



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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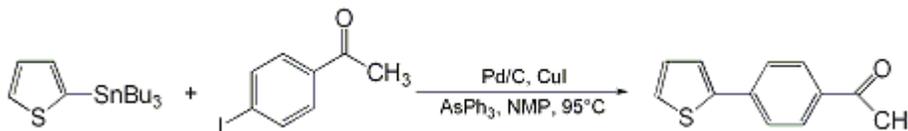
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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STILLE COUPLINGS CATALYZED BY PALLADIUM-ON-CARBON WITH CuI AS A COCATALYST: SYNTHESIS OF 2-(4'-ACETYLPHENYL)THIOPHENE ¹



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1. Procedure

A 200-mL, flame-dried Schlenk flask is purged with nitrogen and charged with 10.0 g (40.6 mmol) of 4-iodoacetophenone (Note 1), 770 mg (4.1 mmol) of copper(I) iodide (CuI) (Note 2), 2.5 g (8.1 mmol) of triphenylarsine (Note 3), and 150 mL of anhydrous 1-methyl-2-pyrrolidinone (Note 4). The dark solution is degassed for 15 min (nitrogen sparge) and then 14.1 mL (44.7 mmol) of 2-(tributylstannyl)thiophene (Note 5) is added. The reaction flask is immersed in a preheated oil bath at 95°C and 215 mg (0.2 mmol) of 10% palladium on activated carbon (Note 6) is added under a positive nitrogen pressure. The mixture is kept at 95°C for 24 hr (Note 7) and then allowed to cool to 25°C and diluted with 300 mL of ethyl acetate. The dark mixture is poured into 200 mL of an aqueous saturated sodium fluoride solution (Note 8) and stirred vigorously for 30 min. The green-yellow heterogeneous mixture is passed through a sand pad contained in a medium-frit filter, aided by a water aspirator (Note 9). The filtrate is partitioned in a separatory funnel and the aqueous layer is extracted with two 100-mL portions of ethyl acetate. The organic extracts are combined and stirred with 200 mL of fresh saturated aqueous sodium fluoride solution for 30 min. The mixture is then passed through a sand pad as described above. The pad is rinsed with 50 mL of ethyl acetate. The mixture is partitioned again and the aqueous layer is extracted with two 50-mL portions of ethyl acetate. The organic extracts are combined and washed with five 100-mL portions of water and finally with 100 mL of brine (Note 10). The dark yellow solution is dried over anhydrous magnesium sulfate (MgSO₄) (Note 11) and filtered. The used MgSO₄ is washed with 50 mL of ethyl acetate. The solvent is removed under reduced pressure to give a dark yellow solid that is dissolved in the minimum amount of dichloromethane and adsorbed onto 20 g of silica gel (Note 12). The solvent is thoroughly removed under reduced pressure and the resulting solid is charged into a medium-pressure liquid chromatography column (silica gel, 3 × 15 cm) (Note 13). The product (6.6 g, 80%) (Note 14) is purified as described by Baeckström et al.⁴ (Note 15).

2. Notes

1. 4-Iodoacetophenone was purchased from Aldrich Chemical Company, Inc., and used without purification.
2. Copper(I) iodide was purchased from Aldrich Chemical Company, Inc., and purified according to a literature procedure.⁵
3. *Caution: Triphenylarsine is highly toxic and must be handled with gloves in a well-ventilated hood.* It was purchased from Aldrich Chemical Company, Inc., and used as received.
4. Anhydrous 1-methyl-2-pyrrolidinone was purchased from Aldrich Chemical Company, Inc., and used without further drying. The water content was determined to be 117 ppm using a Coulomatrix K-F Titrimeter.
5. 2-(Tributylstannyl)thiophene was purchased from Aldrich Chemical Company, Inc., and is used without additional purification.
6. 10% Palladium on activated carbon was purchased from Alpha Division.
7. The reaction can be monitored by quenching small aliquots with water and extracting with a small amount of diethyl ether. The ethereal layer is spotted on an analytical silica gel TLC plate (0.25 mm thickness, from EM Separations Technology) (10% ethyl acetate in hexanes, using 254 nm UV light to

visualize the spots). The following are the R_f s of the components of the mixture: 2-(tributylstannyl)thiophene (0.86), triphenylarsine (0.62), 4-iodoacetophenone (0.48), and 2-(4'-acetylphenyl)thiophene, (0.38 fluorescent). Trace amounts of 4-butylbenzophenone (R_f 0.52) were observed at the end of the reaction.

8. *Caution: Sodium fluoride is highly toxic and should be handled with gloves in a well-ventilated hood.* It was purchased from Spectrum Chemical Mfg. Corp. and used without purification.

9. If crystallization underneath the frit occurs during the filtration process, the sand pad is washed with 20 mL of ethyl acetate. The sand pad was changed three times during the filtration of the whole mixture to avoid clogging.

