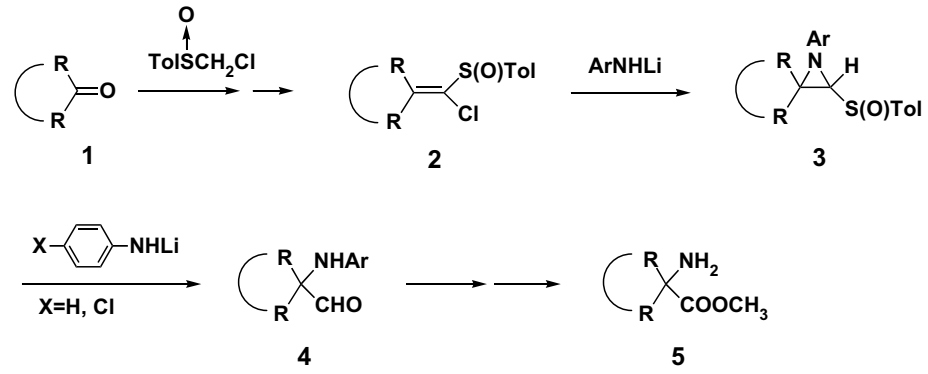
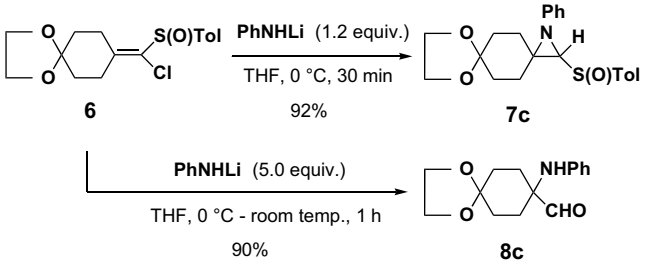


Scheme 1.



Scheme 2.

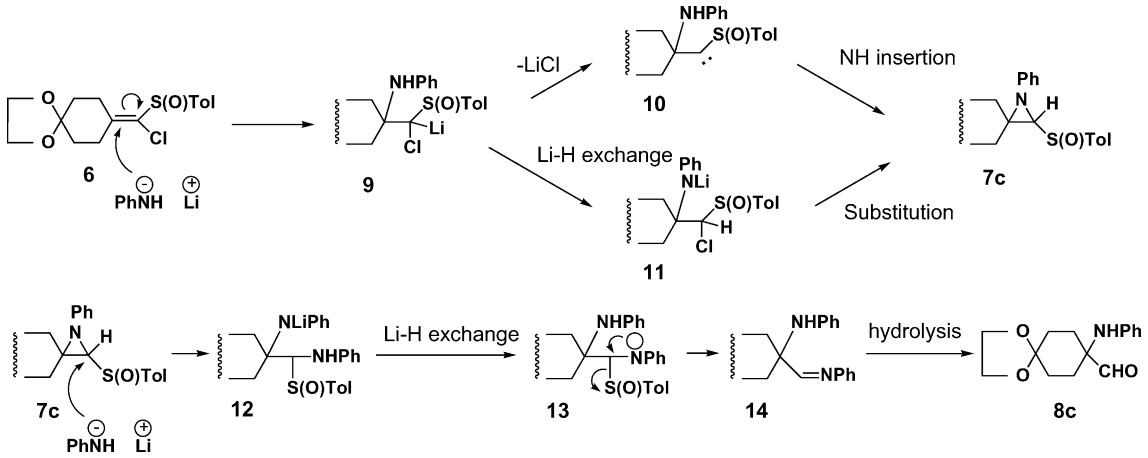
temperature resulted in the formation of α-amino aldehyde **8c** in high yield (vide infra, Table 3, entry 4).

