Indium(III) Chloride-Catalyzed Conversion of {[(Benzyloxy)carbonyl]amino}-Substituted Sulfones with 2-[(Trimethylsilyl)oxy]furan: A Facile Access to γ-Butenolactone Derivatives Containing a Protected Amino Group[1])

by **Biswanath Das***, **Chithaluri Sudhakar**, **Parigi Raghavendar Reddy**, and **Jajula Kashanna**

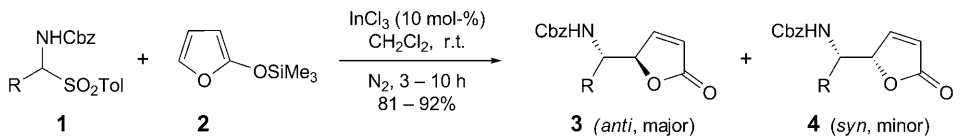
Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India (phone: +91-40-7193434; fax: +91-40-7160512; e-mail: biswanathdas@yahoo.com)

Treatment of {[(benzyloxy)carbonyl]amino}-substituted sulfones **1** with 2-[(trimethylsilyl)oxy]furan (**2**) in the presence of $InCl_3$ as a catalyst at room temperature produced the γ-butenolactone derivatives **3** and **4** containing a protected amino group (*Scheme 1*). The products were formed in high yields (81–92%) within 3–10 h favoring the *anti*-isomer **3**.

Introduction. – The γ-butenolactone moiety is frequently found in various natural products [1–3]. Compounds containing this moiety have been known to possess different important biological properties including anticancer [4–6], antiviral [7], antibiotic [8], and anti-inflammatory activities [9]. Some of the γ-butenolactone derivatives exhibit pesticidal properties [10][11]. Additionally, γ-butenolactones are versatile precursors for the preparation of bioactive natural products [12–14]. Thus, the synthesis of these compounds has attracted much attention of organic chemists [15–22]. Here, we report a simple method for the synthesis of these compounds under mild reaction conditions.

Results and Discussion. – In continuation of our work [23–25] on the development of useful synthetic methodologies by means of α-amido-substituted sulfones (= *N*-(sulfonylmethyl)amides), we observed that these compounds, *i.e.*, racemic {{[(benzyloxy)carbonyl]amino}methyl}-substituted sulfones (= benzyl *N*-(sulfonylmethyl)carbamates) **1**, when treated with 2-[(trimethylsilyl)oxy]furan (**2**) at room temperature in the presence of a catalytic amount of $InCl_3$, afforded γ-butenolactone derivatives **3** and **4** containing a Cbz-protected amino group (Cbz = $PhCH_2OCO$) (*Scheme 1*).

Scheme 1

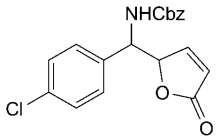
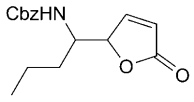


R = aryl, alkyl; Cbz = $PhCH_2OCO$

[1]) Part 210 in the series 'Studies on Novel Synthetic Methodologies'.

Initially, {[(benzyloxy)carbonyl]amino}-substituted sulfones **1** derived from 4-chlorobenzaldehyde or butanal were treated with 2-[(trimethylsilyl)oxy]furan (**2**) in the presence of various *Lewis* acid catalysts (→ **3b**/**4b** or **3k**/**4k**, resp.; *Table 1*). Considering the reaction times and yields, $InCl_3$ was found to be the most effective. Subsequently, $InCl_3$ was utilized for the reaction of various {[(benzyloxy)carbonyl]-amino}-substituted sulfones **1** with 2-[(trimethylsilyl)oxy]furan (**2**) (*Table 2*). The products were racemic γ-substituted butenolactone derivatives **3** and **4** having a Cbz-protected amino group. Both the *anti*- and *syn*-isomers **3** and **4**, respectively, were formed but the *anti*-isomer **3** was the major component. The two isomers could be separated, and as their yields were good, they can be utilized for further conversions. The structures of the products were established from their IR, ^{1}H- and ^{13}C-NMR, and ESI-mass spectra and anal. data. The ratio of the two isomers was determined from ^{1}H-NMR spectra and HPLC analysis of the crude products as well as from the yields of the pure isomers after separation. The configuration of the *anti*- and *syn*-isomers was suggested by comparison of their ^{1}H- and ^{13}C-NMR data with those reported earlier for related compounds [21].

