Lithiation of Aryl Bromides Possessing α-Proton of Carbonyl Groups

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Abstract: A new methodology for metalation of aryl bromide possessing an active methylene adjacent to carbonyl groups is described. In order to avoid self-quenching, selective deprotonation was necessary prior to halogen-metal exchange reaction. For this purpose, mesityllithium was found to be the best choice. Subsequent treatment with *n*-BuLi resulted in the lithium-bromine exchange to generate the dianion, which was successfully trapped with some electrophiles in good yield. This method was applied to the efficient synthesis of a novel carbapenem.

Key words: aryllithium, active methylene, lithium-bromine exchange reaction, intramolecular protonation, enolate, mesityllithium

Metal-halogen exchange reaction is an important transformation, which mediates functionalization of aryl and vinyl compounds in synthetic organic chemistry. Metalation of a variety of functionalized aryls and vinyls using Zn and Mg have been reported to date.[1] However, there is no report on metal-halogen exchange reaction of aryl halides possessing an acidic proton at the carbon adjacent to functional groups such as carbonyl, nitrile, and sulfonyl groups, which stabilize their α-carbanions, probably due to the self protonation/deprotonation.[2] In the course of studies toward a practical and large scale synthesis of our drug candidate, carbapenem **1** (Figure 1),[3] we required a clean metalation of β-(4-bromophenyl)alanine side structure **3** for an efficient synthesis of the thiol side chain **2** (Scheme 1).[4] Herein we wish to report metal-halogen exchange reaction of aryl bromide possessing an active methylene adjacent to carbonyl groups, and its application to the lithiation of β-(4-bromophenyl)alanine side structure **3**.

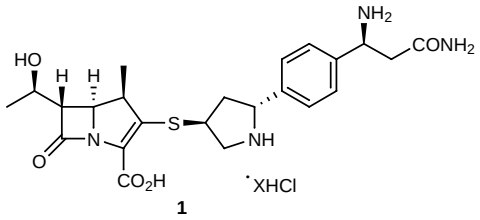

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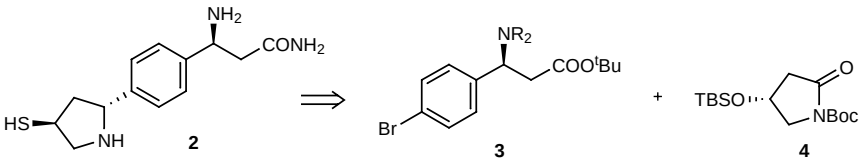
Figure 1

Reactions of *tert*-butyl 3-(4-bromophenyl)propionate **5a** as a representative of aryl halide having a proton α to an ester group with various metalating agents are summarized in the Table. Treatment of **5a** with *sec*-BuLi at –78 °C, followed by quenching with water gave the protonated product **7a** in 53% yield, indicating that the bromine-lithium exchange reaction certainly took place.[5,6] Attack of *sec*-BuLi on the ester was observed as a major side reaction. To our surprise, quenching with DMF instead of water did not give the formylated product **6a**, and the protonated product **7a** was obtained (Figure 3) in a similar



2 **3** **4**

Scheme 1

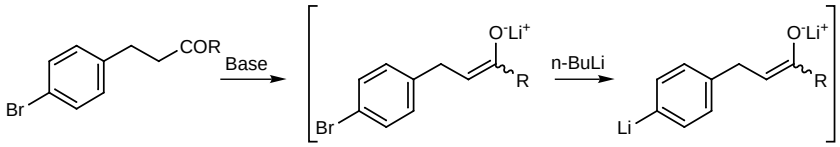


Figure 2

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yield as above (entry 1). It is most likely that the aryllithium generated from the bromine-lithium exchange reaction was quenched with the acidic proton(s) on the carbon adjacent to the ester group. Therefore, we desired a new methodology to obviate the intramolecular quenching. Our initial concept involved deprotonation of an acidic proton first with a non-nucleophilic base (which is not capable of metal-halogen exchange reaction) and subsequent metal-halogen exchange on the aromatic ring with *n*-BuLi (Figure 2).[7]

