γ-Substituted Organoalkali Compounds; Preparation and Synthetic Applications

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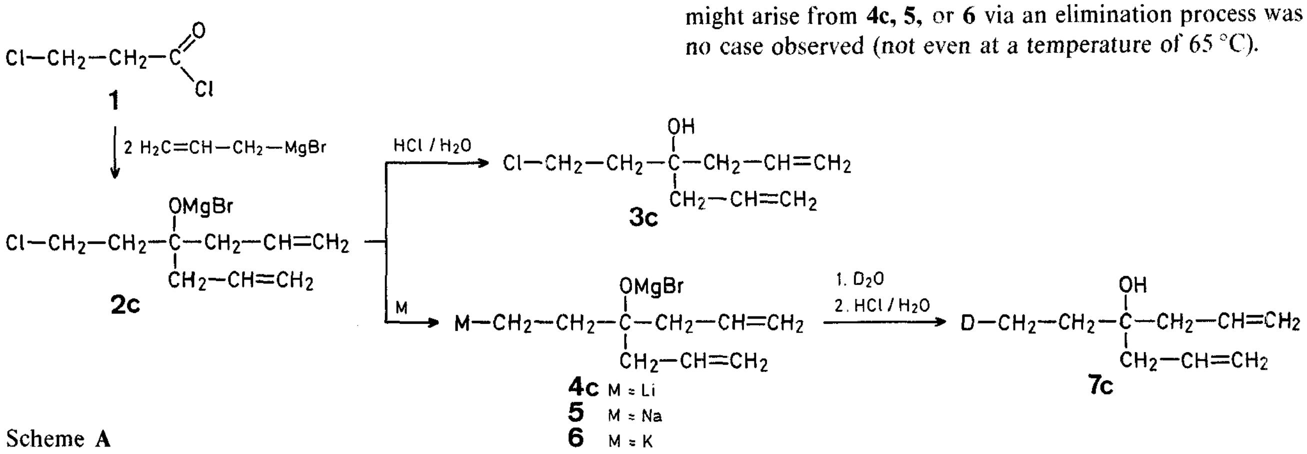
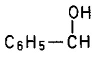
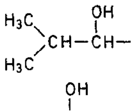
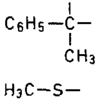
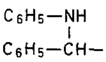
The preparation of functionalized organometallic compounds derived from main-group metals has received interest due to the possibility of obtaining bifunctionalized organic compounds by reaction of these intermediates with electrophilic agents. In connection with our studies on the preparation and reactivity of β-substituted organoalkali compounds[1] and their application in the synthesis of olefins[2], we report here the preparation and synthetic application of the homologous γ-substituted organoalkali compounds[3], mainly the lithium derivatives.

We found that treatment of 3-chloropropanoyl chloride (**1**) with allylmagnesium bromide in a 1 : 2 molar ratio leads to the formation of an intermediate **2c**. Compound **2c** may be metallated in the reaction mixture by treatment with lithium powder, sodium, or potassium plates[4] in tetrahydrofuran at −15° to −20 °C to afford the corresponding 3-substituted alkyllithium (**4c**), alkylsodium (**5**), or alkylpotassium (**6**) compounds, respectively. These latter compounds were characterized as their hydrolysis or deuterolysis products **3c** or **7c** (Scheme **A**). The formation of 1,1-diallylcyclopropane which might arise from **4c**, **5**, or **6** via an elimination process was in no case observed (not even at a temperature of 65 °C).



