



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

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In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

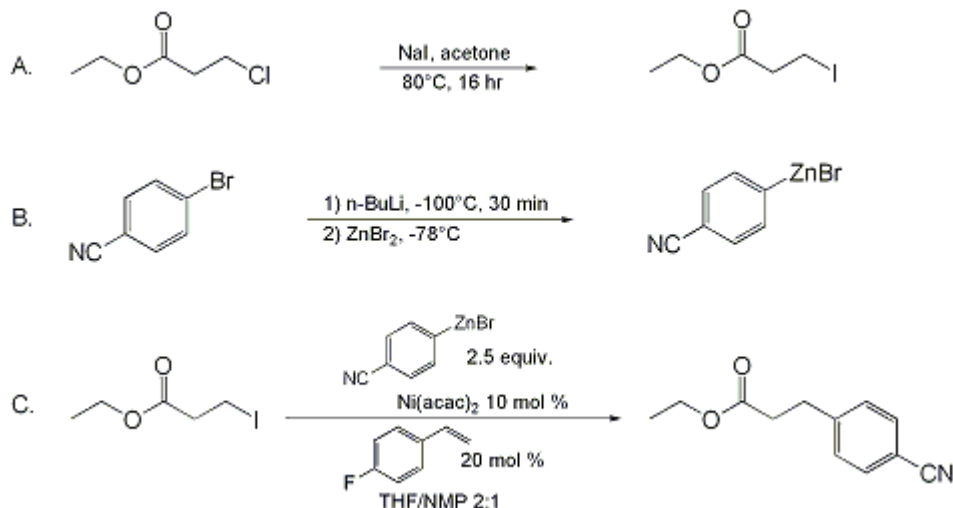
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

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ETHYL 3-(p-CYANOPHENYL)PROPIONATE FROM ETHYL 3- IODOPROPIONATE AND p-CYANOPHENYLZINC BROMIDE

[Benzenepropanoic acid, 4-cyano-, ethyl ester]



Submitted by Anne Eeg Jensen, Florian Kneisel, and Paul Knochel¹.
Checked by V. Girijavallabhan and Marvin J. Miller.

1. Procedure

A. Ethyl 3-iodopropionate. A 1-L, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser is charged with ethyl 3-chloropropionate (27.3 g, 0.2 mol) (Note 1) and acetone (400 mL). Sodium iodide (300 g, 2 mol) (Note 2) is added to the clear solution and the mixture is refluxed for 16 hr. The resulting pale yellow reaction mixture is cooled to room temperature, the stirring bar and reflux condenser are removed and the acetone is removed on a rotary evaporator at 40°C/550 mbar (412 mm). The residue is taken up in diethyl ether (300 mL) and washed with a saturated aqueous solution of sodium thiosulfate (3 × 100 mL). The ethereal phase is dried over anhydrous magnesium sulfate, filtered and the ether is removed by rotary evaporation at 40°C. The resulting yellow oil is purified by distillation with a membrane pump 90°C/25 mbar (18.7 mm) yielding 36.8 g of ethyl 3-iodopropionate as a clear oil (82%) (Note 3).

B. 4-Cyanophenylzinc bromide. A dry, 250-mL, three-necked flask equipped with an argon inlet and a stirring bar is charged with 4-bromobenzonitrile (9.1 g, 50 mmol) (Note 4) and evacuated for 5 min. The flask is flushed with argon, dry tetrahydrofuran (THF, 100 mL) (Note 5) is added, and the flask is equipped with an internal thermometer. The solution is cooled to -100°C in a diethyl ether/liquid nitrogen bath and left for 5 min before slowly adding butyllithium (BuLi, 32 mL, 1.56 M in hexanes, 50 mmol) (approx. 20 min). After complete addition the mixture is stirred at -100°C for an additional 30 min before it is allowed to warm to -78°C. At this temperature, a solution of zinc bromide (ZnBr₂, 36.6 mL, 1.5 M in THF, 55 mmol) (Note 6) is slowly added (approx. 20 min). After complete addition, the reaction mixture is kept at -78°C for 5 min, then the flask is warmed with an ice bath to 0°C and left for 10 min at this temperature before allowing it to warm to room temperature. The yield of the zinc reagent is checked by hydrolysis and iodolysis (Note 7) before concentrating it under reduced pressure to 2.0-2.2 M (22-25 mL).

