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Selective monolithiation of 2,5-dibromopyridine with butyllithium

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Abstract

Selective monolithiation of 2,5-dibromopyridine at either the 2-position or the 5-position is reported. Solvent and concentration strongly influence the selectivity. Coordinating solvents and higher concentration favor the 5-position while non-coordinating solvents and lower concentration favor the 2-position. © 2000 Published by Elsevier Science Ltd.

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As part of our drug development research, we required an efficient method for preparing 5-bromo-2-lithiopyridine and 2-bromo-5-lithiopyridine. A literature search revealed several reports for preparation of 5-bromo-2-lithiopyridine, but none for 2-lithio-5-bromopyridine. Bolm[1] and others[2] have reported selective monolithiation of 2,5-dibromopyridine at the 5-position. Thus, 2-bromo-5-lithiopyridine was generated by lithiation of 2,5-dibromopyridine with BuLi in ether, which, upon quenching with several electrophiles, provided the expected products in 61–83% yield. Bolm also noted that the lithiation gave complex mixtures if THF was employed as solvent. The fact that solvents can profoundly influence the formation, structure and properties of organolithiums[3] led us to examine other solvents for the lithiation of 2,5-dibromopyridine in order to find suitable conditions for selective monolithiation, especially at the previously inaccessible 2-position. In this communication, we would like to report our preliminary findings for the monolithiation of 2,5-dibromopyridine in a variety of solvents at different temperatures and concentrations.

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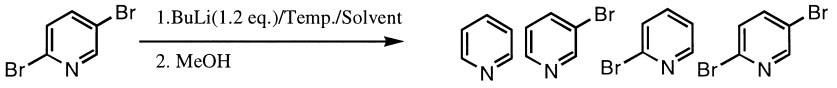
First we examined the use of coordinating solvents ether, MTBE, and THF following the published procedures.[1,2] Thus, BuLi (2.5 M in hexanes, 1.2 equiv.) was added to 2,5-dibromopyridine (0.085 M) in the appropriate solvent at –78°C. After 40 minutes the reaction was quenched with MeOH (10 mL) and the products quantified by HPLC (Table 1, entries 1–5). In coordinating solvents, 2-bromo-5-lithiopyridine is the dominant species. The selectivity of the reactions in ether, MTBE and THF are 12:1, 6.3:1 and 5.8:1, respectively. These results are consistent with the published[1,2] observations. We also noticed a pronounced concentration effect. At lower concentration (0.017 M, ether, –78°C) the selectivity for the 5-position decreases from 12:1 to 4:1 (Table 1, entry 3). At higher concentration (0.28 M, ether, –78°C) the quantity of 2,5-dibromopyridine is increased (Table 1, entry 4).

Table 1
Monolithiation of 2,5-dibromopyridine using BuLi



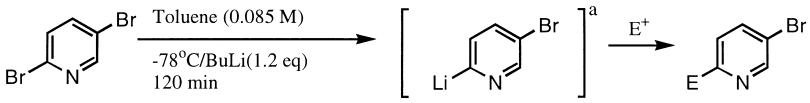
Entry	Solvent(s)	Temp.	Rxn time	Concn.	Products' Distribution (%)[a]			
1	THF	-78°C	40 min 2 hr	0.085 M	12.3 12.3	11.5 12.0	66.5 65.6	9.8 10.1
2	Ether	-78°C	40 min 2 hr 18 hr	0.085 M	4.8 4.3 8.6	6.9 10.6 11.3	84.9 81.7 78.0	3.4 3.4 2.2
3	Ether	-78°C	20 min 2 hr	0.017 M	0.3 2.7	10.7 27.2	44.8 65.7	44.4 4.4
4	Ether	-78°C	40 min 160 min 4 hr	0.28 M[b]	9.6 10.2 6.5	6.7 11.2 22.2	81.6 72.4 59.8	2.1 6.2 11.5
5	MTBE	-78°C	40 min 2 hr 7.5 hr	0.085 M	5.4 5.2 5.1	12.8 17.4 24.9	80.7 76.4 68.5	1.1 1.0 1.5
6	CH_2Cl_2	-78°C	40 min 2 hr	0.085 M	0.4 0.7	83.1 90.3	7.9 8.5	8.6 0.6
7	Toluene	-78°C	30 min 2 hr 3 hr	0.085 M	5.2 5.5 5.0	72.8 83.5 86.8	4.4 4.2 4.2	17.7 6.3 4.0
8	Toluene	-78°C	1 hr 7 hr	0.017 M	0.5 0.6	67.6 94.2	3.0 2.7	29.0 2.5
9	Toluene	-78°C	50 min	0.28 M[b]	6.7	71.8	11.7	9.8
10	Toluene	-50°C	40 min 2 hr	0.085 M	1.5 1.9	90.4 90.2	7.5 7.0	0.5 0.9
11	Ether	-50°C	40 min 2 hr 22 hr	0.085 M	15.1 12.8 8.0	9.1 16.6 40.7	74.8 69.0 50.2	1.0 1.6 1.1

a. Determined by HPLC (Zorbax SB C18, 5 micron, 250x4.6, 0.1% H_3PO_4/ACN 5-95% 12 mins hold, 5 mins, 2 mL/min, 35°C, 235 nM).
b. 2,5-Dibromopyridine and its lithiated pyridines are not completely soluble at this concentration.

