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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.

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MAGNESIATION OF WEAKLY ACTIVATED ARENES USING tmp₂Mg·2LiCl: SYNTHESIS OF *TERT*-BUTYL ETHYL PHTHALATE



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1. Procedure

A. Preparation of tmpMgCl·LiCl. A dried and nitrogen-flushed 1-L Schlenk flask (Note 1), equipped with a magnetic stirring bar and rubber septum, is charged with *i*PrMgCl·LiCl (792 mL, 1.2 M in THF,³ 950 mmol) (Note 2) then 2,2,6,6-tetramethylpiperidine (141.3 g, 1.00 mol) (Note 3) is added dropwise within 5 min via syringe. The mixture is stirred until gas evolution ceases (24–48 h) (Note 4). Titration prior to use shows a concentration of 0.95 M (Notes 4 and 5).^{4,5}

B. Preparation of $tmp_2Mg \cdot 2LiCl$ and synthesis of tert-butyl ethyl phthalate. A flame-dried and nitrogen-flushed 500-mL Schlenk flask (Note 1), equipped with a magnetic stirring bar and rubber septum, is charged with 100 mL of dry THF (Note 7) cooled in a -40 °C cooling bath (Note 8) and stirred for 15 min at this temperature. Then *n*-BuLi (45.5 mL, 2.22 M in hexanes, 100 mmol, 1.1 equiv) (Note 9) is added at once via syringe. After stirring for 15 min at -40 °C, 2,2,6,6-tetramethylpiperidine (14.1 g, 100 mmol, 1.1 equiv) (Note 3) is added at once via syringe. The resulting mixture is stirred at -40 °C for 5 min and the flask is then transferred to an ice bath (0 °C) and is stirred for 30 min. Then, tmpMgCl·LiCl (105 mL, 0.95 M in THF, 100 mmol, 1.1 equiv.) is added dropwise via syringe in one portion (addition time < 1 min.). The mixture is stirred in a 0 °C bath for 30 minutes and at 25 °C for another 60 minutes. The rubber septum is removed and the flask is stoppered with a glass stopper. The solvents are removed *in*

vacuo using a rotary vane vacuum pump and liquid nitrogen cooled cooling trap (25 °C at 1.5 mmHg). The stopper is replaced by a septum and the resulting pale brown solid is redissolved in 112 mL of dry THF (Note 11) and stirred for 10 minutes at 25 °C. Ethyl benzoate (13.5 g, 90.0 mmol, 1.0 equiv) (Note 12) is added at once via syringe (addition time < 1 min.). The greenish brown solution immediately turns deep red. The reaction mixture is stirred at 25 °C for 30 minutes (Note 13). The red solution is cooled in a -40 °C cooling bath. After stirring for 10 min, Boc₂O (28.0 g, 130 mmol, 1.44 equiv) (Note 14) is added in one portion via syringe (addition time < 1 min.). After the addition, the reaction mixture is stirred at 25 °C until a slightly exothermic reaction starts. Then, the flask is put into a water bath (~20 °C) to moderate the exotherm. The reaction is stirred for a further 30 min (Note 15).

At this time, 300 mL of a saturated aqueous NH₄Cl solution is added. Large amounts of a precipitate are formed, which are removed by suction filtration (Note 16). The precipitate is washed with approx. 800 mL of diethyl ether until it is colorless. The resulting mixture is brought into a 2-L separatory funnel, rinsing with 50 mL of diethyl ether. The phases are separated and the organic layer is extracted with a saturated aqueous NH₄Cl solution (3 x 300 mL). The combined aqueous layers are extracted with ethyl acetate (400 mL). The combined organic layers are washed with 300 mL of brine and dried by stirring for 15 min over 110 g of anhydrous MgSO₄ (Note 17). After filtration, the solvents are removed under reduced pressure using a rotary evaporator and vacuum (40 °C, 720 to 50 mmHg). The resulting red oil is loaded on 25.5 g of silica gel, dried for 2 h under high vacuum (Note 18), and purified by column chromatography (Note 19). The solvents are evaporated under reduced pressure using a rotary evaporator and vacuum (40 °C, 720 to 50 mmHg) and dried for 4 h at 25 °C using a rotary vane pump yielding 15.1 g of *tert*-butyl ethyl phthalate (60.3 mmol, 67 %) as a red oil. (Notes 20 and 21)

2. Notes

1. The glassware was oven-dried overnight and evacuated using high vacuum (1 mmHg) and backfilled with nitrogen (this procedure was repeated three times). All syringes, cannulas and needles were purged with nitrogen prior to use.

2. *i*-PrMgCl·LiCl was purchased from Aldrich and the solution was titrated using iodine (1 mmol) in 2 mL of dry THF.³ The submitters purchased *i*-PrMgCl·LiCl from Chemetall GmbH (Frankfurt, Germany).

3. 2,2,6,6-Tetramethylpiperidine was purchased from TCI America and the material was distilled before use (120 °C, 75 mmHg). The submitters purchased 2,2,6,6-tetramethylpiperidine from Evonik Industries AG (Essen, Germany).

