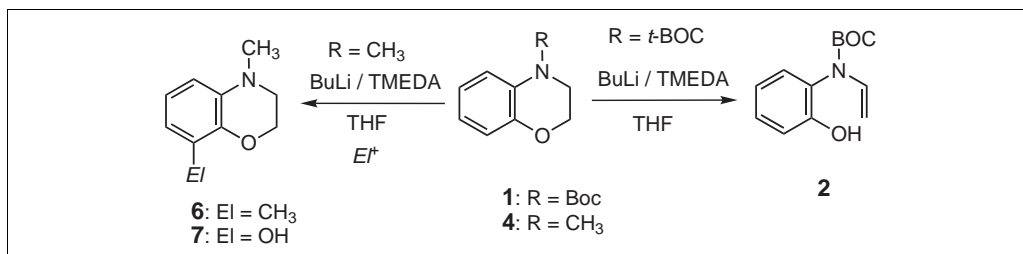# Lithiation of *N*-Protected-dihydro-1,4-benzoxazines

Yansong J. Lu, Bin Hu,* Mahavir Prashad,* Shaum Kabadi [1], Oljan Repič
and Thomas J. Blacklock

Process R&D, Chemical and Analytical Development
Novartis Pharmaceuticals Corporation
One Health Plaza, East Hanover, NJ 07936, USA.
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Lithiation of *N*-protected-2,3-dihydro-1,4-benzoxazines is described. Lithiation of *N*-(*tert*-butoxycarbonyl)-2,3-dihydro-1,4-benzoxazine (**1**) with BuLi/TMEDA occurred in the α-position to nitrogen on the heterocyclic ring, leading to the unexpected ring-opened product **3**. On the other hand, lithiation of *N*-methyl-2,3-dihydro-1,4-benzoxazine (**4**) took place at the oxygen-adjacent *ortho*-position of the aromatic ring.
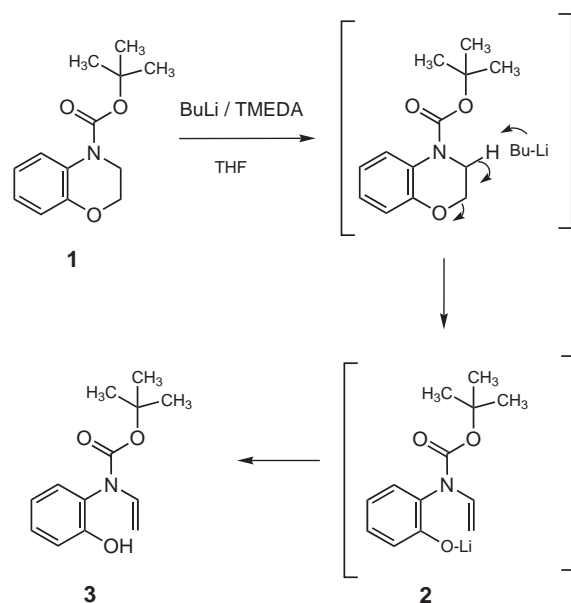
Introduction.

Neighboring group-assisted metalation is a powerful method in the synthesis of substituted aromatic compounds [2,3,4]. The *N-tert*-butoxycarbonyl (Boc) group has been reported to facilitate the *ortho*-lithiation of anilines [5] and α-lithiation of piperidines [6,7]. In tetrahydroquinoline only *ortho*-lithiation in the aromatic ring is reported [7]. However, metalation at the 2-position in tetrahydroquinoline occurred if *N*-COOLi [8] was used instead of *N-tert*-butoxycarbonyl (Boc) group as the directing group. Methoxy group is also known to be a stronger directing metalation group than –NMe$_2$ [9,10]. Therefore, *N*-protected 2,3-dihydro-1,4-benzoxazines present an interesting heterocyclic system to study the lithiation to determine whether the *ortho*-lithiation will be directed by the *N*-Boc or the O-CH$_2$ group. To the best of our knowledge such a study with this heterocyclic system has not been reported in the literature [11]. In this article we describe our results on the directed lithiation of *N*-Boc and *N*-Me 2,3-dihydro-1,4-benzoxazines (**1** and **4** respectively).

Results and Discussion.

