Regioselective lithiations of 2-(3,5-dichlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane

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Dedicated to Professor Henk van der Plas on the occasion of his 80th birthday

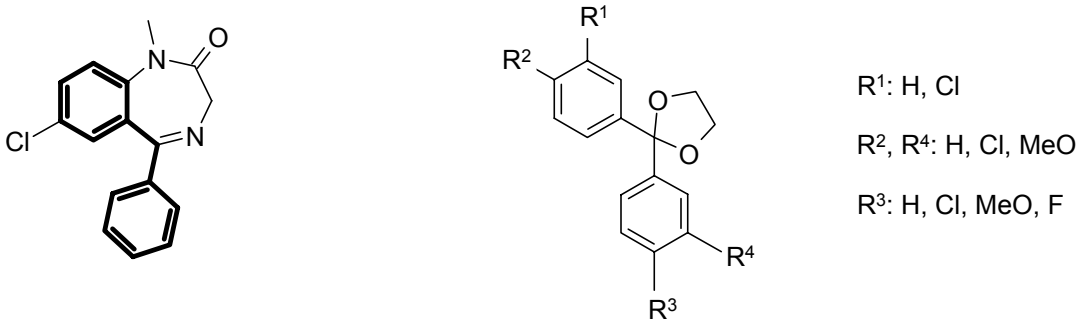
Abstract
2-(3,5-Dichlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane on treatment with butyllithium undergoes deprotonation at the 4-position flanked by the two chloro substituents. The corresponding 4-trimethylsilyl derivative was regioselectively lithiated with butyllithium at the 2-position of the dichlorophenyl ring. Deprotonation with butyllithium complexed with *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine occurred at the site adjacent to the fluorine of the fluorophenyl ring.

Keywords: Lithiation, regioselectivity, butyllithium, chlorotrimethylsilane, protecting groups, *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine

Introduction

Since the discovery of diazepam (**1**) (Figure 1) and the related anxiolytic 1,4-benzodiazepines,[1] substituted diphenylmethane fragments have been considered as important substructures in medicinal chemistry. The key intermediates in the synthesis of benz-anellated heterocycles exhibiting diphenylmethane moieties are the corresponding *ortho*-functionalized benzophenones.

We have previously reported[2] the synthesis of new *ortho*-functionalized benzophenone derivatives by lithiation[3-6] of 2-aryl-2-(chloroaryl)-1,3-dioxolanes (**2**) followed by treatment with various electrophiles. In addition to the synthetic utility of the new compounds prepared by this sequence, the benzophenone ketals **2** proved to be interesting substrates for the study of intramolecular competition of variously substituted phenyl rings in lithiation reactions.[7]



1, diazepam **2**

Figure 1

As a part of our continuing efforts to synthesize new *ortho*- functionalized benzophenone derivatives we report on the lithiation reactions of 2-(3,5-dichlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane (**4**, Figure 3) under various conditions. The results obtained in lithiations of the related 2-(3-chlorophenyl)-, 2-(4-chlorophenyl)-, and 2-(3,4-dichlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolanes are shown in Figure 2. The regioselectivities observed have been explained by the long-range (*meta*) electron-withdrawing (acidifying) effect [8] of the chloro substituent, in addition to the *ortho*-directing aptitude of the chloro and ketal groups.[2,7] In spite of this experience, the prediction of the outcome of lithiation reactions of ketal **4** is uncertain.

