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Working with Hazardous Chemicals

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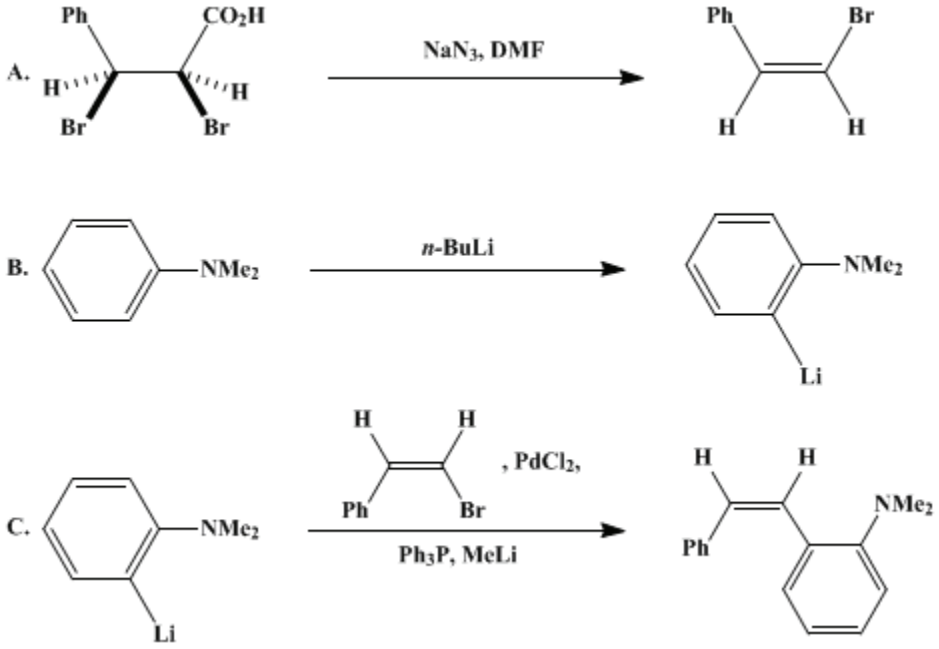
These paragraphs were added in September 2014. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.062.0039

Organic Syntheses, Coll. Vol. 7, p.172 (1990); Vol. 62, p.39 (1984).

PALLADIUM-PHOSPHINE-COMPLEX-CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES: (*Z*)-β-[2-(*N*,*N*-DIMETHYLAMINO)PHENYL]STYRENE

[Benzenamine, *N*,*N*-dimethyl-2-(2-phenylethenyl)-, (*Z*)-]



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Checked by Joseph Fortunak and Ian Fleming.

1. Procedure

Caution! The reaction described in Section (Step) A (Note 1) should be carried out in a well-ventilated hood because bromine is toxic.

A. *(Z)-β-Bromostyrene.* In a 1-L, round-bottomed flask equipped with a magnetic stirring bar are placed 30.8 g (0.100 mol) of *erythro*-α,β-dibromo-β-phenylpropionic acid (Note 1), 13.0 g (0.200 mol) of sodium azide (Note 2), and 500 mL of dry *N,N*-dimethylformamide (Note 3). The reaction mixture is stirred at room temperature for 8 hr and poured into a mixture of 300 mL of ether and 300 mL of water. The organic layer is separated, washed with three 100-mL portions of water, dried over magnesium sulfate, and filtered. After evaporation of the filtrate with a rotary evaporator, the residual liquid is distilled under reduced pressure, giving 13.5–13.9 g (74–76%) of (*Z*)-β-bromostyrene, bp 54–56°C (1.5 mm) (Note 4).

B. *2-(N,N-Dimethylamino)phenyllithium.* A 100-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser connected to a nitrogen-inlet tube is capped with serum stoppers and flushed with nitrogen. The flask is charged with 18.2 g (0.150 mol) of *N,N*-dimethylaniline (Note 5) and 33.4 mL (0.050 mol) of a 1.50 *M* solution of butyllithium in hexane (Note 6). While a continuous positive nitrogen pressure is maintained, the solution is heated at reflux (in a 90–95°C bath) with stirring for 20 hr and then cooled to room temperature (Note 7).

