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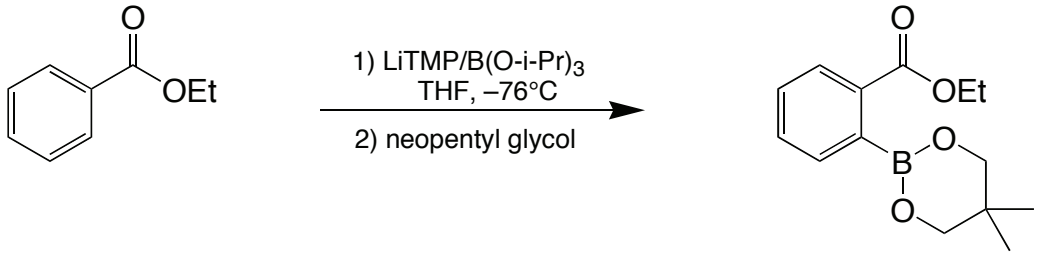
September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.081.0134
Organic Syntheses, Vol. 81, p. 134-139 (2005); Coll. Vol. 11, p. 1015-1019 (2009).

SYNTHESIS OF ORTHO SUBSTITUTED ARYLBORONIC ESTERS BY IN SITU TRAPPING OF UNSTABLE LITHIO INTERMEDIATES: 2-(5,5-DIMETHYL-1,3,2-DIOXABORINAN-2-YL)BENZOIC ACID ETHYL ESTER

[Benzoic acid, 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-, ethyl ester]



Submitted by Jesper Langgaard Kristensen, Morten Lysén, Per Vedsø and Mikael Begtrup.[1]
Checked by Günter Seidel and Alois Fürstner.

1. Procedure

2-(5,5-Dimethyl-1,2,3-dioxaborinan-2-yl)benzoic acid ethyl ester. An oven-dried, three-necked, 2-L, round-bottomed flask fitted with a thermometer, mechanical stirrer, and a 500-mL pressure-equalizing addition funnel (with volume graduation) capped with a rubber septum and nitrogen inlet is charged with 2,2,6,6-tetramethylpiperidine (51.2 g, 367 mmol) (Note 1) and 400 mL of anhydrous tetrahydrofuran (Note 2). The mixture is cooled to –30 °C (internal temperature) in a dry ice-acetone bath and 243 mL of *n*-butyllithium solution (1.49M in hexanes, 362 mmol) (Note 3) is cannulated directly into the addition funnel from a 1-L sure-seal flask. The *n*-butyllithium solution is added dropwise to the stirred reaction mixture over 30 min while the temperature is maintained between –30 and –35 °C resulting in an orange-yellow solution. The addition funnel is washed with two 10-mL portions of tetrahydrofuran and the reaction mixture is stirred an additional 10 min at –30 °C before being cooled to –76 °C (Note 4). Triisopropyl borate (112 mL, 483 mmol) (Note 5) is cannulated into the addition funnel directly from a sure-seal flask and then added dropwise (Note 6) to the creamy yellow suspension over 20 min while the internal

temperature is maintained below –73 °C. Ethyl benzoate (35.7 g, 238 mmol) (Note 7) is added via syringe to the addition funnel and added dropwise to the reaction mixture over 10 min, causing a slight reddening of the suspension. The addition funnel is washed with two 10-mL portions of tetrahydrofuran, and the reaction mixture is stirred for 3.5 h at –73 °C. The resulting deep red suspension is taken out of the cooling bath, and after approximately 20 min the internal temperature rises to –30 °C. Glacial acetic acid (20.7 mL, 362 mmol) is then added dropwise over 5 min via the addition funnel, causing the internal temperature to rise to –10 °C while the color of the reaction mixture changes from red to yellow. The addition funnel is removed, neopentyl glycol (37.1 g, 356 mmol) (Note 8) is added in one portion, and stirring is continued for 2 h. The mixture is decanted from a white precipitate into a 3-L separatory funnel, and 1 L of dichloromethane is added to the separatory funnel (Note 9). The resulting solution is washed with three 300-mL portions of a 1:1 mixture of saturated aqueous NH_4Cl and water, two 300-mL portions of saturated $NaHCO_3$ solution, and two 300-mL portions of water, dried over 100 g of Na_2SO_4, filtered into a 1-L round-bottomed flask, and concentrated by rotary evaporation at 40 °C. When no more solvent can be distilled, a large teflon-coated magnetic stirbar is added to the flask, and the oily residue is stirred overnight at room temperature under reduced pressure (0.3 mm) to give 58.12 g (95%) of 2-(5,5-dimethyl-[1,3,2]dioxaborinan-2-yl)benzoic acid ethyl ester as a golden-brown oil which is pure enough for most purposes (Note 10). Analytically pure material is obtained as a colorless oil by distillation under high vacuum to give 50.3 g (82%), bp 105-110 °C ($1x10^{-5}$ Torr) (Notes 11, 12).