In order to know what kind of amines afford the sulfinylaziridine **7**, the vinyl sulfoxide **6** was treated with various *N*-lithio arylamines and *N*-lithio alkylamines, and the results are summarized in Table 1. As shown in Table 1, arylamines gave sulfinylaziridine **7** in good to high yields (entries 1–5), except *p*-nitroaniline (entry 6). Quite interestingly, no alkylamine gave the desired sulfinyl aziridine **7**. The reaction with about 2 equiv of *N*-lithio alkylamines did not proceed; however, with large excess of *N*-lithio alkylamines, the reaction only resulted in decomposition of **6** (entries 7–9).

The results for a trial to synthesize the α-amino aldehydes **8** directly from **6** are summarized in Table 2. The reaction was conducted with large excess of various *N*-lithio arylamines at room temperature. As shown in Table 2, very limited arylamines gave the desired α-amino aldehyde **8** (entries 3 and 4). It is interesting to note that *o*-methoxy and *p*-methoxy aniline gave a mixture of the aldehyde **8** and imine **14** (entries 1 and 2). From these results, we concluded that there is little prospect for the synthesis of α-amino aldehydes by this direct procedure.

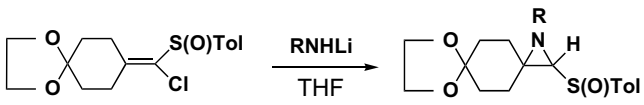
Next, we investigated the reaction of the sulfinyl aziridine **7** with various *N*-lithio arylamines and found that *N*-lithio aniline and *N*-lithio *p*-chloroaniline gave good to high yields of the desired α-amino aldehyde **8** (Table 3). As can be expected, this reaction with *N*-lithio 4-methoxyaniline gave a mixture of the aldehyde **8** and the imine **14**.

Finally, the α-amino aldehyde **8a** (the product in Table 3, entry 1) was converted to cyclic α-quaternary α-amino acid methyl ester **16** (Scheme 4). Because highly oxidizable nitrogen is present in **8a**, a mild oxidizing reagent for the conversion of aldehyde to carboxylic acid must be selected. We found that iodine and a base in methanol were the reagent of choice.[12] The α-amino



Scheme 3. A plausible mechanism for the formation of sulfinylaziridine **7c** and α-amino aldehyde **8c**.

Table 1. Synthesis of sulfinylaziridine **7** from 1-chlorovinyl *p*-tolyl sulfoxide **6** with various *N*-lithio amines

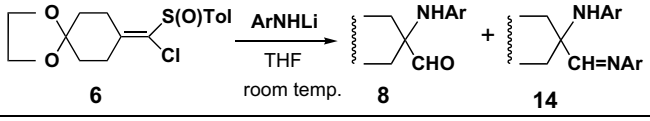


6 **7**

Entry	RNHLi		Temperature °C	**7** Yield %
	R	(Equivalents)		
1	*o*-$MeOC_6H_4$	(2.1)	0	**7a** 80
2	*p*-$MeOC_6H_4$	(1.3)	0	**7b** 90
3	C_6H_5	(1.2)	0	**7c** 92
4	*p*-ClC_6H_4	(1.7)	0	**7d** 93
5	*p*-CNC_6H_4	(2.3)	0	**7e** 84
6	*p*-$NO_2C_6H_4$	(1.7)	0 to rt	—[a]
7	CH_2=$CHCH_2$	(5.3)	0	—[b]
8	$CH_3(CH_2)_5$	(5.2)	0	—[b]
9	$PhCH_2$	(2.2)	0	—[b]

[a] No reaction.
[b] A complex mixture.