N-(*tert*-Butoxycarbonyl)-2,3-dihydro-1,4-benzoxazine (**1**) [12] can be readily prepared from 2-aminophenol in two steps. Treatment of **1** with 2.0 equiv of BuLi/TMEDA interestingly led to the lithiation at the α-position to nitrogen in the heterocyclic ring leading to the unexpected ring-opening product **3** in 60% yield (Scheme 1). The structure of **3** was assigned based on

spectroscopic data and confirmed by X-ray crystallography (ORTEP, Figure 1). The α-lithiation in the heterocyclic ring in **1** was in sharp contrast to the results reported with tetrahydroquinoline where *ortho*-lithiation exclusively occurred in the aromatic ring [7] suggesting that the ring oxygen in **1** is playing a significant role in the reversal of the directed lithiation [13].
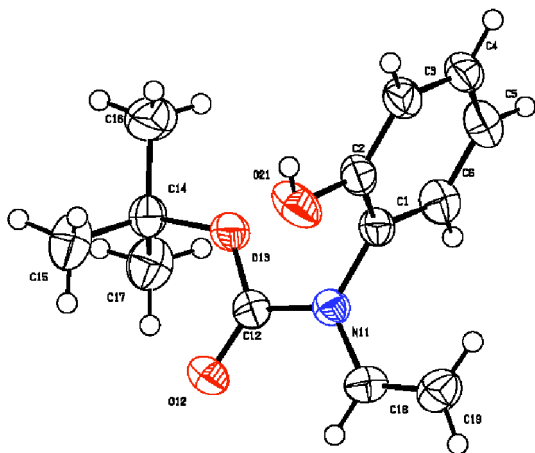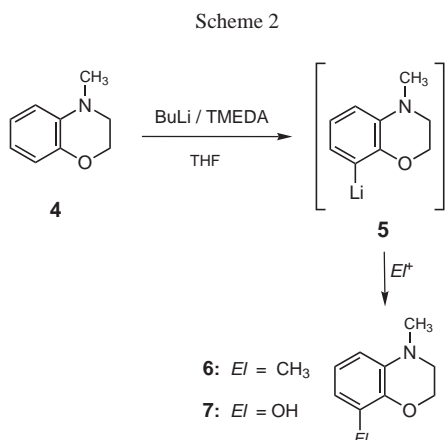
Scheme 1

Figure 1. ORTEP representation of the crystal structure of compound **3**.

We then decided to study the lithiation with *N*-methyl-2,3-dihydro-1,4-benzoxazine (**4**) [14]. The desired compound **4** was obtained in quantitative yield in two steps by the treatment of compound **1** with conc. HCl in MeCN (to deprotect the *N*-Boc group), followed by *N*-methylation of the resulting intermediate with BuLi/MeI. The lithiation in **4** occurred at the oxygen-adjacent *ortho*-position of the aromatic ring. Thus, when **4** was treated with 4.0 equiv of BuLi/TMEDA, followed by treatment of the resulting lithiated species **5** with MeI afforded **6** in 50% yield (Scheme 2). Similar results were obtained with *sec*-BuLi/TMEDA. The structure of **6** was confirmed by comparison of the spectral data with those of an authentic sample that was prepared starting from 2-amino-6-methylphenol using the same method as used for the preparation of compound **4**. Similarly, treatment of the lithiated species **5** with bis(trimethylsilyl)peroxide [15] afforded the phenol **7** in 30-40% yield (due to incomplete reaction). These results demonstrated that the lithiation in *N*-methyl-2,3-dihydro-1,4-benzoxazine (**4**) was directed by the O-CH$_2$ group over CH$_3$-N-CH$_2$.

Scheme 2

6: *El* = CH$_3$

7: *El* = OH

EXPERIMENTAL

Reaction of *N*-(*tert*-Butoxycarbonyl)-2,3-dihydro-1,4-benzoxazine (**1**) with Butyllithium.

