Gallium(III) Chloride-catalyzed Sakurai Reaction of α-Amido Sulfones with Allyltrimethylsilane: Access to Synthesis of 2,6-Disubstituted Piperidine Alkaloid Derivatives

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The Sakurai reaction of *N*-alkoxycarbonylamino sulfones (α -amido sulfones) with allyltrimethylsilane in the presence of gallium(III) chloride (5 mol %) proceeded smoothly to afford the corresponding protected homoallylamines in high yields (82–96%). As an application of this methodology, two-step synthesis of biologically active natural products, 2,6-disubstituted piperidine alkaloid derivatives was carried out.

Over the past few decades, Lewis acid catalyzed allylation has become an important carbon-carbon bond-forming reaction in organic synthesis.¹ Allylation of aldimines provides a useful synthetic method for homoallylamines, which are versatile building blocks for the synthesis of β -amino acids, β -lactams, γ -lactams, aziridines, amines, HIV-protease inhibitors, and biologically active nitrogen-containing natural products.^{2,3} In general, homoallylamines are prepared either by the addition of organometallic reagents to imines or by the nucleophilic addition of allylsilane, allylstannane, allylborane, or allylgermane reagents to imines in the presence of acid catalysts.⁴ Consequently, several methods have been reported for the allylation of aldimines in the presence of Lewis acids, such as TiCl₄, Sc(OTf)₃, BF₃·OEt₂, PdCl₂(PPh₃)₂, PtCl₂(PPh₃)₂, Selectfluor, Bi(OTf)₃, and iodine.⁵ However, imines in general tend to unstable during purification and methods involving in situ formation of imines are preferable. It is well known that N-acyliminiums are attractive alternatives, which are prepared⁶ from stable precursors.

As shown in Scheme 1, *N*-alkoxycarbonylamino sulfones (generally referred as α -amido sulfones) have been prepared⁷ from aldehydes, sodium *p*-toluenesulfinate or benzenesulfinate, and a suitable carbamate. They are converted to *N*-alkoxycarbonyl imine derivatives through treatment with Lewis acid (Scheme 1).⁸ Thus, Lewis acid catalyzed Sakurai reaction of these sulfones with the allyltrimethylsilane constitutes an important method for the synthesis of homoallylamines.

In continuation of our efforts to develop useful synthetic methodologies,⁹ herein we wish to report gallium(III) chloridecatalyzed Sakurai reaction of α -amido sulfones with allyltrimethylsilane, which produces homoallylamines in high yields at room temperature (Scheme 2). In addition, two-step synthesis of 2,6-disubstituted piperidine derivatives is also reported as an application of this methodology.

To define the optimal reaction conditions, we have studied the Sakurai reaction of α -amido sulfone **1a** (R = C₇H₁₅) and allyltrimethylsilane (**2**) as model substrates to afford the homoallylamine. Optimization experiments with respect to the cata-







^aYields of pure isolated compounds after column chromatography. ^bReaction conditions: α -amido sulfone (1 mmol), allyltrimethyl silane (1.3 mmol), GaCl₃ *x* mol%, and the reaction was carried out at rt.

lyst revealed that 5 mol % of the GaCl3 was found to be the most effective (Table 1) as observed by the TLC monitoring, which indicated the total disappearance of the starting material after 3 h. Moreover, a decreased quantity of GaCl₃ (1% vs. 5%) led to the low yield of the homoallylamines. However, higher amounts of the catalyst (10 mol %) did not improve the yields even after prolonged reaction times. We have also examined several Lewis acids such as Bi(OTf)₃, InCl₃, ZrCl₄, and CuBr₂ for this transformation (Table 2). Among these, GaCl₃ was found to be an efficient catalyst for the formation of the corresponding Cbz-protected homoallylamines in excellent yield after extractive work up and purification. Encouraged by the results, we studied the scope of this reaction with respect to the α -amido sulfones employed in the process (results are summarized in Table 3). Interestingly, a wide range of substrates including aromatic, aliphatic, heteroaromatic, and alicyclic sulfones reacted efficiently under similar conditions to give the corresponding homoallylamines in excellent yields. To the best of our knowledge, to date only two catalytic Sakurai reactions of α -amido sulfones with allyltrimethylsilane have been reported using bismuth triflate and indium chloride.^{8,10} These protocols suffer from longer reaction times (generally 9-44 h) and low yields (generally 50-75%). For comparison, in preparation of **31** with $Bi(OTf)_3$ and InCl₃ the reaction times are 26 and 10 h, yields are 74 and 78% respectively,^{8,10} whereas the present method requires only 3 h and yield is 90%. Moreover, sulfones derived from the aliphatic aldehyde 1a requires much longer times (Table 2). There are advantages with gallium(III) chloride for this conversion, which require neither harsh conditions nor long reaction times. In addition, the present method is equally effective for α -amido sulfones derived from aliphatic aldehydes (open chain and cyclic), aromatic aldehydes (bearing electron-donating and electron-withdrawing substituents), sterically hindered aldehyde (2-naphthaldehyde, Table 3, Entry j), and acid-sensitive aldehyde (furfuraldehyde, Table 3, Entry k) to afford excellent yields in a short period (Table 3). The present method is mild to toler-

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Table 2.