Table 1. *Catalytic Activity of Different Catalysts for the Synthesis of γ-Butenolactone Derivatives* **3b**/**4b** or **3k**/**4k**[a])

Products	Catalyst	Time [h]	Yield [%][b])
 **3b/4b**	$InCl_3$	5	89
	$BF_3 \cdot OEt_2$	12	59
	$Sc(OTf)_3$	12	51
	$Bi(OTf)_3$	12	45
	$FeCl_3$	12	59
	$ZrCl_4$	12	31
	VCl_3	12	18
 **3k/4k**	$InCl_3$	6	87
	$BF_3 \cdot OEt_2$	12	56
	$Sc(OTf)_3$	12	48
	$Bi(OTf)_3$	12	42
	$FeCl_3$	12	58
	$ZrCl_4$	12	24
	VCl_3	12	12

[a]) Reaction conditions: {[(benzyloxy)carbonyl]amino}-substituted sulfone **1** (R = 4-Cl–C_6H_4 or Pr; 1 mmol), 2-[(trimethylsilyl)oxy]furan (**2**; 1 mmol), and catalyst (10 mol-%) were stirred at room temperature. [b]) Yield after purification.

The racemic {[(benzyloxy)carbonyl]amino}-substituted sulfones **1** can conveniently be prepared from aldehydes and are generally stable [26]. They were prepared here from aromatic, heteroaromatic, and aliphatic aldehydes. Aromatic aldehydes contained both electron-donating and electron-withdrawing groups at the aromatic rings. The sulfone derivatives prepared from naphthalene-2-carboxaldehyde also underwent the conversion smoothly (→ **3i**/**4i**; *Table 2*). Different functionalities such as ether, halogen, and nitrile remained intact during the conversion.

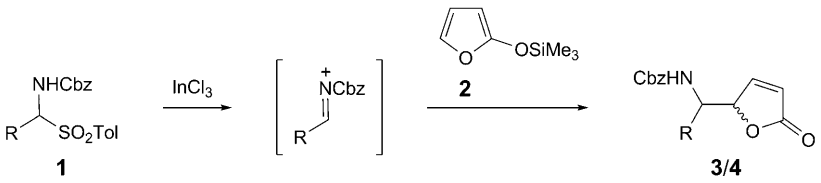
Table 2. *Synthesis of γ-Butenolactone Derivatives* **3** *and* **4**[a])

R	Time [h]	Products[b])	Yield [%][c])	*anti*/*syn*[d])
4-Me–C_6H_4	5	**3a**/**4a**	91	72 : 28
4-Cl–C_6H_4	5	**3b**/**4b**	89	71 : 29
4-F–C_6H_4	7	**3c**/**4c**	89	67 : 33
4-^{i}Pr–C_6H_4	4	**3d**/**4d**	91	72 : 28
3,4,5-$(MeO)_3C_6H_2$	3	**3e**/**4e**	92	65 : 35
4-CN–C_6H_4	10	**3f**/**4f**	81	61 : 39
Furan-2-yl	8	**3g**/**4g**	81	64 : 36
2-Thienyl	7	**3h**/**4h**	91	66 : 34
Naphthalen-2-yl	6	**3i**/**4i**	88	67 : 33
Et	6	**3j**/**4j**	87	68 : 32
Pr	6	**3k**/**4k**	87	68 : 32
Me_2CHCH_2	6	**3l**/**4l**	88	69 : 31

[a]) Reaction conditions: {[(benzyloxy)carbonyl]amino}-substituted sulfone **1** (1 mmol), 2-[(trimethylsilyl)oxy]furan (**2**; 1 mmol), and $InCl_3$ (10 mol-%) were stirred at room temperature. [b]) The structures of the products were established from their IR, ^{1}H- and ^{13}C-NMR, and ESI-mass spectra and anal. data. [c]) Yield after purification. [d]) The ratio of the two isomers was determined by ^{1}H-NMR and HPLC analysis and from the yields of the pure isomers after separation.

