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REGIOSELECTIVE ORTHO LITHIATION OF HALOPYRIDINES

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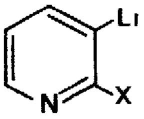
Summary Regioselective ortho lithiation of 2-, 3-, and 4-halopyridines is achieved with lithium diisopropylamide (-78°, tetrahydrofuran) to afford, upon quenching with electrophilic reagents, 2,3- and 3,4-disubstituted pyridines in good to excellent yield.

In connection with synthetic efforts underway in our laboratory, we required an efficient preparation of 3,4-disubstituted pyridines. The enhanced kinetic acidity of the ortho protons in aryl halides[1] and the relative kinetic acidity of the protons in pyridine $(4>3>2)$[2] implied that highly regioselective ortho metalation[3] of halopyridines would obtain. Surprisingly, only a few reports of pyridine metalation, not involving subsequent pyridyne formation, have been recorded.[4-6]

We now report that 2-, 3-, and 4-halopyridines are regioselectively lithiated with lithium diisopropylamide (LDA) at -78° in tetrahydrofuran (THF) to afford the relatively stable 2-halo-3-lithio- (1), 3-halo-4-lithio- (2), and 3-lithio-4-halopyridines (3), respectively. Quenching these anions at low temperatures, to forestall pyridyne formation, with various electrophilic reagents gives the expected disubstituted pyridines in good to excellent yield (Table).



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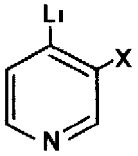

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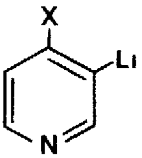

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The stability of the 3-halo-4-lithiopyridines (2) appears to be in the decreasing order $X=F \gg Cl > Br \gg I$, as judged by visual decomposition of the reaction mixture (presumably via 3-pyridyne). Thus, while 2 (X=I) is only fleetingly stable at -95°, 2 (X=Br) is stable for 10-15 min at -78° and 2 (X=Cl) is stable for at least an hour at -78°. In contrast, 2 (X=F) is stable at higher temperatures and, in fact, only succumbs to iodine quenching at about -30°.

The lithiation of 3-chloropyridine appears to be about 96% regioselective at C-4, giving 2 (X=Cl). This was established by subliming the crude material from the reaction of 2 (X=Cl) with iodine, and then subjecting the sublimate to medium pressure preparative liquid chromatography.[8] This afforded 93% of pure 3-chloro-4-iodopyridine (mp 105.5-106°),[9] 3% of 3-chloro-4,5-diiodopyridine (mp 150-151°),[9,10] and 4% of an inseparable mixture[9] of 2-iodo-3-chloropyridine and 3-chloro-5-iodopyridine (ca. 55:45 by nmr) as evidenced by their cleanly separated and distinctive ^{1}H-nmr spectra. Thus, the regiolithiation of 3-chloropyridine is about 96% H-4[11] and 2% each H-2 and H-5, in qualitative agreement with kinetic acidity data.[2b] Future work will establish the precise regiolithiation of the other halopyridines.

Some of the problems encountered with this methodology are worthy of note. If the temperature of the lithiohalopyridine is not maintained at or below -65° during the exothermic quenchings (e.g., those with iodine and diphenyldisulfide), then pyridyne formation will ensue and the yield of disubstituted pyridine will be lowered. However, if the electrophile is added too slowly, then exchange lithiation can occur to give other products. This latter phenomenon is also observed during attempted alkylation of **2** (X=Cl). Treatment of **2** (X=Cl) with *n*-butyl iodide gives a mixture of 3-chloro-4-*n*-butylpyridine and 3-chloro-4-(4-octyl)pyridine. Presumably, inverse quenching will circumvent this exchange lithiation and we will report on this in due course, as well as on the chemistry of these pyridines. For example, we find that 3-pyridyne can be generated and trapped with furan (38% yield of Diels-Alder adduct) by treating 3-chloro-4-iodopyridine with *n*-butyllithium (-78°, THF).[12,13]

