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Remarkable effect of water in a regioselective lithiation of 5-(*tert*-butoxycarbonyl)-7-methoxy-1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline

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Abstract

5-(*tert*-Butoxycarbonyl)-7-methoxy-1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**1b**) was lithiated regioselectively at C-6 with *sec*-BuLi (3.0 equiv.) in the presence of water (1.0 equiv.) in ether at –78°C. Under conventional conditions, **1b** was lithiated non-regioselectively at the C-6, C-8 and C-2 positions.

Keywords: lithiation; regioselection; indoles; marine metabolites.

Directed lithiation is an extremely powerful method for regioselective functionalization of aromatic and heteroaromatic compounds.[1] The site selectivities of the lithiation of multi-substituted substrates are controlled mainly by the relative *ortho*-directing abilities of the hetero-atom-containing substituents on the substrates. In some cases, however, lithiating agents, solvents, and additives also exert remarkable effects on the regioselectivities.[2] Recently, we have reported C-6-selective lithiation of 5-(*tert*-butoxycarbonyl)-1-triisopropylsilyl-7-methoxy-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**1a**) and its application to the first total synthesis of veiutamine (**2**),[3] a new type of anti-tumor pyrroloiminoquinone marine alkaloid having a *p*-hydroxybenzyl substituent at C-6.[4] We planned to extend this strategy for the synthesis of 6-substituted 1-methyl-pyrroloiminoquinone alkaloids, such as isobatzellines A and C (**3a**, **b**),[5] via directed lithiation of an analogous 1-methylated compound **1b**. In this letter, we wish to report an amazing effect of water as an additive for the regioselective lithiation of **1b**, which was discovered serendipitously during the course of this work.

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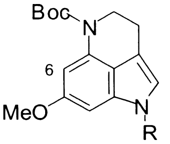
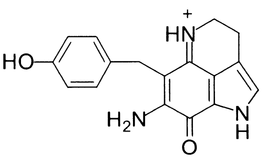


1a: R=Si(i-Pr)$_3$
1b: R=Me



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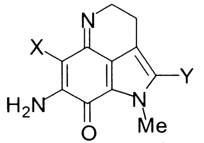
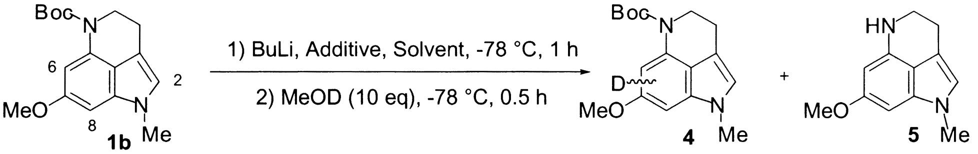


3a: X=Cl, Y=SMe
3b: X=Cl, Y=H

The results of the lithiation of **1b** followed by MeOD quenching are summarized in Table 1. In general, the ring-deuterated compound **4** and the Boc-deprotected by-product **5** were formed. The compound **5**, which must be formed by nucleophilic attack of BuLi against Boc carbonyl, was readily removed by flash chromatography. The regioselectivity of the lithiation was estimated by ^{1}H NMR analysis of the recovered substrate.[6] In entry 1, we tested the standard lithiation conditions (*sec*-BuLi, TMEDA, ether, –78°C, 1 h), which were successfully employed for the C-6-selective lithiation of **1a**.[3] To our surprise, the lithiation was non-regioselective and deuterium was incorporated in ca. 1:1:1 ratio at the C-6, C-8 and C-2 positions. This result indicated that *ortho*-directing ability of the *N*-Boc group[7] was not strong enough to effect clean *ortho* lithiation at C-6 under these conditions. In entry 2, we omitted the use of TMEDA in order to enhance the coordinating effect of the Boc group on *sec*-BuLi. However, the lithiation was again non-regioselective.

Table 1
Lithiation-deuteration of 5-Boc-7-methoxy-1-methyl-1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline (**1b**)



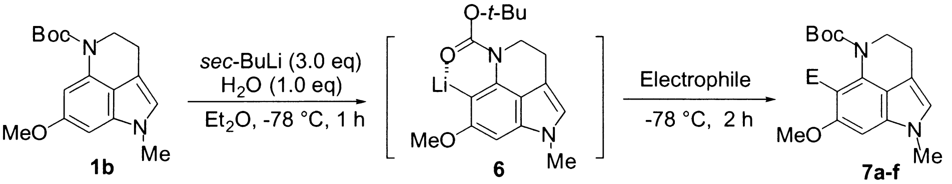
Entry	BuLi (eq)[a]	Additive (eq)[a]	Solvent	**1b**+**4** (%)[b]	Deuterium content (%)[c]				**5** (%)[b]
					C-6	C-8	C-2	Total	
1	*sec* (1.5)	TMEDA (1.8)	Et$_2$O	76	23	29	25	77	14
2	*sec* (1.5)	——	Et$_2$O	65	24	25	25	74	30
3	*sec* (2.0)	H$_2$O (1.0)	Et$_2$O	77	39	2	0	41	11
4	*sec* (3.0)	H$_2$O (1.0)	Et$_2$O	70	91	1	0	92	23
5	*sec* (3.0)	H$_2$O (0.5)	Et$_2$O	65	95	1	1	97	34
6	*sec* (3.0)	H$_2$O (1.0)	THF	90	20	44	32	96	9
7	*n* (3.0)	H$_2$O (1.0)	Et$_2$O	98	2	0	0	2	0
8	*tert* (3.0)	H$_2$O (1.0)	Et$_2$O	40	26	22	23	71	13
9	*sec* (3.0)	MeOH (1.0)	Et$_2$O	68	63	13	10	86	22
10	*sec* (3.0)	*tert*-BuOH (1.0)	Et$_2$O	57	21	19	16	56	35
11	*sec* (2.0)	LiOH (1.0)	Et$_2$O	67	84	3	0	87	27

