δ-Substituted Organoalkaline Metal Compounds; Preparation and Synthetic Applications

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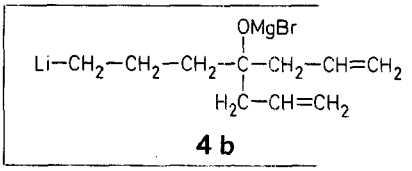
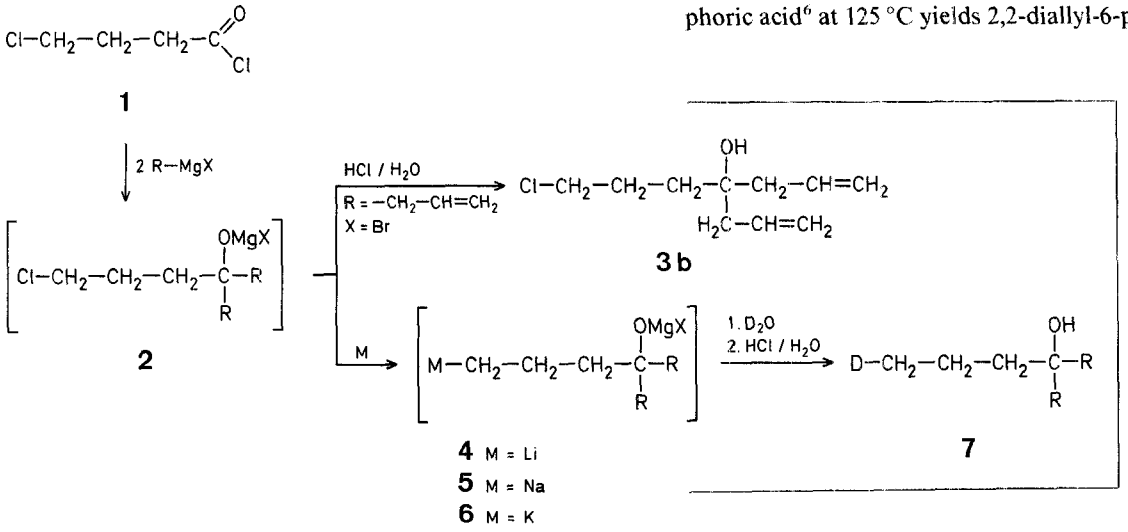
Substituted organometal compounds derived from the main-group metals have preparative interest because of their ability to react with electrophiles to give directly bifunctionalized organic compounds. We have recently described the preparation and synthetic application of β-[1] and γ-substituted[2] organoalkaline metal compounds. Herein, we report the synthesis of the homologous δ-substituted systems and their chemical behaviour.



4b

When 4-chlorobutanoyl chloride (**1**) was treated with allylmagnesium bromide (1:2 molar ratio) the intermediate **2b** (R = allyl) was formed, which was metallated *in situ* with lithium powder or sodium or potassium plates[3] to give the corresponding δ-substituted organoalkaline metal compounds **4b**, **5b**, and **6b**, respectively. These intermediates were chemically characterized by hydrolysis or deuterolysis reactions giving products **3b** or **7b**. The use of other Grignard reagents and lithium metal leads to the corresponding organolithium intermediates **4** which were also characterized by treatment with deuterium oxide (formation of compounds **7**).



