Alkylation of Haloquinolines by Grignard Reagents with Nickel-Phosphine Complex Catalysts (1)

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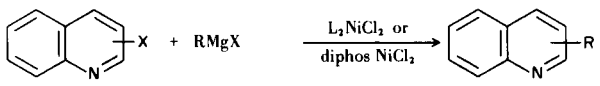
It was recently reported (2) that chlorobenzenes and vinyl chlorides could be alkylated in good yield with alkyl or aryl Grignard reagents if dichlorodiphosphinenickel complexes were used as catalysts. We have discovered that this reaction can be used to synthesize alkylated quinolines in high yield according to the following equation:



[L = $(C_6H_5)_3P$; diphos = $(C_6H_5)_2PCH_2CH_2P(C_6H_5)_2$]

We have found this alkylation to be considerably easier for the preparation of a variety of alkylated quinolines than are syntheses using alkyl lithiums. The reaction should prove complementary to the Taylor and Martin procedure (3) for alkylation and alkenylation of haloheterocycles with Wittig reagents.

Our results are given in Table I and merit some comments. Thus, we have used two slightly different nickel complexes as catalysts depending upon the type of Grignard reagent used. When the Grignard reagent possessed hydrogen bonded to an sp^3 hybridized β carbon atom, we used dichloro[1,2-bis(diphenylphosphino)eth-

TABLE I

Alkylations of 2-Chloroquinoline with Grignard Reagents (RMgX)

R	Catalyst (a)	% Yield (b)	Picrate M.p., °C
Benzyl	A	23 (e)	154-155 (h)
Benzyl	B	57	
Allyl	A	17	(i)
Allyl	B	54	
Phenethyl	A	15 (f)	131-132 (j)
Phenethyl	B	78	
Cyclopentyl (c)	A	72	152-154 (c)
Cyclohexyl (d)	A	90	160-162 (d)
n-Butyl	B	0 (g)	

(a) Catalyst A was dichloro[1,2-bis(diphenylphosphino)ethane] nickel (II) and catalyst B was dichlorobis(triphenylphosphine) nickel (II). (b) Of isolated 2-substituted quinoline based on 2-chloroquinoline. (c) B.p. 76-80° @ 0.05 mm; Lit 163° @ 10 mm, C. Schuster, German Patent, 858,698; *Chem. Abstr.*, 52, 5484b (1958). Picrate: *Anal.* Calcd. for $C_{20}H_{18}N_4O_7$: C, 56.34; H, 4.26; N, 13.14. Found: C, 56.46; H, 4.51; N, 13.02. (d) *Anal.* Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 8.11; N, 6.63. Found: C, 85.24; H, 7.94; N, 6.71. Picrate: *Anal.* Calcd. for $C_{21}H_{20}N_4O_7$: C, 57.27; H, 4.58; N, 12.72. Found: C, 57.18; H, 4.60; N, 12.42. T. Kato, H. Yamanaka, and M. Hikichi, *Yakugaku Zasshi*, 85, 331 (1965); *Chem. Abstr.*, 63, 4250b (1965). (e) Bibenzyl observed as chief product. (f) Styrene observed as major product. (g) Quinoline isolated as only product. (h) Lit. m.p. 154-155° Ref. (2). (i) Product identified by its nmr spectrum. Aryl, 7.1-8.3 δ (m, 6H): $-CH_2^-$, 3.8 δ (doublet of triplets, 2H); vinyl $-CH^-$, 6.1 δ (m, 1H); vinyl CH_2, 5.2 δ (m, 2H). Attempts at purification led to mixtures containing 2-allyl and 2-*cis* and *trans*-propenyl quinoline. (j) Lit. m.p. 131.5-133°, M. Avaramoff and Y. Sprinzak, *J. Am. Chem. Soc.*, 78, 4090 (1956).

TABLE II

Alkylation of Some Haloquinolines with CH_3MgBr

Quinoline	Products	% Yield (a)	M.p., °C	Picrate M.p., °C
4,7-Dichloro	7-Chloro-4-methyl (b)	77	57-58	
	4,7-Dimethyl (c)	trace		228-229 dec. (c)
3-Bromo	3-Methyl	65		187-188 (d)
	2,3-Dimethyl	trace	69-70 (e)	222-224 (f)

(a) Based on starting quinoline. (b) *Anal.* Calcd. for $C_{11}H_{11}N$: C, 67.62; H, 4.54; N, 7.89. Found: C, 67.47; H, 4.71; N, 7.60. (c) Compound identified by its nmr spectrum; Picrate Lit. m.p. 224°, A. J. Ewins and H. King, *J. Chem. Soc.*, **103**, 110 (1913). (d) Lit. m.p. 185-186°, R. H. F. Manske, L. Marion, and F. Leger, *Can. J. Research*, **20B**, 132 (1942). (e) Lit. m.p. 67.5-69°, E. J. Poth, *et al.*, *J. Am. Chem. Soc.*, **52**, 1249 (1930). (f) Lit. m.p. 225°, J. Eliasberg and P. Friedländer, *Ber.*, **25**, 1754 (1892).

ane] nickel (II) (4) as the catalyst since use of the alternate dichlorobis(triphenylphosphine) nickel (II) (5) resulted in elimination to the alkene of the reagent and reduction of the haloquinoline to quinoline. On the other hand, if the bis(diphenylphosphino)ethane catalyst was used with allyl and benzyl magnesium halides the predominant reaction was homo-coupling of the Grignard reagent. In this case, the bis(triphenylphosphine) nickel catalyst gave good yields of the substituted quinolines. Thus, the catalysts are complementary. If no catalyst at all is employed, only complex, intractable mixtures were formed and no alkylated quinolines could be isolated. As far as we are aware, this is the first report of such different behavior for these two (or any similar) catalysts and these selectivities are worthy of further delineation.

We also found that 4,7-dichloroquinoline could be selectively alkylated at the 4-position and that alkylation was possible at the normally unreactive 3-position. These results are reported in Table II.

Although we have not tried alkylating other *N*-heteroaromatic compounds there seems to be no reason to believe that this will not be a general reaction of wide applicability in these systems.

EXPERIMENTAL

All melting points are uncorrected. Nmr spectra were determined on either a Varian A60A or T60 spectrometer using deuterochloroform as solvent and tetramethylsilane as internal standard. Elemental analyses were performed by Chemalytics, Inc., Tempe, Arizona.

Since the procedure used was the same for all the alkylquinolines prepared, only a general procedure will be given.

A 50 ml. 3-neck flask was charged with a magnetic stirring bar, 10.0 mmoles of the haloquinoline and 30-40 mg. of the appropriate catalyst. The flask was fitted with a septum-stoppered, pressure equalized addition funnel, a gas inlet and a second septum covering the remaining neck. The system was then evacuated and flushed with argon several times. Finally, the gas inlet was connected to a mercury trap to relieve pressure built up during the reaction.

Ether (4 ml.) was then added to the flask with a syringe and the funnel was charged with 10.0 mmoles of the alkylmagnesium halide in ether. The flask and its contents were cooled in an ice bath while the Grignard reagent was added with stirring (5-7 minutes). The reaction mixture was stirred as it was allowed to come to room temperature (*ca.* 1 hour) followed by continued stirring for a total of 24 hours. The reaction mixture was then poured into saturated ammonium chloride (20 ml.) and the ether layer was separated and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure to yield the product. The products were purified *via* recrystallization of the picrates and liberation of the quinoline with aqueous ammonia. Final purification was by microdistillation.

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