A Novel Method for Furan Annelation by the Regioselective Acylation of Allylic Sulfides *via* α-Silyl Intermediates

Kunio Hiroi,* Hiroyasu Sato

Department of Synthetic Organic Chemistry, Tohoku College of Pharmacy, 4-4-1 Komatsushima, Sendai, Miyagi 983, Japan

Aluminum chloride-catalyzed acylations of allylic phenyl sulfides **3** with acid chlorides **5** were carried out *via* α-silyl intermediates **4** to give γ-acylated vinylic sulfides **6** with complete regioselectivity. Treatment of the γ-acylated compounds with concentrated sulfuric acid in refluxing benzene led to the formation of α-phenylthiofurans **7**, which on reductive desulfurization with Raney nickel afforded various furan derivatives **8**.

Recently much attention has been devoted to the regioselective alkylation of allylic systems. Methodologies reported include the use of lithium[1] and copper(I)[2] as a metal cation with alkylborane[3] or alkylaluminium,[4] and allylic sulfides involving special functions (thioamides,[5] 2-pyridyl,[6] 2-thiazolinyl,[7] and 2-imidazolyl[8]) in the substituents next to the sulfenyl groups for the stabilization of the α-carbanions by chelation.

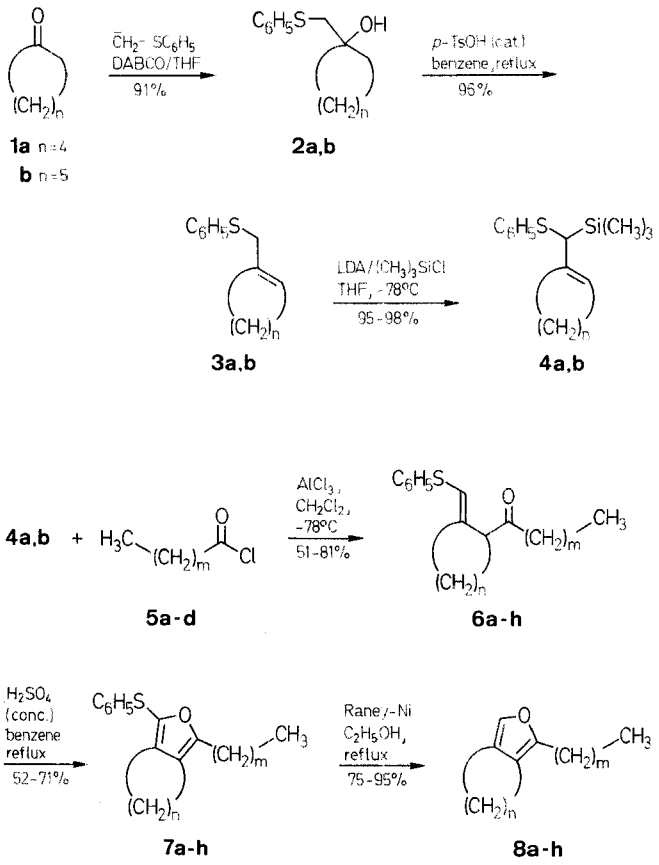
We have already reported a regioselective acylation of allylic sulfides *via* their α-silyl intermediates[9] and developed a novel method for cyclopentannelation using this method.[10] We wish to communicate herein a novel method for furan annelation using an acid-catalyzed acylation of α-silylallylic sulfides.

Allylic sulfides **3a, b** were easily obtainable by addition of the α-carbanion of methyl phenyl sulfide to cycloalkanones **1a, b** in the presence of 1,4-diazabicyclo[2.2.2]octane followed by the acid-catalyzed dehydration of the resulting hydroxy compounds **2a, b** (heating in refluxing benzene with a catalytic amount of *p*-toluenesulfonic acid). Treatment of the allylic sulfides **3a, b** with lithium diisopropylamide at −78 °C followed by addition of chloro-trimethylsilane led to an α-regioselective silylation to give α-silylallylic sulfides **4a, b** in excellent yields (98 and 95%).