The amounts of all liquids used in the synthesis were determined by weighing them in a syringe, since this method is more accurate than the determination of the volumes by the scales of the syringes used.

4. Titration of the base was performed in a dried 10-mL Schlenk tube (Note 1). The base was titrated against benzoic acid (1 mmol) using (4-phenylazo)diphenylamine (3 mg, Aldrich) as indicator in 1 mL dry THF. Color change from orange to dark violet indicated the end of the titration (consumption 1.05 mL). The submitters purchased (4-phenylazo)diphenylamine from Acros.

5. The checkers used the base of known concentration in subsequent reactions. The submitters also checked complete formation of the base by quenching an aliquot with benzaldehyde. Absence of 2-methyl-1-phenylpropan-1-ol (detected by GC/MS; $M^+=150$) indicates full consumption of the Grignard reagent. The submitters performed GC/MS-analysis using an HP 6890 Series GC system equipped with an Agilent 5973 Network Mass Selective Detector. Column HP-5MS (J&W Scientific) (15 m x 0.25 mm x 0.25 µm). Oven program for GC/MS-Analysis: Starting temperature 70 °C for 0.5 min; heating to 250 °C at a rate of 50 °C/min; 5 min at 250 °C; heating to 300 °C at a rate of 50 °C/min, 3 min 300 °C. Aliquots of the base were quenched with benzaldehyde (approx. 0.2 mL) then diethyl ether was added (1 mL). The mixture was extracted with a saturated aqueous NH₄Cl solution.

6. It is not mandatory to prepare the tmpMgCl·LiCl on this large scale. It is possible to prepare the base in just the amount needed for this reaction. The description of the preparation refers to a synthesized batch in the submitter's group's usual scale. The submitter has reported that it can be stored at room temperature under nitrogen for more than 6 months without losing efficiency.⁵

7. The checkers purchased all solvents from Fischer and THF (99%) was distilled and then constantly refluxed from sodium/benzophenone. The other solvents were used by the checkers without further purification. The

submitters purchased THF (95 %) from BASF (Ludwigshafen, Germany), distilled and then constantly refluxed from sodium/benzophenone, all other solvents were purchased from Biesterfeld AG (Hamburg, Germany) and distilled before use.

8. The checkers performed constant cooling using a NESLAB CC-100 cooling device and a stirred ethanol bath. The submitters used a ThermoHaake EK90 cooling device and a stirred ethanol bath.

9. *n*-BuLi was purchased from Aldrich and titrated using menthol (1 mmol) in 1 mL of dry THF and (4-phenylazo)diphenylamine (3 mg) (Aldrich) as indicator.⁴ The submitters purchased *n*-BuLi from Chemtall GmbH (Frankfurt, Germany), and (4-phenylazo)diphenylamine and used the same titration method.

10. Vacuum was 1 mmHg. During the evaporation process the flask is stored in a water bath ($\sim 20^{\circ}$ C) to maintain the temperature and ensure steady evaporation.

11. The actual quantity of dry THF needed may vary up to 10%.

12. Ethyl benzoate (99%) was purchased from Aldrich and used without further purification The submitters purchased ethyl benzoate (99%) from Merck.

13. The checkers continued with the subsequent addition after the reaction had stirred for 30 minutes. The submitters confirmed full consumption of the starting material by GC analysis of iodolyzed reaction aliquots. The submitters performed GC analysis using an Agilent Technologies 6850 Series equipped with an HP-5 column (J&W Scientific) (15m x 0.25mm x 0.25 μ m). Oven program for GC analysis: Starting temperature 70 °C for 0.5 min; heating to 250 °C at a rate of 50 °C/min; 5 min at 250 °C. Reaction aliquots were quenched with 0.2 mL of a 0.5 M I₂ solution in dry THF mixed with approx. 1 mL of a sat. aq. NH₄Cl and 1 mL of a sat. aq. Na₂S₂O₃ solution and extracted with diethyl ether (1 mL). The conversion was monitored by GC by controlling the production of ethyl 2-iodobenzoate (retention time 3.45 min) and the consumption of ethyl benzoate (retention time: 2.31 min).

14. Boc₂O (99%) was purchased from Aldrich and melted in a water bath (40 °C) to facilitate the weighing and adding processes. The submitters purchased Boc₂O (99%) from Merck.

15. The checkers quenched the reaction after 30 minutes. The submitters followed the progress of the reaction by quenching reaction aliquots with 1 mL of a saturated NH₄Cl solution and extracting with diethyl

ether. GC analysis after 30 minutes showed the complete absence of ethyl benzoate. The retention time of *tert*-butyl ethyl benzoate was 3.75 min.

16. A glass filter with P3 pore size and a volume of 500 mL were used. Filtration was carried out under reduced pressure (300 mmHg).

17. MgSO₄ was purchased from Fischer and used as received. The submitters purchased MgSO₄ from Grüssing (Filsum, Germany).

