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

R. Sateesh Chandra Kumar, G. Venkateswar Reddy, K. Suresh Babu, and J. Madhusudana Rao*
Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500 607, India

(Received February 19, 2009; CL-090173; E-mail: janaswamy@iict.res.in)

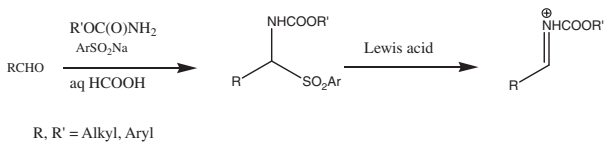
The Sakurai reaction of *N*-alkoxycarbonylamino sulfones (α-amido sulfones) with allyltrimethylsilane in the presence of gallium(III) chloride (5 mol %) proceeded smoothly to afford the corresponding protected homoallylamines in high yields (82–96%). As an application of this methodology, two-step synthesis 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 $TiCl_4$, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$, $PdCl_2(PPh_3)_2$, $PtCl_2(PPh_3)_2$, 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 prepared[6] from stable precursors.

As shown in Scheme 1, *N*-alkoxycarbonylamino sulfones (generally referred as α-amido sulfones) have been prepared[7] 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.

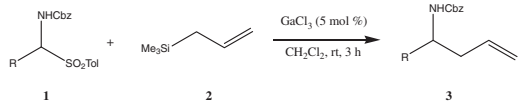
In continuation of our efforts to develop useful synthetic methodologies,[9] herein we wish to report gallium(III) chloride-catalyzed Sakurai reaction of α-amido sulfones with allyltrimethylsilane, which produces homoallylamines in high yields at room temperature (Scheme 2). In addition, two-step synthesis 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 = C_7H_{15}) and allyltrimethylsilane (**2**) as model substrates to afford the homoallylamine. Optimization experiments with respect to the catalyst revealed that 5 mol % of the $GaCl_3$ 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 $GaCl_3$ (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 $Bi(OTf)_3$, $InCl_3$, $ZrCl_4$, and $CuBr_2$ for this transformation (Table 2). Among these, $GaCl_3$ 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 **3l** with $Bi(OTf)_3$ and $InCl_3$ 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-



R, R' = Alkyl, Aryl

Scheme 1.



1 2 3

Scheme 2.

Table 1.

Entry	Catalyst loading (*x* mol %)	Time/h	Yield/%[a,b]
1	1	3	35
2	2	3	50
3	5	3	94
4	5	9	96
5	10	3	95

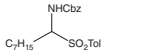
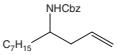
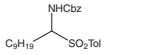
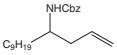
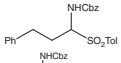
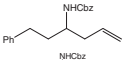
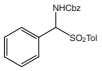
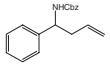
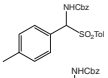
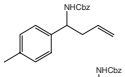
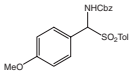
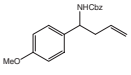
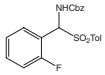
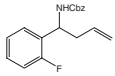
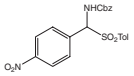
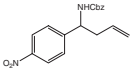
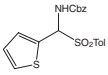
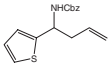
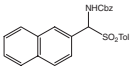
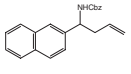
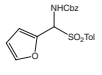
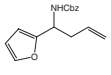
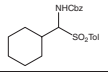
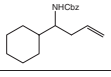
[a]Yields of pure isolated compounds after column chromatography. [b]Reaction conditions: α-amido sulfone (1 mmol), allyltrimethyl silane (1.3 mmol), $GaCl_3$ *x* mol %, and the reaction was carried out at rt.

Table 2.

Catalyst	Catalyst loading (x mol %)	Time/h	Yield/%[a,b]
$Bi(OTf)_3 \cdot 4H_2O$	2	44	66
$Bi(OTf)_3 \cdot 4H_2O$	5	24	69
$InCl_3$	5	9	76
$InCl_3$	10	9	78
$GaCl_3$	5	3	94
$CuBr_2$	5	3	10

[a]α-Amido sulphone **1a** (1 mmol) treated with 1.3 mmol allyltrimethylsilane in CH_2Cl_2 at rt. [b]Isolated yield after column chromatography.

Table 3. $GaCl_3$-catalyzed allylation of α-amido sulphones **1** with allyltrimethylsilane **2**

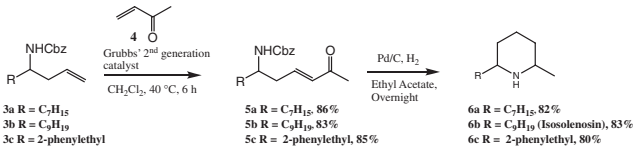
Entry	α-Amido sulphone **1**	Homoallyl amine **3**	Time/h	Yield/%[a]
a			3	94
b			3	94
c			3	94
d			3	95
e			3	94
f			3	93
g			3	92
h			6[b]	92
i			3	85
j			3	88
k			6	82[c]
l			3	90

[a]Yields of pure isolated compounds after column chromatography. [b]Reaction was not completed in 3 h, extended up to 6 h at rt. [c]Reaction 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 CH_2Cl_2 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 ^{1}H NMR spectrum.



Scheme 3.

The presence of the doublet at δ 6.02 and multiplet at δ 6.69 in the ^{1}H NMR 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 (^{1}H NMR, ^{13}C NMR, 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.

The authors thank to CSIR, UGC New Delhi for financial assistance.

References and Notes

1 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.
6 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 $GaCl_3$ (5 mol %) in CH_2Cl_2 (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 CH_2Cl_2 (3×10 mL). The combined organic portions were washed with water (2×10 mL) and saturated aqueous NH_4Cl (2×10 mL), and dried over anhydrous Na_2SO_4 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.

Published on the web (Advance View) May 16, 2009; doi:10.1246/cl.2009.564