The regioselective acylation of the α-silylallylic sulfides **4a, b** was carried out by reacting **4a, b** with acid chlorides **5a–d** in dichloromethane at −78 °C for 6 h with catalysis by aluminum chloride (1.5 equivalents), giving exclusively γ-acylated enol thioethers **6a–h**.[10]

Treatment of the acylated compounds **6a–h** with an equimolar amount of concentrated sulfuric acid in refluxing benzene for 15 h led to an acid-catalyzed cyclization and subsequent oxidation to produce α-phenylthiofuran derivatives **7a–h**. The structures of these compounds were confirmed by IR, NMR, mass spectral data and exact mass determination (Table 1).

The reductive desulfurization of **7a–h** with Raney nickel afforded furan derivatives **8a–h** in good yields (Table 2).



DABCO = 1,4-diazabicyclo[2.2.0]octane
Ts = *p*-toluenesulfonyl
LDA = lithium diisopropylamide

5	m
a	2
b	3
c	5
d	6

6–8	n	m	6–8	n	m
a	4	2	e	5	2
b	4	3	f	5	3
c	4	5	g	5	5
d	4	6	h	5	6

Other methods for the preparation of furans have previously been devised involving the condensation of carbonyl compounds such as ketene dithioacetals[11] or α-*n*-butylthiomethylene ketones[12] with dimethylsulfonium methylide under basic conditions. The present method, however, was performed under acidic conditions starting from allylic sulfides. This route provides a facile entry to furan derivatives **7a–h** and **8a–h** by the furan annelation of cyclic ketones **1a, b** involving regioselective acylation and subsequent acid-catalyzed cyclization.

Table 1. 2-Acyl-1-(phenylthiomethylene)cycloalkanes **6a–h** Prepared

Product	Yield (%)	Molecular Formula	HRMS (70 eV) *m/e* (M^+)[a]		IR (Neat)[b] ν (cm^{-1})	^{1}H-NMR (CCl_4)[c] δ, J (Hz)
			calc.	found		
6a[d]	65	$C_{17}H_{22}OS$ (274.4)	274.1390	274.1363	1715, 1660 1585	0.99 (t, 3H, J = 7); 1.17–2.87 (m, 10H); 2.53 (t, 2H, J = 7); 2.87–3.32, 3.63–3.95 (2m, 1H each); 5.92, 6.03 (2s, 1H each); 6.90–7.57 (m, 5H)
6b[d]	80	$C_{18}H_{24}OS$ (288.5)	288.1548	288.1550	1710, 1660, 1585	0.85 (t, 3H, J = 6); 1.03–2.80 (m, 14H); 3.00–3.27, 3.68–3.90 (2m, 1H, each); 5.90, 6.00 (2s, 1H each); 6.93–7.40 (m, 5H)
6c[d]	81	$C_{20}H_{28}OS$ (316.5)	316.1861	316.1881	1705, 1640, 1580	0.87 (t, 3H, J = 5); 1.00–2.80 (m, 18H); 3.00–3.28, 3.70–3.90 (2m, 1H each); 5.93, 6.03 (2s, 1H each); 6.93–7.40 (m, 5H)
6d[d]	74	$C_{21}H_{30}OS$ (330.5)	330.2016	330.2009	1710, 1650, 1580	0.88 (t, 3H, J = 5); 1.03–2.90 (m, 20H); 3.03–3.30, 3.70–3.93 (2m, 1H each); 5.95, 6.05 (2s, 1H each); 6.90–7.47 (m, 5H)
6e	51	$C_{18}H_{24}OS$ (288.5)	288.1549	288.1569	1710, 1660, 1580	0.95 (t, 3H, J = 7); 1.03–2.85 (m, 14H); 3.10–3.45, 3.70–4.03 (2m, 1H each); 5.91, 6.03 (2s, 1H each); 7.00–7.50 (m, 5H)
6f	57	$C_{19}H_{26}OS$ (302.5)	302.1705	302.1706	1710, 1665, 1580	0.93 (t, 3H, J = 4); 1.10–2.90 (m, 16H); 3.27, 3.83 (2t, 1H each, J = 8); 5.95, 6.05 (2s, 1H each); 6.90–7.50 (m, 5H)
6g	67	$C_{21}H_{30}OS$ (330.5)	330.2017	330.2027	1705, 1660, 1580	0.90 (t, 3H, J = 4); 1.07–2.80 (m, 20H); 3.30 (t, 1H, J = 8); 3.87 (t, 1H, J = 7); 6.00, 6.10 (2s, 1H each); 7.00–7.50 (m, 5H)
6h	59	$C_{22}H_{32}OS$ (344.6)	344.2172	344.2164	1710, 1650, 1580	0.85 (t, 3H, J = 4); 1.00–2.80 (m, 22H); 3.23 (t, 1H, J = 8); 3.80 (t, 1H, J = 7); 5.90, 6.00 (2s, 1H each); 7.00–7.40 (m, 5H)