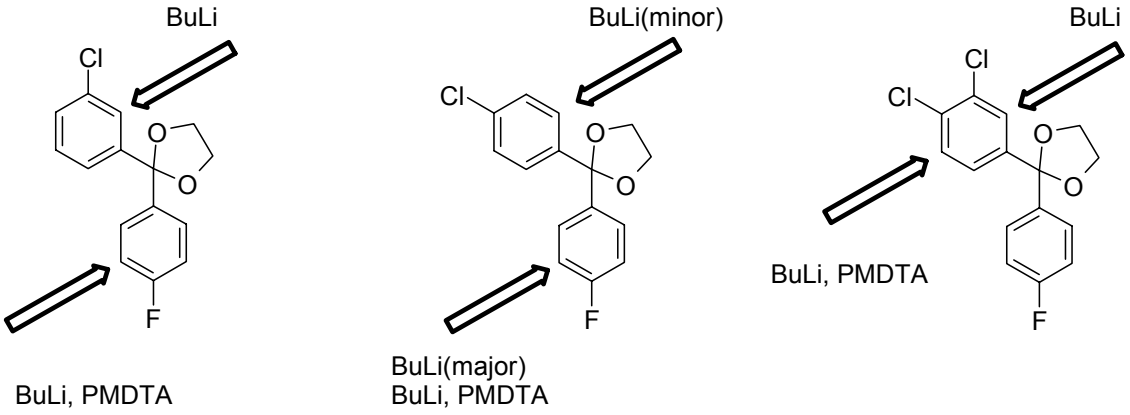
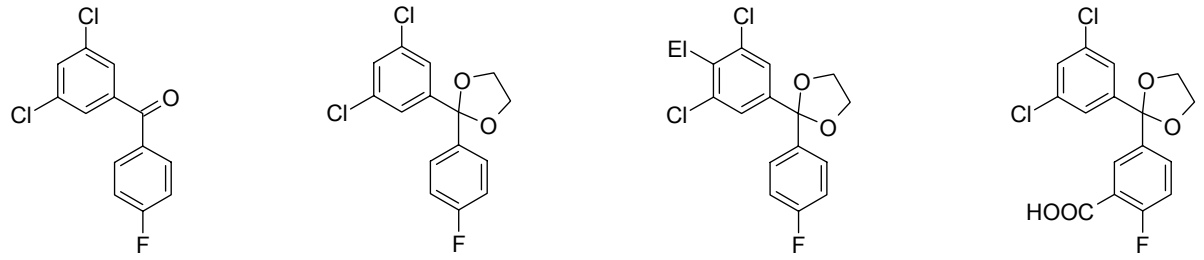


Figure 2

Results and Discussion

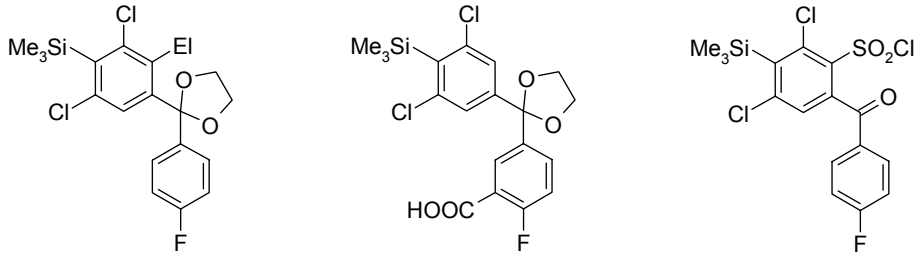
Compound **4** was synthesized by Friedel-Crafts reaction of 3,5-dichlorobenzoyl chloride with fluorobenzene, followed by ketalization of the benzophenone **3** with ethylene glycol under microwave heating[9] (Figure 3).

Lithiation of compound **4** with butyllithium at –78 °C in THF occurred regioselectively at the common *ortho*- site of the two chlorine atoms, as indicated by the formation of the carboxylic acid **5** as the single product after treatment with carbon dioxide. This result shows that - under these conditions – the *p*-fluorophenyl ring cannot compete with the 3,5-dichlorophenyl ring for the lithium, and that the combined *ortho*-directing aptitude of the two chloro groups is more powerful than that of the chloro and the 1,3-dioxolan-2-yl substituents.



3 **4** **5** (El=COOH) **6**

7 (El=$SiMe_3$)



8 (El=COOH) **10** **11**

9 (El=SO_2Cl)

Figure 3

Lithiation of the ketal **4** with butyllithium complexed with *N*,*N*,*N'*,*N''*,*N''*-pentamethyl-diethylenetriamine (PMDTA),[10,11] followed by carboxylation, gave a mixture of carboxylic acids **5** and **6** in a molar ratio of 1:1, as determined by ^{1}H-NMR analysis of the product mixture. This result suggested that a regioselectivity suitable for our purpose, *i.e.,* lithiation *ortho* to the 1,3-dioxolan-2-yl group, could be achieved only if the common *ortho* position to the two chloro

substituents is blocked, *e.g.*, by introducing the easily removable trimethylsilyl group.[12,13] Thus, the lithio derivative obtained by reaction of **4** with butyllithium at –78 °C in THF was treated with chloro(trimethyl)silane, affording compound **7** in high yield.

As expected from our earlier studies (Figure 2), lithiation of the silylated derivative **7** with butyllithium in THF at –78 ° occurred exclusively in the chloro-substituted ring, as demonstrated by the formation of derivatives **8** and **9**, respectively, after reaction with the corresponding electrophiles. According to our expectations,[7,14,15,16] lithiation of the ketal **7** with butyllithium complexed with PMDTA, and subsequent carboxylation, resulted in product **10,** demonstrating that lithiation took place at the site adjacent to fluorine.