Next, we investigated the non-coordinating solvents toluene and dichloromethane and, to our delight, the selectivity is completely reversed (Table 1, entries 6–10). After 2 hours reaction time at –78°C, the selectivity of monolithiation in CH_2Cl_2 (0.085 M) was 11:1 in favor of the 2-position, while in toluene (0.085 M) it was at 20:1. The concentration also plays an important role in the selectivity of monolithiation in toluene. The more dilute the solution the better the selectivity for the 2-position is. For example, at a concentration of 0.017 M, the selectivity for 5-bromo-2-lithiopyridine over 2-bromo-5-lithiopyridine reached equilibrium at 34:1 after 7 hours. Furthermore, at this low concentration, only a small amount of 2,5-dilithiopyridine (0.61%) and 2,5-dibromopyridine (2.5%) were detected (Table 1, entry 8). We also carried out the following trapping experiment to further verify the kinetic regioselectivity in toluene. To a solution of 2,5-dibromopyridine (1.0 equiv.) and TMSCl (2.0 equiv.) in toluene (0.085 M) at –78°C was added BuLi (1.2 equiv.). After the reaction mixture was warmed to room temperature and subjected to normal workup, 2-trimethylsilyl-5-bromopyridine (49%) and 2-bromo-5-trimethylsilylpyridine (3%) were isolated in a ratio of 16 to 1, consistent with the result in entry 7. It should also be noted that 1.2 equiv. of BuLi are necessary as the lithiation using less than 1.2 equiv. of BuLi has a substantial amount of 2,5-dibromopyridine (> 10%) remaining.

In all solvents at –78°C, as the reaction time increased the ratio of 5-bromo-2-lithiopyridine over 2-bromo-5-lithiopyridine increased. This strongly suggests that under these reaction conditions, 5-bromo-2-lithiopyridine is thermodynamically more stable than 2-bromo-5-lithiopyridine. In coordinating solvents, 2-bromo-5-lithiopyridine is kinetically favored. On the other hand, in non-coordinating solvents, 5-bromo-2-lithiopyridine is both kinetically and thermodynamically favored. All the lithiated pyridines are stable, at a concentration of 0.28 M or lower, in THF, ether and toluene for up to 12 hours at –78°C. However, decomposition of these species was especially noticeable in MTBE and CH_2Cl_2 at –78°C after 2 hours reaction time.

Table 2
Monolithiation of 2,5-dibromopyridine in toluene



Entry	E^+	E	Yield (%)[b]	M.p. (°C)	lit. M.p. (°C)
1	DMF	CHO	49	96.4-97.3	78-80[c]
2	DMF/$NaBH_4$[d]	CH_2OH	78	60.1-60.7	52-54[c]
3	TMSCl	TMS	51	Oil	New compd
4	MeSSMe	SMe	80	39.0-39.6	38-39[e]
5	MSSMe/Oxone[f]	SO_2Me	77	94.7-96.6	95-96[e]
6	PhCOMe	C(OH)MePh	81	69.3-70.8	New compd
7	Me_2CO	$C(OH)Me_2$	79	Oil	New compd
8	PhCHO	CH(OH)Ph	82	Oil	N/A[g]

a. ^1H NMR of 2-lithio-5-bromopyridine (Toluene-d_8, -78 °C): δ 6.1-6.2 (m, 2H), 7.8 (s, 1H). b. Isolated yields after flash column chromatography. c. See reference 7. d. *In situ* treatment of $NaBH_4$ (2 eq.) gave the alcohol directly. e. See reference 8. f. *In situ* treatment of H_2O/ MeOH / Oxone (3 eq.) afforded the sulfone directly. g. See reference 9.

We also ran the experiments at –50°C and found that the temperature is not a major factor in controlling the initial selectivity, although the equilibrium is achieved in a shorter period of time (Table 1, entries 10 and 11). Decomposition of the lithiated pyridines began after 1 hour at –50°C even in THF, ether and toluene.

We then briefly examined the scope of the reaction of 2-lithio-5-bromopyridine with several electrophiles under our reaction conditions. The results are summarized in Table 2.[4] Especially worth noting are the reactions with enolizable ketones[5] (acetophenone and acetone), which gave the tertiary alcohols[6] in very good yields (Table 2, entries 6 and 7). Also, no other regioisomers were detected in the reaction mixtures.

From a practical point of view, we recommend that the lithiation reactions to form 2-bromo-5-lithiopyridine and 5-bromo-2-lithiopyridine be run in ether and toluene at –78°C, respectively. In the case of 2-bromo-5-lithiopyridine, the electrophile should be added within 40 minutes of the addition of BuLi. However, in the case of 5-bromo-2-lithiopyridine the electrophile should be added at least 2 hours after the addition of BuLi. We have successfully applied these reaction conditions to the synthesis of adducts of 2-bromo-5-lithiopyridine and 5-bromo-2-lithiopyridine in ether and toluene on 500 g scales.

In conclusion, we have discovered an efficient procedure to generate previously inaccessible 2-lithio-5-bromopyridine (up to 34:1 selectivity ratio) via monolithiation of 2,5-dibromopyridine using BuLi (1.2 equiv.) in toluene at –78°C. We also identified two key factors that strongly influence the selectivity of this reaction: solvent and concentration.

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4. All products exhibited satisfactory physical data (^{1}H NMR, ^{13}C NMR and HRMS) consistent with their assigned structures.
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6. Representative procedure: To a solution of 2,5-dibromopyridine (1.0 g, 4.2 mmol) in toluene (50 mL) at –78°C was slowly added BuLi (2.5 M in hexanes, 2.0 mL, 5.0 mmol). The reaction mixture was aged for 2 hours. Electrophile (5.5 mmol) was added. The solution was stirred for 1 hour at –78°C and then warmed to –10°C. NH_4Cl saturated aqueous solution (10 mL) was added and the mixture was warmed to rt. Separation of two phases gave toluene solution, which was concentrated to dryness. Purification by flash column chromatography afforded the desired product.
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