Protection of Amino and Hydroxy Groups in the Ullmann Reaction and Related Organocopper Couplings

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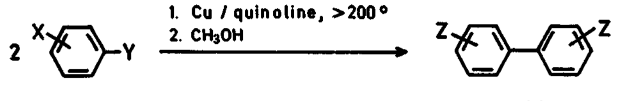
The presence of hydroxy and amino groups in reacting halogenoaryl substrates, as well as of auxiliary agents such as benzoic acid, are reported completely to prevent the formation of biaryls (and of copper halides in some instances), in the Ullmann reaction[1]. Yields from couplings involving authentic organocopper reagents may also be reduced by proton or hydrogen radical capture, although the more thermally stable alkynylcoppers are not so affected[2].

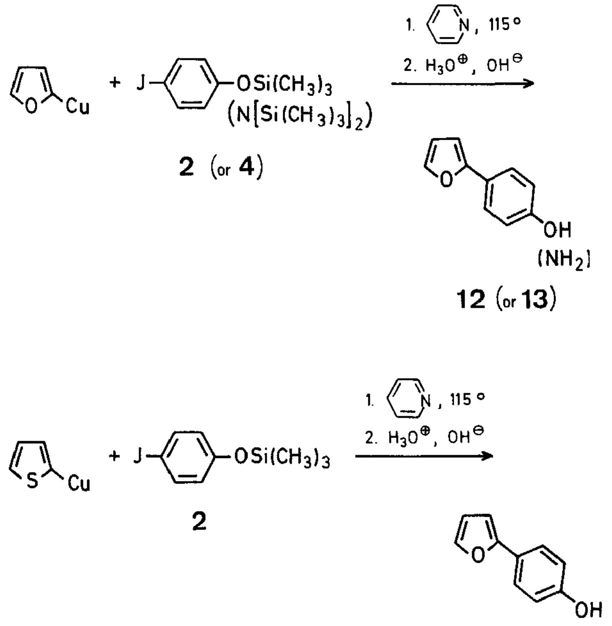
We find that trimethylsilyl groups may be used successfully to protect acidic functions in both areas of synthesis as described below.

The silylated reagents, **1–6**, (Scheme A and Table) couple under standard Ullmann conditions (quinoline, >200°) to give biaryls, which may be desilylated without isolation of the intermediates, to give the free hydroxy- or amino-containing products (**7–11**). Since both the silylation and desilylation steps are virtually quantitative, the only loss in yield is sustained at the Ullmann coupling step. The second area is exemplified by 2-furyl- and 2-thienylcopper which couple with **2** and **4** to give silylated intermediates. Methanolysis yields the free 2-arylfuran or -thiophene (Scheme **B**).



1-6 **7-11**

Scheme A



Scheme B

Preparation of Silylated Precursors (1–5):

Diethylamine was continuously fractionated from a refluxing mixture of the appropriate halogeno-phenol, -benzoic acid, or benzyl alcohol (1 mol) and diethylamino(trimethyl)silane (1.2 mol) and the residual liquid was distilled to give the products **1**,**2**,**3**,**5**, and **6** in >95% yield.

O-Trimethylsilyl 2-Iodobenzoate (**5**):

$C_{10}H_{13}IO_2Si$	calc.	C 37.63	H 4.12
(320.22)	found	37.50	4.07

^{1}H-N.M.R. (CCl_4): $\delta = 7.72$ (m, 2H, aryl), 7.00 (m, 2H, aryl), 0.34 ppm [s, 9H, $Si(CH_3)_3$].

4-Bromobenzyloxy(trimethyl)silane (**6**); m.p. 29–30°:

$C_{10}H_{15}BrOSi$	calc.	C 46.33	H 5.83
(259.25)	found	46.07	5.80

^{1}H-N.M.R. (CCl_4): $\delta = 7.24$ (q, 4H, p-C_6H_4), 4.70 (s, 2H, CH_2), 0.20 ppm [s, 9H, $Si(CH_3)_3$].

Analogous treatment of *p*-iodoaniline (1 mol) with diethylamino(trimethyl)silane (2.2 mol) in the presence of a catalytic quantity of ammonium sulphate (0.01 mol) gave *p*-iodo-*N*,*N*-bis[trimethylsilyl]aniline (**4**); yield: 80%.

Ullmann Reactions:

Preparation of 2,2'- and 4,4'-Dihydroxybiphenyl (7, 8):

A suspension of copper bronze (40 g) in quinoline (150 ml) containing dissolved **1** or **2** (39.2 g, 0.1 mol) was heated to 240° for 60 h with efficient stirring. The resulting dark-red mixture was cooled to 60° and petroleum ether (150 ml, 60–80° fraction) was added. Precipitated copper salts were removed by filtration and the filtrate was distilled under reduced pressure. The fraction b.p. 100–150°/0.001 torr was dissolved in methanol (30 ml) and the methanol solution was diluted with water (120 ml) and extracted with ether (5 × 100 ml). The ether extracts were dried ($MgSO_4$) and concentrated by rotary evaporation to give **7**; yield: 25%; m.p. 108° (from ethanol) (lit.[6] m.p. 108°); diacetyl derivative m.p. 95° (lit.[6] m.p. 95°) or **8**; yield: 55%; m.p. 270° (lit.[7] m.p. 272°); diacetyl derivative m.p. 160° (lit.[7] m.p. 160–161°). An identical coupling using **3** in place of **2** gave **8** in 20% yield.