Scheme **A**

Table 1. Preparation of Compounds **3c**, **7a–e**, and **8–18**

Compound	X	Reaction conditions		Yield[a] [%]	b.p.[b]/torr [°C]	Molecular formula[c]	
		Temperature [°C]	Time [h]				
3c	—	−15° to 20°/—[d]	2/—[e]	96	48–52°/0.1	$C_9H_{15}ClO$	(174.7)
7a	—	−20° to 20°/−20° to 20°[d]	2/6[e]	52	40–44°/15	$C_7H_{15}DO$	(117.2)
7b	—	−15° to 20°/−15° to 20°[d]	2/13[e]	39	52–56°/15	$C_9H_{19}DO$	(145.3)
7c	—	−15° to 20°/−15° to 20°[d]	2/6[e]	71[f]	54–58°/15	$C_9H_{15}DO$	(141.2)
		−15° to 20°/20°[g]	2/10[g]	52[h]; 47[i]			
7d	—	−15° to 20°/−15° to 20°[d]	2/13[e]	31	36–40°/0.1	$C_{11}H_{23}DO$	(173.3)
7e	—	−20° to 20°/−20° to 20°[d]	2/17[e]	56	93–97°/0.001	$C_{17}H_{19}DO$	(241.3)
8	H	20°[j]	0.25[k]	70	55–58°/15	$C_9H_{16}O$	(140.2)
9	OH	−30° to −15°[j]	2[k]	42	71–75°/0.001	$C_9H_{16}O_2$	(156.2)
10	—	−40° to 20°[j]	4[k]	53	46–50°/0.001	$C_{10}H_{14}O_2$	(166.2)
11	 $C_6H_5-CH(OH)-$	20°[j]	5[k]	86	140–150°/0.001[l]	$C_{16}H_{22}O_2$	(246.3)
12	 $(H_3C)_2CH-CH(OH)-$	20°[j]	13[k]	60	85–89°/0.001	$C_{13}H_{24}O_2$	(212.3)
13	 $C_6H_5-C(OH)(CH_3)-$	20°[j]	3.5[k]	65	112–115°/0.001	$C_{17}H_{24}O_2$	(260.4)
14	H_3C-S-	20°[j]	3[k]	58	57–61°/0.001	$C_{10}H_{18}OS$	(186.3)
15	$C_6H_5-CH_2-$	20°[j]	2[k]	27	60–70°/0.001	$C_{16}H_{22}O$	(230.3)
16	$(H_3C)_3Si-$	20°[j]	5[k]	49	41–44°/0.001	$C_{12}H_{24}OSi$	(212.4)
17	 $C_6H_5-CH(NH-C_6H_5)-$	20°[j]	5[k]	63	—[m]	$C_{22}H_{27}NO$	(321.5)
18	—	125°[n]	1[n]	78[o]	65–70°/0.001	$C_{16}H_{20}O$	(228.3)

[a] Yield of isolated product based on starting material **1**.

[b] Distillation interval. Purity >95% from G.L.C. analysis (Chromosorb OV-101).

[c] The microanalyses were in good agreement with the calculated values: C, ±0.18; H/D, ±0.12.

[d] Temperature in the reaction with alkylmagnesium bromide/with lithium.

[e] Time of the reaction with alkylmagnesium bromide/with lithium.

[f] Via intermediate **4c**.

[g] Reaction conditions when sodium or potassium were used as metallation agent.

[h] Via intermediate **5**.

[i] Via intermediate **6**.

[j] Temperature in the reaction of **4c** with the electrophilic agent *El*.

[k] Time of the reaction of **4c** with *El*.

[l] Bath temperature.

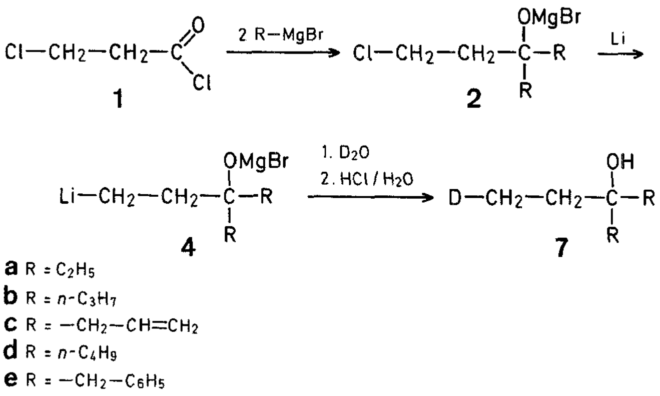
[m] Oil.

