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Lithiation of 2-(chloroaryl)-2-methyl-1,3-dioxolanes and application in synthesis of new *ortho*-functionalized acetophenone derivatives

Gyula Lukács, Márta Porcs-Makkay and Gyula Simig*

Chemical Research Division, EGIS Pharmaceuticals Ltd, PO Box 100, H-1475 Budapest, Hungary

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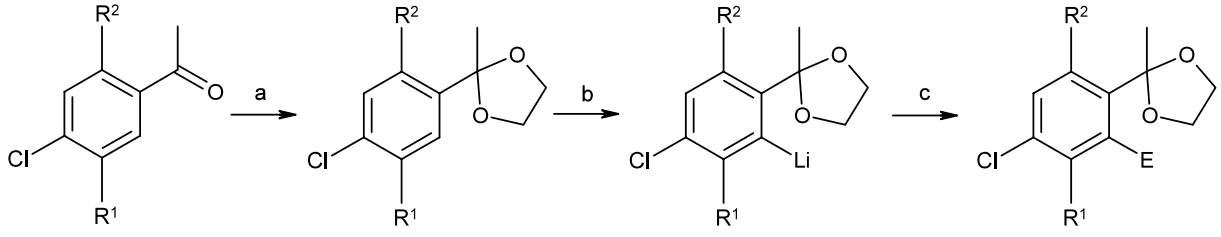
Abstract—2-(4-Chlorophenyl)-2-methyl-1,3-dioxolane **2a** was lithiated *ortho* to the ketal group by treatment with butyllithium in THF at 0°C. Related 2-aryl-2-methyl-1,3-dioxolanes possessing a chlorine substituent at the *meta* position of the aryl group **2b**,**c** were lithiated with butyllithium in THF at −78°C at the position between the two directing groups. The lithio species thus generated were treated with various electrophiles to give *ortho*-functionalized acetophenone derivatives.

Cyclization of *ortho* disubstituted benzene derivatives is an important strategy for the synthesis of benzanellated heterocyclic compounds. A widely used route of forming *ortho* disubstituted ring closure precursors involves a sequence of *ortho* lithiation assisted by one of the functional groups and then addition of an electrophile to generate the required second functionality.[1–4] As a part of our work in medicinal chemistry we became interested in an approach to chloro substituted heterocycles that would rely on *ortho*-functionalized acetophenone precursors (exemplified by the corresponding ethylene ketals **4**, Scheme 1).

Ethylene ketals **2** were prepared starting from known acetophenones **1**[5,6] by conventional methods.[7] For yields, bp's and ^{1}H NMR data of ketals **2** see Table 1. The *ortho* directing ability of aromatic acetals and ketals in lithiation reactions has been demonstrated.[8–13] Since chlorine is also known to promote *ortho* lithiation,[14–21] the result of lithiation of *para* disubstituted



1,2,3	R1	R2
a	H	H
b	Cl	H
c	Cl	CH_3

Scheme 1. *Reaction conditions*: (a) Ethylene glycol, PTSA/toluene; (b) butyllithium/THF; (c) electrophilic reagent.

Keywords: *ortho* lithiation; *ortho* directing group; butyllithium; 1,3-dioxolane derivatives; aryllithium derivatives.
* Corresponding author. Tel.: +36-1-2655543; fax: +36-1-2655613; e-mail: chemistry.rd@egis.hu

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Table 1.