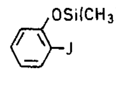
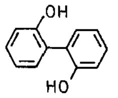
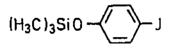
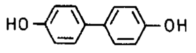
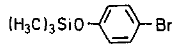
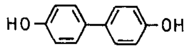
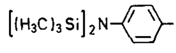
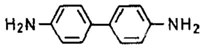
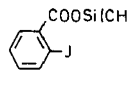
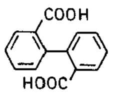
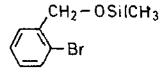
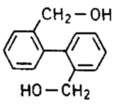
Preparation of 4,4'-Diaminobiphenyl (9):

The dark-red distillate, b.p. 130–170°/0.001 torr, obtained upon working up reaction of **4** (36.5 g, 0.1 mol) with copper bronze (40 g) in quinoline (150 ml) at 240° for 60 h, as described above, was shaken with 2 *M* hydrochloric acid (100 ml). Hexamethyldisiloxane was extracted with ether and the aqueous layer, after removal of traces of dissolved ether under reduced pressure, was made alkaline with 5 *M* aqueous sodium hydroxide (50 ml) and boiled briefly. Upon cooling, crystals of **9** were obtained; yield: 60%; m.p. 126–128° (lit.[8] m.p. 128°); diacetyl derivative m.p. 316–317° (lit.[8] m.p. 317°).

Preparation of 2,2'-Biphenic acid (10):

Compound **5** (32 g, 0.1 mol) was reacted with copper bronze (40 g) and quinoline (150 ml) at 200° for 60 h. After cooling the mixture to 60°, addition of petroleum ether and filtration, the distillate obtained at 0.001 torr was treated with 5 *M* aqueous hydrochloric acid (200 ml) to remove quinoline. The petrol layer was combined with ether (2 × 50 ml) extracts of the aqueous acid layer and concentrated by rotary evaporation to leave a red oil. The oil was dissolved in ether (50 ml) and extracted with 2 *M* aqueous sodium hydroxide (200 ml). Dissolved ether was removed under reduced pressure from the alkaline extract which upon acidification gave **10**; yield: 70%; m.p. 228–229° (from water; lit.[9] m.p. 228°).

Table. Silylated Precursors 1–6 and Ullmann Reaction thereof

Precursor	B.p./torr (Lit. b.p./torr)	n_D (Lit. n_D)	Biaryl	Yield (%)
1 	102–103°/3 (134°/25)[3]	n_D^{25} 1.5449 (n_D^{25} 1.5441)[3]	**7** 	25
2 	100–102°/3 (102°/3)[4]	n_D^{25} 1.5480 (n_D^{20} 1.5487)[4]	**8** 	55
3 	98–99°/7 (126°/25)[3]	n_D^{20} 1.5148 (n_D^{25} 1.5123)[3]	**8** 	20
4 	104–105°/1 (103–104°/0.8)[5]	n_D^{20} 1.5384 (n_D^{20} 1.5380)[5]	**9** 	60
5 	85–87°/0.2	n_D^{25} 1.5475	**10** 	70
6 	90–92°/1	—	**11** 	35

Preparation of 4,4′-(Dihydroxymethyl)-biphenyl (11):
Compound **6** (26 g, 0.1 mol), copper bronze (40 g) and quinoline (150 ml) were heated together at 240° for 120 h. Addition of petroleum ether to the cooled mixture, filtration and distillation gave material b.p. 120–150°/0.001 torr which was treated with aqueous methanol and worked up by the procedure described for the isolation of **7** and **8** to give **11**; yield: 35%; m.p. 193–194° (from 100–120° petroleum ether; lit.[10] m.p. 190–191°).

Preparation of *p*-(2-Furyl)-phenol (12):
n-Butyllithium (62 ml of 1.6 *M* solution in hexane) was added during 30 min to a solution of furan (7.5 g, 0.11 mol) in ether (100 ml) at 0°. The reaction mixture was stirred at this temperature for 1 h, then boiled under reflux for 15 min and added at −20° to a vigorously stirred suspension of copper(I) iodide (30 g, 0.1 mol) in ether (30 ml). After 1 h, ether was removed *in vacuo* and replaced by pyridine (150 ml). Compound **3** (29.2 g, 0.1 mol) was then added and the mixture was initially heated at 115° for 3 h, then stirred for 12 h at 20° and diluted with petroleum ether. Precipitated salts were filtered off and the filtrate concentrated by rotary evaporation and distilled. The fraction b.p. 55–60°/0.02 torr was poured into 2 *M* aqueous sodium hydroxide and extracted with ether. The aqueous phase was acidified with hydrochloric acid and extracted with ether (4 × 70 ml). The extract was dried ($MgSO_4$) and concentrated to leave a colourless oil which was recrystallised from 3:2 petroleum ether (60–80° fraction)/chloroform to give pure **12**; yield: 40%; m.p. 135–136° (lit.[11] m.p. 136°).

Preparation of *p*-(2-Furyl)-aniline (13) and *p*-(2-Thienyl)-phenol (14):
The distillate, b.p. 70–72°/0.005 torr resulting from an identical 0.1 mol scale coupling to 2-furylcopper with **4** was acidified with hydrochloric acid. Organic by-products were extracted with ether and the aqueous layer was made alkaline and extracted with ether. The ether extracts were dried and concentrated to give **13**; yield: 34%; m.p. 53–54° (from 60–80° petroleum ether) (lit.[12] m.p. 54°); phenyl urea derivative, m.p. 226–228° (lit.[12] m.p. 227 to 228°).

Thiophene (0.11 mol) was metallated with butyllithium (0.11 mol) at 0° then treated successively with copper iodide and **3** (0.11 mol) as described for the coupling of furylcopper with **3**. An identical work-up procedure including extraction of the required phenolic product with alkali gave **14**; yield: 55%; m.p. 148–149° [from 1:1 petroleum ether (100–120°)/chloroform] (lit.[13] m.p. 148 to 149°).

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