[n] Temperature and time in the reaction of compound **11** with H_3PO_4.

[o] Based on compound **11**.

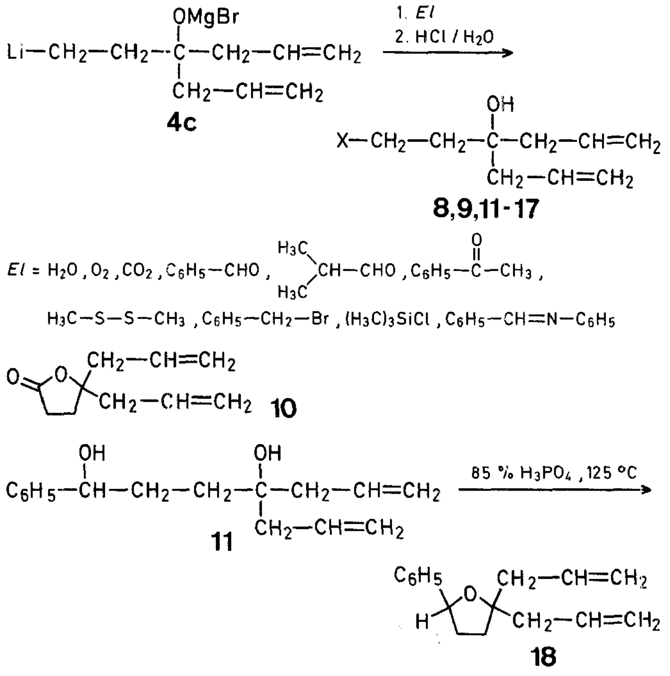
All intermediates **4**, **5**, and **6** exhibit a behavior different from that of the lower homologous 2-substituted compounds which easily undergo β-elimination to alkenes[2].

The intermediates **4** formed in an analogous manner from the reaction of 3-chloropropanoyl chloride (**1**) with other organomagnesium bromides were also characterized as the hydrolysis products **7** obtained with deuterium oxide (Scheme **B** and Table 1).



Scheme **B**

The synthetic utility of intermediates **4** is demonstrated by the reaction of **4c** with a variety of electrophilic compounds (*El*) to give, after hydrolysis, the bifunctional compounds **8-17** (Scheme **C**). The reaction of **4c** with carbon dioxide affords lactone **10** directly. The possibility of preparing tetrahydrofurans via intermediates **4** is shown by the conversion of diol **11** into 2,2-diallyl-5-phenyltetrahydrofuran (**18**) by heating with phosphoric acid.



