Dichlorobis(triphenylphosphine)nickel (II) Catalysis of Cross Coupling of Grignard Reagents to Halopyridines

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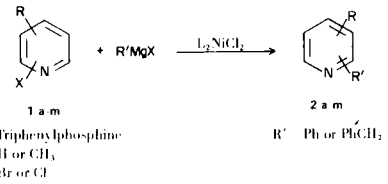
To prepare selected benzomorphans for study of certain nmr spectral properties, we have utilized in this laboratory a nickel-phosphine complex as a catalyst in the homolytic coupling of a Grignard reagent to the pyridine ring (1,2,3). An initial study has been reported involving halogenated quinolines (2) but no other substituents were present which could sterically complicate the coupling. Since quinolines are in general more reactive than pyridines, due to the presence of an adjacent aromatic ring which would stabilize any developing incipient charge on the hetero-aromatic ring, we are prompted to report our results with pyridine derivatives.

The pyridine ring system proved to be particularly well suited for studies on the electronic and steric requirements of the nickel-phosphine complex because of the difference in reactivities of its three potential sites for coupling. Moderate to good yields were obtained from most of the halopyridines studied as summarized in Table I.



1 a-m

2 a-m

L Triphenylphosphine
R H or CH_3
X Br or Cl
R' Ph or $PhCH_2$

A decrease in the formation of coupled product **2** normally resulted under the standard reaction conditions (see general procedure) when the halogen and methyl group were bonded to adjacent carbons (see entries **1d**, **h**, **i**, **k**, and **l**). For pyridines **1h** and **1i** the high reactivity of the 4-halogen apparently partially compensates for the evident unfavorable steric interaction exhibited by the adjacent 3-methyl on the large-nickel-phosphine complex. This is supported by the low yields of **2k** and **2l** derived from the much less reactive 3-bromine (see Table I). Further, after the normal reaction time for **1k** and **1l** (*ca.* 24 hours), vpc analysis (4) of the isolated crude basic fraction of the reaction mixture after hydrolysis and subsequent basification ascertained the presence of substantial starting material in each case, 58% and 52% respectively.

The relatively unreactive 3-bromopyridine gave a moderate yield of the cross-coupled product (see entry **1j**) on treatment with phenylmagnesium bromide but was recovered unchanged after treatment with *t*-butylmagnesium chloride. 2-Bromopyridine after a similar treatment with *t*-butylmagnesium chloride gave an intractable mixture. This latter result was anticipated since β-elimination in alkyl Grignard reagents has been previously reported using dichlorobis(triphenylphosphine)nickel (II) (2). The utility of this reaction involving pyridines should prove to be of synthetic value in the preparation of more complex heterocyclic materials, specifically those requiring the preparation of benzyl picolines (11). An investigation to find a suitable catalyst for arylation and alkylation with Grignard reagents possessing β-hydrogens is underway.

EXPERIMENTAL (12)

General Procedure.

Using the procedure of Thorsett and Stermitz (2), but with slight revisions, a 100 ml. 3-neck flask containing a magnetic stirring bar was fitted with a nitrogen inlet tube, a calcium chloride drying tube and a pressure equalized addition funnel stoppered with a rubber septum. After the flask was flame dried, the catalyst (*ca.* 120 mg.) and 6 ml. of ether were added, followed by the bulk addition of the halopyridine (17.5 mmoles) in 6 ml. of ether. The flask was then cooled by an ice-water bath and with efficient stirring the appropriate Grignard reagent (21 mmoles) in ether was added slowly (*ca.* 15 minutes) from the funnel. The reaction mixture was then stirred at ambient temperature 24 hours under positive nitrogen pressure then poured into cold dilute hydrochloric acid. The acidic layer was washed several times with ether then basified with potassium carbonate and extracted with ether. The combined and dried (potassium carbonate) ether extracts were concentrated and the residue was distilled *in vacuo* to yield the alkylated (arylated) pyridine.

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Table I

Dichlorobis(triphenylphosphine)nickel (II) Catalysis of Coupling of Grignard Reagents to Pyridines **1a-m**(a)

Pyridine **1**	Product **2**	B.p. °C (mm) of **2**	Yield (b) of **2**,%
a 2-Bromo	2-Benzyl	144-146 (0.2)	80
b 2-Bromo	2-Phenyl	135 (0.6)	80
c 2-Bromo-4-methyl	2-Benzyl-4-methyl (c)	134 (0.2)	71
d 2-Bromo-3-methyl	2-Benzyl-3-methyl (d)	124-130 (0.02)	19
e 2-Bromo-6-methyl	2-Benzyl-6-methyl (e)	128-129 (0.15)	81
f 2-Bromo	2-*tert*-Butyl	----------	---
g 2-Chloro	4-Benzyl	120 (0.6)	40
h 4-Chloro-3-methyl	4-Benzyl-3-methyl (f) (j)	159-162 (0.2)	55
i 4-Chloro-3-methyl	3-Methyl-4-phenyl (g)	128-129 (0.15)	54
j 3-Bromo	3-Phenyl	130-140 (0.2)	54
k 3-Bromo-4-methyl	3-Benzyl-4-methyl (h)(j)	140-153 (0.13)	32
l 3-Bromo-4-methyl	4-Methyl-3-phenyl (i)	105 (0.06)	36
m 3-Bromo	3-*tert*-Butyl	----------	---

(a) Usually, 40 mg. of catalyst was employed per gram of halopyridine. The Grignard reagent was prepared from either benzyl chloride, *t*-butyl chloride or bromobenzene. (b) Based on distilled isolated products. Optimum yield is not meant to be implied. (c) M.p. (picrate) 146-148°; lit (5), 149°. (d) M.p. (picrate) 137-138.5°; lit (6), 133°. (e) M.p. (picrate) 145-147°; lit (7), 146-147°. (f) M.p. [picrate (ethanol) 161-162°; lit (8) (water) 135-136°]; (HCl) 184-185.5°. (g) M.p. [picrate (ethanol) 162.5-164°; lit (9) (benzene) 168-169°]. (h) M.p. (picrate) 148-149.5°; (HCl) 201-203°. (i) M.p. (picrate) 144-145°; lit (10), 145°; (HCl) 169-171°; (j) Compound **2h**, *Anal.* Calcd. for $C_{13}H_{14}ClN$: C, 71.1; H, 6.4; N, 6.4. Found: C, 71.1; H, 6.6; N, 6.9. Compound **2k**, *Anal.* Calcd. for $C_{13}H_{14}ClN$: C, 71.7; H, 6.4; N, 6.4. Found: C, 71.1; H, 6.5; N, 6.3.

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(4) Glpc analyses were performed on a Perkin-Elmer 800 gas chromatograph using a 3 ft. x .25 in. 15% Apiezon L on Chromosorb W (80/100 mesh) column at 190°.

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(12) Melting points were taken on a Mel-Temp apparatus and are uncorrected. Proton nmr spectra were obtained on a Hitachi R-20A spectrometer in carbon tetrachloride with tetramethylsilane as internal reference. Infrared spectra were taken with a Perkin-Elmer 237B spectrophotometer. Elementary analyses were performed by Chemalytics Inc., Tempe, Arizona.

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