1

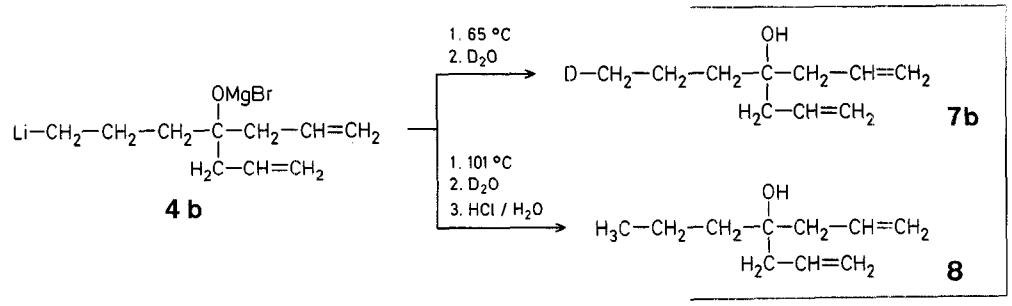
2

3b

4 M = Li
5 M = Na
6 M = K

7

In a study of the thermal stability of intermediate **4b**, we found that refluxing a solution of **4b** in tetrahydrofuran followed by treatment with D_2O affords compound **7b** whereas heating of **4b** in the higher boiling dioxan followed by treatment with D_2O and acid hydrolysis leads to the formation of alcohol **8** due to proton abstraction from the reaction medium by intermediate **4b**. 1,1-Diallylcyclobutane, which might have been formed by a δ-elimination process, was in no case isolated.



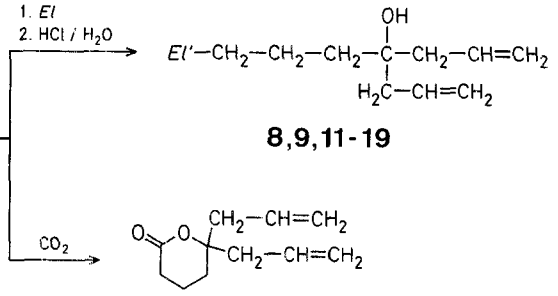
4b

7b

8

It is noteworthy that the thermal behaviour of the δ-substituted organolithium intermediate **4b** is analogous to that of the γ-substituted systems[2]. In contrast, the homologous β-substituted compounds easily decompose to olefins via a β-elimination process[5].

The synthetic utility of intermediates **4** was studied by treatment of intermediate **4b** with a series of electrophiles. These



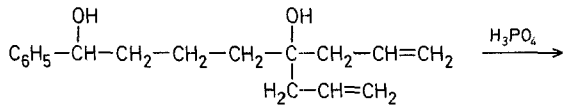
8,9,11-19

10

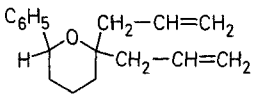
reactions, followed by hydrolysis, led to the formation of the bifunctional aliphatic compounds **8**, **9**, **11-19** in moderate to good yields.

The reaction of intermediate **4b** with carbon dioxide as electrophile under the same conditions affords directly lactone **10**.

Treatment of the bifunctional product **12** with 85% phosphoric acid[6] at 125 °C yields 2,2-diallyl-6-phenyltetrahydropyran (**20**) while diols of the type **9** are under the same conditions cyclocondensed to the corresponding tetrahydrofuran derivatives[2].



12



20

4-(3-Chloropropyl)-4-hydroxy-1,6-heptadiene (3b) via Intermediate 2b:
A solution of 4-chlorobutanoyl chloride (**1**, Aldrich; 2.82 g, 20 mmol) in ether (25 ml) is added dropwise, over 30 min, to a stirred solution of allylmagnesium bromide (40 mmol) in ether at −10 °C. The temperature is thereafter allowed to rise to 20 °C within 2 h. The mixture containing intermediate **2b** is then hydrolyzed with water (20 ml) and neutralized (pH 7) with dilute hydrochloric acid. The resultant mixture is extracted with ether (3 × 15 ml). The ether extract is washed with water (15 ml) and dried with sodium sulfate. The solvents are removed under reduced pressure (15 torr), and the residue is distilled in vacuo (0.1 torr) to give **3b**; yield: 3.25 g (86%); b.p. 55–60 °C/0.1 torr.

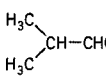
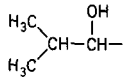
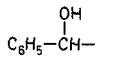
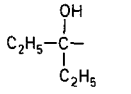
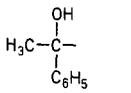
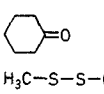
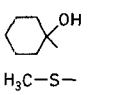
4-(3-Deuteriopropyl)-4-hydroxy-1,6-heptadiene (7b) via Intermediates 2b and 4b; Typical Procedure:
To a stirred mixture containing intermediate **2b** (prepared as above) at −10 °C is added lithium powder (60 mg-atom) and the temperature is allowed to rise to 20 °C during 6 h. The resultant black suspension containing intermediate **4b** is hydrolyzed successively with deuterium oxide (2 ml) and water (20 ml) and neutralized with dilute hydro-