Lithium amides such as LDA was not valuable for this purpose since the resulting amine can act as a proton source (entry 2). Metal hydride such as sodium hydride might be useful, however, evolution of hydrogen gas is not amenable to large-scale synthesis. Alkyllithiums like as MeLi and PhLi ended in competition with attack at the ester group (entries 3 and 4). It has been reported that bulky, non-nucleophilic mesityllithium is able to cleanly produce enolates of carbonyl compounds.[8] In addition, the resulting mesitylene no longer acts as a proton source. In this regard, the combination of mesityllithium (as a base to generate the ester enolate) and *n*-BuLi (as an agent to raise the bromine-metal exchange reaction) seemed to be of the best choice. In fact, treatment of **5a** with 1.1 equivalents of mesityllithium, followed by 1 equivalent of *n*-BuLi generated the dianion, which was trapped with DMF to afford the desired the formylated product in 74% yield (entry 5).[9] Mesityllithium has been recently reported to undergo iodine-lithium exchange reaction, but such reaction was not observed in this case.[10] Even when 2 equivalents of mesityllithium were used, the second mesityllithium left the bromide intact (entry 6). Mesityllithium did not attack a smaller alkyl ester such as ethyl ester **5b** (entry 7) and tolerated the diethylamide **5c** (entry 8). Thus, mesityllithium was found to be a very useful base for the enolate formation, with no reaction with arylbromide and regeneration of a proton donor.

Table Reactions of *tert*-Butyl 3-(4-Bromophenyl)propionate **5a** with Various Metalating Agents

Entry	R	Base/Metalating Agent	**5**	**6**	**7**
1	*t*-BuO	*sec*-BuLi	n.d.[a]	n.d.	53
2	*t*-BuO	LDA (1.1 equiv)/ *n*-BuLi (2.6 equiv)	n.d.	18	64
3	*t*-BuO	MeLi (1.2 equiv)/ *n*-BuLi (2.2 equiv)	16	n.d.	21
4	*t*-BuO	PhLi (1.2 equiv)/ *n*-BuLi (1.3 equiv)	10	n.d.	13
5	*t*-BuO	Mesityllithium (1.1 equiv)/*n*-BuLi (1 equiv)	n.d.	74	<5
6	*t*-BuO	Mesityllithium (2 equiv)	95	n.d.	n.d.
7	EtO	Mesityllithium (1.1 equiv)/*n*-BuLi (1 equiv)	n.d.	71	<5
8	NEt_2	Mesityllithium (1.1 equiv)/*n*-BuLi (1 equiv)	n.d.	67	<5

[a] n.d. = not determined

Next, we applied this methodology to the synthesis of the thiol side chain of novel carbapenem **1**. β-Amino acid fragment **11** was prepared as shown in Scheme 2. 4-Bromobenzaldehyde (**8**) was converted to α,β-unsaturated *t*-butyl ester **9** by Horner–Emmons reaction (96%). Subsequent asymmetric Michael reaction using (*R*)-*N*-(α-methylbenzyl)benzylamine (**10**) gave **11** in good yield and selectivity (95%, 94% de).[11,12]

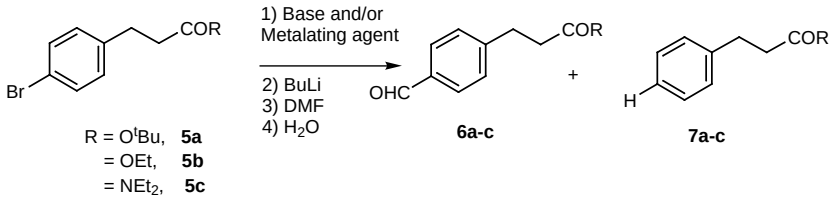
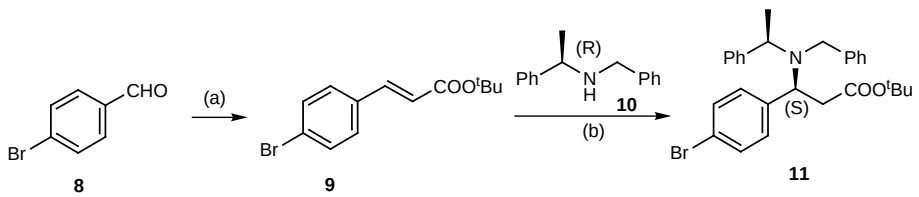


Figure 3



Scheme 2 *Reagents and conditions*: (a) $(EtO)_2P(O)CH_2COO$-*t*-Bu, NaH, toluene (b) **10** (2 equiv), *n*-BuLi (2 equiv), THF, –78 °C.

With the desired β-(4-bromophenyl)alanine fragment **11** in hand, we then implemented our protocol. Treatment of **11** with mesityllithium followed by treatment with *n*-BuLi generated the dianion **12** (Figure 4), which was quenched with DMF to afford the desired formylated product **13** (Figure 4) in 87% yield.