C. *(Z)-β-[2-(N,N-Dimethylamino)phenyl]styrene.* A 1-L. three-necked, round-bottomed flask equipped with a magnetic stirring bar, a reflux condenser connected to a nitrogen-inlet tube, and a 300-mL, pressure-equalizing dropping funnel is capped with serum stoppers. The flask is flushed with nitrogen and charged with 0.433 g (0.0025 mol) of palladium chloride (Note 8), 2.62 g (0.010 mol) of

triphenylphosphine (Note 9) and 300 mL of benzene (Note 10). While a continuous positive nitrogen pressure is maintained, the mixture is stirred at gentle reflux for 30 min, and then 4.25 mL (0.0060 mol) of a 1.41 *M* solution of methyllithium in ether (Note 11) is added with a syringe. After an additional 10 min at reflux, 9.15 g (0.050 mol) of (*Z*)-β-bromostyrene as prepared in Section A is added in one portion with syringe, and the mixture is heated at reflux for 10 min. The solution of 2-(*N,N*-dimethylamino)phenyllithium prepared as described in Section B is transferred to the dropping funnel with a syringe and diluted by adding 150 mL of benzene (Note 10) and (Note 12). The resulting solution is then added dropwise to the mixture with stirring at reflux over a period of 30 min (Note 13). After additional stirring for 10 min, the resulting red solution is cooled to room temperature with the help of an ice bath and quenched by adding 100 mL of saturated aqueous ammonium chloride. The organic layer is separated, washed successively with 100 mL of water and 100 mL of saturated aqueous sodium chloride, and then dried over magnesium sulfate and filtered. The solvent is evaporated with a rotary evaporator, and the residue is distilled under reduced pressure to give a forerun (ca. 11 g) of excess *N,N*-dimethylaniline, bp 31–51°C (1 mm), followed by 7.4–7.5 g (66–67%) of (*Z*)-β-[2-(*N,N*-dimethylamino)phenyl]styrene, bp 90.0–92.0°C (0.035 mm), 82–84°C (0.01 mm), as a pale-yellow liquid (Note 14).

2. Notes

1. *erythro*-α,β-Dibromo-β-phenylpropionic acid is prepared from *trans*-cinnamic acid (mp 133–134°C) (Nakarai Chemicals, Japan) by the method used for ethyl α,β-dibromo-β-phenylpropionate (Abbott T. W.; Althousen, D. *Org. Synth., Coll. Vol. II* **1943**, 270) in 83% yield, mp 199–200°C. The checkers used benzene (400 mL per mol) in place of the carbon tetrachloride, because the mixture was then easier to stir and the reaction was more reproducible. The yield before purification was 89% (mp 174–191°C); the yield after recrystallization was 81% (mp 198–199°C). Crude material could be used without appreciable loss of yield.
2. Sodium azide from Wako Pure Chemical Ind., Japan, was used without purification.
3. *N,N*-Dimethylformamide is distilled over calcium hydride.
4. Gas chromatographic analysis of the distillate (10% PEG-20M on 60–80-mesh, Celite 545 AW, 1-m × 4-mm column, column temperature 100–220°C, injection temperature 200°C) shows that the product is 100% isomerically pure. The spectral properties of the (*Z*)-β-bromostyrene are as follows: IR (neat) cm^{-1}: strong absorptions at 3095, 3040, 1620, 1500, 1450, 1333, 1032, 930, 920, 830, 770, and 700; ^1H NMR ($CHCl_3$) δ: 6.43 (doublet, 1 H, J = 8, PhCH=C), 7.08 (doublet, 1 H, J = 8, PhC=CHBr), 7.22–7.85 (multiplet, 5 H, aromatic). The checkers also purified the residual oil before distillation by filtration in 250 mL of pentane through three times its weight of silica gel (70–230-mesh) followed by evaporation. The yield before distillation was then reproducibly 84%, distillation was avoided, and the next step proceeded with undiminished yield.
5. *N,N*-Dimethylaniline from Nakarai Chemicals was dried over calcium hydride and freshly distilled. Three molar equivalents of *N,N*-dimethylaniline are used to achieve complete conversion of the butyllithium, because in the present particular case free butyllithium, if present, causes the isomerization of the (*Z*)-alkene to the (*E*)-isomer.
6. A solution of butyllithium in hexane was obtained from Aldrich Chemical Company, Inc. Before use the solution is titrated with a 1 *M* solution of 2-butanol in xylene according to the procedure of Watson and Eastham[2] (see Gall, M.; House, H. O. *Org. Synth. Coll. Vol. VI* **1988**, 121) with 2,2'-biquinoline as indicator.
7. The resulting cloudy, yellowish orange solution should be used within 3–4 hr.
8. Palladium chloride from Inuisho Precious Metal Company, Japan, was used without purification.
9. Triphenylphosphine from Nakarai Chemicals, Japan, was used without purification.
10. Benzene is distilled over benzophenone ketyl and stored under a nitrogen atmosphere.
11. A solution of methyllithium in ether is prepared from lithium wire and methyl bromide according to the literature procedure[3] and titrated by the same method as (Note 6). The checkers used 1.1 *M* methyllithium from Aldrich Chemical Co., Inc.
12. Without the dilution, (*Z*)-1,4-diphenyl-1-buten-3-yne is detected, apparently formed from the cross-coupling with phenylacetylide, derived from lithiation of β-bromostyrene, followed by E2cB elimination or Fritsch–Butlenberg–Wiechell-type rearrangement.
13. Prolonged reaction time causes the isomerization of (*Z*)-β-[2-(*N,N*-dimethylamino)phenyl]styrene to the (*E*)-isomer.

