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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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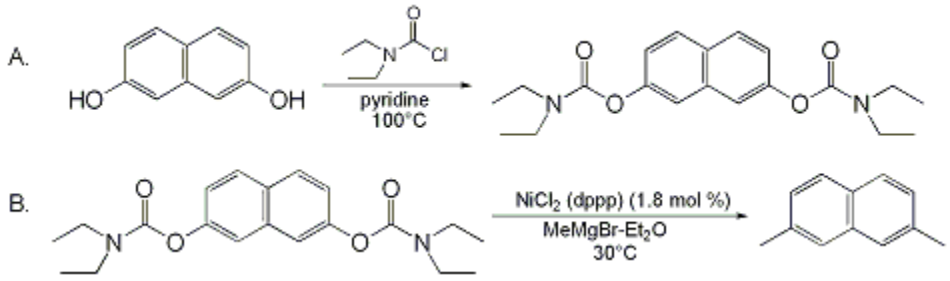
NICKEL-CATALYZED COUPLING OF ARYL O-CARBAMATES WITH GRIGNARD REAGENTS: 2,7-DIMETHYLNAPHTHALENE

[Naphthalene, 2,7-dimethyl-]



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Checked by Mitsuru Kitamura and Koichi Narasaka.

1. Procedure

A. 2,7-Bis(diethylcarbamoyloxy)naphthalene .[2] Into a dry, 1-L, three-necked, round-bottomed flask, equipped with a mechanical stirrer and a condenser, are added 2,7-dihydroxynaphthalene(49.7 g, 0.310 mol , Note 1) and pyridine (700 mL , Note 2) under nitrogen. A dry, 200-mL pressure-equalizing dropping funnel fitted with a rubber septum is installed and charged with N,N-diethylcarbamoyl chloride (120 mL, 0.900 mol ; Note 3). After the reaction flask is cooled in an ice bath for 30 min, N,N-diethylcarbamoyl chloride is added within 5 min to the vigorously stirred mixture. The ice bath is removed and the dark-brown solution is warmed to room temperature. The dropping funnel is removed under a stream of nitrogen and a thermometer is installed. The solution is heated to 100°C (±5°C) for 2 days. TLC indicates a complete reaction (SiO_2, 2,7-dihydroxynaphthalene, R_f = 0.46; acetone / hexane : 40/60). After the flask is cooled in an ice bath, hydrochloric acid (6 M, 250 mL) is poured into it over 10 min with vigorous stirring. A light-brown solid is formed. The brown mixture is poured into a 3-L Erlenmeyer flask and more hydrochloric acid (6 M, 350 mL) is added, followed by water (600 mL) in order to precipitate the compound further. The solid is filtered with a Büchner funnel and washed with water (500 mL). The crude product is dried under vacuum for several hours until a constant weight is obtained. The purity is found to be sufficient for the subsequent steps (111.0 g, 99% yield; mp 89.0-90.0°C, Note 4). However, a recrystallization is achieved by dissolving the crude compound in boiling 95% ethanol (300 mL), followed by the addition of water (200 mL). After the flask stands for 8 hr at room temperature, light-brown needles can be collected and washed with a solution of ethanol and water (50:50, 150 mL). The crystals are dried under vacuum to give pure 2,7-bis(N,N-diethylcarbamoyloxy)naphthalene (89.8 g, 0.250 mol, 81% yield; mp 89.6-90.5°C , Note 5). The filtrate is warmed, water (175 mL) is added, and the mixture is allowed to stand for 8 hr at room temperature to give additional crystals (14.0 g, 0.0391 mol, 13% yield; mp 89.0-90.0°C). The filtrate is cooled at 5°C to give a brown solid (5.7 g; mp 83.5-86.5°C), which is recrystallized from boiling hexanes (120 mL), to give needles of 2,7-bis(N,N-diethylcarbamoyloxy)naphthalene (3.22 g, 8.98 mmol; mp 88.0-89.5°C). The overall yield is 107 g, 0.299 mol, 97%.