To a cold (−20 °C) solution of TMEDA (tetramethylethylenediamine) (1.16 g, 10 mmol) in dry THF (20 mL), was added a solution of 1.6 *M* BuLi in hexane (6.25 mL, 10 mmol). The mixture was stirred at −20 °C for 10 min. Then a solution of *N*-(*tert*-butoxycarbonyl)-2,3-dihydro-1,4-benzoxazine (**1**; 1.175 g; 5.0 mmol) in THF (3 mL) was added at −20 °C. The reaction mixture was stirred at −20 °C for 1 h and then at 20 °C for 2 h. The reaction mixture was cooled to −20 °C and quenched with aqueous NH$_4$Cl (3.0 mL). THF was removed and isopropyl acetate (30 mL) and water (10 mL) were added to the mixture. This solution was washed with 20% citric acid (15 mL), water (20 mL), sat. aqueous NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and chromatographed over silica gel (some decomposition of the product was observed on silica gel) using *i*-PrOAc/heptane mixture as the eluant to afford pure 2-*N*-(*tert*-butoxycarbonyl)-*N*-vinyl-amino)phenol (**3**): 0.7 g (60%). mp: 114-116 °C. ^{1}H NMR (600 MHz, CDCl$_3$): δ 7.31 (dd, J = 15.8 & 9.0 Hz, 1H), 7.28-7.23 (m, 2H), 7.07 (d, J = 9.0 Hz, 1H), 7.02 (d, J = 9.0 Hz, 1H), 6.99-6.93 (m, 1H), 5.16 (br s, 1H), 4.29 (d, J = 9.0 Hz, 1H), 3.96 (d, J = 15.8 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 152.65, 151.78, 133.25, 129.59, 129.48, 124.58, 121.12, 117.00, 94.05, 82.22, 28.07; m/z 221 [(M+1)$^+$-Me], 136 [(M+1)$^+$-BOC].

Anal. Calcd for C$_{13}$H$_{17}$NO$_2$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.24; H, 6.95; N, 6.02.

Reaction of *N*-Methyl-2,3-dihydro-1,4-benzoxazine (**4**) with Butyllithium and Iodomethane.

To a cold (−20 °C) solution of TMEDA (2.32 g, 20 mmol) in dry THF (20 mL), was added a solution of 1.6 *M* BuLi in hexane (12.5 mL, 20 mmol). The mixture was stirred at −20 °C for 10 min. Then a solution of *N*-methyl-2,3-dihydro-1,4-benzoxazine (**4**; 0.745 g; 5.0 mmol) in THF (3 mL) was added at −20 °C. The reaction mixture was stirred at −20 °C for 1 h and then at 20 °C for 2 h. The reaction mixture was cooled to −20 °C and iodomethane (22.5 mmol) was added. THF was removed and isopropyl acetate (30 mL) and water (10 mL) were added to the mixture. This solution was washed with 20% aqueous citric acid (15 mL), water (20 mL), sat. aqueous NaHCO$_3$ (20 mL) and water (20 mL). The organic layer was dried over anhydrous sodium sulfate, concentrated and chromatographed over silica gel using *i*-PrOAc/heptane mixture as the eluant to afford the pure 4,8-dimethyl-3,4-dihydro-2*H*-benzo[1,4]oxazine (**6**): 0.41 g (50%). ^{1}H NMR (600 MHz, CDCl$_3$): δ 6.85-6.70 (m, 1H), 6.65-6.50 (m, 2H), 4.40-4.25 (m, 2H), 3.35-3.20 (m, 2H), 2.87 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$): δ 142.40, 136.25, 125.19, 120.47, 120.21, 110.53, 64.80, 49.35, 39.13, 15.93; m/z 164 [(M+1)$^+$].

Anal. Calcd for C$_{10}$H$_{13}$NO: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.61; H, 8.03; N, 8.38.

Reaction of *N*-Methyl-2,3-dihydro-1,4-benzoxazine (**4**) with Butyllithium and Bis(trimethylsilyl)peroxide.

An analogous reaction was performed employing *N*-methyl-2,3-dihydro-1,4-benzoxazine (**4**; 0.745 g; 5.0 mmol) and

bis(trimethylsilyl)peroxide (22.5 mmol) instead of iodomethane as the reagent. The crude product was chromatographed over silica gel using *i*-PrOAc/heptane mixture as the eluant to afford the pure 4-methyl-3,4-dihydro-2*H*-benzo[1,4]oxazin-8-ol (**7**): 0.33 g (40%). mp: 62-64 °C; ^{1}H NMR (600 MHz, CDCl$_3$): δ 6.72 (t, J = 8.0 Hz, 1H), 6.38 (dd, J= 8.0 Hz & 1.5 Hz, 1H), 6.27 (dd, J = 8.0 & 1.5 Hz, 1H), 5.40 (br s, 1H), 4.34 (t, J = 4.5 Hz, 2H), 3.27 (t, J = 4.5 Hz, 2H), 2.87 (s, 3H); ^{13}C NMR (150 MHz, CDCl$_3$): δ144.58, 136.72, 131.14, 120.96, 105.13, 104.87, 65.11, 49.19, 38.82; m/z 166 [(M+1)$^+$].

Anal. Calcd for C$_9$H$_{11}$NO$_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.54; H, 6.80; N, 8.86.

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