[a] Recorded on a JEOL JMS-01 SG-2 high resolution mass spectrometer.
[b] Recorded on a Hitachi 215 grating infrared spectrophotometer.
[c] Obtained on a Hitachi R-24B high resolution NMR spectrometer.
[d] Compounds previously prepared (Ref. 10), but no physical and spectral data were reported.

Table 2. Synthesis of α-Phenylthiofuran Derivatives **7a–h**

Product	Yield[a] (%)	Molecular Formula	HRMS (70 eV) *m/e* (M^+)[b]		IR (Neat)[c] ν (cm^{-1})	^{1}H-NMR (CCl_4)[d] δ, J (Hz)
			calc.	found		
7a	52 (61)	$C_{17}H_{20}OS$ (272.4)	272.1232	272.1266	1625, 1585	0.92 (t, 3H, J = 7); 1.17–1.97 (m, 6H); 2.23–2.67 (m, 6H); 6.73–7.43 (m, 5H)
7b	47 (57)	$C_{18}H_{22}OS$ (286.4)	286.1392	286.1398	1620, 1580	0.90 (t, 3H, J = 5); 1.10–1.90 (m, 8H); 2.23–2.67 (m, 6H); 6.70–7.57 (m, 5H)
7c	41 (52)	$C_{20}H_{26}OS$ (314.5)	314.1705	314.1726	1625, 1590	0.87 (t, 3H, J = 5); 1.03–1.90 (m, 12H); 2.10–2.63 (m, 6H); 6.73–7.45 (m, 5H)
7d	46 (59)	$C_{21}H_{28}OS$ (328.5)	328.1860	328.1845	1625, 1590	0.85 (t, 3H, J = 5); 1.00–1.95 (m, 14H); 2.10–2.65 (m, 6H); 6.65–7.40 (m, 5H)
7e	68	$C_{18}H_{22}OS$ (286.4)	286.1390	286.1375	1625, 1585	0.87 (t, 3H, J = 7); 1.30–1.95 (m, 8H); 2.20–2.70 (m, 6H); 6.67–7.67 (m, 5H)
7f	56	$C_{19}H_{24}OS$ (300.5)	300.1549	300.1552	1625, 1585	0.87 (t, 3H, J = 5); 1.03–1.90 (m, 10H); 2.20–2.67 (m, 6H); 6.73–7.50 (m, 5H)
7g	53	$C_{21}H_{28}OS$ (328.5)	328.1859	328.1844	1625, 1585	0.88 (t, 3H, J = 5); 1.03–1.90 (m, 14H); 2.23–2.70 (m, 6H); 6.67–7.50 (m, 5H)
7h	54 (71)	$C_{22}H_{30}OS$ (321.5)	342.2018	342.2030	1625, 1585	0.85 (t, 3H, J = 7); 1.00–1.83 (m, 16H); 2.17–2.67 (m, 6H); 6.65–7.43 (m, 5H)

[a] Corrected yield based on the recovered starting materials are listed in parentheses.
[b–d] Refers to footnotes a–c in Table 1.

1-(Phenylthiomethyl)cycloalkanols 2a, b; General Procedure:
A dry 100 mL two-necked flask equipped with a septum inlet and a magnetic stirring bar is flushed with nitrogen and maintained under a positive pressure of nitrogen. A solution of 1,4-diazabicyclo[2.2.2]-octane (2.39 g, 21.3 mmol) in THF (25 mL) is added to the flask, followed by addition of a solution of methyl phenyl sulfide (2.64 g, 21.3 mmol) in THF (1 mL). The solution is cooled to 0 °C and a 1.5 normal hexane solution of *n*-butyllithium (14.2 mL, 1.36 g, 21.3 mmol) is added to the above solution. After stirring at 0 °C for 15 min and at room temperature for 1.5 h, the appropriate cycloalkanone **1a** or **b** (20.8 mmol) is added at 0 °C and the mixture is allowed to stir at 0 °C for 1 h and at room temperature for 1 h. The mixture is diluted with ether (3 × 30 mL), washed with 10% aqueous HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL) and saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue is subjected to column chromatography on silica gel (ether/hexane, 1:4) to give the cycloalkanol **2a** or **b** as a pale yellow oil.