18. The checkers loaded the crude product onto 25.5 g of silica. It was added to the oil and dried in high vacuum for 2 h. The submitters loaded the crude product onto 25.5 g of Isolute (Biotage) and dried it in high vacuum for 1 h. Isolute is comparable to loading on silica, but it offers very sharp bands as it plays no part in the chromatographical process.

19. Column chromatography was carried out using a 10-cm diameter column packed with 787 g of silica gel (the checkers used Siliaflash 60, 0.040-0.060 mm; the submitters used Gelduran SI60 from Merck 0.040-0.063 mm) using *n*-pentane:diethyl ether 4:1 as eluent (R_f =0.62, TLC aluminium sheets, silica gel 60 F254, Merck). The product is visible under UV radiation as a bright blue fluorescent band. After 2.6 L of eluent, the band is ready to be collected. Collection is stopped when the fluorescence subsides; approx 1.5 L.

20. The product exhibits the following properties ¹H-NMR (400 MHz, CDCl₃) δ : 1.38 (t, *J* = 7.0 Hz, 3 H), 1.58 (s, 9 H), 4.37 (q, *J* = 7.2 Hz, 2 H), 7.48 (m, 2 H), 7.67 (m, 2 H); ¹³C-NMR (100 MHz, CDCl₃) δ : 13.9, 27.8, 61.3, 81.8, 128.4, 128.8, 130.45, 130.5, 132.3, 133.2, 166.3, 167.8; MS (70 ev, EI) *m/z*: 251 (29), 246 (21), 195 (100), 177 (23) [M⁺-CO₂Et], 150 (4), 149 (35); HRMS (ESI) calcd. for C₁₄H₁₉O₄ 251.1278 found: 251.1280; IR (Film) \tilde{v} (cm⁻¹): 2979 (w), 1715 (vs), 1599 (w), 1579 (w), 1477 (w), 1447 (w), 1392 (w), 1367 (vs), 1286 (s), 1255 (s), 1172 (S), 1123 (vs), 1072 (vs), 1038 (vs), 1017 (vs), 845 (vs), 784 (w), 737 (s), 705 (vs); CHN Analysis for C₁₄H₁₈O₄: calcd.: C, 67.18; H, 7.25; found: C, 67.46; H, 7.48.

21. A ³/₄-scale run afforded 12.1 g (71%) of analytically pure product.

Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

Directed lithiations are important reactions for the functionalization of aromatics and heterocycles.⁶ The high reactivity of the organolithium reagents leads to low functional group tolerance. In contrast, magnesium reagents offer also high reactivity in combination with high tolerance of functional groups such as ester, cyano and keto groups. We have shown that the use of magnesium bases like tmpMgCl·LiCl are suitable for the deprotonation of a wide range of aromatic and heteroaromatic substrates.⁵ However, some poorly activated substrates like ethyl benzoate do not undergo metallation at all or the metallation does not lead to satisfactory results. Eaton demonstrated that tmp₂Mg offers high reactivity and functional group tolerance.⁷ The limited solubility in common organic solvents, as well as the use in high excess (of the reagent and the electrophile) to achieve full conversion, precluded further use in organic synthesis.⁸ During the studies on Grignard reagents we realized that the addition of LiCl could enhance the reactivity and solubility dramatically.⁹ Therefore, the addition of two equivalents of LiCl leads to the highly soluble and reactive complex tmp₂Mg·2LiCl. This composition facilitates the metallation of moderately activated aromatic substrates such as ethyl benzoate, benzonitrile, ethyl naphthanoate or derivatives thereof. The metallation of heteroaromatic subtrates like ethyl nicotinate or diethyl pyridine-3,5-dicarboxylate proceeds without any problems.⁸ These organomagnesium reagents can now be used in any typical trapping process, for example Negishi cross coupling reactions,¹⁰ copper(I) mediated acylations¹¹ or iodo- or bromolysis (Table 1), leading to the expected products in good to excellent yields.⁸



Table 1 Products of type 4 obtained by the magnesiation of aromatics andheterocycles with tmp_2Mg ·2LiCl and reactions with electrophiles.^a

^aReactions performed on 1-2 mmol scale. ^bIsolated yield of analytically pure product. ^cTransmetalation with CuCN-2LiCl (0.2 mol%) was performed. ^dObtained by palladium-catalyzed cross-coupling after transmetalation with ZnCl₂ (1.2 to 1.3 equiv).

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Appendix Chemical Abstracts Nomenclature; (Registry Number)

*i*PrMgCl·LiCl: isopropylmagnesium chloride lithium chloride complex; (807329-97-1)

2,2,6,6-Tetramethylpiperidine; (768-66-1)

Ethyl benzoate: Benzoic acid, ethyl ester; (93-89-0)

Boc₂O: Dicarbonic acid, *C*,*C*'-bis(1,1-dimethylethyl) ester; (244424-99-5)

tert-Butyl ethyl phthalate: 1,2-Benzenedicarboxylic acid, 1,2-bis[2-[3,5-

bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl] ester; (259254-67-6)



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