Scheme **C**

Table 2. Spectrometric Data for Compounds **3c**, **7a-e**, and **8-18**

Compound	I.R. (film)[a] ν_{OH} [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int})[b] δ [ppm]	^{13}C-N.M.R. (CCl_4)[b] δ [ppm][c]
3c	3420	1.9 (t, 2H, J=9 Hz, Cl—C—CH_2); 2.2 (d, 4H, J=8 Hz, 2=C—CH_2); 2.95 (s, 1H, OH); 3.6 (t, 2H, J=9 Hz, Cl—CH_2); 4.9-5.25 (m, 4H, 2=CH_2); 5.5-6.25 (m, 2H, 2CH)	39.6, 42.0, 43.7, 73.0, 118.6, 133.1
7a	3400	0.8 (t, 8H, J=6 Hz, 2CH_3 and CH_2D); 1.2-1.6 (m, 6H, 3CH_2); 2.05 (s, 1H, OH)	7.1 (t, J_{CD}=19.2 Hz), 7.3, 30.2, 73.8
7b	3400	0.65-1.1 (m, 8H, 2CH_3 and CH_2D); 1.15-1.5 (m, 10H, 5CH_2); 2.45 (s, 1H, OH)	7.3 (t, J_{CD}=19.1 Hz), 14.5, 16.5, 31.3, 41.0, 73.8
7c	3400	0.8 (t, 2H, J=7 Hz, CH_2D); 1.4 (t, 2H, J=7 Hz, D—C—CH_2); 2.1 (d, 4H, J=8 Hz, 2=C—CH_2); 2.2 (s, 1H, OH); 4.8-5.1 (m, 4H, 2=CH_2); 5.5-6.1 (m, 2H, 2CH)	6.9 (t, J_{CD}=19.1 Hz), 31.3, 43.1, 73.2, 117.6, 133.7[d]
7d	3400	0.6-1.05 (m, 8H, 2CH_3 and CH_2D); 1.1-1.7 (m, 14H, 7CH_2); 3.65 (br. s, 1H, OH)	7.2 (t, J_{CD}=18.8 Hz), 13.7, 23.2, 25.5, 31.2, 38.2, 73.8
7e	3460	0.65-1.0 (m, 2H, CH_2D); 1.05-1.4 (m, 2H, O—C—CH_2); 1.5 (s, 1H, OH); 2.6 (s, 4H, 2C_6H_5—$C\underline{H}_2$); 7.0 (m, 10H, 2C_6H_5)	7.9 (t, J_{CD}=19.3 Hz), 30.4, 44.9, 74.1, 126.0, 127.8, 130.5, 137.4
8	3400	0.8 (t, 3H, J=7 Hz, CH_3); 1.3 (q, 2H, J=7 Hz, H_3C—$C\underline{H}_2$); 2.05 (d, 4H, J=8 Hz, 2=C—CH_2); 2.6 (s, 1H, OH); 4.75-5.1 (m, 4H, 2=CH_2); 5.5-6.05 (m, 2H, 2CH)	7.8, 31.7, 43.6, 73.8, 117.7, 134.5
9	3350	1.65 (t, 2H, J=6 Hz, O—C—CH_2); 2.2 (d, 4H, J=8 Hz, 2=C—CH_2); 3.45, 3.75 (2t, 2H, J=6 Hz, O—CH_2); 4.15 (s, 2H, 2OH); 4.85-5.25 (m, 4H, 2=CH_2); 5.5-6.1 (m, 2H, 2CH)	39.5, 43.9, 58.3, 74.0, 117.8, 133.9
10	—[e]	1.75-2.15 (m, 2H, O=C—C—CH_2); 2.3-2.7 (m, 2H, O=C—CH_2); 2.4 (d, 4H, J=8 Hz, 2=C—CH_2); 4.95-5.25 (m, 4H, 2=CH_2); 5.5-6.1 (m, 2H, 2CH)	28.7, 29.3, 43.3, 87.2, 119.4, 132.2, 175.5
11	3350	1.2-1.9 (m, 4H, CH_2—CH_2); 2.1 (d, 4H, J=8 Hz, 2=C—CH_2); 3.9 (s, 2H, 2OH); 4.45 (m, 1H, O—CH); 4.8-5.1 (m, 4H, 2=CH_2); 5.4-5.9 (m, 2H, 2=CH); 7.1 (m, 5H, C_6H_5)	32.7, 35.1, 43.3, 43.7, 73.5, 74.2, 117.8, 125.8, 126.9, 128.0, 133.8, 144.8
12	3400	0.85 (d, 6H, J=6 Hz, 2CH_3); 1.5 (m, 5H, CH_2—CH_2 and H_3C—$C\underline{H}$); 2.2 (d, 4H, J=8 Hz, 2=C—CH_2); 3.2 (m, 1H, O—CH); 3.7 (s, 2H, 2OH); 4.85-5.1 (m, 4H, 2=CH_2); 5.5-6.1 (m, 2H, 2=CH)	17.7, 18.8, 27.1, 33.5, 35.4, 43.2, 44.2, 73.3, 76.5, 117.5, 134.2
13	3400	1.25-1.65 (m, with s at 1.55, 5H, C_6H_5—C—C—$C\underline{H}_2$ and CH_3); 1.8-2.05 (m, 2H, C_6H_5—C—$C\underline{H}_2$); 2.1-2.25 (m, 4H, 2=C—CH_2); 2.6 (s, 2H, 2OH); 4.85-5.2 (m, 4H, 2=CH_2); 5.45-6.0 (m, 2H, 2CH); 7.15-7.5 (m, 5H, C_6H_5)[d]	30.1, 33.0, 37.3, 43.6, 43.8, 73.3, 74.0, 117.8, 124.9, 126.1, 127.8, 133.9, 148.2