	R^1	R^2	E	Yield (%)	bp or mp (°C)	Molecular formula	^{1}H NMR ($CDCl_3$)
2a	H	H	–	91	bp: 72–74 (0.3 mmHg)[a,b]	$C_{10}H_{11}ClO_2$ (198.65)	7.42 (2H, d, J=8.4 Hz), 7.28 (2H, d, J=8.4 Hz), 4.09–3.92 (2H, m), 3.81–3.65 (2H, m), 1.62 (3H, s).
2b	Cl	H	–	91	bp: 112–114 (0.4 mmHg)[b]	$C_{10}H_{10}Cl_2O_2$ (233.09)	7.59 (1H, d, J=1.8 Hz), 7.41 (1H, d, J=8.4 Hz), 7.32 (1H, dd, J=8.4 Hz, J=1.8 Hz), 4.08–4.01 (2H, m), 3.80–3.73 (2H, m), 1.63 (3H, s).
2c	Cl	CH_3	–	86	bp: 124–126 (0.5 mmHg)[b]	$C_{11}H_{12}Cl_2O_2$ (247.12)	7.62 (1H, s), 7.22 (1H, s), 4.07–4.00 (2H, m), 3.76–3.69 (2H, m), 2.43 (3H, s), 1.64 (3H, s).
4a	H	H	CH_3	95	bp: 78–80 (0.2 mmHg)[b]	$C_{11}H_{13}ClO_2$ (212.67)	7.47 (1H, d, J=8.1 Hz), 7.12–7.07 (2H, m), 4.04–3.97 (2H, m), 3.72–3.66 (2H, m), 2.46 (3H, s), 1.64 (3H, s).
4b	H	H	COOH	91	mp: 129–130 (ethyl acetate/hexane 1:1)[c]	$C_{11}H_{11}ClO_4$ (242.66)	8.90 (1H, bs), 7.55 (1H, d, J=8.4 Hz), 7.54 (1H, d, J=2.5 Hz), 7.42 (1H, dd, J=8.4 Hz, J=2.5 Hz), 4.10–4.03 (2H, m), 3.75–3.68 (2H, m), 1.84 (3H, s).
4c	H	H	SO_2Cl	67	mp: 117–118 (2-propanol)[c]	$C_{10}H_{10}Cl_2O_4S$ (297.16)	8.24 (1H, d, J=2.2 Hz), 7.86 (1H, d, J=8.4 Hz), 7.66 (1H, dd, J=8.4 Hz, J=2.2 Hz), 4.16–4.09 (2H, m), 3.82–3.75 (2H, m), 1.88 (3H, s).
4d	Cl	H	CH_3	69	bp: 108–110 (0.2 mmHg)[b]	$C_{11}H_{12}Cl_2O_2$ (247.12)	7.45 (1H, d, J=8.5 Hz), 7.26 (1H, d, J=8.5 Hz), 4.05–4.01 (2H, m), 3.74–3.71 (2H, m), 2.58 (3H, s), 1.67 (3H, s).
4e	Cl	H	COOH	91	mp: 153–154 (ethyl acetate/hexane 1:1)[c]	$C_{11}H_{10}Cl_2O_4$ (277.10)	8.70 (1H, bs), 7.51 (1H, d, J=8.4 Hz), 7.43 (1H, d, J=8.4 Hz), 4.09–4.02 (2H, m), 3.80–3.73 (2H, m), 1.74 (3H, s).
4f	Cl	H	SO_2Cl	87	mp: 99–100 (ethanol)[c]	$C_{10}H_9Cl_3O_4S$ (331.61)	7.80 (1H, d, J=8.4 Hz), 7.73 (1H, d, J=8.4 Hz), 4.10–4.03 (2H, m), 3.65–3.57 (2H, m), 1.99 (3H, s).
4g	Cl	CH_3	CH_3	71	bp: 136–138 (0.3 mmHg)[b]	$C_{12}H_{14}Cl_2O_2$ (261.14)	7.09 (1H, s), 3.99–3.92 (2H, m), 3.58–3.52 (2H, m), 2.57 (3H, s), 2.43 (3H, s), 1.72 (3H, s).
4h	Cl	CH_3	COOH	72	mp: 171–172 (ethyl acetate/hexane 1:1)[c]	$C_{12}H_{12}Cl_2O_4$ (291.13)	9.30 (1H, bs), 7.33 (1H, s), 4.03–3.98 (2H, m), 3.79–3.75 (2H, m), 2.49 (3H, s), 1.77 (3H, s).
4i	Cl	CH_3	SO_2Cl	65	mp: 97–98 (2-propanol)[c]	$C_{11}H_{11}Cl_3O_4S$ (345.64)	7.52 (1H, s), 4.10–4.00 (1H, bs), 4.00–3.90 (1H, bs), 3.80–3.60 (1H, bs), 3.40–3.20 (1H, bs), 2.56 (3H, s), 2.07 (3H, s).

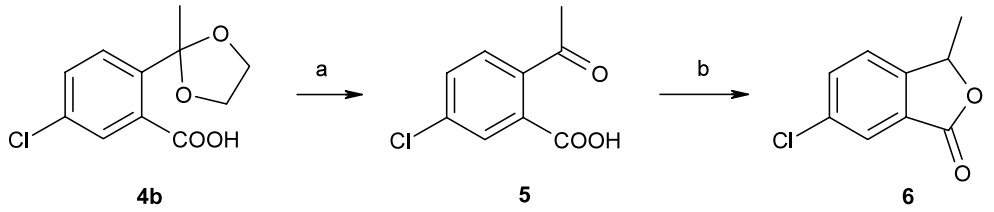
[a] Lit.:[30] mp 34°C; lit.:[31] described **2a** as an oil.
[b] Compounds **2a**–**c**, **4a**, **4d** and **4g** are colourless oils.
[c] Compounds **4b**, **4c**, **4e**, **4f**, **4h** and **4i** are colourless crystals.

compound **2a** will depend on the relative directing abilities of the two substituents which are generally considered as poor *ortho* directing metallation groups. In the case of ketal **2b** lithiation at the common *ortho* site is expected as a result of the cooperative effects of the 1,3-interrelated chlorine and 2-methyl-1,3-dioxolane-2-yl groups. *Ortho* and lateral metallation may occur in the lithiation reaction of toluene derivative **2c**.

Previous reports described that lithiations *ortho* to both chlorine and 1,3-dioxolane groups were accompanied with important side reactions. Benzynes are generated from *ortho*-lithiochlorobenzenes when the temperature of the reaction mixture exceeds about –60°C.[14,22,23] Ketal ring cleavage of 2-aryl-1,3-dioxolanes in lithiation reactions has also been described.[10,24] In order to avoid side reactions, the reaction conditions of metallations involving these directing groups have to be strictly controlled.