Table 1. Preparation of Compounds **3b** and **7**

Product	Intermediate	R	X	M	Reaction conditions[a] temperature [°C], time [h]	Yield[b] [%]	b.p.[c]/torr [°C]	Molecular formula[d]
3b	**2b**	$-CH_2-CH=CH_2$	Br	—		86	55–60°/0.1	$C_{10}H_{17}ClO$ (188.7)
7a	**4a**	CH_3	J	Li	−10° to 20°, 6	45	35–38°/15	$C_6H_{12}DO$ (103.2)
7b	**4b**	$-CH_2-CH=CH_2$	Br	Li	−10° to 20°, 6	71	66–70°/15	$C_{10}H_{17}DO$ (155.3)
7b	**5b**	$-CH_2-CH=CH_2$	Br	Na	20°, 10	68		
7b	**6b**	$-CH_2-CH=CH_2$	Br	K	20°, 12	47		
7c	**4c**	n-C_3H_7	Br	Li	−10° to 20°, 6	52	69–71°/15	$C_{10}H_{21}DO$ (159.3)
7d	**4d**	i-C_3H_7	Br	Li	−10° to 20°, 6	63	71–74°/15	$C_{10}H_{21}DO$ (159.3)
7e	**4e**	C_6H_5	Br	Li	−10° to 20°, 6	57	93–95°/0.001	$C_{16}H_{17}DO$ (227.3)
7f	**4f**	$-CH_2-C_6H_5$	Br	Li	−10° to 20°, 6	65	99–101°/0.001	$C_{18}H_{23}DO$ (255.4)

[a] In the step **2** → **4**, **5b**, or **6b** (see experimental).
[b] Yield of isolated product based on starting material **1**.
[c] Distillation interval.
[d] The microanalyses were in good agreement with the calculated values: C, ±0.26; H or H/D, ±0.15.

Table 2. Preparation of Compounds **8–20** via Intermediate **4b**

El	Product	*El'*	Reaction conditions, temperature [°C], time [h]	Yield[a] [%]	b.p.[b]/torr [°C]	Molecular formula[c]
H_2O	**8**	H	20°, 0.25	91	68–71°/15	$C_{10}H_{18}O$ (154.2)
O_2	**9**	OH	−20°, 2	53	75–78°/0.001	$C_{10}H_{18}O_2$ (170.2)
CO_2	**10**	(see text)	−40°, 10	58	100–105°/0.001	$C_{11}H_{17}O_2$ (180.2)
	**11**		20°, 12	75	92–95°/0.001	$C_{14}H_{26}O_2$ (226.4)
C_6H_5-CHO	**12**		20°, 12	51	110–115°/0.001	$C_{17}H_{24}O_2$ (260.4)
	**13**		20°, 12	56	110–112°/0.001	$C_{15}H_{28}O_2$ (240.4)
	**14**		20°, 12	64	115–120°/0.001	$C_{18}H_{26}O_2$ (274.4)
	**15**		20°, 12	82	113–118°/0.001	$C_{16}H_{28}O_2$ (252.4)
$H_3C-S-S-CH_3$	**16**	H_3C-S-	20°, 12	72	85–87°/0.1	$C_{11}H_{20}OS$ (200.3)
$H_2C=CH-CH_2-Br$	**17**	$H_2C=CH-CH_2-$	20°, 12	79	58–60°/0.001	$C_{13}H_{22}O$ (194.3)
$(H_3C)_3SiCl$	**18**	$(H_3C)_3Si-$	20°, 12	68	123–126°/15	$C_{13}H_{26}OSi$ (226.4)
$C_6H_5-CH=N-C_6H_5$	**19**	$C_6H_5-CH(C_6H_5-NH)-$	20°, 12	68	oil[d]	$C_{23}H_{29}NO$ (335.5)
[$C_6H_5-CHO \rightarrow$ **12**]	**20**	(see text)	125°[e], 1	77[f]	75–80°/0.001	$C_{17}H_{22}O$ (242.4)

[a] Yield of isolated product based on starting material **1**.
[b] Distillation interval.
[c] The microanalyses were in good agreement with the calculated values: C, ±0.19; H, ±0.17; N, ±0.03.
[d] Not distilled.
[e] Temperature and time in the reaction of compound **12** with H_3PO_4.
[f] Based on compound **12**.

chloric acid (pH 7). The mixture is extracted with ether (3 × 15 ml) and the ether layer is washed with water (15 ml) and dried with sodium sulfate. The solvents are removed under reduced pressure (15 torr) and the residue is carefully distilled in vacuo (15 torr) to afford the pure product **7b**.