C. Ethyl 3-(4-cyanophenyl)propionate. A dry, 100-mL, three-necked flask, equipped with an argon inlet and a stirring bar, is charged with nickel acetylacetonate (Ni(acac)₂, 520 mg, 2 mmol) and evacuated for 10 min before flushing with argon. THF (6.7 mL), N-methylpyrrolidinone (NMP, 3.3 mL) (Note 8), 4-fluorostyrene (496 mg, 4 mmol) (Note 9) and ethyl 3-iodopropionate (4.56 g, 20 mmol) are

successively added and the flask is equipped with an internal thermometer. The reaction mixture is cooled to -60°C before slowly adding the zinc reagent with a syringe through a large diameter cannula. After complete addition, the reaction mixture is allowed to warm to -14°C in a cryostat. (The checkers used a dry ice/ethylene glycol bath). The conversion is complete within 12-15 hr (Note 10), when it is quenched with saturated aqueous ammonium chloride solution (15 mL) and allowed to warm to room temperature. The quenched reaction mixture is extracted with diethyl ether (7×150 mL), the ethereal extracts are dried over magnesium sulfate, filtered, and evaporated to dryness by rotary evaporation at 40°C . The resulting yellow oil is purified by column chromatography (Note 11) affording 2.42 g (11.9 mmol) of ethyl 3-(4-cyanophenyl)propionate as a pale yellow oil (60%) (Note 12).

2. Notes

1. Ethyl 3-chloropropionate from Aldrich Chemical Company, Inc., was used as obtained.
2. Sodium iodide was purchased from Acros Organics as water free, 99+%.
3. Spectral data are as follows: IR (KBr) cm^{-1} : 2981 (m), 1372 (m), 1213 (s); ^1H NMR (300 MHz, CDCl_3) δ : 1.26 (t, 3 H, $J = 7.1$), 2.95 (t, 2 H, $J = 7.5$), 3.32 (t, 2 H, $J = 7.5$), 4.15 (q, 2 H, $J = 7.1$); ^{13}C NMR (75 MHz, CDCl_3) δ : -3.3, 14.6, 39.0, 61.3, 171.4. MS (EI, 70 eV): 228 (33), 183 (27), 155 (67), 101 (100), 73 (49). Anal. Calcd for $\text{C}_5\text{H}_9\text{IO}_2$: C, 26.34; H, 3.98. Found: C, 26.27; H, 3.96.
4. 4-Bromobenzonitrile from ABCR Germany is used as obtained.
5. THF is dried by distillation under argon from sodium/benzophenone.
6. Anhydrous ZnBr_2 is dried for 5 hr at 150°C under oil pump vacuum, then cooled to room temperature and flushed with argon before adding dry THF. The concentration is determined by transferring a 1-mL aliquot to a dry tared flask, then evaporating the THF.
7. Hydrolysis: An aliquot of the reaction mixture is quenched with saturated aqueous ammonium chloride solution and extracted with ether, then injected on GC to verify that all the 4-bromobenzonitrile has been consumed. Iodolysis: An aliquot of the reaction mixture is added to a dry vial containing iodine; after 10 min ether is added and the ethereal solution is washed with an aqueous solution of sodium thiosulfate. The organic phase is injected on GC to verify the formation of the zinc reagent. Decane was used as internal standard in the reaction.
8. NMP is dried by stirring overnight with calcium hydride, then refluxing for 5 hr followed by distillation under argon from calcium hydride.
9. 4-Fluorostyrene 99% from Aldrich Chemical Company, Inc., is used as obtained.
10. The reaction is monitored by GC analysis of worked-up aliquots. Tetradecane is used as internal standard for the cross-coupling reaction.
11. The oil is taken up in diethyl ether and absorbed onto approximately 15 g of flash silica (Merck silica gel 60 mesh 0.040-0.063 mm), then applied to a 10-cm diameter column packed with 500 g of flash silica eluting the product with pentane/diethyl ether 85:15. (The checkers used 10:1 hexanes/ether for improved resolution.)
12. Spectral data are as follows: IR (KBr) cm^{-1} : 2983 (m), 2228 (m), 1732 (s), 1688 (m), 1186 (m). ^1H NMR (300 MHz, CDCl_3) δ : 1.20 (t, 3 H, $J = 7.1$), 2.60 (t, 2 H, $J = 7.5$), 3.00 (t, 2 H, $J = 7.5$), 4.10 (q, 2 H, $J = 7.1$), 7.30 (d, 2 H, $J = 7.8$), 7.60 (d, 2 H, $J = 7.8$); ^{13}C NMR (75 MHz, CDCl_3) δ : 14.5, 31.3, 35.4, 61.0, 110.6, 119.2, 129.6, 132.6, 146.6, 172.5. MS (EI, 70 eV): 203 (26), 129 (100), 116 (39), 103 (12). Anal. Calcd. for $\text{C}_{12}\text{H}_{13}\text{NO}_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.61; H, 6.20; N, 6.74.