14. Gas chromatographic analysis of the product (5% silicone SE 30 on 80–100-mesh Chromosorb W AB, 0.5-m × 4-mm column, column temperature 100–250°C, injection temperature 180°C) shows that the product is at least 98% (*Z*)-isomer. The spectral properties of the (*Z*)-alkene are as follows; IR (neat) cm^{-1}: strong absorptions at 3070, 3025, 2950, 2870, 2835, 2780, 1600, 1490, 1450, 1320, 1190, 1160, 1140, 1100, 1050, 950, 780, 750, and 690; ^1H NMR (CCl_4) δ: 2.76 (singlet, 6 H, CH_3-N), 6.38 (doublet, 1 H, J = 12.3, PhC=CH), 6.63 (doublet, 1 H, J = 12.3, PhCH=C), 6.50–7.30 (multiplet, 9 H, aromatic).

3. Discussion

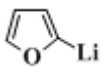
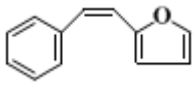
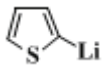
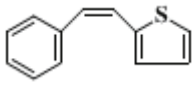
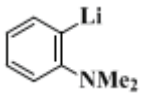
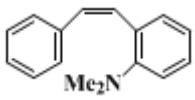
The starting materials, (*Z*)-β-bromostyrene[4] and 2-(*N*,*N*-dimethylamino)phenyllithium[5] have been prepared in satisfactory yields by known procedures after slight modifications. The azide procedure[4] gives higher stereospecificity than the earlier procedure using sodium bicarbonate.[6]

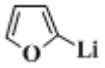
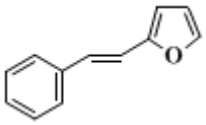
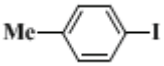
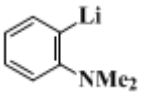
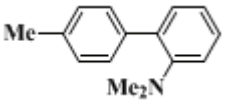
This procedure illustrates a general method for the preparation of alkenes from the palladium(O)-catalyzed reaction of vinyl halides with organolithium compounds,[7] which can be prepared by various methods, including direct regioselective lithiation of hydrocarbons.[8] The method is simple and has been used to prepare a variety of alkenes stereoselectively. Similar stoichiometric organocopper reactions sometimes proceed in a nonstereoselective manner[9] and in low yields.[10] Nickel catalysts can be used efficiently for the reaction of alkenyl halides with Grignard reagents but not with organolithium compounds.[11] Highly reactive zerovalent palladium catalyst can be directly generated in situ from $PdCl_2$–PPh_3–CH_3Li. Tetrakis(triphenylphosphine)palladium can be used alternatively. Grignard reagents undergo the reaction as well with vinyl halides. Organolithium compounds require the limited reaction conditions under which the elimination of alkenyl halides producing lithium acetylides is slower than the cross-coupling reaction.[7] The choice of benzene as a solvent and the dilution of the solution satisfy the above conditions. The palladium-catalyzed alkylation of aryl halides with organolithium compounds proceeds efficiently without such difficulty.[7] Similar reactions with lithium thiolates give the corresponding alkenyl sulfides.[7] Representative reactions of organolithium compounds are shown in Table I.