a) Equivalent against the substrate **1b**. b) Isolated yield. c) Deuterium content was estimated by ^{1}H nmr analysis.

After a number of disappointing experiments, we happened to succeed in the selective C-6 lithiation. After careful inspection of the reaction conditions, we speculated that water contaminated in **1b** could be the origin of this success. Thus, we tested a lithiation using completely dried **1b** in the presence of a controlled amount of water, and confirmed excellent regioselectivity at C-6 (entry 3). Under the optimized conditions [*sec*-BuLi (3.0 equiv.), H_2O (1.0 equiv.), ether, –78°C, 1 h], the substrate was recovered in 70% yield and the deuterium incorporation at C-6 was over 90% (entry 4). It was of interest that a lesser amount (0.5 equiv.) of water was also effective to achieve selective C-6 lithiation (entry 5). It was found that utilization of ether as a solvent was essential for the C-6 regioselectivity. When THF was employed, the reaction became non-regioselective (entry 6). The use of *sec*-BuLi as a lithiating agent was also essential. *n*-BuLi was not basic enough to effect deprotonation (entry 7). *tert*-BuLi resulted in non-regioselective lithiation (entry 8). The effects of other hydroxylic additives, such as MeOH and *tert*-BuOH, were also examined. Although MeOH induced moderate C-6-selectivity (entry 9), the more bulky and hydrophobic *tert*-BuOH resulted in less efficient and non-regioselective lithiation (entry 10). Finally, we found that utilization of dried LiOH in place of water was also effective for selective C-6 lithiation, though LiOH was slightly soluble in ether (entry 11).

Having established the conditions for C-6-selective lithiation of **1b** by deuteration experiments, we examined the functionalization of **1b**. Thus, **1b** was treated with 3.0 equiv. of *sec*-BuLi in the presence of 1.0 equiv. of water in ether at –78°C for 1 h, and the resulting lithio species **6** was reacted with a series of common electrophiles. After usual workup and chromatographic purification, the C-6-substituted compounds were isolated in good yields. The results are summarized in Table 2.

Table 2
Synthesis of C-6-substituted 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline derivatives **7a**–**f**



Entry	Electrophile	Product	E	Yield (%)[a)]
1	MeI	**7a**	Me	52
2	Me_2NCHO	**7b**	CHO	70
3	MeSSMe	**7c**	MeS	60
4	Cl_3CCCl_3	**7d**	Cl	65
5	$BrCF_2CF_2Br$	**7e**	Br	65
6	*p*-MeO-C_6H_4-CHO	**7f**	*p*-MeO-C_6H_4-CH(OH)	70

a) Isolated yield.

In conclusion, we have discovered a remarkable effect of water for the regioselective lithiation of **1b**. Although a variety of additives have been employed to change the reactivity of organolithium reagents,[2,8] utilization of water for this purpose has so far not been reported. This is apparently due to a preconception of organic chemists, i.e., that completely dried conditions are essential for organolithium reactions. However, now we can propose a *sec*-BuLi–H_2O (probably *sec*-BuLi–LiOH mixed aggregate generated in situ[9]) system is a useful lithiating agent and is worth trying when selective lithiation cannot be achieved under conventional lithiation conditions.

General experimental procedure for the lithiation of ***1b*** *followed by the reaction with electrophiles:* Under an atmosphere of Ar, water (6 μL, 0.33 mmol) was added via a microsyringe to a solution of **1b** (100 mg, 0.33 mmol) in dry ether (3.3 mL) at room temperature. After stirring at –78°C for 20 min, 0.91 M solution of *sec*-BuLi in hexane–cyclohexane (1.10 mL, 0.99 mmol, Kanto Chemical Co., Inc.) was added dropwise, and the mixture was stirred for an additional 1 h. An appropriate electrophile (1.0 mmol) was added as a neat liquid or as an ether solution. After stirring at –78°C for 2 h, the reaction mixture was quenched with saturated aqueous NH_4Cl. The mixture was allowed to warm to room temperature and the products were extracted with ether. The extract was washed sequentially with water and brine solution, dried over Na_2SO_4, and evaporated. The residue was purified by flash chromatography over silica gel using hexane:ethyl acetate (10:1∼5:1) to give the product **7**.

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