Representative Procedure. 3-Chloro-4-trimethylsilylpyridine- An oven-dried 100ml 3-neck round bottom flask fitted with an internal thermometer, addition funnel, nitrogen adapter, rubber septum, and magnetic stirring bar was charged with dry THF (20ml) (distilled from Na/Ph$_2$CO) and dry diisopropylamine (26.4mmol, 3.70ml) (distilled from NaH). To this was added *n*-butyllithium (16.5ml of 1.6M in hexane, 30mmol) at -78° under N$_2$ with magnetic stirring. This solution was stirred at -78° for 20 min and then to this solution of LDA was added over 15 min a solution of 3-chloropyridine (2.51ml, 26.4mmol) in dry THF (5ml) with magnetic stirring and keeping the temperature below -78°. The resulting 3-chloro-4-lithiopyridine precipitated as a white solid in a light yellow solution. The mixture was stirred for 30 min at -78° and then treated over 5-10 min with a solution of chlorotrimethylsilane (3.60ml, 28.4mmol) in dry THF (15ml) keeping the temperature at -78°. The mixture was allowed to warm to room temperature overnight, partially concentrated *in vacuo*, poured into 50ml of 5% aq. NaHCO$_3$, and extracted with ether (3x100ml). The ether extract was washed with water (1x75ml) and brine (2x75ml), dried (K$_2$CO$_3$), and concentrated *in vacuo* to afford 5.37 g of a light amber oil. Distillation gave 4.72 g (96%) of 3-chloro-4-trimethylsilylpyridine, bp 75-77°/1 torr, nmr (CDCl$_3$) δ 0.40 (s, 9H), 7.32 (d, J=5, 1H), 8.50 (d, J=5, 1H), and 8.55 (s, 1H) ppm. Anal. Calcd for C$_8$H$_{12}$NClSi: C, 51.73, H, 6.51, N, 7.54, Cl, 19.09. Found: C, 51.67, H, 6.60, N, 7.51, Cl, 19.05.

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Table Reactions of 2-Halo-3-lithio-, 3-Halo-4-lithio-, and 3-Lithio-4-halopyridines with Electrophiles

Pyridine Anion[a]	X	Electrophile[b]	Product[c]	% Yield[d]	M.P. (B.P./torr)
1	Cl	Me_3SiCl	2-Chloro-3-trimethylsilylpyridine[e]	74	(54-62°/0.4)
2	F	Me_3SiCl	3-Fluoro-4-trimethylsilylpyridine[e]	87	(40-42°/0.5)
2	F	I_2	3-Fluoro-4-iodopyridine	50	80-81°[f]
2	Cl	Me_3SiCl	3-Chloro-4-trimethylsilylpyridine[e]	96	(75-77°/1)
2	Cl	I_2	3-Chloro-4-iodopyridine	65	105.5-106°[g]
2	Cl	PhSSPH	3-Chloro-4-thiophenylpyridine[e]	75	52.5-53°
2	Cl	PhCHO	α-Phenyl-α-(3-chloro-4-pyridyl)methanol[e]	57	140-140.5°
2	Cl	Ph_2CO	α,α-Diphenyl-α-(3-chloro-4-pyridyl)methanol[e]	65	210-211°
2	Cl	Me_2CO	2-(3-Chloro-4-pyridyl)-2-propanol[e]	28[h]	77-78°
2	Br	PhSSPh	3-Bromo-4-thiophenylpyridine[e]	61	53.5-54°
3	Cl	Me_3SiCl	4-Chloro-3-trimethylsilylpyridine[e]	92	(52°/0.65)

[a] Generated by slowly adding with efficient stirring a solution of the halopyridine in THF (4.5M) to a solution of equimolar LDA prepared by treating diisopropylamine in THF (1.2M) with n-butyllithium/hexane at -78°. The lithiopyridines frequently precipitated at -78°.

[b] Slowly added as a solution in THF (2.0M) to the lithiopyridine, keeping the temperature below -65°. The reaction mixture was then slowly warmed to room temperature over 12h.