1-(Phenylthiomethyl)cyclohexanol (**2a**); yield: 4.19 g (91%).
HRMS: *m/e* = 222.1050 (calc. for $C_{13}H_{18}OS$ = 222.1079).
IR (Neat): ν = 3400 (OH), 1580 cm^{-1} (phenyl).
^{1}H-NMR (CCl_4): δ = 1.20–1.80 (10H, m); 2.10 (1H, brs); 2.93 (2H, s); 6.90–7.40 (5H, m).

Table 3. Synthesis of Furan Derivatives **8a–h**

Product	Yield (%)	b.p.[a] (°C)/mbar	Molecular Formula	HRMS (70 eV) *m/e* (M^+)[b] calc.	found	IR (Neat)[c] ν (cm^{-1})	^{1}H-NMR (CCl_4)[d] δ, *J* (Hz)
8a	75	42–45/1.6	$C_{11}H_{16}O$ (164.3)	164.1200	164.1200	1640, 1610	0.90 (t, 3H, *J* = 7); 1.37–2.03 (m, 6H); 2.03–2.67 (m, 6H); 6.83 (s, 1H)
8b	84	50–53/2	$C_{12}H_{18}O$ (178.3)	178.1358	178.1360	1625, 1600	0.85 (t, 3H, *J* = 6); 1.07–1.83 (m, 8H); 2.17–2.60 (m, 6H); 6.78 (s, 1H)
8c	94	55–60/3	$C_{14}H_{22}O$ (206.3)	206.1670	206.1685	1640, 1605	0.90 (t, 3H, *J* = 5); 1.07–2.00 (m, 12H); 2.10–2.63 (m, 6H); 6.85 (s, 1H)
8d	89	55–59/2	$C_{15}H_{24}O$ (220.4)	220.1826	220.1823	1640, 1605	0.90 (t, 3H, *J* = 4); 1.07–1.90 (m, 14H); 2.23–2.67 (m, 6H); 6.87 (s, 1H)
8e	95	43–47/1.5	$C_{12}H_{18}O$ (178.3)	178.1358	178.1386	1640, 1605	0.80 (t, 3H, *J* = 7); 1.25–1.90 (m, 8H); 2.13–2.53 (m, 6H); 6.75 (s, 1H)
8f	77	53–57/2	$C_{13}H_{20}O$ (192.3)	192.1513	192.1483	1640, 1605	0.87 (t, 3H, *J* = 7); 1.05–1.85 (m, 10H); 2.17–2.83 (m, 6H); 6.73 (s, 1H)
8g	88	59–63/3	$C_{15}H_{24}O$ (220.4)	220.1825	220.1819	1640, 1605	0.87 (t, 3H, *J* = 5); 1.07–2.00 (m, 14H); 2.13–2.60 (m, 6H); 6.82 (s, 1H)
8h	76	63–67/3	$C_{16}H_{26}O$ (234.4)	234.1983	234.1978	1635, 1600	0.85 (t, 3H, *J* = 5); 1.03–1.97 (m, 16H); 2.15–2.70 (m, 6H); 6.72 (s, 1H)

[a] Oil bath temperature.

[b–d] Refers to footnotes a–c in Table 1.

1-(Phenylthiomethyl)cycloheptanol **(2b)**: yield: 4.47 g (91%).

HRMS: *m/e* = 236.1223 (calc. for $C_{14}H_{20}OS$ = 236.1233).

IR (Neat): ν = 3450 (OH), 1580 cm^{-1} (phenyl).

^{1}H-NMR (CCl_4): δ = 0.90–2.10 (12H, m); 2.18 (1H, brs); 3.00 (2H, s); 6.90–7.50 (5H, m).