Catalyst	Catalyst loading (x mol %)	Time/h	Yield/% ^{a,b}
Bi(OTf)3·4H2O	2	44	66
Bi(OTf)3·4H2O	5	24	69
InCl ₃	5	9	76
InCl ₃	10	9	78
GaCl ₃	5	3	94
CuBr ₂	5	3	10

 ${}^{a}\alpha$ -Amido sulphone **1a** (1 mmol) treated with 1.3 mmol allyltrimethylsilane in CH₂Cl₂ at rt. ^bIsolated yield after column chromatography.

Table	3.	GaCl ₃ -catalyzed	allylation	of	α -amido	sulphones	1	with	allyltri
methyl	sila	ane 2							

Entry	α -Amido sulphone 1	Homoallyl amine 3	Time/h	Yield/% ^a
а	NHCbz	NHCbz	3	94
	C7H15 SO2TOI	C7H15		
b	NHCbz	NHCbz		
	C9H19 SO2TOI	C9H19	3	94
с	NHCbz	NHCbz		
	Ph SO ₂ Tol	Ph	3	94
	↓ NHCbz	NHCbz		
d	SO ₂ Tol		3	95
	NHCbz	NHCbz		
e	SO ₂ Tol		3	94
c			2	02
Ι	SO ₂ Tol		3	93
	MeO NHCbz	NHCbz		
g	SO ₂ Tol		3	92
0	F F			
	ŅHCbz	NHCbz		
h	SO ₂ Tol		6 ^b	92
		O,N		
	NHCbz	NHCbz		
i	SO ₂ Tol		3	85
	Ls	Ls		
	NHCbz	NHCbz		
j	SO ₂ Tol	$\bigwedge \bigwedge \bigwedge \bigwedge$	3	88
	NHCbz	NHCbz		
k	SO ₂ Tol	$\langle \gamma \rangle \sim \langle \gamma \rangle$	6	82 ^c
	<u>L</u> 0	∖ _ó		
1	NHCbz	NHCbz	2	00
	SO ₂ Tol	() Ť Ň	5	90

^aYields of pure isolated compounds after column chromatography. ^bReaction was not completed in 3 h, extended up to 6 h at rt. ^cReaction carried out with 2 equivalents of allyltrimethylsilane upto 6 h at rt.

ance of a wide range of functionalities such as methoxy, methyl, halogen, and nitro groups.¹¹

We applied the present strategy for the synthesis of 2,6-disubstituted piperidine derivatives, some of them have been found in certain members of pine and fire-ant species.¹² Some of the analogues of the 2,6-disubstituted piperidines have been studied as hemolytic, insecticidal, and antibiotic agents, and are therefore of considerable biological significance.¹³

As shown in Scheme 3, the requisite starting materials **3a**–**3c** were obtained through the Sakurai reaction of the α -amido sulfones **1a–1c** with allyltrimethylsilane, which were subjected to crossed metathesis in CH₂Cl₂ with methyl vinyl ketone **4** in the presence of Grubbs' second-generation catalyst to afford α , β -unsaturated ketones **5a–5c**. The stereochemistry of the double bond of the compounds **5a–5c** was confirmed as E by the coupling constant (J = 17 Hz) from the ¹H NMR spectrum.



The presence of the doublet at δ 6.02 and multiplet at δ 6.69 in the ¹HNMR spectrum attested to the α and β protons of α , β -unsaturated ketones. Finally, cyclization through reductive amination of **5a–5c** in the presence of Pd/C under hydrogen atmosphere afforded 2,6-disubstituted piperdine alkaloids **6a–6c**.¹⁴ The structures of the products were established from their spectral (¹HNMR, ¹³CNMR, IR, and MS) data.¹⁵

In conclusion, we have developed an efficient method for the synthesis of homoallylamines via Sakurai reaction of α amido sulfones with allyltrimethylsilane. Short reaction times, low catalyst loading, and high yields are the advantages of the present method. We have utilized this protocol for the synthesis of 2,6-disubstituted piperidine alkaloid derivatives.