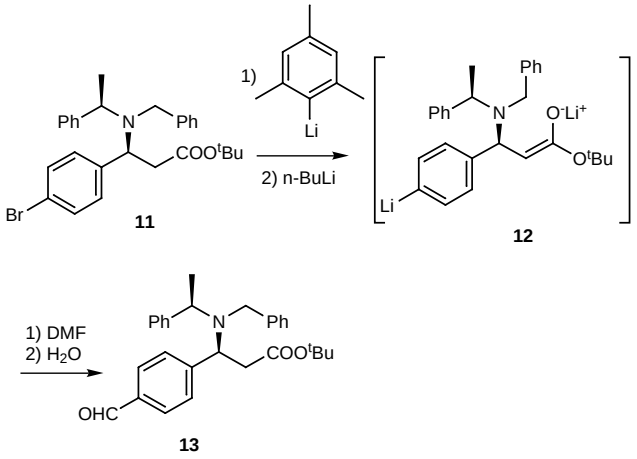


Figure 4

As we confirmed that the mesityllithium/*n*-BuLi protocol successfully produced the dianion **12**, the reaction with 4-TBSoxy-*N*-Boc-pyrrolidin-2-one (**4**) was finally attempted. Addition of the dianion **12** to **4** proceeded cleanly and the desired coupling adduct **14** was obtained in 74% yield (Figure 5). Compound **14** could be converted to the thiol side chain **2** for the synthesis of a novel carbapenem **1**. The whole synthetic work will be reported elsewhere as a full article.

In conclusion, it was found that mesityllithium could act as a non-nucleophilic base without reaction with aryl bromide and regeneration of a proton donor. Combination of mesityllithium with *n*-BuLi allowed us to develop a new synthetic technique for metalation of aryl bromides possessing active methylene adjacent to carbonyl groups.

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(5) The reaction with *n*-BuLi resulted in attack on the ester.

(6) Magnesium- or zinc-based approaches were all unsuccessful: *i*-PrMgCl, (*i*-Pr)$_2$Mg, Bu$_3$MgLi, Me$_4$ZnLi$_2$ and Rieke Mg–Zn left the substrate unreacted.

(7) *n*-BuLi should be used because thus any nucleophiles would not attack the enolate thus formed.

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(9) Typical experimental procedure: To a solution of mesityl bromide (876 mg, 4.4 mmol) in THF (15 mL) at –78 °C was added dropwise *n*-BuLi (2.9 mL of 1.5 M solution in heptane, 4.40 mmol) to form white suspension. The mixture was stirred for 30 min at the same temperature. Arylbromide **5a** (1.14 g, 4.40 mmol, dissolved in 7.8 mL of THF) was added to the mixture at –78 °C to form yellow solution which indicated enolate was formed, and stirred for 30 min at the same temperature. *n*-BuLi (2.7 mL of 1.5 M solution in heptane, 4.0 mmol) was added dropwise at –78 °C and stirred for additional 30 min at the same temperature to complete the reaction. DMF (0.37 mL, 4.8 mmol) was added dropwise to the solution and was stirred for 30 min at the

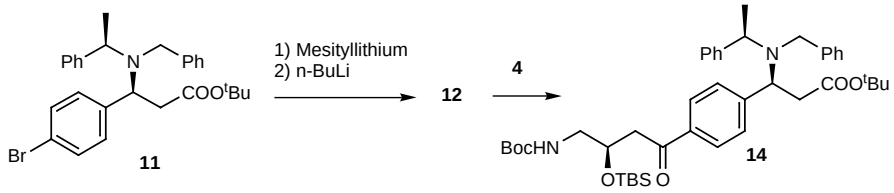

Figure 5

same temperature. Aq NH_4Cl was added to the solution and the product was extracted with EtOAc. The organic layer was washed with water, dried over anhyd Na_2SO_4 and was concentrated in vacuo to yield crude product which was purified by column chromatography using silica to afford **6a** (690 mg, 2.95 mmol) in 74% yield.

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(12) The diastereoselectivity was determined after conversion of **11** to amine **15** (Figure 6) by hydrogenation using Pd/C. Enantiomeric purity was determined by HPLC with comparison of a standard sample **17,** which was prepared from conjugated ester **9**.

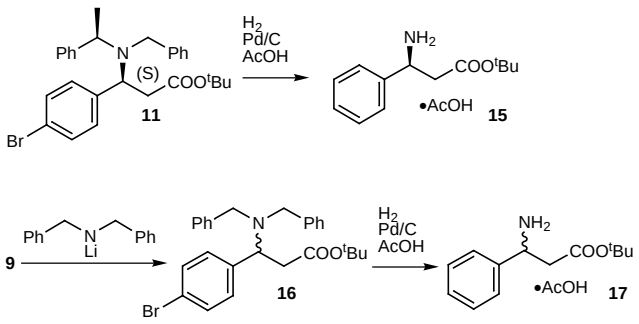

Figure 6