H, 8.86; N, 11.19. Found: C, 66.89; H, 8.75; N, 11.12.

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Registry No. 1, 826-36-8; 2, 73018-15-2; 3, 73018-16-3; chloroform, 67-66-3; $PhCH_2NEt_3^+Cl^-$, 56-37-1; 18-crown-6, 17455-13-9.

Facile Synthesis of 8-Substituted Quinolines

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8-Substituted quinolines are useful molecular frameworks for studying the interaction of various metals with organic functional groups. Information on the aldehyde decarbonylation reaction,[1] hydroacylation,[2] and metal insertion into carbon–hydrogen bonds[3] has been obtained by using this class of compounds. We wanted a general method for placing groups such as vinyl, propenyl, and aldehyde, which engage in transition-metal-mediated reactions at the 8-postion of quinolines, for our studies on the interaction of metals with carbon–hydrogen, carbon–carbon, and carbon–heteroatom bonds. The classical Skraup synthesis[4] is limited to substituents which can survive strongly acidic reaction conditions. A more flexible synthesis of 8-substituted quinolines appeared to proceed by generation of 8-lithioquinoline via metal–halogen exchange and elaboration of the lithium reagent (or its derived cuprate).[5]

The ease with which the quinoline ring is attacked by nucleophiles[6] limits the conditions under which metal–halogen exchange can occur. In an earlier study, Pearson and co-workers had reported that substituted 8-bromoquinolines underwent lithium–bromine exchange at −70 °C with *n*-butyllithium in THF, using 2 equiv of lithium reagent.[7] They proposed that 2 equiv of lithium reagent was needed due to the coordination of the lithium cation to the quinolinyl nitrogen and the resulting deactivation. This report was surprising in view of the ability of tertiary amines such as TMEDA to promote metalation of hydrocarbons (although we are not aware of any reports on the effect of TMEDA upon metal–halogen exchange).[8]

Our results on the metalation of 8-bromoquinoline are summarized in Table I. Any deactivating effect of the quinolinyl nitrogen is small, since we find excess *n*-butyllithium gives only slightly better yields of 8-methylquinoline. A superior procedure involved the use of *sec*-butyllithium as the metalation reagent. Due to its greater reactivity, excess *sec*-butyllithium was deleterious since products arising from addition to the imine double bond were formed. The use of *tert*-butyllithium gave approximately equal amounts of addition and exchange products. The superiority of *sec*-butyllithium for lithium–bromine exchange has also recently been observed with vinyl bromides.[9] As in Pearson's work, we found 8-chloroquinoline gave only ring addition products.

Table I. Formation of 8-Lithioquinoline

8-BrQuin + RLi → + CH_3I → 8-MeQuin

T, °C	solvent	R	t,[a] min	% 8-MeQuin
−100	THF	*sec*-butyl	60	49
−78	THF	*sec*-butyl	60	73
−78	THF	*sec*-butyl	5	87
−78	ether	*sec*-butyl	60	46
−78	THF	*tert*-butyl	10	*b*
−78	THF	*sec*-butyl[c]	5	56
−78	THF	*sec*-butyl[d]	5	50
−78	THF	*n*-butyl	15	58
−78	THF	*n*-butyl[c]	15	66

[a] Time between addition of the lithium reagent to the cold solution of 8-bromoquinoline and addition of methyl iodide. [b] The reaction contained products from addition to the ring as well as from metal–halogen exchange. [c] Two equivalents of lithium reagent was used. [d] Addition of 8-bromoquinoline as a THF solution to the lithium reagent.

Table II. Synthesis of 8-Substituted Quinolines

electrophile	yield,[a] %	R[d]
$DCON(CD_3)_2$	43	CDO
$HCON(CH_3)_2$	42[b]	CHO
CH_3CHO	64	$CH_3CH(OH)$
$H_2C{=}CHCH_2Br$[c]	65	$CH_2CH{=}CH_2$
PPh_2Cl	32	PPh_2
CH_3I	87[b]	CH_3
$Sn(CH_3)_3Cl$	55	$Sn(CH_3)_3$
ethylene oxide[c]	71[b]	CH_2CH_2OH

[a] Isolated yields of chromatographically homogeneous products. All new products gave satisfactory analytical and spectral data. [b] Determined by NMR integration, with acetophenone as a standard. [c] Prepared via the cuprate reagent. [d] R is the 8-substituent on quinoline.