Table 2. Synthesis of α-amino aldehyde **8** from 1-chlorovinyl *p*-tolyl sulfoxide **6** with various *N*-lithio arylamines



6 **8** **14**

Entry	ArNHLi		**8** Yield %	**14** Yield %
	Ar	(Equivalents)		
1	*o*-$MeOC_6H_4$	(12.4)	**8a** —[a]	**14a** —[a]
2	*p*-$MeOC_6H_4$	(7.5)	**8b** —[b]	**14b** —[b]
3	C_6H_5	(4.0)	**8c** 90	0
4	*p*-ClC_6H_4	(8.3)	**8d** 80	0
5	*p*-CNC_6H_4	(6.2)	0[c]	0

[a] An inseparable mixture of α-amino aldehyde **8a** and imine **14a**; 84% yield.
[b] An inseparable mixture of α-amino aldehyde **8b** and imine **14b**; 40% yield.
[c] The product of this reaction was the sulfinylaziridine **7e** (Table 1, entry 5; yield 75%).

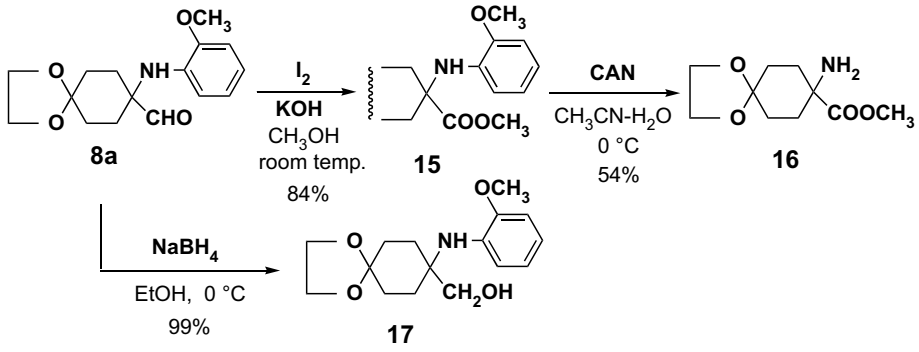
Table 3. Synthesis of α-amino aldehyde **8** from sulfinylaziridine **7**

7 **8**

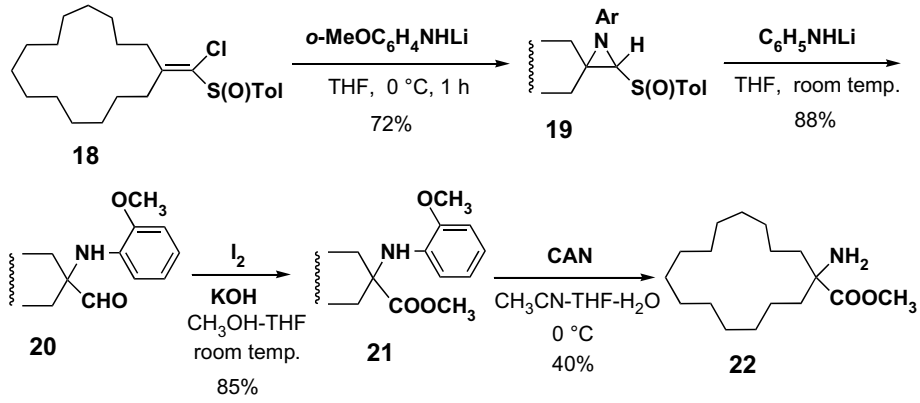
Entry	Ar	Ar′	(Equivalents)[a]	**8** Yield %
1	*o*-$MeOC_6H_4$	C_6H_5	(5.5)	**8a** 90
2	*p*-$MeOC_6H_4$	C_6H_5	(4.0)	**8b** 76
3	*p*-$MeOC_6H_4$	*p*-ClC_6H_4	(5.5)	**8b** 91
4	C_6H_5	C_6H_5	(4.0)	**8c** 94
5	*p*-ClC_6H_4	*p*-ClC_6H_4	(4.5)	**8d** 90
6	*p*-CNC_6H_4	C_6H_5	(8.5)	0[b]

[a] Use of less amount of aniline or *p*-chloroaniline gave incomplete reaction.
[b] A complex mixture.

aldehyde **8a** was treated with a solution of iodine and KOH in methanol to give the methyl ester **15** in 84% yield. Finally, the methyl ester **15** was treated with celic ammonium nitrate (CAN).[13] This reaction gave the desired free amine **16** in moderate yield. Reduction of the aldehyde **8a** with $NaBH_4$ in ethanol gave the desired



Scheme 4.