2. Notes

1. 2,2,6,6-Tetramethylpiperidine (99+%) was purchased from Aldrich Chemical Company, Inc. and used as received.

2. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under a nitrogen atmosphere.

3. Butyllithium (1.6M solution in hexanes) was purchased from Aldrich Chemical Company, Inc. Three sequential titrations using *N*-pivaloyltoluidine (see: Suffert, J. *J. Org. Chem*. **1989**, *54*, 509) gave titers of

1.47M, 1.48M, and 1.51M, and on that basis the titer was assumed to be 1.49M.

4. At approximately –60 °C the mixture becomes cloudy.

5. Triisopropyl borate (98+%) was purchased from Aldrich Chemical Company, Inc. and used as received.

6. Care should be taken that the triisopropyl borate drops directly into the solution and does not run down the side of the flask, as this will cause the triisopropyl borate to precipitate from the reaction mixture.

7. Ethyl benzoate (99+%) was purchased from Aldrich Chemical Company, Inc. and used as received.

8. Neopentyl glycol (2,2-dimethyl-1,3-propanldiol) (99%) was purchased from Aldrich Chemical Company, Inc. and used as received.

9. Ca. 200 mL of the dichloromethane is used to rinse the 2-L flask before being added to the separatory funnel.

10. GC-MS analysis showed the crude material to be 95% pure. The title compound is the only detectable species in the NMR-spectrum. The submitters obtained 61.8 g (99%)of the product which was 99.5% pure by GC-MS analysis.

11. High vacuum is necessary for the success of the distillation. Attempted distillation at 0.3 mm results in decomposition of the material at a bath temperature of approximately 150 °C.

12. The product exhibits the following properties: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.11 (s, 6H), 1.39 (t, 3H, J = 7.1 Hz), 3.79 (s, 4H), 4.38 (q, 2H, J = 7.1 Hz), 7.42-7.35 (m, 1H), 7.52-7.48 (m, 2H), 7.93 (td, 1H, J = 7.8, 0.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 14.3, 21.9, 31.6, 61.6, 72.4, 128.3, 128.6, 131.2, 131.9, 133.1, 168.6; ^{11}B NMR (96 MHz, $CDCl_3$) δ 28.1 ppm. Anal. Calcd for $C_{14}H_{19}BO_4$: C 64.15, H 7.31. Found: C 64.02, H 7.46.

2. Waste Disposal Information

All toxic materials were disposed of in accordance with ”Prudent Practices in the Laboratory”; National Academy Press; Washington, DC, 1995.

3. Discussion

The procedure described herein is an improved version of our previously reported synthesis,[2] circumventing the need for an intermediate aqueous work-up, thereby providing the title compound in a one-pot procedure.

The transition metal catalyzed cross coupling of an organohalide with a boronic acid derivative, the Suzuki-Miyaura coupling, has become one of the most popular ways of preparing biaryls.[3] The reaction is very robust and can easily be scaled to provide multigrams of material.[4]

Arylboronic acids have traditionally been prepared via the addition of an organomagnesium or organolithium intermediate to a trialkyl borate. Subsequent acidic hydrolysis produces the free arylboronic acid. This limits the type of arylboronic acids one can access via this method, as many functional groups are not compatible with the conditions necessary to generate the required organometallic species, or these species may not be stable intermediates.

Complete characterization of arylboronic acids is often difficult because they are readily transformed into stable cyclic anhydrides called boroxines[5] and other polymeric species. Arylboronic acids are also known to be hygroscopic. Thus, arylboronic acids are often prepared and used directly as a mixture of different entities. Commercial arylboronic acids will very often contain varying amount of anhydrides.

The procedure described herein illustrates two important points:

(1) The in situ trapping of unstable lithio-intermediates as a way of circumventing the above mentioned limitations, and

(2) The direct isolation of the well defined and stable neopentyl glycol arylboronic esters, without the need for an intermediate aqueous work-up.

As first described by Krizan and Martin,[6] the in situ trapping protocol, i.e., having the base and electrophile present in solution simultaneously, makes it possible to lithiate substrates that are not applicable in classical *ortho*-lithiation reactions.[7] Later, Caron and Hawkins utilized the compatibility of lithium diisopropylamide and triisopropyl borate to synthesize arylboronic acid derivatives of bulky, electron deficient neopentyl benzoic acid esters.[8] As this preparation illustrates, the use of lithium tetramethylpiperidide instead of lithium diisopropylamide broadens the

scope of the reaction, and makes it possible to functionalize a simple alkyl benzoate.[2]

The conversion of arylboronic acids to the corresponding neopentyl glycol arylboronic esters has several advantages: The esters are readily soluble in organic solvents, shelf stable, non-hygroscopic and easily characterized as a single entity.[9] Furthermore, boronic esters can be utilized in many of the transformations where arylboronic acids usually are employed, making them an attractive alternative from a practical point of view.