B. 2,7-Dimethylnaphthalene . A 2-L, three-necked, round-bottomed flask is equipped with a mechanical stirrer, reflux condenser, nitrogen inlet adapter and a 300-mL pressure-equalizing dropping funnel fitted with a rubber septum. All the glassware is oven-dried before assembly. Under a flow of nitrogen, the flask is charged with crystalline 2,7-bis(N,N-diethylcarbamoyloxy)naphthalene (70.3 g; 0.196 mol) , the catalyst $NiCl_2(dppp)_2$ (1.90 g; 3.51 mmol, 1.8 mol % relative to 2,7-bis(N,N-diethylcarbamoyloxy)naphthalene, Note 6) and anhydrous diethyl ether (550 mL , Note 7). A red mixture is obtained. The dropping funnel is charged with an ethereal solution of methylmagnesium bromide (3 M in diethyl ether, 235 mL, 0.705 mol , Note 8), which is added dropwise over a period of 25 min. During the addition, the reaction mixture changes from red to pale brown and to green. The

mixture is stirred at 30°C for 13 hr in order to complete the reaction (Note 9). TLC is used to follow the reaction [SiO_2, 2,7-bis(diethylcarbamoyloxy)naphthalene, R_f = 0.10; 2,7-dimethylnaphthalene, R_f = 0.74, (hexane/ethyl acetate: 80/20)]. The resulting dark brown mixture is cooled in an ice bath and the dropping funnel is charged with aqueous hydrochloric acid (6 M, 300 mL), which is slowly added to the reaction mixture over 25 min in order to maintain a gentle reflux. The aqueous layer is separated and extracted further with diethyl ether (50 mL). The combined organic layers are washed with aqueous hydrochloric acid (6 M, 3 × 100 mL), distilled water (150 mL), brine (200 mL), and dried over anhydrous sodium sulfate (25 g). After filtration and evaporation of the solvent, the compound is dried under vacuum to a constant weight, to afford a beige solid (30.2 g). The crude product is recrystallized from boiling 95% ethanol (350 mL) to give colorless crystals of 2,7-dimethylnaphthalene (22.1 g). Concentration of the mother liquors and another recrystallization, provides an additional amount of product (5.3 g). 2,7-Dimethylnaphthalene (overall: 27.4 g, 0.175 mol, 89%, mp 95-96°C , lit.[7]: mp 95-96°C, (Note 10) is obtained as fluffy colorless leaflet crystals.

2. Notes

1. 2,7-Dihydroxynaphthalene (97%) was purchased from Aldrich Chemical Company, Inc., Acros Organics, or Tokyo Chemical Industry Co.
2. Laboratory grade pyridine was distilled from calcium hydride under nitrogen or used as received from Acros Organics (reagent grade, <0.1% water).
3. N,N-Diethylcarbamoyl chloride was used as received from Aldrich Chemical Company, Inc. (99%) or Tokyo Chemical Industry Co. (>95%). It was transferred to the dropping funnel via a syringe.
4. The purity was estimated from ^{1}H NMR (250 MHz, $CDCl_3$) and melting point.
5. The physical properties are as follows: R_f = 0.65 (SiO_2, acetone/hexane = 40/60); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.25 (broad s, 12 H), 3.45 (broad s, 8 H), 7.25 (dd, 2 H, J = 2.2, 8.7), 7.50 (d, 2 H, J = 2.2), 7.77 (d, 2 H, J = 8.9) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 13.9, 14.7, 42.6, 118.5, 121.6, 129.3, 135.0, 150.3, 154.7 ; IR (CCl_4) cm^{-1}: 1724, 1155 ; MS (EI) m/e 358 (M^{+}·, 26%).
6. $NiCl_2$(dppp): [1,3-Bis(diphenylphosphino)propane]dichloronickel(II) . **Important**: A loading of catalyst less than 1.8 mol % relative to the amount of 2,7-bis(N,N-diethylcarbamoyloxy)naphthalene gave erratic results. For example, 1.2-1.3 mol % sometimes gave an incomplete conversion, but additional catalyst (1.0 mol %) ensured completion of the reaction. This step was checked at least five times, each time with reproducible yields in the range of 86-89%. $NiCl_2$(dppp) was used as received from Acros Organics.
7. Diethyl ether was dried and purified by distillation under nitrogen from sodium and benzophenone, or was used as received from Kanto Chemical Co. (reagent grade, <0.005% water).
8. 3.0 M Methylmagnesium bromide solution in diethyl ether was purchased from Aldrich Chemical Company, Inc. and used without standardization. The Grignard reagent was transferred from the original bottle into the dropping funnel via a cannula under nitrogen.
9. In general, it was found that a dark brown color was indicative of a successful reaction. At 20°C, the reaction sometimes proceeds very slowly with poor reproducibility. The checkers recommended a temperature of = 30°C.
10. The physical properties are as follows: R_f = 0.74 (SiO_2, hexane/ethyl acetate = 80/20). ^{1}H NMR (250 MHz, $CDCl_3$) δ: 2.49 (s, 6 H), 7.22 (d, 2 H, J = 8.0), 7.50 (s, 2 H), 7.65 (d, 2 H, J = 8.0) ; ^{13}C NMR (62.9 MHz, $CDCl_3$) δ: 21.7, 126.3, 127.2, 127.4, 130.0, 134.0, 135.4 ; MS (EI) m/e 156 (M^{+}·, 100%).