1-(Phenylthiomethyl)cycloalkenes 3a, b; General Procedure:

A solution of the appropriate alcohol **2a** or **b** (21.3 mmol) in benzene (40 mL) is refluxed for 7 h in the presence of a catalytic amount of *p*-toluenesulfonic acid using Dean-Stark apparatus. After cooling, the mixture is extracted with ether (3 × 30 mL), washed with saturated aqueous $NaHCO_3$ (2 × 10 mL) and saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. The residue is subjected to column chromatography on silica gel (ether/hexane, 1:4) to give the allylic sulfide **3a** or **b** as a yellow oil.

1-(Phenylthiomethyl)cyclohexene **(3a)**: yield: 4.13 g (95%).

HRMS: *m/e* = 204.0947 (calc. for $C_{13}H_{16}S$ = 204.0973).

IR (Neat): δ = 1660 (C=C); 1580 cm^{-1} (phenyl).

^{1}H-NMR (CCl_4): δ = 1.40–2.20 (8H, m); 3.33 (2H, s); 5.20–5.50 (1H, m); 6.80–7.54 (5H, m).

1-(Phenylthiomethyl)cycloheptene **(3b)**: yield: 4.46 g (96%).

HRMS: *m/e* = 218.1135 (calc. for $C_{14}H_{18}S$ = 218.1130).

IR (Neat): ν = 1660 (C=C); 1595 cm^{-1} (phenyl).

^{1}H-NMR (CCl_4): δ = 1.10–2.50 (10H, m); 3.27 (2H, s); 5.50 (1H, t, *J* = 6 Hz); 6.90–7.50 (5H, m).

1-[Phenylthio(trimethylsilyl)methyl]cycloalkenes 4a, b; General Procedure:

A dry 100 mL two-necked flask equiped with a septum inlet and a magnetic stirring bar is flushed with nitrogen and maintained under a positive pressure of nitrogen. A solution of diisopropylamine (2.12 g, 20.9 mmol) in THF (5 mL) is added to the flask, followed by addition of a 1.5 normal hexane solution of *n*-butyllithium (13.9 mL, 1.34 g, 20.9 mmol) at 0°C. After stirring at 0°C for 30 min, the mixture is cooled to −78°C and a solution of the appropriate allylic sulfide **3a** or **3b** (13.9 mmol) in THF (6 mL) is added to the solution. After stirring at −78°C for 2 h, chlorotrimethylsilane (2.27 g, 20.9 mmol) is added to the solution at −78°C and the mixture is allowed to stir at the same temperature for 4 h. The mixture is diluted with ether (3 × 30 mL), washed with 10% aqueous HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and saturated aqueous NaCl (2 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue is subjected to column chromatography on silica gel (ether/hexane, 1:30) to give **4a** or **b** as a yellow oil.

1-[Phenylthio(trimethylsilyl)methyl]cyclohexene **(4a)**: yield: 3.76 g (98%).

HRMS: *m/e* = 276.1313 (calc. for $C_{16}H_{24}SSi$: 276.1348).

IR (Neat): ν = 1650 (C=C); 1590 cm^{-1} (phenyl).

^{1}H-NMR (CCl_4): δ = 0.10 (9H, s); 1.10–2.60 (8H, m); 3.03 (1H, s); 5.20–5.40 (1H, m); 6.90–7.60 (5H, m).

1-[Phenylthio(trimethylsilyl)methyl]cycloheptene **(4b)**: yield: 3.83 g (95%).

HRMS: *m/e* = 290.1531 (calc. for $C_{17}H_{26}SSi$ = 290.1524).

IR (Neat): ν = 1645 (C=C); 1585 cm^{-1} (phenyl).

^{1}H-NMR (CCl_4): δ = 0.07 (9H, s); 1.00–2.30 (10H, m); 3.08 (1H, s); 5.42 (1H, t, *J* = 6 Hz); 6.90–7.30 (5H, m).