The compounds synthesized are useful intermediates for the synthesis of heterocyclic derivatives. The trimethylsilyl [13,17] and ethylene ketal [2,18,19] protecting groups can be removed at a convenient stage of the subsequent synthetic route under conventional conditions. Just as examples, compound **6** was prepared by desilylation of the derivative **10**, and the ketal **9** was hydrolyzed to the benzophenone **11**.

Conclusions

Regioselective functionalizations of 2-(3,5-dichlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane (**4**) have been carried out *via* lithiation reactions under various conditions, as demonstrated by the formation of the substituted benzoic acids **5**, **8** and **10**.

Experimental Section

General Procedures. Melting points are uncorrected. Infrared spectra were recorded as KBr pellets. ^{1}H NMR spectra were recorded at 200 MHz. All unspecified reagents were from commercial sources. Yields are not optimized.

(3,5-Dichlorophenyl)-(4-fluorophenyl)methanone (3). 3,5-Dichlorobenzoic acid (12.5 g, 65 mmol) was heated at reflux with thionyl chloride for 4 h. After removal of the thionyl chloride, fluorobenzene (5.6 mL, 5.76 g, 60 mmol) and anhydrous aluminum chloride (8.53 g, 64 mmol) were added to the oily residue and the reaction mixture was stirred at 140 °C for 3 h. After cooling to 70 °C, it was poured under vigorous stirring onto ice-water (500 g). The crude product was filtered off, washed with water, and recrystallized from ethanol to give compound **3** (11.9 g, 73.6 %) as colorless crystals. Mp. 65-67 °C (ethanol); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.85 (2H, dd, J = 8.8 Hz, $^4J_{HF}$ = 5.5 Hz); 7.61 (2H, d, J = 1.8 Hz); 7.58 (1H, d, J = 1.8 Hz); 7.20 (2H, t, J = 8.8 Hz). IR (KBr): 1663, 1598 cm^{-1}. Anal. Calcd for $C_{13}H_7Cl_2FO$ (269.10): C, 58.02; H, 2.62; Cl, 26.35. Found: C, 57.80; H, 2.60; Cl, 26.07 %.

2-(3,5-Dichlorophenyl)-2-(4-fluorophenyl)-1,3-dioxolane (4).[9] A solution of (3,5-dichlorophenyl)-(4-fluorophenyl)methanone (**3**, 11.90 g, 44 mmol), ethylene glycol (13.64 g, 12.3 mL, 220 mmol) and *p*-toluenesulfonic acid (0.25 g) in toluene (59 mL) was heated at reflux (boiling temperature**,** 118–120°C) in a Dean-Stark apparatus in a microwave reactor under irradiation with a constant 650W energy for 6 h. The reaction mixture was washed with aqueous $NaHCO_3$ solution (5 %, 50 mL) and water, dried**,** and evaporated. The residue was triturated with hexane and filtered to give compound **4** (12.95 g, 94 %) as colorless crystals. Mp. 75-77 °C (ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.45 (2H, dd, J = 8.8 Hz, $^4J_{HF}$ = 5.5 Hz); 7.39 (2H, d, J = 1.8 Hz); 7.28 (1H, d, J = 1.8 Hz); 7.02 (2H, t, J = 8.8 Hz); 4.05 (4H, s). Anal. Calcd for $C_{15}H_{11}Cl_2FO_2$ (313.16)**:** C**,** 57.53**;** H**,** 3.54**;** Cl**,** 22.64**.** Found**:** C**,** 57.19**;** H**,** 3.61**;** Cl, 22.37%.

2,6-Dichloro-4-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]benzoic acid (5). Butyllithium (5 mL of a 2.5 M solution in hexane, 12.5 mmol) was added to a solution of **4** (2.96 g, 9.5 mmol) in THF (20 mL), under argon at –78 °C and the mixture was stirred for 2 h. The resulting suspension was poured onto a large excess of solid CO_2. After 2 h, water (50 mL) and diethyl ether (30 mL) was added, the layers were separated, the aqueous layer was acidified with 10 % aqueous hydrochloric acid. The solid precipitate was filtered off, and recrystallized from ethyl acetate/ hexane to give compound **5** (2.57 g; 76 %) as colorless crystals. Mp. 157-159 °C (ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 8.23 (1H, bs); 7.50 (2H, s); 7.45 (2H, dd, J = 8.8 Hz, $^4J_{HF}$ = 5.1 Hz); 7.05 (2H, t, J = 8.8 Hz); 4.13-4.08 (2H, m); 4.08-4.02 (2H, m). IR (KBr): 2900, 1717, 1602 cm^{-1}. Anal. Calcd for $C_{16}H_{11}Cl_2FO_4$ (357.17): C, 53.81; H, 3.10; Cl, 19.85. Found: C, 53.68; H, 3.09; Cl; 19.56%.