It is known [27][28] that α-amido-substituted sulfones are converted into the corresponding (protected) *N*-acyliminium ions on treatment with a *Lewis* acid. These iminium ions can easily undergo nucleophilic addition. Thus, 2-[(trimethylsilyl)oxy]-furan (**2**) reacts with the iminium ions derived from {[(benzyloxy)carbonyl]amino}-substituted sulfones **1** in the presence of $InCl_3$ to produce the γ-butenolactone derivatives **3** and **4** (*Scheme 2*).

Scheme 2



R = aryl, alkyl; Cbz = $PhCH_2OCO$

Conclusions. – We developed an efficient method for the synthesis of racemic γ-butenolactone derivatives having a protected amino group by the reaction of {[(benzyloxy)carbonyl]amino}-substituted sulfones with 2-[(trimethylsilyl)oxy]furan in the presence of $InCl_3$ as a catalyst at room temperature. The method is simple and mild and gives high yields of products.

The authors thank *CSIR*, New Delhi, for financial assistance.

Experimental Part

General Procedure. Under N_2, 2-[(trimethylsilyl)oxy]furan (**2**; 1.0 mmol) was added dropwise to a soln. of {[(benzyloxy)carbonyl]amino}-substituted sulfone **1** (1.0 mmol) and $InCl_3$ (10 mol-%) in CH_2Cl_2 (5 ml). The mixture was stirred at r.t. (TLC monitoring). After completion, the reaction was quenched with dist. H_2O (5 ml), and the mixture was extracted with AcOEt (3 × 10 ml). The extract was washed with H_2O (2 × 10 ml), dried (Na_2SO_4), and concentrated and the crude product subjected to column chromatography (silica gel, 20 → 40% AcOEt/hexane): pure racemic *anti*- and *syn*-isomers **3** and **4**, resp. The spectral and analytical data of some representative products are given below.

Phenylmethyl N-*{(*RS*)-[(2*SR*)-2,5-Dihydro-5-oxofuran-2-yl](4-methylphenyl)methyl}carbamate* (**3a** (*anti*)): IR: 3323, 1758, 1710, 1529, 1246. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38 – 7.21 (*m*, 6 H); 7.14 – 7.03 (*m*, 4 H); 5.89 (*dd*, *J* = 7.0, 1.5, 1 H); 5.69 (*d*, *J* = 7.0, 1 H); 5.37 – 5.33 (*m*, 1 H); 5.12 – 4.99 (*m*, 3 H); 2.29 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 172.5; 155.7; 153.2; 139.4; 135.4; 133.2; 129.9; 129.0; 128.9; 128.7; 126.1; 122.7; 85.0; 67.1; 55.8; 20.6. ESI-MS: 355 ($[M + NH_4]^+$). Anal. calc. for $C_{20}H_{19}NO_4$: C 71.22, H 5.64, N 4.15; found: C 71.14, H 5.71, N 4.19.

Phenylmethyl N-*{(*RS*)-[(2*RS*)-2,5-Dihydro-5-oxofuran-2-yl](4-methylphenyl)methyl}carbamate* (**4a** (*syn*)): IR: 3323, 1758, 1710, 1529, 1246. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.35 – 7.18 (*m*, 8 H); 7.08 (*d*, *J* = 8.0, 2 H); 5.99 (*dd*, *J* = 7.0, 2.0, 1 H); 5.51 (*d*, *J* = 7.0, 1 H); 5.24 – 5.20 (*m*, 1 H); 5.02 (*d*, *J* = 8.0, 1 H); 5.01 (*s*, 2 H); 2.31 (*s*, 3 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 173.0; 156.2; 154.5; 138.8; 136.1; 134.9; 129.9; 128.8; 128.7; 128.5; 127.3; 123.0; 85.1; 67.4; 55.4; 21.1. ESI-MS: 355 ($[M + NH_4]^+$). Anal. calc. for $C_{20}H_{19}NO_4$: C 71.22, H 5.64, N 4.15; found: C 71.33, H 5.59, N 4.20.