Preparation of 2-Acyl-1-(phenylthiomethylene)cycloalkanes 6a–h by Acylation of α-Silylallylic Sulfides 4a, b; General Procedure:

A dry 15 mL two-necked flask, equipped with a septum inlet and a stirring bar containing aluminum chloride (145 mg, 1.09 mmol) is flushed with nitrogen and maintained under a positive pressure of nitrogen. Anhydrous CH_2Cl_2 (1 mL) is added, followed by the addition of the appropriate acyl chloride **5a–d** (0.87 mmol) in CH_2Cl_2 (1.5 mL) at −78°C. A solution of **4a** or **4b** (0.72 mmol) in CH_2Cl_2 (1.5 mL) is added dropwise to the above mixture at −78°C and the reaction mixture is allowed to stir at −78°C for 6 h. The flask is removed from the dry ice-acetone bath, and the mixture is diluted with ether (30 mL). The solution is washed sequentially with saturated aqueous NaCl (5 mL), saturated aqueous $NaHCO_3$ (2 × 5 mL), and saturated aqueous NaCl (2 × 5 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude products are subjected to preparative TLC (silica gel plates; ether/hexane, 1:20) to give the products **6a–h** as oils. See Table 1.

1-Alkyl-3-phenylthio-4,5,6,7-tetrahydroisobenzofurans 7a–d and 1-Alkyl-3-phenylthio-5,6,7,8-tetrahydro-4*H*-cyclohepta[*c*]furans 7e–h; General Procedure:

A solution of **6a–h** (0.16 mmol) in benzene (5 mL) is refluxed in the presence of concentrated sulfuric acid (16 mg, 0.16 mmol) for 15 h. After cooling, the mixture is diluted with ether (20 mL). The ethereal solution is washed with 10% aqueous NaOH (2 × 5 mL) and saturated aqueous NaCl (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude products are subjected to preparative TLC (silica gel plates, hexane) to give the products **7a–h** as oils. See Table 2.

1-Alkyl-4,5,6,7-tetrahydroisobenzofurans 8a–d and 1-Alkyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*c*]furans 8e–h; General Procedure:

A mixture of **7a–h** (0.10 mmol) and Raney Ni-W_4 (0.3 mL) [deactivated by refluxing in acetone for 3 h] in ethanol (5 mL) is refluxed for 2 h. The catalyst is filtered with celite-545, and the filtrate is concentrated under reduced pressure. The residual oil is subjected to preparative TLC (silica gel plates, hexane) to give the products **8a–h**. See Table 3.

Received: 26 June 1986; revised: 13 March 1987

(1) Biellmann, J.F., Ducep, J.B. *Tetrahedron Lett.* **1968**, 5629.
Still, W.S., Macdonald, T.L. *J. Org. Chem.* **1976**, *41*, 3620.
Atlani, P.M., Biellmann, J.F., Dube, S., Vicens, J.J. *Tetrahedron Lett.* **1974**, 2665.
(2) Oshima, K., Yamamoto, H., Nozaki, H. *J. Am. Chem. Soc.* **1973** *95*, 7926.
(3) Yamamoto, Y., Yatagi, H., Maruyama, K. *Chem. Lett.* **1979**, 385
(4) Yamamoto, Y., Yatagi, H., Maruyama, K. *J. Org. Chem.* **1980**, *45* 195.
(5) Hayashi, T. *Tetrahedron Lett.* **1974**, 339.
Hayashi, T., Fujitaka, N., Oishi, T., Takeshima, T. *Tetrahedron Lett.* **1980**, 303.
(6) Mukaiyama, T., Narasaka, K., Maekawa, K., Furusato, M. *Bull Chem. Soc. Jpn.* **1971**, *44*, 2285.
(7) Hirai, K., Kishida, Y. *Tetrahedron Lett.* **1972**, 2743.
(8) Evans, D.A., Andrews, G.C. *Acc. Chem. Res.* **1974**, *7*, 147.
(9) Hiroi, K., Chen, L.-M. *J. Chem. Soc. Chem. Commun.* **1981**, 377
(10) Hiroi, K., Sato, H., Kotsuji, K. *Chem. Lett.* **1986**, 743.
(11) Okazaki, R., Negishi, Y., Inamoto, N. *J. Chem. Soc. Chem Commun.* **1982**, 1055.
Okazaki, R., Negishi, Y., Inamoto, N. *J. Org. Chem.* **1984**, *49* 3819.
(12) Garst, M.E., Spencer, T.A. *J. Am. Chem. Soc.* **1973**, *95*, 250.