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 performance of cross-coupling reactions between aryl organometallics and alkyl iodides is not well known. Only the reaction of diarylcuprates with alkyl iodides may be considered for performing such cross-couplings.² The present procedure³ describes a convenient way for performing the cross-coupling between an arylzinc bromide and an alkyl iodide. The reaction is catalyzed by $\text{Ni}(\text{acac})_2$ (10 mol %) and the addition of commercially available 4-fluorostyrene (20 mol %). The role of 4-fluorostyrene is to reduce the electron density of the nickel intermediate $[(\text{Ar})\text{Ni}(\text{Alkyl})]$ by

coordinating to the nickel center and removing electron density, thereby favoring the reductive elimination leading to Ar-Alkyl. The key role of several electron-poor styrenes such as *m*- or *p*-trifluoromethylstyrene has been noticed in related cross-couplings between two Csp³-centers.⁴ The reaction tolerates a broad range of functional groups such as ester, nitrile, amide, and halogen (Table 1).

The functionalized arylzinc reagents are best prepared either starting from an aryllithium obtained by halogen-lithium exchange followed by a low-temperature (−80°C) transmetalation⁵ with ZnBr₂ or by performing an iodine-magnesium exchange reaction. The latter reaction tolerates temperatures up to −30°C and is more convenient for industrial applications.⁶

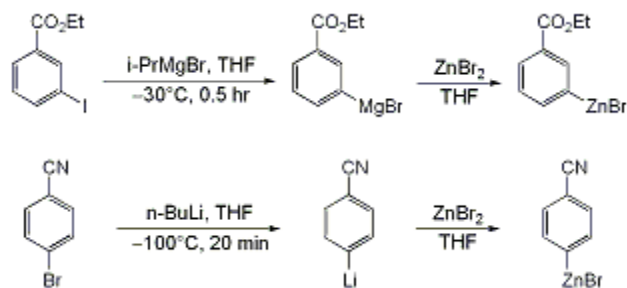
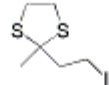
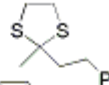
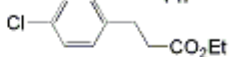
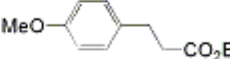
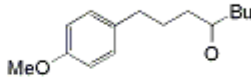
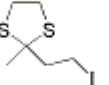
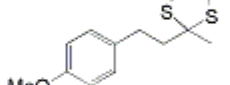
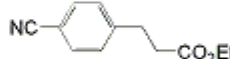
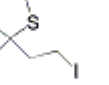
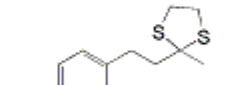
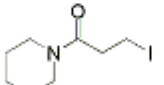
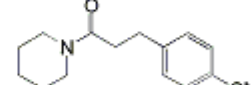
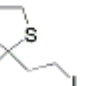
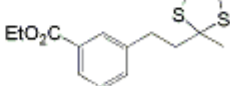
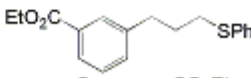
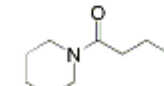
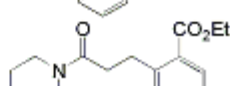