Table 2. (Continued)

Compound	I.R. (film)[a] ν_{OH} [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int})[b] δ [ppm]	^{13}C-N.M.R. (CCl_4)[b] δ [ppm][c]
14	3460	1.75 (m, 2H, O—C—CH_2); 2.1 (s, 4H, CH_3 and OH); 2.25 (d, 4H, $J=8$ Hz, 2=C—CH_2); 2.6 (m, 2H, S—CH_2); 4.9-5.2 (m, 4H, 2=CH_2); 5.5-6.1 (m, 2H, 2CH)[d]	15.2, 28.1, 38.5, 43.7, 73.2, 118.1, 133.7
15	3400	1.1-1.9 (m, 5H, CH_2—CH_2—C—OH); 2.05 (d, 4H, $J=8$ Hz, 2=C—CH_2); 2.45 (t, 2H, $J=6$ Hz, C_6H_5—$\underline{C}H_2$); 4.75-5.05 (m, 4H, 2=CH_2); 5.4-5.9 (m, 2H, 2CH); 7.0 (m, 5H, C_6H_5)	25.0, 36.2, 38.6, 43.7, 73.1, 117.6, 125.5, 128.0, 128.1, 134.0, 142.0
16	3440	0.05 (s, 9H, 3Si—CH_3); 0.4-0.65 (m, 2H, Si—CH_2); 1.3-1.6 (m, 2H, O—C—CH_2); 1.75 (s, 1H, OH); 2.25 (d, 4H, $J=8$ Hz, 2=C—CH_2); 4.95-5.25 (m, 4H, 2=CH_2); 5.6-6.15 (m, 2H, 2CH)	−1.9, 9.5, 32.9, 43.2, 73.9, 118.5, 134.2
17	3440[f]	1.2-1.85 (m, 4H, CH_2—CH_2); 2.05 (d, 4H, $J=8$ Hz, 2=C—CH_2); 3.0 (s, 2H, OH and NH); 4.1 (t, 1H, $J=6$ Hz, N—CH); 4.75-5.05 (m, 4H, 2=CH_2); 5.3-5.9 (m, 2H, 2=CH); 6.25-7.25 (m, 10H, 2C_6H_5)[d]	31.8, 34.9, 42.9, 43.3, 58.0, 72.7, 112.9, 116.6, 117.8, 125.8, 126.3, 127.9, 128.5, 133.2, 143.5, 146.9[d]
18	—[g]	1.7 (m, 4H, CH_2—CH_2); 2.3 (d, 4H, $J=8$ Hz, 2=C—CH_2); 4.8 (m, 1H, O—CH); 4.85-5.2 (m, 4H, 2=CH_2); 5.55-6.0 (m, 2H, 2=CH); 7.2 (m, 5H, C_6H_5)	34.4, 35.2, 43.8, 44.4, 80.5, 84.3, 117.4, 117.5, 125.4, 126.7, 127.9, 134.5, 134.6, 143.1

[a] Recorded in a Pye Unicam SP-1000 I.R. spectrometer.
[b] Recorded in a Varian FT-80 spectrometer with a D_2O capillary.
[c] Referred to the solvent CCl_4 (or $CDCl_3$).
[d] In $CDCl_3$.
[e] $\nu_{C=O} = 1775$ cm^{-1}.
[f] This band includes the ν_{NH} absorption.
[g] $\nu_{C-O} = 1030$ cm^{-1}.