Phenylmethyl N-*{(*RS*)-[(2*SR*)-2,5-Dihydro-5-oxofuran-2-yl][4-(1-methylethyl)phenyl]methyl}carbamate* (**3d** (*anti*)): IR: 3332, 1752, 1716, 1516, 1242. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.38 – 7.25 (*m*, 6 H); 7.19 – 7.06 (*m*, 4 H); 5.93 (*dd*, *J* = 7.0, 1.5, 1 H); 5.61 (*d*, *J* = 7.0, 1 H); 5.41 – 5.37 (*m*, 1 H); 5.12 – 5.00 (*m*, 3 H); 2.83 – 2.81 (*m*, 1 H); 1.21 (*d*, *J* = 7.0, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.2; 156.0; 153.7; 149.2; 136.0; 135.8; 134.0; 129.1; 129.0; 128.9; 126.1; 123.2; 84.9; 65.4; 55.4; 34.0; 24.1. ESI-MS: 383 ($[M + NH_4]^+$). Anal. calc. for $C_{22}H_{23}NO_4$: C 72.33, H 6.30, N 3.84; found: C 72.45, H 6.23, N 3.92.

Phenylmethyl N-*{(*RS*)-[(2*RS*)-2,5-Dihydro-5-oxofuran-2-yl][4-(1-methylethyl)phenyl]methyl}carbamate* (**4d** (*syn*)): IR: 3332, 1752, 1716, 1516, 1242. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.44 – 7.20 (*m*, 8 H); 7.18 (*d*, *J* = 8.0, 2 H); 5.98 (*dd*, *J* = 7.0, 2.0, 1 H); 5.79 (br. *s*, 1 H); 5.24 – 5.18 (*m*, 1 H); 5.10 – 5.01 (*m*, 3 H); 2.91 – 2.87 (*m*, 1 H); 1.21 (*d*, *J* = 7.0, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.6; 156.2; 154.8; 149.4; 136.1; 136.0; 135.2; 129.5; 129.2; 129.0; 126.6; 123.2; 85.0; 65.2; 55.3; 34.5; 24.2. ESI-MS: 383 ($[M + NH_4]^+$). Anal. calc. for $C_{22}H_{23}NO_4$: C 72.33, H 6.30, N 3.84; found: C 72.26, H 6.24, N 3.78.

Phenylmethyl N-*{(*RS*)-[(2*SR*)-2,5-Dihydro-5-oxofuran-2-yl](naphthalen-2-yl)methyl}carbamate* (**3i** (*anti*)): IR: 3419, 1748, 1693, 1612, 1452, 1271. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.41 – 7.20 (*m*, 7 H); 5.90 (*dd*, *J* = 7.0, 1.5, 1 H); 7.33 – 7.30 (*m*, 1 H); 5.02 (*s*, 2 H); 4.85 – 4.79 (*m*, 1 H); 2.03 – 1.99 (*m*, 1 H); 1.70 – 1.52 (*m*, 2 H); 0.83 (*d*, *J* = 7.0, 1 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.6; 158.1; 154.4; 136.1; 128.0; 127.5; 127.4; 122.2; 85.0; 67.2; 50.0; 40.6; 30.0; 23.1. ESI-MS: 321 ($[M + NH_4]^+$). Anal. calc. for $C_{17}H_{21}NO_4$: C 67.33, H 6.93, N 4.62; found: C 67.25, H 6.87, N 4.55.

Phenylmethyl N-*{(*RS*)-[(2*RS*)-2,5-Dihydro-5-oxofuran-2-yl](naphthalen-2-yl)methyl}carbamate* (**4i** (*syn*)): IR: 3419, 1748, 1693, 1612, 1452, 1271. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.42 – 7.20 (*m*, 7 H); 6.14 (*dd*, *J* = 7.0, 2.0, 1 H); 5.32 – 5.29 (*m*, 1 H); 5.02 (*s*, 2 H); 4.82 – 4.79 (*m*, 1 H); 1.99 – 2.03 (*m*, 1 H); 1.71 – 1.52 (*m*, 2 H); 0.82 (*d*, *J* = 7.0, 6 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 174.8; 159.2; 154.7; 137.4; 129.2; 129.0; 128.8; 124.5; 85.3; 67.0; 51.3; 41.0; 29.9; 23.6. ESI-MS: 321 ($[M + NH_4]^+$). Anal. calc. for $C_{17}H_{21}NO_4$: C 67.33, H 6.93, N 4.62; found: C 67.38, H 7.01, N 4.66.