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References and Notes

- a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207. b) C. K. Z. Andrade, N. R. Azevedo, G. R. Oliveira, *Synthesis* **2002**, 928.
- 2 a) J. C. A. Hunt, P. Laurent, C. J. Moody, Chem. Commun. 2000, 1771. b) M. Brands, R. Endermann, R. Gahlmann, J. Kruger, S. Raddatz, Bioorg. Med. Chem. Lett. 2003, 13, 241. c) K. J. Hale, M. M. Domostoj, D. A. Tocher, E. Irving, F. Scheinmann, Org. Lett. 2003, 5, 2927. d) P. V. Ramachandran, T. E. Burghardt, Chem.-Eur. J. 2005, 11, 4387, and references cited therein. e) M. Atobe, N. Yamazaki, C. Kibayashi, Tetrahedron Lett. 2005, 46, 2669.
- 3 a) Comprehensive Organic Synthesis, ed. by B. M. Trost, I. Fleming, C. H. Heathcock, Pergamon Press, Oxford, 1992, Vol. 2. b) E. Juaristi, Enantioselective Synthesis of β-amino Acids, Viley-VCH, London, 1997, and references cited therein. c) R. Bloch, Chem. Rev. 1998, 98, 1407. d) S. Kobayashi, H. Ishitani, Chem. Rev. 1999, 99, 1069.
- 4 a) T. H. Chan, W. Lu, *Tetrahedron Lett.* **1998**, *39*, 8605. b) T. Akiyama, J. Iwai, *Synlett* **1998**, 273. c) S. Itsuno, K. Watanable, K. Ito, A. A. El-Shehawy, A. A. Sarhan, *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 109. d) P. C. Andrews, A. C. Peatt, C. L. Raston, *Green Chem.* **2001**, *3*, 313. e) P. C. Andrews, A. C. Peatt, C. L. Raston, *Tetrahedron Lett.* **2002**, *43*, 7541. f) P. C. Andrews, A. C. Peatt, C. L. Raston, *Tetrahedron Lett.* **2004**, *45*, 243. g) R. Bloch, *Chem. Rev.* **1998**, *98*, 1407.
- 5 a) J. S. Yadav, B. V. S. Reddy, A. K. Raju, *Synthesis* **2003**, 883. b) J. Liu, C.-H. Wong, *Tetrahedron Lett.* **2002**, *43*, 3915. c) T. Ollevier, T. Ba, *Tetrahedron Lett.* **2003**, *44*, 9003. d) P. Phukan, *J. Org. Chem.* **2004**, *69*, 4005. e) S. Kobayashi, *Chem. Commun.* **1998**, 19. f) H. Nakamura, H. Iwama, Y. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 6641.
- a) T. Mecozzi, M. Petrini, J. Org. Chem. 1999, 64, 8970. b) M. Petrini, Chem. Rev. 2005, 105, 3949. c) T. Mecozzi, M. Petrini, R. Profeta, J. Org. Chem. 2001, 66, 8264. d) M. Petrini, E. Torregiani, Tetrahedron Lett. 2005, 46, 5999.
- 7 W. H. Pearson, A. C. Lindbeck, J. W. Kampf, J. Am. Chem. Soc. 1993, 115, 2622.
- 8 T. Ollevier, Z. Li, Org. Biomol. Chem. 2006, 4, 4440.
- 9 a) V. Anuradha, P. V. Srinivas, R. R. Rao, K. Manjulatha, M. G. Purohit, J. M. Rao, *Bioorg. Med. Chem.* **2006**, *14*, 6820. b) A. S. Rao, P. V. Srinivas, K. S. Babu, J. M. Rao, *Terahedron Lett.* **2005**, *46*, 8141.
- 10 B. Das, K. Damodar, D. Saritha, N. Chowdhury, M. Krishnaiah, *Tetrahedron Lett.* 2007, 48, 7930.
- 11 General experimental procedure for the synthesis of homoallylamines 3: To a solution of α -amido sulfone 1 (1 mmol) and GaCl₃ (5 mol%) in CH₂Cl₂ (5 mL) was added allyltrimethylsilane 2 (1.3 mmol) dropwise under nitrogen atmosphere. The mixture was stirred at room temperature. After completion (TLC), the reaction was quenched with distilled water (5 mL) and the mixture was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic portions were washed with water (2 × 10 mL) and saturated aqueous NH₄Cl (2 × 10 mL), and dried over anhydrous Na₂SO₄ and concentrated under vacuum. The crude product was subjected to column chromatography (silica gel 100–200, hexane–EtOAc) to obtain compounds 3.
- 12 S. Leclercq, I. Thirionet, F. Broeders, D. Daloze, R. V. Meer, J. C. Braeckman, *Tetrahedron* 1994, 50, 8465.
- 13 G. A. Adrouny, V. J. Derbes, R. C. Jung, Science 1959, 130, 449.
- 14 S. Randl, S. Blechert, *Tetrahedron Lett.* 2004, 45, 1167.
- 15 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.