Lithiation of *para* disubstituted derivative **2a** with 1.6 equiv. of butyllithium in THF at 0°C followed by quenching the aryllithium **3a** with methyl iodide and carbon dioxide gave products **4a** and **4b**, respectively, in good yields. Lithiation conducted at 0°C is expected to occur at the position *ortho* to the ketal substituent since *ortho*-lithiochlorobenzenes are not stable at this temperature. Nevertheless, the structure of **4b** was proved by its transformation to phthalide **6**[25,26] via derivative **5**[27,28] (Scheme 2). Sulfonyl chloride **4c** was obtained by trapping aryllithium **3a** with sulfur dioxide and treating the isolated lithium arylsulfinate with sulfuryl chloride.[29]

Lithiation of compounds **2b** and **2c** with 1.6 equiv of butyllithium in THF at –78°C and subsequent reaction with various electrophiles afforded products demonstrating lithiation at the common site of the *ortho* directing groups (**3b**,**c**). Trapping with methyl iodide



Scheme 2. *Reaction conditions*: (a) Aq. HCl (10%); (b) 1. $NaBH_4$, MeOH, 2. aq. HCl (10%).

and carbon dioxide gave the expected products **4d**,**g** and **4e**,**h**, respectively. Sulfonyl chlorides **4f** and **4i** were obtained by the sequence described above for **4c**. For yields, mp's (bp's) and ^1H NMR data of compounds **4** see Table 1.

Experimental procedures

Lithiation of 2-(chloroaryl)-2-methyl-1,3-dioxolanes 2

To a solution of **2** (0.10 mol) in THF (100 mL) under argon was added butyllithium (100 mL of a 1.6 M solution in hexane, 0.16 mol) at 0°C (**2a**) or at −78°C (**2b**,**c**) and the mixture was stirred at 0°C (**2a**) or at −78°C (**2b**,**c**) for 2 h. The resulting suspension of **3** was treated with the appropriate electrophile to give compounds **4**.

Methylation of lithio derivatives 3

To a suspension of the lithio derivatives **3a**–**c** prepared as described above was added a solution of iodomethane (25.0 mL, 56.8 g, 0.40 mol) in THF (25 mL) at 0°C (**3a**) or at −78°C (**3b**,**c**) and the mixture was stirred at ambient temperature for 1 h. Water (100 mL) and diethyl ether (50 mL) were added and the layers were separated. The aqueous layer was extracted with diethyl ether (2×50 mL). The combined extracts were washed with water (50 mL), dried ($MgSO_4$) and evaporated. The oily residue was distilled to give **4a**, **4d** and **4g** as colourless oils.

Carboxylation of lithio derivatives 3

A suspension of the lithio derivative **3** prepared as described above was poured onto a large excess of dry ice (200 g). After 1 h, water (100 mL) was added, the layers were separated. The aqueous layer was extracted with diethyl ether (50 mL). To the aqueous layer was added an aqueous solution of hydrochloric acid (10%, 100 mL) and the mixture was extracted with diethyl ether (3×50 mL). The ethereal solution was dried ($MgSO_4$), evaporated and the residue was triturated with hexane to give **4b**, **4e**, and **4h** as colourless crystals.

Chlorosulfonation of lithio derivatives 3

At 0°C (**3a**) or at −78°C (**3b**,**c**), to a stirred solution of sulfur dioxide (30 g, 0.47 mol) in THF (1000 mL) was added a suspension of the lithio derivative **3** prepared as described above. The mixture was stirred at ambient temperature for 12 h and the solid product (lithium sulfinate) was filtered. To the suspension of the solid in hexane (1000 mL) was added sulfuryl chloride (24.3 mL, 4.5 g, 0.3 mol) in hexane (50 mL) at 0°C. After stirring for 30 min at 0°C, the solvent was evaporated, water (200 mL) was added to the residue and the mixture was stirred for 30 min. The crystalline product was filtered to give **4c**, **4f**, and **4i** as colourless crystals.

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26. **6-Chloro-3-methylbenzo[*c*]furan-1(3*H*)-one (6)**: mp 44–46°C (ethyl acetate/hexane, 1:1) (lit.[25] mp 45°C). ^{1}H NMR ($CDCl_3$): δ 7.85 (1H, d, $J=1.8$ Hz), 7.65 (1H, dd, $J=8.4$ Hz, $J=1.8$ Hz), 7.39 (1H, d, $J=8.4$ Hz), 5.55 (1H, q, $J=6.6$ Hz), 1.64 (3H, d, $J=6.6$ Hz). IR (cm^{-1}): 1753. Anal. calcd for $C_9H_7ClO_2$ (182.60): C, 59.19, H, 3.86, Cl, 19.42. Found: C, 59.23, H, 3.93, Cl, 19.07.
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