[c] All products exhibited satisfactory ^{1}H-NMR spectra, showing essentially pure ortho-disubstituted pyridine.

[d] Yields refer to isolated (distilled, recrystallized, or sublimed) product.

[e] This new pyridine gave a satisfactory elemental analysis (C,±0.19%, H,±0.09%, N,±0.07%, Cl,±0.15%, Br,±0.02%, S,±0.04%).

[f] Lit. mp = 87°; T. Talik and Z. Talik, Rocz. Chem , 42, 1861 (1968).

[g] Lit. mp = 105-106°, T. Talik, Rocz. Chem., 36, 1049 (1962).

[h] The predominant pathway appears to be enolate formation, resulting in recovered 3-chloropyridine

References and Notes

1. For example, the protons in fluorobenzene exhibit these relative kinetic acidities (deuterium exchange with lithium cyclohexylamide) ortho, 630,000, meta, 110, para 11, benzene, 1 (A Streitwieser, Jr , and F. Mares, *J Am. Chem. Soc.*, 90, 644 (1968))

2. (a) The relative kinetic acidities in pyridine are H-4, 12, H-3, 9.3, H-2, 1 0 (CH_3ONa/CH_3OD), J A Zoltewicz, G Grahe, and C L Smith, *J Am Chem Soc* 91, 5501 (1969) (b) In 3-chloropyridine H-4 is 53 times more acidic than H-2 and H-5 (CH_3ONa/CH_3OD), J A Zoltewicz and C L. Smith, *Tetrahedron*, 25, 4331 (1969).

3. H. W Gschwend and H. R Rodriguez, *Org Reactions*, 26, 1(1979)

4. Lithiation of 3-chloropyridine with *n*-butyllithium is much less regioselective than it is with LDA and results in substantial *n*-butyllithium addition to the pyridine ring F. Marsais, M Mallet, G Queguiner, and P Pastour, *Comptes rendus*, 275, C, 1535 (1972)

5. Pyridine itself, with LDA/THF, is reported to form 2,2'-bipyridine A J Clarke, S. McNamara, and O. Meth-Cohn, *Tetrahedron Lett* , 2373 (1974).

6. (a) A. I. Meyers and R A. Gabel, *Tetrahedron Lett.*, 227 (1978), report regiometalation (MeLi) of pyridyloxazolines, (b) Lithiation with *n*-butyllithium occurs selectively at the 4-position in 2,3,6-trichloropyridine: N. J. Foulger and B. J Wakefield, *J Organomet. Chem.*, 69, 161 (1974)

7. This effectively separates the chloroiodopyridines from the dark polymeric material (pyridyne derived?) and the small amount of 3-chloropyridine which distills into the trap

8. Patterned after the design by A I. Meyers, J. Slade, R K. Smith, E. D Mihelich, F. M Hershenson, and C D Liang, *J Org Chem* , 44, 2247 (1979)

9 This material gave satisfactory ^{1}H-nmr and mass spectra The ^{13}C-nmr spectrum of 3-chloro-4-iodopyridine was also satisfactory

10 This compound may result from I_2 quenching of 3-chloro-4-iodo-5-lithiopyridine formed by exchange lithiation between 3-chloro-4-iodopyridine and 3-chloro-4-lithiopyridine

11. This value may actually be 93% if the 3-chloro-4,5-diiodopyridine arised from 3-chloro-5-iodopyridine by exchange lithiation

12, The other major product is 3-chloro-4-*n*-butylpyridine (45%). The use of *t*-butyllithium (2 eq) should militate against this alkylation side reaction, see E J Corey and D J Beames, *J Am. Chem. Soc.*, 94, 7210 (1972).

13. This method of 3-pyridyne generation is superior to those involving strong base and 3-halopyridines (M. Mallet, F Marsais, G Queguiner, and P Pastour, *Comptes rendus*, 275, C, 1439 (1972)) or alkali metals and 3,4-dihalopyridines (Th Kauffmann and F. P. Boettcher, *Chem. Ber* , 95, 949 (1962)), both of which give the furan adduct in low yield 15% and 4 5%, respectively

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