Table 3. Spectrometric Data of Compounds **3b, 7a-f, 8-20**

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]
3b	3420	1.3–1.85 (m, 4H, O—C—CH_2—CH_2); 2.05 (d, 4H, J=8 Hz, 2 =C—CH_2); 2.15 (s, 1H, OH); 3.35 (t, 2H, J=6 Hz, Cl—CH_2); 4.8–5.15 (m, 4H, 2 =CH_2); 5.1–6.0 (m, 2H, 2 CH)	26.7, 36.3, 43.7, 45.2, 72.9, 118.2, 133.6
7a	3380	0.75 (m, 2H, CH_2D); 1.0 (s, 6H, 2 CH_3); 1.25 (m, 4H, O—C—CH_2—CH_2); 3.1 (br. s, 1H, OH)	11.2 (t, J_{CD}=19.1 Hz), 17.3, 28.9, 46.3, 70.3
7b	3440	0.9 (m, 2H, CH_2D); 1.34 (m, 4H, O—C—CH_2—CH_2); 1.9 (s, 1H, OH); 2.15 (d, 4H, J=8 Hz, 2 =C—CH_2); 4.85–5.25 (m, 4H, 2 =CH_2); 5.5–6.1 (m, 2H, 2 CH)	14.0 (t, J_{CD}=19.2 Hz), 16.2, 41.4, 43.7, 73.7, 117.3, 134.1
7c	3380	0.8–1.05 (m, 8H, 2 CH_3 + CH_2D); 1.25–1.55 (m, 12H, 3 O—C—CH_2—CH_2); 3.25 (s, 1H, OH)	13.4 (t, J_{CD}=19.1 Hz), 13.7, 18.7, 39.6, 70.4
7d	3380	0.8–1.0 (m, 14H, 4 CH_3 + CH_2D); 1.25–1.7 (m, 6H, O—C—CH_2—CH_2 + 2 CH); 3.45 (s, 1H, OH)	13.6 (t, J_{CD}=19.1 Hz), 17.2, 18.6, 19.0, 33.5, 36.2, 75.7
7e	3500	0.65–1.25 (m, 4H, CH_2—CH_2D); 1.75 (s, 1H, OH); 1.95–2.2 (m, 2H, O—C—CH_2); 6.85–7.3 (m, 5H_{arom})	13.8 (t, J_{CD}=19.4 Hz), 16.6, 22.7, 77.7, 125.8, 126.9, 127.6, 147.1
7f	3480	0.75–1.0 (m, 2H, CH_2D); 1.2–1.45 (m, 4H, O—C—CH_2—CH_2); 2.65 (s, 2H, C_6H_5—CH_2); 2.7 (s, 1H, OH); 7.1–7.25 (m, 5H_{arom})	14.0 (t, J_{CD}=19.5 Hz), 16.9, 40.6, 45.4, 73.9, 126.0, 127.7, 130.5, 137.4
8	3420	0.9 (m, 3H, CH_3); 1.4 (m, 4H, O—C—CH_2—CH_2); 2.15 (s, 1H, OH); 2.2 (d, 4H, J=8 Hz, 2 =C—CH_2); 4.85–5.2 (m, 4H, 2 =CH_2); 5.5–6.1 (m, 2H, 2 CH)	14.4, 16.4, 41.5, 43.8, 73.3, 117.4, 134.2
9	3360	1.4–1.8 (m, 4H, O—C—CH_2—CH_2); 2.15 (d, 4H, J=8 Hz, 2 =C—CH_2); 3.7 (t, 2H, J=6 Hz, O—CH_2); 4.75–5.2 (m, 4H, 2 =CH_2); 5.4–5.95 (m, 2H, 2 CH); 6.5, 7.2 (2s, 2H, 2 OH)	25.9, 33.7, 43.5, 67.4, 83.8, 117.2, 134.5
10	—[d]	1.3–1.95 (m, 6H, 3 CH_2); 2.15, 2.35 (2d, 4H, J=8 Hz, 2 =C—CH_2); 4.8–5.2 (m, 4H, 2 =CH_2); 5.5–6.05 (m, 2H, 2 CH)	16.3, 29.0, 29.2, 43.3, 84.0, 118.9, 132.3, 169.9
11	3420	0.9 (d, 6H, J=6 Hz, 2 CH_3); 1.4 (m, 5H, O—C—CH_2—CH_2—CH_2 + O—C—CH); 2.2 (d, 4H, J=8 Hz, 2 =C—CH_2); 3.25 (m, 1H, O—CH); 3.65 (s, 2H, 2 OH); 4.85–5.25 (m, 4H, 2 =CH_2); 5.6–6.15 (m, 2H, 2 =CH)	17.8, 18.9, 19.2, 33.7, 34.2, 38.8, 43.6, 73.5, 75.6, 117.5, 134.2