Table 1

Table 1: Polyfunctional products obtained by the Ni(II)-catalyzed cross-coupling of Arylzinc bromides and alkyl iodides in the presence of 4-(trifluoromethyl)styrene.

| Entry | ArZnBr | Alkyl iodide | Product | Yield (%) |
|-------|---|---|--|-----------|
| 1 | Ph ^b | PivO(CH ₂) ₂ I | PivO(CH ₂) ₂ Ph | 71 |
| 2 | Ph ^b |  |  | 75 |
| 3 | p-Cl-C ₆ H ₄ ^b | EtO ₂ C(CH ₂) ₂ I |  | 71 |
| 4 | p-MeO C ₆ H ₄ ^b | EtO ₂ C(CH ₂) ₂ I |  | 78 |
| 5 | p-MeO C ₆ H ₄ ^b | BuCO(CH ₂) ₃ I |  | 72 |
| 6 | p-MeO C ₆ H ₄ ^b |  |  | 77 |
| 7 | p-CN C ₆ H ₄ ^b | EtO ₂ C(CH ₂) ₂ I |  | 75 |
| 8 | p-CN C ₆ H ₄ ^b |  |  | 80 |
| 9 | p-CN C ₆ H ₄ ^b |  |  | 71 |
| 10 | m-EtO ₂ C-C ₆ H ₄ ^c |  |  | 72 |
| 11 | m-EtO ₂ C-C ₆ H ₄ ^c | PhS(CH ₂) ₃ I |  | 75 |
| 12 | o-EtO ₂ C-C ₆ H ₄ ^c |  |  | 72 |

^aIsolated yield of analytically pure products. ^bPrepared from the corresponding lithium reagent. ^cPrepared from the corresponding magnesium reagent.

References and Notes

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

Ethyl 3-(4-cyanophenyl)propionate:
Benzenepropanoic acid, 4-cyano-, ethyl ester (12); (116460-89-0)

Ethyl 3-iodopropionate:
Propanoic acid, 3-iodo-, ethyl ester (9); (6414-69-3)

Ethyl 3-chloropropionate:
Propionic acid, 3-chloro-, ethyl ester (8);
Propanoic acid, 3-chloro-, ethyl ester (9); (623-71-2)

Sodium iodide (8,9); (7681-82-5)

p-Cyanophenylzinc bromide:
Zinc, bromo(4-cyanophenyl)- (12); (131379-14-1)

4-Bromobenzonitrile:
Benzonitrile, p-bromo- (8);
Benzonitrile, 4-bromo- (9); (623-00-7)

Butyllithium:
Lithium, butyl- (8,9); (109-72-8)

Zinc bromide (8,9); (7699-45-8)

Nickel acetylacetonate:
Nickel, bis(2,4-pentanedionato-) (8);
Nickel, bis(2,4-pentanedionato-O, O')-, (sp-4-1)- (9); (3264-82-2)

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

p-Fluorostyrene:
Styrene, p-fluoro- (8);
Benzene, 1-ethenyl-4-fluoro- (9); (405-99-2)