The described procedure can also be applied for *ortho*-borylation of chloro, fluoro and cyanonaphthalenes[10] or pyridines.[11]

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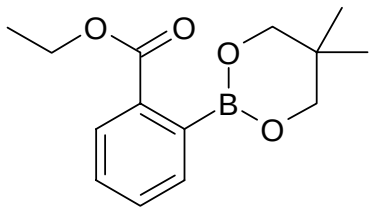
Appendix
Chemical Abstract Nomenclature (Registry Number)

2,2,6,6-Tetramethylpiperidine; Piperidine, 2,2,6,6-tetramethyl-; (768-66-1)
n-Butyllithium: Lithium, butyl-; (109-72-8)
Triisopropyl borate: Boric acid (H_3BO_3), tris(1-methylethyl) ester; (5419-55-6)
Ethyl benzoate: Benzoic acid ethyl ester; (93-89-0)
Neopentyl glycol: 1,3-Propanediol, 2,2-dimethyl-; (126-30-7)
2-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)benzoic acid ethyl ester: Benzoic acid, 2-(5,5)- dimethyl-1,3,2-dioxaborinan-2-yl)-, ethyl ester; (346656-34-6)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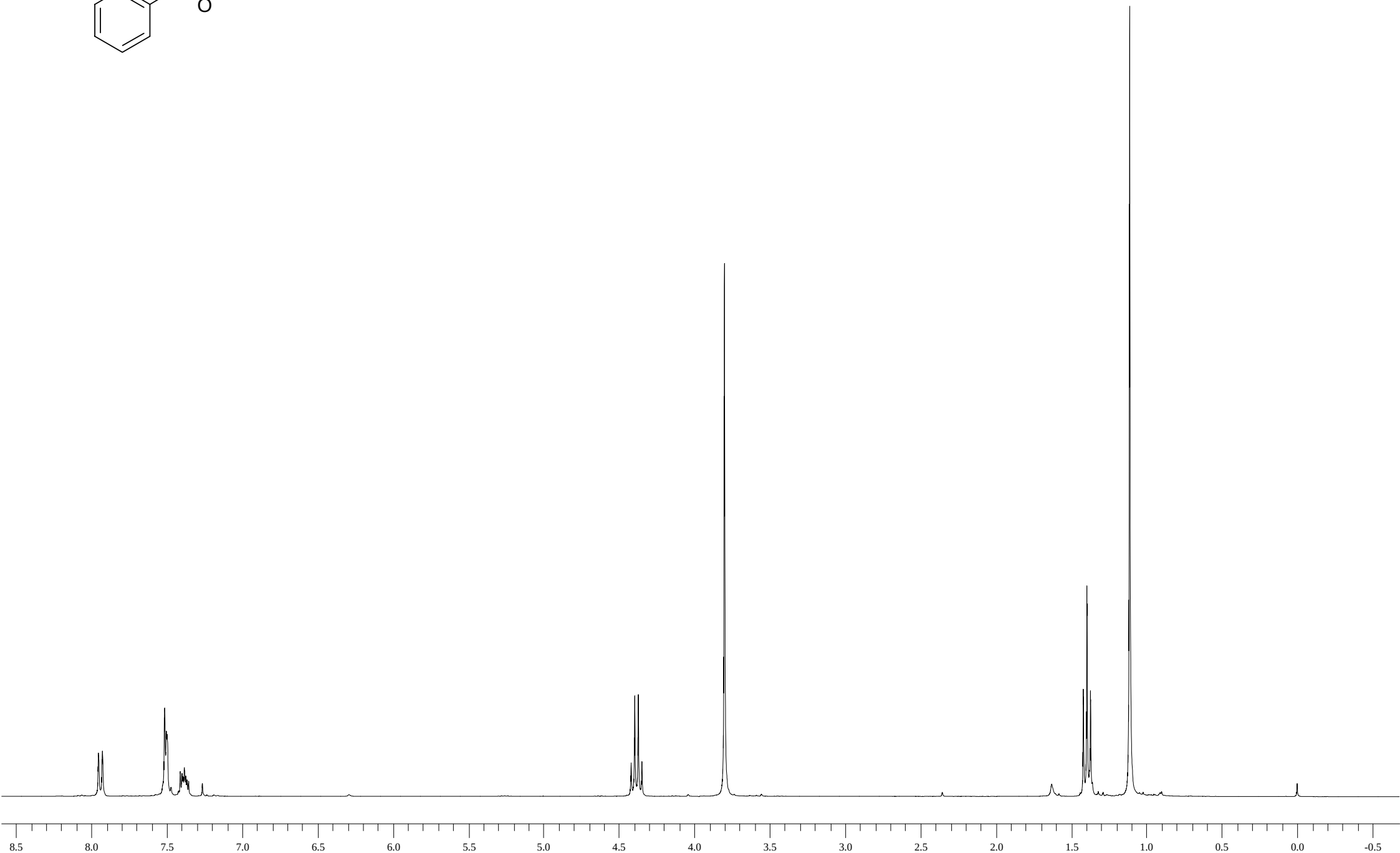
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