4-(2-Chloroethyl)-4-hydroxy-1,6-heptadiene (3c) via Hydrolysis of Intermediate 2c:

A solution of 3-chloropropanoyl chloride (**1**, Aldrich; 2.54 g, 20 mmol) in tetrahydrofuran (25 ml) is added dropwise, over a period of 30 min, to a stirred ether solution of allylmagnesium bromide (40 mmol) under an argon atmosphere at −15 °C. The temperature is allowed to rise to 20 °C within 1.5 h, the mixture then hydrolyzed with water (25 ml) and neutralized (pH 7) with hydrochloric acid. The resultant mixture is extracted with ether (3 x 15 ml). The organic extract is washed with water (2 x 10 ml), dried with sodium sulfate, and evaporated at 15 torr. The residue is distilled in vacuo to give **3c**; yield: 3.3 g (96%); b.p. 48-52 °C/0.1 torr.

$C_9H_{15}ClO$	calc.	C 61.89	H 8.65
(174.7)	found	61.75	8.71

4-(2-Deuterioethyl)-4-hydroxy-1,6-heptadiene (7c); Typical Procedure:

A solution of 3-chloropropanoyl chloride (**1**; 2.54 g, 20 mmol) in tetrahydrofuran (25 ml) is added dropwise, over a period of 30 min, to a stirred ether solution of allylmagnesium bromide (40 mmol) under an argon atmosphere at −15 °C. The temperature is allowed to rise to 20 °C within 1.5 h. The mixture is then again cooled to −15 °C, lithium powder (416 mg, 60 mmol) is added, and the temperature is allowed to rise to 20 °C during 6 h. The resultant black suspension containing intermediate **4c** is stirred with deuterium oxide (2 ml) for 15 min, then hydrolyzed with water (20 ml), and neutralized (pH 7) with hydrochloric acid. The mixture is extracted with ether (3 x 15 ml). The organic extract is washed with water (2 x 10 ml), dried with sodium sulfate, and evaporated at 15 torr. The residue is carefully distilled in vacuo to afford product **7c**; yield: 2.0 g (71%); b.p. 54-58 °C/15 torr.

$C_9H_{15}DO$	calc.	C 76.54	H/D 12.13
(141.2)	found	76.38	12.02

The intermediates **5** and **6** are prepared as described above for the lithio derivative **4c** with the modification that sodium and potassium are used as plates obtained by dissolving the metal in liquid ammonia at −50 °C and then evaporating the solvent[4] at 0.1 torr.

Bifunctional Compounds 8-17 according to Scheme C; General Procedure:

The black suspension of intermediate **4c** is prepared as described above and filtered through a G-3 funnel. The filtrate is stirred at 20 °C and the electrophile (*El*) is added in a 1 : 1 molar ratio. Stirring is continued for 0.25 to 13 h (Table 1), the mixture then hydrolyzed with water (20 ml), neutralized (pH 7) with hydrochloric acid, and extracted with ether (3 x 15 ml). The organic extract is washed with water (2 x 10 ml), dried with sodium sulfate, and evaporated at 15 torr. The residual product is purified by distillation in vacuo.

When oxygen is used as the electrophile *El*, a precooled (−30 °C) stream of dry oxygen is bubbled through the solution of **4c** at −30° to −15 °C for 2 h and the mixture then hydrolyzed and worked up as above.

The reaction with carbon dioxide[6] is carried out by adding a precooled (−40 °C) solution of **4c** to excess anhydrous solid carbon dioxide. The resultant mixture is stirred for 4 h and then hydrolyzed and worked up as described above.

2,2-Diallyl-5-phenyltetrahydrofuran (18):

A mixture of 4-allyl-1-phenyl-6-heptene-1,4-diol (**11**; 3.7 g, 15 mmol) and 85% phosphoric acid (1.0 ml, 15 mmol) is stirred at 125 °C (bath temperature) for 1 h, then cooled, and extracted with ether (3 x 15 ml). The organic extract is washed with water (2 x 10 ml), dried with sodium sulfate, and evaporated at 15 torr. The residue is distilled in vacuo to give **18**; yield: 2.7 g (78%); b.p. 65-70 °C/0.001 torr.

$C_{16}H_{20}O$	calc.	C 84.16	H 8.83
(228.3)	found	84.20	8.88

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