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Working with Hazardous Chemicals

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These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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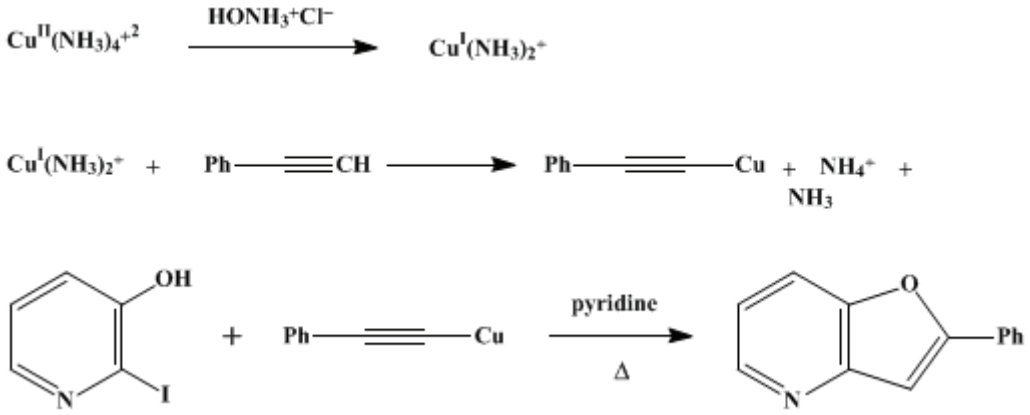
SUBSTITUTION OF ARYL HALIDES WITH COPPER(I) ACETYLIDES: 2-PHENYLFURO[3,2-*b*]PYRIDINE

[Furo[3,2-*b*]pyridine, 2-phenyl-]



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1. Procedure

A. *Copper(I) phenylacetylide*. A 2-l. Erlenmeyer flask fitted with a large magnetic stirring bar (Note 1) and an ice-water cooling bath is charged with a solution of 25.0 g. (0.100 mole) of copper(II) sulfate pentahydrate (Note 2) in 100 ml. of concentrated aqueous ammonia. The solution is stirred with cooling for 5 minutes while a stream of nitrogen is passed over the solution (Note 3). Water (400 ml.) is added, and stirring and cooling under a nitrogen atmosphere (Note 3) are continued for 5 minutes. Solid hydroxylamine hydrochloride (13.9 g., 0.200 mole, (Note 4)) is added to the reaction solution, with continuous stirring and cooling under nitrogen, over 10 minutes (Note 5). A solution of 10.25 g. (0.1005 mole) of phenylacetylene (Note 6) in 500 ml. of 95% ethanol is then added rapidly to the pale blue solution. The reaction flask is swirled by hand, copper(I) phenylacetylide separates as a copious yellow precipitate, and an additional 500 ml. of water is added. After the mixture has been allowed to stand for 5 minutes, the precipitate is collected on a sintered glass filter (Note 7) and washed successively with five 100-ml. portions of water, five 100-ml. portions of absolute ethanol, and five 100-ml. portions of anhydrous diethyl ether. The copper(I) acetylide is dried in a 250-ml., round-bottom flask heated to 65° for 4 hours under reduced pressure on a rotary evaporator, yielding 14.8–16.4 g. (90–99%) of a bright yellow solid. The dry acetylide may be stored under nitrogen in a brown bottle (Note 8).

B. 2-*Phenylfuro*[3,2-b]*pyridine*. A 300-ml., three-necked flask fitted with a nitrogen inlet stopcock, a magnetic stirring bar, and a condenser attached to a nitrogen outlet stopcock and a mercury trap is charged with 2.47 g. (0.0150 mole) of copper(I) phenylacetylide. The system is purged with nitrogen for 20 minutes before 80 ml. of pyridine (Note 9) is added. The resulting mixture is stirred for 20 minutes under a nitrogen atmosphere (Note 10), and 3.30 g. (0.0149 mole) of 3-hydroxy-2-iodopyridine (Note 11) is added. The mixture, which changes in color from yellow to dark green as the acetylide dissolves (Note 12), is warmed in an oil bath at 110–120° for 9 hours with continuous stirring under a nitrogen atmosphere (Note 10). The reaction solution is transferred to a 500-ml., round-bottom flask and concentrated to a volume of 20 ml. at 60–70° (20–80 mm.) with a rotary evaporator. The pyridine solution is treated with 100 ml. of concentrated aqueous ammonia, and the resulting deep-blue mixture is stirred for 10 minutes and extracted with five 100-ml. portions of ether. The combined ethereal extracts are washed with three 250-ml. portions of water, dried over anhydrous magnesium sulfate, and concentrated with a rotary evaporator. The crude product, 2.6–2.76 g. of orange semisolid, is dissolved in 100 ml. of boiling cyclohexane. The solution is filtered, concentrated to a volume of about 30 ml., and cooled in an ice bath. The partially purified product crystallizes as 2.3–2.7 g. of orange solid, m.p.