5-[2-(3,5-Dichlorophenyl)-1,3-dioxolan-2-yl]-2-fluorobenzoic acid (6).[17] To a solution of compound **10** (1.0 g, 2.3 mmol) in THF (5 mL) was added tetrabutylammonium fluoride trihydrate (0.73 g, 2.3 mmol)and the mixture was heated at reflux for 10 min. After cooling to RT, an aqueous solution of citric acid (10 %, 10 mL), and ethyl acetate (10 mL) were added. The layers were separated, the organic layer dried with $MgSO_4$, the solvent removed, and the solid residue crystallized from a mixture of ethyl acetate and hexane to give compound **6** (0.49 g, 60 %) as colorless crystals. Mp. 143-145 °C (ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 8.17 (1H, dd, $^4J_{HF}$ = 7.0 Hz, J = 2.6 Hz); 7.66 (1H, ddd, J = 8.8 Hz, $^4J_{HF}$ = 7.0 Hz, J = 2.6 Hz.); 7.39 (2H, d, J = 1.8 Hz); 7.30 (1H, t, J = 1.8 Hz); 7.15 (1H, t, J = 8.8 Hz); 4.08 (4H, s). IR (KBr): 3085, 2897, 1696, 1616 cm^{-1}. Anal. Calcd for $C_{16}H_{11}Cl_2FO_4$ (357.17): C, 53.81; H, 3.10; Cl, 19.85. Found: C 54.05; H, 3.23; Cl, 20.09%.

{2,6-Dichloro-4-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]phenyl}(trimethyl)silane (7). Butyl lithium (16 mL of a 2.5 *M* solution in hexane, 40 mmol) was added to a solution of **4** (7.83 g, 25 mmol) in THF (50 mL) under argon at –78 °C, and the mixture was stirred for 30 min. Chloro(trimethyl)silane (5.43 g, 6.2 mL; 50 mmol) was added at –78 °C and stirred at RT until a solution formed. Water (50 mL) was added, the layers were separated, and the aqueous layer extracted with ethyl acetate (50 mL). The combined organic layer was dried, and evaporated to give **7** (9.00 g, 93.4 %) as a yellow oil. ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.44 (2H, dd, J =

8.8 Hz, $^4J_{HF}$ = 5.1 Hz); 7.36 (2H, s); 7.02 (2H, t, *J* = 8.8 Hz); 4.05 (4H, s); 0.48 (9H, s). IR (KBr): 2957, 2895, 1606, 1591, 1532, 1508 cm^{-1}. Anal. Calcd for $C_{18}H_{19}Cl_2FO_2Si$ (385.34): C, 56.11; H, 4.97; Cl, 18.40. Found: C, 56.20; H, 5.01; Cl, 18.16 %.

2,4-Dichloro-6-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]-3-(trimethylsilyl)benzoic acid (8). Butyllithium (5 mL of a 2.5 *M* solution in hexane, 12.5 mmol) was added to a solution of **7** (2.96 g, 9.5 mmol) in THF (20 mL) under argon at –78 °C and the mixture was stirred for 30 min. The resulting suspension was poured onto a large excess of solid CO_2. After 2 h, water (50 mL) and diethyl ether (50 mL) were added, the layers were separated, and the aqueous layer acidified with 10 % aq. hydrochloric acid. The solid precipitate was filtered off and crystallized from a mixture of ethyl acetate and hexane to give compound **8** (2.53 g; 62 %) as colorless crystals. Mp. 178-180 °C (ethyl acetate-hexane). ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.52 (2H, dd, *J* = 8.8 Hz, $^4J_{HF}$ = 5.1 Hz); 7.37 (1H, s); 7.01 (2H, t, *J* = 8.8 Hz); 4.15-4.07 (2H, m); 4.07-3.99 (2H, m); 0.51 (9H, s). IR (KBr): 2986, 2959, 2900, 1714 cm^{-1}. Anal. Calcd for $C_{19}H_{19}Cl_2FO_4Si$ (429.35): C, 53.15; H, 4.46; Cl, 16.51. Found: C, 53.36; H, 4.48; Cl, 16.14 %.