12	3380	1.2–1.7 (m, 6H, O—C—CH_2—CH_2—CH_2); 2.1 (d, 4H, J=8 Hz, 2 =C—CH_2); 4.3 (s, 2H, 2 OH); 4.5 (m, 1H, O—CH); 4.8–5.1 (m, 4H, 2 =CH_2); 5.4–5.9 (m, 2H, 2 =CH); 7.0–7.5 (m, 5H_{arom})	19.3, 38.7, 39.4, 43.5, 73.7, 117.7, 125.8, 126.8, 127.9, 133.9, 145.0
13	3350[e]	0.85 (t, 6H, J=6 Hz, 2 CH_3); 1.2–1.55 (m, 10H, 2 H_3C—CH_2 + O—C—CH_2—CH_2—CH_2); 2.2 (d, 4H, J=8 Hz, 2 =C—CH_2); 2.75 (br. s, 2H, 2 OH); 4.85–5.2 (m, 4H, 2 =CH_2); 5.5–6.1 (m, 2H, 2 CH)	7.8, 16.6, 30.7, 38.6, 39.6, 43.7, 73.3, 74.1, 117.6, 134.3
14	3410[e]	1.2–1.75 (m with s at 1.45, 5H, O—C—C—CH_2 + CH_3); 1.95–2.5 (m with s at 2.25, 10H, 4 O—C—CH_2 + 2 OH); 4.8–5.25 (m, 4H, 2 =CH_2); 5.45–6.05 (m, 2H, 2 CH); 6.95–7.55 (m, 5H_{arom})	15.4, 29.9, 35.4, 38.6, 43.6, 73.1, 74.0, 117.6, 125.8, 127.0, 127.8, 133.8, 147.9
15	3400[e]	1.1–1.55 (m, 16H, 5 $CH_{2\,ring}$ + O—C—CH_2—CH_2—CH_2); 2.1 (d, 4H, J=8 Hz, 2 =C—CH_2); 2.3 (br. s, 2H, 2 OH); 4.8–5.1 (m, 4H, 2 =CH_2); 5.5–6.05 (m, 2H, 2 CH)	16.3, 22.1, 25.8, 37.4, 39.6, 42.7, 43.7, 71.0, 73.4, 117.8, 134.0
16	3410	1.4 (m, 4H, O—C—CH_2—CH_2); 1.95 (s, 3H, CH_3); 2.1 (d, 4H, J=8 Hz, 2 =C—CH_2); 2.35 (s, 1H, OH); 2.4 (t, 2H, J=6 Hz, S—CH_2); 4.85–5.15 (m, 4H, 2 =CH_2); 5.5–6.05 (m, 2H, 2 CH)	15.1, 22.8, 34.6, 38.1, 43.7, 73.1, 117.7, 134.0
17	3380	1.0–1.5 (m, 6H, O—C—CH_2—CH_2—CH_2); 1.7–2.1 (m with d at 1.95, 6H, J=8 Hz, 3 =C—CH_2); 2.45 (s, 1H, OH); 4.55–4.95 (m, 4H, 2 =CH_2); 5.25–5.9 (m, 2H, 2 CH)	22.6, 29.3, 33.6, 38.9, 43.7, 73.4, 114.2, 117.5, 134.1, 138.4
18	3400	0.05 (s, 9H, 3CH_3); 0.5 (m, 2H, Si—CH_2); 1.35–1.6 (m, 4H, O—C—CH_2—CH_2); 1.9 (br. s, 1H, OH); 2.2 (d, 4H, J=8 Hz, 2 =C—CH_2); 4.9–5.25 (m, 4H, 2 =CH_2); 5.55–6.15 (m, 2H, 2 CH)	−6.6, 12.3, 12.4, 38.3, 38.8, 68.4, 112.5, 129.2
19	3410[e,f]	1.25–1.95 (m, 6H, 3 CH_2); 2.2 (d, 4H, J=8 Hz, 2 =C—CH_2); 2.75–4.0 (broad signal, 2H, NH + OH); 4.35 (t, 1H, J=6 Hz, N—CH); 4.9–5.4 (m, 4H, 2 =CH_2); 5.55–6.1 (m, 2H, 2 =CH); 6.4–7.55 (m, 10H_{arom})[g]	19.9, 38.7, 39.2, 43.7, 57.9, 72.9, 113.2, 117.1, 118.1, 126.1, 126.6, 128.2, 128.8, 133.7, 144.0, 147.1
20	—[h]	1.25–1.9 (m, 6H, $CH_{2\,ring}$); 2.1–2.45 (m, 4H, 2 =C—CH_2); 4.45 (m, 1H, O—CH); 4.85–5.2 (m, 4H, 2 =CH_2); 5.45–6.25 (m, 2H, 2 =CH); 6.95–7.55 (m, 5H_{arom})	19.6, 31.4, 33.6, 36.1, 45.1, 71.7, 75.1, 117.2, 125.6, 126.6, 127.8, 133.8, 134.2, 143.8