Scheme 5.

amino alcohol **17** in a quantitative yield without any problem.

To investigate the generality of these reactions, we further studied this procedure starting from 1-chlorovinyl *p*-tolyl sulfoxide **18** derived from cyclopentadecanone[9] (Scheme 5). The reaction of 1-chlorovinyl *p*-tolyl sulfoxide **18** with *N*-lithio 2-methoxyaniline gave the desired sulfinylaziridine **19** in somewhat lower yield (72%) compared with the examples in Table 1. The amino aldehyde **20** was obtained from **19** by treatment with *N*-lithio aniline in 88% yield. Oxidation of the aldehyde group to a methoxycarbonyl group was successful by the oxidation with iodine to afford the amino acid methyl ester **21** in 85% yield. Finally, the methoxyphenyl group was eliminated with CAN as above to give the cyclic amino acid methyl ester having a large carbon ring **22** in moderate yield.

We are continuing to study the scope and limitation of this procedure and extension of this reaction to the asymmetric synthesis of cyclic and acyclic α-quaternary α-amino aldehydes, amino alcohols, and amino acid derivatives.

Acknowledgements

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References and notes

1. *Chemistry and Biochemistry of the Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985.
2. (a) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon: Oxford, 1989; (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539; (c) Beller, M.; Eckert, M.. *Angew. Chem., Int. Ed.* **2000**, *39*, 1011.
3. (a) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **1998**, *9*, 3517; (b) Cativiela, C.; Diaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645; (c) Sano, S.; Nagao, Y. *J. Synth. Org. Chem. Jpn.* **2000**, *58*, 756; (d) Tanaka, M. *J. Synth. Org. Chem. Jpn.* **2002**, *60*, 125.
4. (a) Cole, D. C. *Tetrahedron* **1994**, *50*, 9517; (b) Juaristi, E.; Quintana, D.; Escalante, J. *Aldrichimica Acta* **1994**, *27*, 3; (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; (d) Davies, S. G.; Ichihara, O. *J. Synth. Org. Chem. Jpn.* **1997**, *55*, 26; (e) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813; (f) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991.
5. Park, K.-H.; Kurth, M. J. *Tetrahedron* **2002**, *58*, 8629.
6. Some recent reviews and papers concerning cyclic amino acids. (a) Czombos, J.; Aelterman, W.; Tkachev, A.; Martins, J. C.; Tourwe, D.; Peter, A.; Toth, G.; Fulop, F.; Kimpe, N. D. *J. Org. Chem.* **2000**, *65*, 5469; (b) Kabalka, G. W.; Das, B. C.; Das, S. *Tetrahedron Lett.* **2001**, *42*,

7145; (c) Volk, F.-J.; Wagner, M.; Frahm, A. W. *Tetrahedron: Asymmetry* **2003**, *14*, 497; (d) Truong, M.; Lecornue, F.; Fadel, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1063; (e) Kotha, S. *Acc. Chem. Res.* **2003**, *36*, 342; (f) Andrei, M.; Undheim, K. *Tetrahedron: Asymmetry* **2004**, *15*, 53.

7. Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149.
8. (a) Satoh, T.; Ota, H. *Tetrahedron Lett.* **1999**, *40*, 2977; (b) Satoh, T.; Ota, H. *Tetrahedron* **2000**, *56*, 5113; (c) Satoh, T.; Yoshida, M.; Ota, H. *Tetrahedron Lett.* **2001**, *42*, 9241; (d) Satoh, T.; Sakamoto, T.; Watanabe, M. *Tetrahedron Lett.* **2002**, *43*, 2043; (e) Satoh, T.; Sugiyama, S.; Ota, H. *Tetrahedron Lett.* **2002**, *43*, 3033; (f) Satoh, T.; Yoshida, M.; Takahashi, Y.; Ota, H. *Tetrahedron: Asymmetry* **2003**, *14*, 281; (g) Satoh, T.; Sugiyama, S.; Kamide, Y.; Ota, H. *Tetrahedron* **2003**, *59*, 4327; (h) Satoh, T.; Sakamoto, T.; Watanabe, M.; Takano, K. *Chem. Pharm. Bull.* **2003**, *51*, 966; (i) Satoh, T.; Wakasugi, D. *Tetrahedron Lett.* **2003**, *44*, 7517; (j) Satoh, T.; Kawashima, T.; Takahashi, S.; Sakai, K. *Tetrahedron* **2003**, *59*, 9599.
9. Satoh, T.; Takano, K.; Ota, H.; Someya, H.; Matsuda, K.; Koyama, M. *Tetrahedron* **1998**, *54*, 5557.
10. Compound **7c**: Colorless crystals; mp 151–154 °C (AcOEt–hexane). IR (KBr) 1595, 1492, 1397, 1272, 1080, 1048, 1030 (SO)/cm; ^{1}H NMR δ 1.12, 1.42, 1.63 (each 1H, m), 1.75 (2H, m), 1.97, 2.20, 2.27 (each 1H, m), 2.45 (3H, s), 3.26 (1H, s), 3.95 (4H, m), 6.89 (2H, d, $J = 7$ Hz), 6.99 (1H, t, $J = 7$ Hz), 7.19 (2H, t, $J = 8$ Hz), 7.39, 7.69 (each 2H, d, $J = 8$ Hz); MS m/z (%) 383 (M^+, trace), 367 (2), 244 (39), 158 (100). Calcd for $C_{22}H_{25}NO_3S$: 383.1555. Found: m/z 383.1545.
11. *n*-BuLi (0.5 mmol) was added dropwise to a solution of aniline (0.5 mmol) in 1 mL of dry THF at 0 °C with stirring. The solution was stirred at 0 °C for 10 min. To this solution was added a solution of **6** (33 mg; 0.1 mmol) in 0.5 mL of THF. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched by adding saturated aq NH_4Cl and the whole was extracted with AcOEt. The product was purified by silica gel column chromatography to give the cyclic amino aldehyde **8c** (23.5 mg; 90%) as colorless crystals; mp 92–94 °C (AcOEt–hexane). IR (KBr) 3392 (NH), 1711 (CO), 1600, 1091/cm; ^{1}H NMR δ 1.74 (4H, m), 1.95 (2H, m), 2.05 (2H, m), 3.95 (4H, m), 6.56 (2H, m), 6.74 (1H, m), 7.19 (2H, m), 9.64 (1H, s, CHO). MS m/z (%) 261 (M^+, 6), 232 (100), 170 (32). Calcd for $C_{15}H_{19}NO_3$: 261.1364. Found: m/z 261.1367.
12. Inch, T. D.; Ley, R. V.; Rich, P. *J. Chem. Soc. (C)* **1968**, 1693.
13. (a) Bravo, P.; Guidetti, M.; Viani, F.; Zanda, M.; Markovsky, A. L.; Sorochinsky, A. E.; Soloshonok, I. V.; Soloshonok, V. A. *Tetrahedron* **1998**, *54*, 12789; (b) Bravo, P.; Capelli, S.; Crucianelli, M.; Guidetti, M.; Markovsky, A. L.; Meille, S. V.; Soloshonok, V. A.; Sorochinsky, A. E.; Viani, F.; Zanda, M. *Tetrahedron* **1999**, *55*, 3025; (c) Fustero, S.; Pina, B.; Garcia de la Torre, M.; Navarro, A.; Ramirez de Arellano, C.; Simon, A. *Org. Lett.* **1999**, 977.