REFERENCES

[1] J. A. Joule, K. Mills, ' Heterocyclic Chemistry', 4th edn., Blackwell Science Publishing, Oxford, UK, 2000.

[2] R. S. Word, in 'Recent Advances in the Chemistry of Lignans', Vol. 24, Part E, Ed. Atta-ur-Rahman, Elsevier, Amsterdam, 2000, pp. 739 – 798.

[3] J. R. Hanson, *Nat. Prod. Rep.* **2002**, *51*, 4571.

[4] S. Raic-Malic, D. Svedruzic, T. Gazivoda, A. Marunovic, A. Hergold-Brundic, A. Nagl, I. Balzarini, E. Declereq, M. Mintas, *J. Med. Chem.* **2000**, *43*, 4806.
[5] D. T. A. Yousef, R. K. Yamaki, M. Kelly, P. J. Scheuer, *J. Nat. Prod.* **2002**, *65*, 2.
[6] C. J. Hernandez-Guerrero, E. Zubia, M. S. Ortega, J. Luiscarballo, *Tetrahedron* **2006**, *62*, 5392.
[7] S. Raic-Malic, A. Hergold-Brundic, A. Nagl, M. Grdisa, *J. Med. Chem.* **1999**, *42*, 2673.
[8] D. Alonso, I. Font, R. M. Ortuno, J. d'Angelo, A. Guingant, C. Bois, *Tetrahedron* **1991**, *47*, 5895.
[9] H. Kikuchi, Y. Tsukitani, I. Shimizu, M. Kobayashi, I. Kitagawa, *Chem. Pharm. Bull.* **1983**, *31*, 552.
[10] B. Terem, P. J. Scheur, *Tetrahedron* **1986**, *42*, 4409.
[11] G. R. Flematti, E. L. Ghisalberti, K. W. Dixon, R. D. Trengova, *Science (Washington, DC, U.S.)* **2004**, *305*, 977.
[12] G. Casiraghi, L. Colomb, G. Rassu, P. Spanu, *J. Org. Chem.* **1990**, *55*, 2565.
[13] G. Casiraghi, L. Colomb, *J. Org. Chem.* **1991**, *56*, 2135.
[14] G. Rassu, L. Pinna, N. Culeddu, G. Casiraghi, G. Gasparti Fava, M. Belicchi Ferrari, G. Pelosi, *Tetrahedron* **1992**, *48*, 727.
[15] J. A. Marshall, E. N. Wallace, P. S. Coan, *J. Org. Chem.* **1995**, *60*, 796.
[16] E. Nagishi, M. Kotora, *Tetrahedron* **1997**, *53*, 6707.
[17] J. Christoffers, *Synlett* **2001**, 723.
[18] S. F. Martini, *Acc. Chem. Res.* **2002**, *35*, 895.
[19] R. Horon, C. Jacquet, *J. Org. Chem.* **2003**, *68*, 1821.
[20] S. Ma, *Acc. Chem. Res.* **2003**, *36*, 701.
[21] S. Ma, Z. Yu, *Chem. – Eur. J.* **2004**, *10*, 2078.
[22] T. Akiyama, Y. Honma, J. Itoh, K. Fuchibe, *Adv. Synth. Catal.* **2008**, *350*, 399.
[23] B. Das, K. Damodar, D. Saritha, N. Chowdhury, M. Krishnaiah, *Tetrahedron Lett.* **2007**, *48*, 7930.
[24] B. Das, K. Damodar, B. Shashi Kanth, Y. Srinivas, I. Kalavathi, *Synlett* **2008**, 3133.
[25] B. Das, K. Damodar, N. Bhunia, *J. Org. Chem.* **2009**, *74*, 5607.
[26] W. H. Pearson, A. C. Lindbeck, J. W. Kampf, *J. Am. Chem. Soc.* **1933**, *115*, 2622.
[27] T. Mecozzi, M. Petrini, *J. Org. Chem.* **1999**, *64*, 8970.
[28] M. Petrini, *Chem. Rev.* **2005**, *105*, 3949; M. Petrini, E. Torregiani, *Synthesis* **2007**, 159.

Received September 27, 2010