This preparation is referenced from:

- Org. Syn. Coll. Vol. 8, 532

TABLE I
PALLADIUM-CATALYZED REACTION OF ORGANOLITHIUM COMPOUNDS AND ALKENYL HALIDES[a]

Halides	RLi	Products	Yield(%)[b]	
(Z)-C_6H_5CH=CHBr	CH_3Li	(Z) C_6H_5CH=$CHCH_3$	90	
	C_4H_9Li	(Z)C_6H_5CH=CHC_4H_9	62	
			85	
			94[c]	
			87 (66-67)[d]	
	C_6H_5SLi	(Z)-C_6H_5CH=$CHSC_6H_5$	95[c]	
		(Z)-		

	C_2H_5SLi	$C_6H_5CH=CHSC_2H_5$	93[c]
(E)-$C_6H_5CH=CHBr$	CH_3Li	(E)-$C_6H_5CH=CHCH_3$	88
			85
			(89)[d]

*a*The reaction was carried out on a 1.0–1.5-mmol scale.
*b*Determined by gas chromatography.
*c*Tetrakis-(triphenylphosphine)palladium was used.
*d*Isolated yield.

References and Notes

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

benzophenone ketyl

erythro-α,β-Dibromo-β-phenylpropionic acid

(Z)-$C_6H_5CH=CHBr$

CH_3Li

C_4H_9Li

C_6H_5SLi

(Z)-$C_6H_5CH=CHSC_6H_5$

C_2H_5SLi

(Z)-$C_6H_5CH=CHSC_2H_5$

(E)-$C_6H_5CH=CHBr$

Benzene (71-43-2)

ether (60-29-7)

ammonium chloride (12125-02-9)

sodium bicarbonate (144-55-8)

sodium chloride (7647-14-5)

bromine (7726-95-6)

carbon tetrachloride (56-23-5)

nitrogen (7727-37-9)

nickel (7440-02-0)

palladium (7440-05-3)

methyl bromide (74-83-9)

xylene (106-42-3)

N,N-dimethylaniline (121-69-7)

Pentane (109-66-0)

sodium azide (26628-22-8)

β-bromostyrene (103-64-0)

palladium chloride,
palladium dichloride (7647-10-1)

Lithium wire (7439-93-2)

magnesium sulfate (7487-88-9)

Ethyl α,β-dibromo-β-phenylpropionate (5464-70-0)

butyllithium (109-72-8)

N,N-dimethylformamide (68-12-2)

hexane (110-54-3)

Methyllithium (917-54-4)

calcium hydride (7789-78-8)

triphenylphosphine,
triphenyl phosphine (603-35-0)

2-Butanol (78-92-2)

(Z)-β-Bromostyrene (103-64-0)

phenylacetylide

Tetrakis(triphenylphosphine)palladium (14221-01-3)

2,2'-biquinoline (119-91-5)

(Z)-β-[2-(N,N-Dimethylamino)phenyl]styrene,
Benzenamine, N,N-dimethyl-2-(2-phenylethenyl)-, (Z)- (70197-43-2)

2-(N,N-Dimethylamino)phenyllithium

trans-cinnamic acid (140-10-3)

(Z)-1,4-diphenyl-1-buten-3-yne

cTetrakis-(triphenylphosphine)palladium