[a] Recorded with a Pye Unicam SP-1025 I.R. spectrometer.
[b] Recorded with a Varian FT-80 spectrometer using a D_2O capillary.
[c] Referred to the solvent CCl_4 (or $CDCl_3$).
[d] $\nu_{C=O}$ = 1735 cm^{-1}.
[e] In Nujol.
[f] This band includes the ν_{NH} absorption.
[g] In $CDCl_3$.
[h] ν_{C-O} = 1025 cm^{-1}.

The intermediates **5b** and **6b** are prepared in the same manner as **4b**. Sodium and potassium are used as plates prepared by dissolving the metal in liquid ammonia at −50 °C and then evaporating the ammonia under reduced pressure (0.1 torr)[5].

Compounds 8, 11–19 by Reaction of Intermediate 4b with Electrophiles; General Procedure:
A suspension containing intermediate **4b** is prepared as above and filtered through a G-3 funnel. To the stirred filtrate, the electrophile *El* (ratio **4b**/*El* = 1/1) is added and the mixture is hydrolyzed and worked up as described for **7b**.

4-Hydroxy-4-(3-hydroxypropyl)-1,6-heptadiene (9):
A stream of precooled (−30 °C) oxygen is bubbled through a filtered solution of intermediate **4b** (prepared as above) at −20 °C for 2 h. Hydrolysis and work-up is performed as described for **7b**.

2,2-Diallyl-6-oxotetrahydropyran (10, 5-Allyl-7-octen-5-olide):
A filtered, precooled (−40 °C) solution of intermediate **4b** (prepared as above) is added with stirring to excess solid carbon dioxide[7]. Stirring is continued for 4 h at −40° to −10 °C temperature and the mixture then hydrolyzed and worked up as described for **7b**.

2,2-Diallyl-6-phenyltetrahydropyran (20):
A mixture of 5-allyl-1,5-dihydroxy-1-phenyl-7-octene (**12**; 3.9 g, 15 mmol) and 85% phosphoric acid (1.0 ml, 15 mmol) is stirred for 1 h at 125 °C (bath temperature). The mixture is then extracted with ether (3 × 15 ml). The organic extract is washed with water (15 ml) and dried with sodium sulfate. The solvent is removed at reduced pressure (15 torr) and the residue distilled in vacuo to give pure **12**; yield: 2.8 g (77%); b.p. 75–80 °C/0.001 torr.

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