83–89°. Further purification is effected by sublimation at 110–120° (0.01–0.2 mm.), yielding 2.2–2.4 g. (75–82%) of a yellow solid, m.p. 90–91° (Note 13).

2. Notes

1. An 8-cm., Teflon-coated stirring bar is convenient.
2. A reagent grade copper(II) sulfate pentahydrate, purchased from either Mallinckrodt Chemical Works or J. T. Baker Chemical Company, may be employed.
3. A nitrogen atmosphere is maintained above the reaction solution throughout the preparation of the copper(I) acetylide.
4. Material of satisfactory purity was obtained either from J. T. Baker Chemical Company or from Matheson, Coleman and Bell.
5. Too rapid an addition of the hydroxylamine salt results in precipitation of a dark solid that dissolves slowly. If solids do separate, they should be pulverized to hasten solution.
6. Phenylacetylene, purchased either from K & K Laboratories or from Aldrich Chemical Company, Inc., was used without purification.
7. A 600-ml., coarse porosity, sintered glass filter is recommended to shorten the filtration time. The filtration may also be hastened by periodically scraping the bottom of the funnel with a spatula.
8. The submitters report that the acetylide is stable for years under these conditions.
9. A reagent grade of pyridine, purchased from either J. T. Baker Chemical Company or Fisher Scientific Company, was employed.
10. Oxygen will convert the acetylide to 1,4-diphenylbutadiyne.[2]
11. This material, obtained from Aldrich Chemical Company, Inc., was used without purification.
12. Although the reaction mixture becomes homogeneous in this example, the submitters report that only partial solution occurs in other successful substitution reactions. The solubilities of the acetylides and the heterogeneous character of the cyclization have been described.[3]
13. The product exhibits UV maxima (95% C_2H_5OH solution) at 312 nm (ε 32,900) and 326 nm (ε 27,100) with ^1H NMR peaks (acetone-d_6) at δ 7.1–8.1 (m, 8H) and 8.49 (d of d, J = 1.4 and 4.7 Hz., 1H). The mass spectrum has the following relatively abundant peaks: *m/e* (rel. int.), 196 (25), 195 (100, M^+), 166 (13), 139 (8), 102 (5), and 39 (6).

3. Discussion

Copper(I) acetylides can be prepared from ammoniacal copper(I) iodide and acetylenes.[4,5] The generation of fresh solutions of the copper(I) salts results in a higher purity acetylide.

The substitution of aryl halides by copper(I) acetylides provides a convenient, high-yield route to aromatic acetylenes.[2,5,6,7,8,9] Aliphatic acetylenes can also be obtained under forcing conditions.[10] The procedure is also useful for the preparation of conjugated acetylenic ketones and alkynyl sulfides.[3] Moreover, the reaction provides the basis for the facile synthesis of an exceedingly broad scope of heterocycles. Thus, a halide bearing an adjacent nucleophilic substituent can be cyclized by the copper (I) salt. The example described is illustrative of the preparation of indoles,[2] benzo[*b*]thiophenes,[11] phthalides,[2] benzofurans,[2] 3(*H*)-isobenzofurans,[3] furans,[10] 1(*H*)-2-benzopyrans,[3] 1(*H*)-thieno[3,4-*b*]-2-pyranones,[12] furo[3,2-*b*]pyridines,[12] furo[3,2-*c*]pyridines,[12] pyrrolo[3,2-*b*]pyridines,[3] and 4,5-dihydro-4-keto[3] benzoxepins. The furo[3,2-*b*]pyridine system has only been prepared by this route.[12]

References and Notes

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

ethanol (64-17-5)

ammonia (7664-41-7)

ether,
diethyl ether (60-29-7)

oxygen (7782-44-7)

nitrogen (7727-37-9)

cyclohexane (110-82-7)

pyridine (110-86-1)

Hydroxylamine hydrochloride (5470-11-1)

Phenylacetylene (536-74-3)

copper(I) iodide (7681-65-4)

magnesium sulfate (7487-88-9)

copper(II) sulfate pentahydrate (7758-99-8)

1,4-diphenylbutadiyne (886-66-8)

copper(I) phenylacetylide (13146-23-1)

copper(I) acetylide

3-hydroxy-2-iodopyridine (40263-57-8)

2-Phenylfuro[3,2-b]pyridine,
Furo[3,2-b]pyridine, 2-phenyl- (18068-82-1)