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

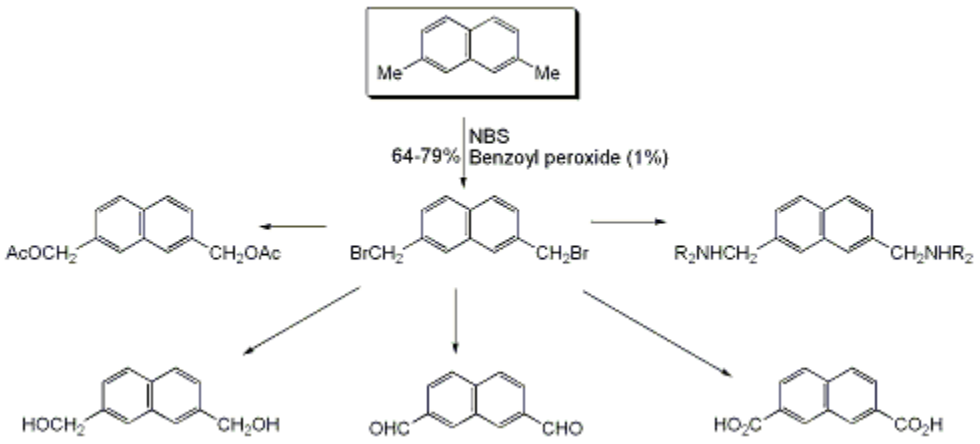
Nickel-catalyzed coupling of aryl O-carbamates and Grignard reagents is a promising methodology in synthetic organic chemistry. [3] Relatively cheap nickel catalysts are used in some efficient coupling procedures with a variety of easily made reagents such as vinyl, aryl and alkyl magnesium halides. The method avoids the classic use of expensive triflates in some palladium-catalyzed coupling procedures (for instance, the Stille coupling with costly and toxic organotins). Furthermore, palladium-catalyzed

alkyl couplings are sometimes problematic because of β-hydride eliminations.