The products derived from 8-quinolinyllithium and various electrophiles are summarized in Table II. 8-Allylquinoline and 8-(2-hydroxyethyl)quinoline could only be prepared in reasonable yields by means of the cuprate in diethyl ether. Interference from the metalation byproduct, *sec*-butyl bromide, was not a problem with any of the electrophiles studied. However, 8-lithioquinoline can be prepared in the absence of alkyl halide by the analogous metalation of 8-(trimethylstannyl)quinoline. 8-Vinylquinoline was best prepared by dehydration of 8-(1-hydroxyethyl)quinoline with Burgess' salt [ethyl(carboxysulfamoyl)triethylammonium hydroxide inner salt].[10]

Experimental Section

8-(1-Hydroxyethyl)quinoline. To a magnetically stirred solution of 3.0 g (14.4 mmol) of 8-bromoquinoline[11] in 50 mL of dry THF at −78 °C under argon was added dropwise 12 mL of a 1.2 M commercial solution (Aldrich) of *sec*-butyllithium in hexane. After 5 min 1.28 g (29 mmol) of acetaldehyde was added

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(11) Prepared via a Skraup synthesis from 2-bromoaniline, glycerine, sulfuric acid, and iodine; purified by neutralization of the reaction mixture, extraction with methylene chloride, bulb-to-bulb distillation, and preparative medium-pressure liquid chromatography. Further purification, if necessary, was accomplished by recrystallization of the 8-bromoquinolinium hexafluorophosphate from water.

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rapidly, and the solution was warmed to room temperature. The solution was neutralized with 3 N HCl, the solvent was removed, and the yellow oil was taken up in CH_2Cl_2, washed with brine, and dried over $MgSO_4$. Purification of the yellow oil (2.7 g) by medium-pressure preparative liquid chromatography (silica gel column, 1:1 ethyl acetate–hexane eluent) gave 8-(1-hydroxyethyl)quinoline: 1.6 g (64%); mp 48–52 °C (ether–hexane); IR (film) 3380, 1594, 1497, 901, 832, 797, 762 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.73 (dd, J = 4, 2 Hz, 1 H, 2 position), 8.07 (dd, J = 8, 2 Hz, 1 H, 4 position), 7.8–7.2 (m, 4 H, ring), 6.04 (br, 1 H, OH), 5.62 (q, J = 7 Hz, 1 H, HC–O), 1.80 (d, J = 7 Hz, 3 H, CH_3). Anal. Calcd for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.47; H, 6.44; N, 7.83.

8-Allylquinoline via the Cuprate. 8-Lithioquinoline was prepared from 8-bromoquinoline (2.08 g, 10 mmol) as above, except the solvent was diethyl ether. It was added rapidly, via a double-tipped needle packed in dry ice, to a suspension of CuI (0.952 g, 5 mmol) in 20 mL of ether at −20 °C under argon. After warming to −5 °C over 20 min, the clear brown solution was quenched with allyl bromide (1.2 g, 10 mmol) and stirred at −5 °C for 1 h and then at 25 °C for 1 h. The solution was washed three times with ammonium hydroxide solution, once with ammonium chloride solution, and once with brine and dried over $MgSO_4$, and solvent was removed to give a yellow oil. Medium-pressure preparative liquid chromatography (silica gel column, 3:1 hexane–ethyl acetate) gave 8-allylquinoline as a clear oil: 0.55 g (65%); IR (film) 1635, 1594, 1496, 910, 825, 792, 757 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.93 (dd, J = 5, 2 Hz, 1 H, 2 position), 8.10 (dd, J = 8, 2 Hz, 1 H, 4 position), 7.8–7.2 (m, 4 H, ring), 6.6–6 (m, 1 H, HC= allyl), 5.1 (m, 2 H, $=CH_2$ allyl), 4.15 (m, 2 H, CH_2 allyl). Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.19; H, 6.50; N, 8.18.

