Mesityllithium as a Reagent for Chemoselective Halogen–Lithium Exchange Reaction
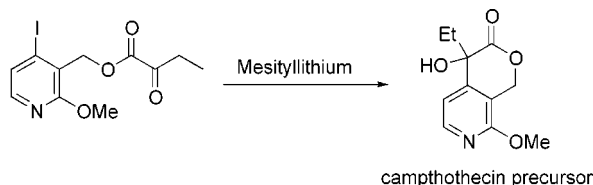
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ABSTRACT

camptothecin precursor

Mesityllithium was found to be an excellent selective lithiating agent to prepare aryllithium compounds having alkoxycarbonyl groups. To extend our studies on chemoselective lithiation, an important precursor for the synthesis of camptothecin was prepared using a halogen–lithium exchange reaction followed by an intramolecular 1,2-addition.

Halogen–metal exchange reaction is one of the most powerful methods for preparing various organometallic compounds among which the preparation of organolithium compounds has been most extensively studied.[1] Organolithium compounds display a strong anionic character that allows reactions with various electrophiles to take place. However, compatibility with electrophilic substituents such as ester groups is limited. To overcome this restriction,[2,3] we employed the combination of a sterically hindered aromatic lithiating agent, such as mesityllithium,[4] and bulky ester groups. An aryllithium with a *tert*-butoxycarbonyl group, which was prepared using mesityllithium as the lithiating agent, was stable enough to react with various electrophiles at −78 °C, without any self condensation. To extend the use of mesityllithium for chemoselective lithiation, an important precursor for the synthesis of camptothecin[5a,b] was prepared by a halogen–lithium exchange reaction prior to a cyclization by an intramolecular 1,2-addition.

First, halogen–lithium exchange reactions involving iodobenzoates were investigated using mesityllithium. Ethyl 2-iodobenzoate was treated with mesityllithium in THF at

(1) (a) Gilman, H.; Jacoby, A. L. *J. Org. Chem.* **1938**, *3*, 108. (b) Gilman, H.; Langham, W.; Jacoby, A. L. *J. Am. Chem. Soc.* **1939**, *61*, 106. (c) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. (d) Wakefield, B. J. *Organolithium Method*; Academic Press: London, 1988. (e) Snieckus, V.; Gray, M.; Tinkl, M. In *Comprehensive Organometallic Chemistry II*; Abel, F. G., Stone, F. G. A., Wilkinson, G., McKillop, A., Eds.; Pergamon Press: Oxford, 1995; Vol. 1, p 1.

(2) For examples of previous approaches in chemoselective lithiation, see: (a) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 2704. (b) Parham, W. E.; Jones, L. D.; Sayed, Y. A. *J. Org. Chem.* **1975**, *40*, 2394. (c) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. (d) Beak, P.; Musick, T. J.; Liu, C.; Cooper, T.; Gallagher, D. J. *J. Org. Chem.* **1993**, *58*, 7330. (e) Gray, M.; Tinkl, M.; Snieckus, V. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Elsevier Science Ltd.: Oxford 1995; Vol. 11, pp 1–92 and references therein.
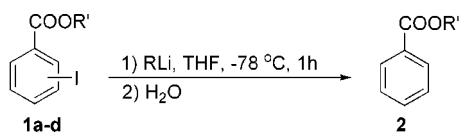
(3) For recent examples of chemoselective aromatic metalation, see: (a) Zhu, R.; Wehmeyer, R. M.; Rieke, R. D. *J. Org. Chem.* **1991**, *56*, 1445. (b) Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 736. (c) Kondo, Y.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1997**, 799. (d) Kondo, Y.; Komine, T.; Fujinami, M.; Uchiyama, M.; Sakamoto, T. *J. Comb. Chem.* **1999**, *1*, 123. (e) Kondo, Y.; Shilai, M.; Uchiyama, M.; Sakamoto, T. *J. Am. Chem. Soc.* **1999**, *121*, 3539. (f) Boymond, L.; Rottlaender, M.; Cahiez, G.; Knochel, P. *Angew. Chem., Int. Ed.* **1998**, *37*, 1701.

(4) For an example of hydrogen–lithium exchange reaction using mesityllithium, see: Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.

(5) (a) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer, K. H.; McPhail. A. T.; Sim, G. A. *J. Am. Chem. Soc.* **1966**, *88*, 3888. (b) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120.

−78 °C for 1 h, and the reaction was quenched with H₂O. The expected ethyl benzoate was not obtained as a result of side reactions during lithiation. When isopropyl 2-iodobenzoate was reacted with mesityllithium, isopropyl benzoate was obtained with a yield of 21%. On the other hand, lithiation of *tert*-butyl 2-iodobenzoate using mesityllithium proceeded smoothly, and *tert*-butyl benzoate was obtained with a yield of 68%. Selective lithiation of *tert*-butyl 4-iodobenzoate using mesityllithium also proceeded smoothly, and the protonated product was obtained with a yield of 57% after treatment with H₂O (Table 1).