An application of the nickel catalysis is shown here in the formation of 2,7-disubstituted derivatives of naphthalene, which are less common in the library of commercial fine chemicals. For these reasons, the submitters developed some synthetic routes to 2,7-bis(diethylcarbamoyloxy)naphthalene, 2,7-dimethylnaphthalene[4] and 2,7-bis(bromomethyl)naphthalene that will facilitate access to a large family of 2,7-disubstituted naphthalenes.[5] The low cost of N,N-diethylcarbamoyl chloride, relative to triflic anhydride (for making aryl triflates), allows the formation of O-carbamates, and assures the incorporation of a wide variety of substituents with some relatively cheap nickel(II) catalysis and Grignard reagents.[3] Scheme 1 indicates a few possible uses of 2,7-dimethylnaphthalene from its Wohl-Ziegler dibromination with N-bromosuccinimide (NBS).[6] Recently, some effective procedures were published for making 2,7-dimethylnaphthalene and 2,7-bis(bromomethyl)naphthalene.[7] The best synthetic route required five steps to 2,7-bis(bromomethyl)naphthalene in an overall yield of ≈34%, including the formation of a Grignard reagent, one separation of isomers and several unwanted by-products during two selective halogenation reactions. In addition, a major reactant was the relatively expensive 3,3-dimethoxy-2-butanone. The submitter's procedure is regiospecific at positions 2 and 7 on the naphthalene system and avoids separation of isomers. Furthermore, the dibromination of 2,7-dimethylnaphthalene could be accomplished by the Wohl-Ziegler reaction, which provided isolated yields equal to the photolytic procedure (64% in ref. 7), but no photolytic equipment was required. All the procedures described used simple purifications by recrystallization.

In spite of the poor availability of 2,7-bis(bromomethyl)naphthalene, it nevertheless has been used as an important convergent spacer and building block in supramolecular chemistry. For example, a bioinorganic model from a complexation with Cu(II), generated supramolecular cyclophanes by self-assembly, and encapsulated Lewis bases.[8] Helicoidal compounds, such as carbohelicenes, have recently been prepared from 2,7-bis(bromomethyl)naphthalene by Reetz[9] and Brunner.[7] Other syntheses are also known.[10] Because of the cost, the rather long synthetic sequences, and scarcity of these 2,7-disubstituted naphthalenes, the submitters believe that their procedures will encourage further uses of these synthons, either as supramolecular spacers with convergent functionalities or as important pharmaceutical intermediates. New receptors and helical structures could also be foreseen.

Scheme 1. A Few Synthetic Uses of 2,7-Dimethylnaphthalene and 2,7-Bis(bromomethyl) naphthalene



References and Notes

1. (a) MDS Pharma Services, 2350 Cohen St., St. Laurent, Montreal, Quebec, Canada H4R 2N6; (b) Université Libre de Bruxelles, CP 160/08, 50 Ave. F. D. Roosevelt, 1050 Brussels, Belgium; (c) Chemical Laboratory of Organic and Metallic Materials (CMOM), Faculty of Sciences, University of Nice-Sophia Antipolis, 28 Avenue Valrose, 06108 Nice Cedex 2, France.
2. Based in part from Kolber, I., Mémoire at Université Libre de Bruxelles, 1997.

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4. Expensive 2,7-dimethylnaphthalene is available in small amounts from Aldrich Chemical Company, Inc. ($144 per gram).
5. Similar synthetic strategies to 2,7-disubstituted naphthalenes, but with different substitutents and Pd-reactions, have already been described: (a) Katz, T. J.; Liu, L.; Willmore, N. D.; Fox, J. M.; Rheingold, A. L.; Shi, S.; Nuckolls, C.; Rickman, B. H. *J. Am. Chem. Soc.* **1997**, *119*, 10054-10063; (b) Takeuchi, M.; Tuihiji, T.; Nishimura, J. *J. Org. Chem.* **1993**, *58*, 7388-7392.
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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

2,7-Dimethylnaphthalene:
Naphthalene, 2,7-dimethyl- (8,9); (582-16-1)

2,7-Dihydroxynaphthalene:
2,7-Naphthalenediol (8,9); (582-17-2)

Diethylcarbamoyl chloride: CANCER SUSPECT AGENT:
Carbamic chloride, diethyl- (8,9); (88-10-8)

[1,3-Bis(diphenylphosphino)propane]dichloronickel(II) CANCER SUSPECT AGENT:
Nickel, dichloro[trimethylenebis[diphenylphosphine]]- (8);
Nickel, dichloro[1,3-propanediylbis[diphenylphosphine]-PP']- (9); (15629-92-2)

Methylmagnesium bromide:
Magnesium, bromomethyl- (8,9); (75-16-1)