2,4-Dichloro-6-[2-(4-fluorophenyl)-1,3-dioxolan-2-yl]-3-(trimethylsilyl)benzenesulfonyl chloride (9). Butyllithium (30 mL of a 2.5 M solution in hexane, 75 mmol) was added to a solution of **7** (21.3 g, 55 mmol) in THF (140 mL) under argon at –78 °C and the mixture was stirred for 30 min. The resulting suspension was added to a solution of sulfur dioxide (25.6 g, 0.40 mol) in THF (50 mL) at –78 °C. After stirring at ambient temperature for 12 h, the solvent was evaporated. The solid residue was suspended in hexane (350 mL) and a solution of sulfuryl chloride (11.5 g, 7.0 mL; 85 mmol) in hexane (90 mL) was added dropwise at 0 °C. After stirring at 0 °C for 10 min, the solvent was evaporated. The residue was crystallized from diethyl ether to give compound **9** (10.0 g, 37.5 %) as yellow crystals. Mp. 180-182 °C (ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 8.00 (1H, s); 7.33 (2H, ddd, *J* = 8.8 Hz, $^4J_{HF}$ = 7.0 Hz, *J* = 2.1 Hz); 7.02 (2H, t *J* = 8.8 Hz); 4.31-4.22 (2H, m); 3.93-3.84 (2H, m); 0.60 (9H, s). IR (KBr): 3443, 2958, 2893, 1683, 1600 cm^{-1}. Anal. Calcd for $C_{18}H_{18}Cl_3FO_4SSi$ (483.86): C, 44.68; H, 3.75; Cl, 21.98; S, 6.62. Found: C, 44.41; H, 3.72; Cl, 21.66; S, 6.55.

5-{2-[3,5-Dichloro-4-(trimethylsilyl)phenyl]-1,3-dioxolan-2-yl}-2-fluorobenzoic acid (10). *N*,*N*,*N'*,*N''*,*N''*-pentamethyldiethylenetriamine (PMDTA, 1.03 g, 1.25 mL, 6 mmol) was added under argon at –78 °C to butyllithium (2.4 mL of a 2.5 *M* solution in hexane, 6 mmol) followed by addition of a solution of ketal **7** (1.52 g, 4 mmol) in THF (10 mL). The reaction mixture was stirred at –78 °C for an additional 30 min. The resulting suspension was poured onto a large excess of solid CO_2. After 3 h, water (20 mL) was added and it was extracted with diethyl ether (30 mL). The aqueous layer was acidified with aqueous (10 %) hydrochloric acid. The solid precipitate was filtered off, and crystallized from a mixture of ethyl acetate and hexane to give **10** (1.34 g, 78 %) as colorless crystals. Mp. 146-148 °C (ethyl acetate-hexane); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 9.78 (1H, bs); 8.20 (1H, dd, $^4J_{HF}$ = 7.0 Hz, *J* = 2.2 Hz); 7.67 (1H, ddd, *J* = 8.4 Hz, $^4J_{HF}$ = 7.0 Hz, *J* = 2.2 Hz); 7.36 (2H, s); 7.15 (2H, t, *J* = 8.8 Hz); 4.07 (4H, s); 0.48 (9H, s). IR (KBr): 2959, 2899, 1702, 1616 cm^{-1}. Anal. Calcd for $C_{19}H_{19}Cl_2FO_4Si$ (429.35): C, 53.15; H, 4.46; Cl, 16.51. Found: C, 53.48; H, 4.53; Cl, 16.51.

2,4-Dichloro-6-[(4-fluorophenyl)carbonyl]-3-(trimethylsilyl)benzenesulfonyl chloride (11).[19] To a suspension of Kieselgel (10 g) in chloroform (145 mL), concentrated sulfuric acid (5.75 mL) was added, and stirred at RT for 10 min. After the addition of **9** (14.28 g, 34 mmol) the suspension was stirred for 8 h at RT. After filtration, the filtrate was washed with aqueous sodium hydrogen carbonate solution (5 %, 100 mL) and water (100 mL), dried, and evaporated. The residue was crystallized from ethanol to give compound **11** (11.0 g, 88 %) as colorless crystals. Mp. 130-131 °C (ethanol); ^{1}H NMR ($CDCl_3$, 200 MHz, 25 °C): δ 7.81 (2H, dd, J = 8.4 Hz, $^4J_{HF}$ = 5.3 Hz); 7.26 (1H, s); 7.17 (2H, t, J = 8.8 Hz); 0.61 (9H, s). IR (KBr): ν = 3065, 2958, 1672, 1598 cm^{-1}. Anal. Calcd for $C_{16}H_{14}Cl_3FO_3SSi$ (439.80): C, 43.70; H, 3.21; Cl, 24.18; S, 7.29. Found: C, 43.31; H, 3.30; Cl, 24.44; S, 7.35.

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