10. The washings are necessary to remove all the 1-methyl-2-pyrrolidinone.

11. Anhydrous magnesium sulfate was obtained from EM Science.

12. Silica gel 60, particle size 0.040-0.063 mm (230-400 mesh) was obtained from EM Separation Technology.

13. The medium-pressure liquid chromatography system (MPLC) was purchased from Baeckström SEPARO AB.

14. The product (a golden flaky solid) exhibits the following properties: mp 118-119°C; IR (CH_2Cl_2) cm^{-1} : 1680, 1601, 1270; ^1H NMR (300 MHz, CDCl_3) δ : 2.6 (s, 3 H), 7.1 (m, 1 H), 7.3 (d, 1 H, $J = 5$), 7.4 (d, 1 H, $J = 3.8$), 7.7 (d, 2 H, $J = 8$), 8.0 (d, 2 H, $J = 9$); ^{13}C NMR (75.5 MHz, CDCl_3) δ : 26.5, 124.6, 125.6, 126.4, 128.3, 129.1, 135.7, 138.7, 142.9, 197.2. Anal. Calcd for $\text{C}_{12}\text{H}_{10}\text{OS}$: C, 71.30; H, 5.00; S, 15.90. Found: C, 71.14; H, 5.03; S, 15.77. (The material obtained by the checkers was a very pale yellow flaky solid.)

15. The purification was carried out using a hexanes/dichloromethane gradient (200 mL of each gradient solution). The gradient started with hexanes at a flow rate of 25 mL/min and the concentration of dichloromethane was increased each time by 10%. A total of fifty 30-mL fractions were collected. Under these conditions, most of the triphenylarsine used was recovered and recycled. (The checkers purified the material using conventional flash chromatography techniques. The crude product adsorbed on 20 g of flash silica gel was dry packed on a 6-cm \times 14-cm column of flash silica gel. Elution with 750 mL of hexanes followed by 500 mL each of a hexane/dichloromethane gradient starting with 10% dichloromethane (CH_2Cl_2)/hexanes and finishing with 100% CH_2Cl_2 . A total of fifty 100-mL fractions were collected. The separation was monitored by analytical TLC as described in (Note 7).)

Waste Disposal Information

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

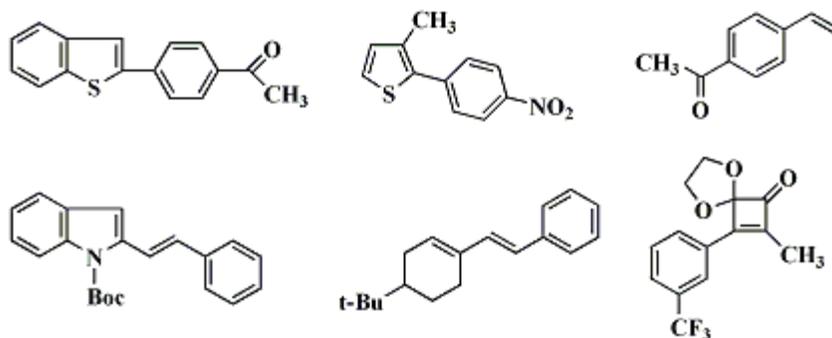
3. Discussion

The rate-enhancing influence of Cu(I) salts (the so-called "Copper Effect") in normally nonproductive and sluggish Stille couplings was first pointed out by Liebeskind et al.⁶ in 1990. A greater insight into this phenomenon was obtained later by Farina and co-workers.⁷ A number of modifications of the Stille reaction have since been reported. Among them are the cross-coupling of organostannanes with organic halides promoted by stoichiometric amounts of Cu(I) salts,⁸⁻¹⁰ and the Cu(I)- or Mn(II)-catalyzed cross-coupling of organostannanes with iodides in the presence of sodium chloride.¹¹

It was also discovered that aryl and vinyl iodides, bromides, and triflates participated efficiently in cross-coupling reactions with organostannanes when catalyzed by palladium-on-carbon in the presence of Cu(I) as cocatalyst.¹

The best conditions were found to be: Pd/C (0.5 mole%), Cu(I) (10 mole%), and AsPh_3 (20 mole%). Besides the advantage of using a stable form of Pd(0), the yield of the products under these conditions was better than that obtained using tris(dibenzylideneacetone)palladium [$\text{Pd}_2(\text{dba})_3$] as the source of Pd(0). Similarly, a slightly lesser amount of the homocoupled product was observed using the Pd/C protocol. Although a significant amount of AsPh_3 is necessary for cross-coupling to take place, it can be efficiently recovered (and recycled) at the end of the reaction by column chromatography.

Other products prepared using the Pd/C protocol are:



References and Notes

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Appendix

Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

4-Iodoacetophenone:
Acetophenone, 4'-iodo- (8);
Ethanone, 1-(4-iodophenyl)- (9); (13329-40-3)

Copper(I) iodide (8,9); (7681-65-4)

Triphenylarsine: HIGHLY TOXIC:
Arsine, triphenyl- (8,9); (603-32-7)

1-Methylpyrrolidinone:
2-Pyrrolidinone, 1-methyl- (8,9); (872-50-4)

2-(Tributylstannyl)thiophene:
Stannane, tributyl-2-thienyl- (9); (54663-78-4)

Sodium fluoride (8,9); (7681-49-4)