Registry No. 8-(1-Hydroxyethyl)quinoline, 73038-00-3; 8-bromoquinoline, 16567-18-3; acetaldehyde, 75-07-0; 8-lithioquinoline, 73038-01-4; allyl bromide, 106-95-6; 8-allylquinoline, 73038-02-5; 8-(formyl-*d*)quinoline, 73038-03-6; 8-formylquinoline, 38707-70-9; 8-(diphenylphosphino)quinoline, 28225-52-7; 8-methylquinoline, 611-32-5; 8-(tetramethylstannyl)quinoline, 73038-04-7; 8-(2-hydroxyethyl)quinoline, 73048-42-7; perfluoro-*N*,*N*-dimethylformamide, 4472-41-7; *N*,*N*-dimethylformamide, 68-12-2; diphenylphosphinous chloride, 1079-66-9; iodomethane, 74-88-4; chlorotrimethylstannane, 1066-45-1; ethylene oxide, 75-21-8.

Regioselective 2-Alkylation and 2-Arylation of Piperidine and Pyrrolidine via Organolithiation of Cyclic Imines[1]

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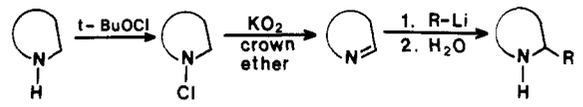
Recently, we reported a reaction of potassium superoxide with primary and secondary organic *N*-chloramines which produces imines in good yield.[2] In our subsequent studies of the mechanism and limitations of this reaction we have examined the reaction of alicyclic *N*-chloramines and found, as expected, that the cyclic imines are formed. In an attempt to characterize these cyclic imines we have taken advantage of the aprotic solvent in which they are generated to study their reaction with organometallics. This paper describes the successful addition of organolithium reagents to the cyclic imines and a new approach to the regioselective alkylation of piperidine and pyrrolidine.

Scheme I

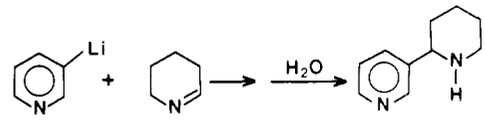


Cyclic imines **1** and **2** can be generated from cyclic

1 2

N-chloramine precursors by reaction with potassium superoxide in ether solution. The solution then can simply be filtered and added dropwise to a solution of excess organolithium. Reaction appears to be immediate at room temperature so that after the addition of a minimum amount of water and subsequent drying of the ether solution, the product can be isolated by distillation. The overall reaction scheme is shown in Scheme I. The yields of 2-alkyl- and 2-arylpiperidines range from 44 to 63% based on the amount of *N*-chloropiperidine used. All attempts to isolate *N*-chloropyrrolidine resulted in its rapid, exothermic decomposition. Thus it was necessary to carry out the reaction without isolation of the chloramine. The yields of 2-substituted pyrrolidines reported here are therefore lower (25–29%). However, if we assume that the yield of *N*-chloropyrrolidine generated in situ is comparable to that of the isolated yield of *N*-chloropiperidine (60%), then the yields of 2-substituted pyrrolidines compare favorably with those of the piperidines. Grignard reagents give no noticeable alkylation or arylation of the cyclic imines under similar conditions.

One of the most interesting applications of our reaction involves the synthesis of the tobacco alkaloid *dl*-anabasine (**7**) or 2-(3′-pyridyl)piperidine (see eq 1). 3-Pyridyllithium



1 7 (1)

is usually generated by metal–halogen exchange between 3-bromopyridine and *n*-butyllithium at low temperature. However, the yields of anabasine are only about 10% when this method is used. The majority of material formed is considerably higher boiling than anabasine. When *tert*-butyllithium is used for the metal–halogen exchange at −120 °C and **1** added to the resulting slurry of pyridyllithium at −100 °C, the yield rises significantly to 44%, and very little high-boiling material is produced. We suspect that the *n*-butyl bromide formed when *n*-butyllithium is used alkylates the piperidide anion but that *tert*-butyl bromide undergoes elimination.

In examining the factors which limit the yields to about 50%, we found that when **1** is the limiting reagent and is added to an excess of *n*-butyllithium, a yield of 58% is obtained. Since the dehydrohalogenation of 40 mmol of *N*-chloropiperidine usually takes about 8 h, we suspected that trimerization accounted for a significant decrease in yield under these conditions. We therefore attempted to quantitate it by allowing a 0.4 M solution of *N*-chloropiperidine to react with KO_2 for 8 h. After removal of the KO_2 by filtration the ether solution was concentrated under vacuum with slight warming. The residue, piperideine trimer, which crystallized overnight, accounted for 35% of the theoretical amount of piperideine formed.

(1) Presented in part before the Division of Organic Chemistry at the 178th National Meeting of the American Chemical Society, Washington, DC, Sept 9–14, 1979.

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