Table 1. Halogen−Lithium Exchange Reaction Performed on Iodobenzoates

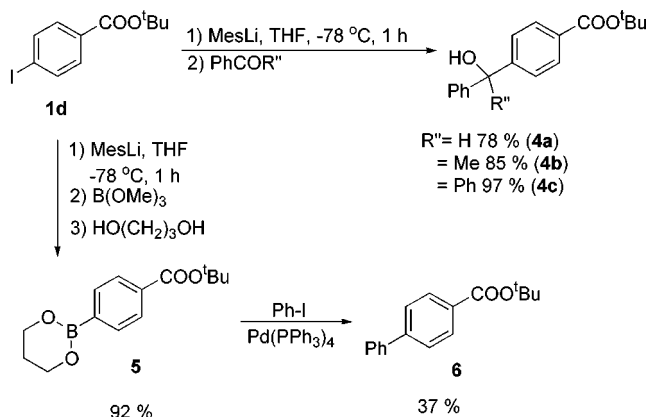| X	R'	RLi	Yield (%)
2-I (**1a**)	Et	MesLi	0
2-I (**1b**)	i-Pr	MesLi	21
2-I (**1c**)	t-Bu	MesLi	68
2-I (**1c**)	t-Bu	n-BuLi	50
2-I (**1c**)	t-Bu	t-BuLi	23
4-I (**1d**)	t-Bu	MesLi	57

tert-Butyl 2-lithiobenzoate prepared from the lithiation of *tert*-butyl 2-iodobenzoate was reacted with several carbonyl compounds. Substituted phthalides were obtained directly with excellent yields (Scheme 1). *tert*-Butyl 4-lithiobenzoate,
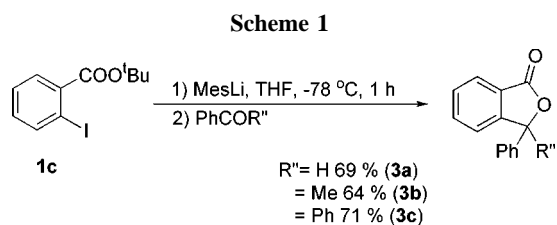
Scheme 1

prepared from *tert*-butyl 4-iodobenzoate and mesityllithium, was also reacted with various carbonyl compounds. Substituted hydroxyesters were obtained with excellent yields (Scheme 2).

Scheme 2

tert-Butyl 4-lithiobenzoate was also reacted with trimethylborate, followed by treatment with 1,3-propanediol to give arylborate **5**. The arylborate **5** was subjected to reaction with iodobenzene in the presence of Pd(PPh₃)₄ in DMF at 100 °C, to give the biaryl ester **6** (Scheme 2).

Next, the chemoselective lithiation of haloaromatics using mesityllithium was applied for the synthesis of a camptothecin precursor. As a preliminary experiment, lithiation−cyclization was investigated using iodobenzyl ketoester **7** as the substrate. The lithiation was carried out using mesityllithium in THF at −78 °C for 1 h, accompanied by the spontaneous intramolecular 1,2-addition to give the hydroxylactone **8** in 70% yield (Scheme 3). The use of other

Scheme 3

organolithium compounds such as *n*-BuLi, *t*-BuLi gave the lactone **8** with low yields (25% and 24%), and no formation of the lactone **8** was observed when phenyllithium was used.
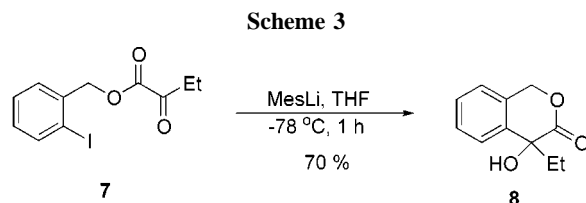
(6) **Typical Procedure for Schemes 1 and 2.** Under an argon atmosphere, *t*-BuLi (1.44 M in *n*-pentane, 2.8 mL, 4.0 mmol) was added to a solution of mesityl bromide (398 mg, 2.0 mmol) in dry THF (7 mL) at −78 °C and stirred at −20 °C for 1 h. The mixture was then cooled to −78 °C and a solution of an alkyl iodobezoate (1.0 mmol) in dry THF (7 mL) was added drop by drop. The mixture was stirred at the same temperature for 1 h, treated with an electrophile (3 mmol), and stirred at the same temperature for 1 h before addition of an aqueous solution saturated with NH₄Cl. The resulting mixture was extracted with Et₂O (20 mL × 3) and washed with brine (30 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was evaporated to give a residue, which was purified by column chromatography to obtain a pure compound.

(7) **Typical Procedure for Scheme 4.** Under an argon atmosphere, *t*-BuLi (1.44 M in *n*-pentane, 2.8 mL, 4.0 mmol) was added to a solution of mesityl bromide (398 mg, 2.0 mmol) in dry THF (7 mL) at −78 °C and stirred at −20 °C for 1 h. The mixture was then cooled to −78 °C and a solution of the iodopyridinylmethyl ketoester **9** (349 mg, 1.0 mmol) in dry THF (5 mL) was added drop by drop. The mixture was stirred at the same temperature for 5 h and an aqueous solution saturated with NH₄Cl was added. The resulting mixture was extracted with Et₂O (20 mL × 3) and washed with brine (30 mL). The organic layer was dried over anhydrous MgSO₄ and the solvent was evaporated to give a residue, which was purified by SiO₂ column chromatography using *n*-hexane/AcOEt (5:1) as the eluent to give a viscous oil (127 mg, 57%): ¹H NMR (CDCl3, 300 MHz) δ 8.24 (d, *J* = 5.2 Hz, 1H), 7.38 (d, *J* = 5.2 Hz, 1H), 5.05 (d, *J* = 17.3 Hz, 1H), 4.84 (d, *J* = 17.3 Hz, 1H), 4.01 (s, 3H), 2.90 (s, 1H), 2.12 (q, *J* = 7.4 Hz, 1H), 1.89 (q, *J* = 7.4 Hz, 1H), 1.01 (t, *J* = 7.4 Hz, 1H); HRMS calcd for C₁₁H₁₃NO₄ (M⁺) 223.0844, found 223.0875.

A similar lithiation—cyclization reaction was conducted using the iodopyridinylmethyl ketoester **9** as the substrate for the synthesis of the precursor for camptothecin and the hydroxylactone **10** was obtained with a yield of 57% (Scheme 4). The conversion of the lactone **10** to campto-

Scheme 4
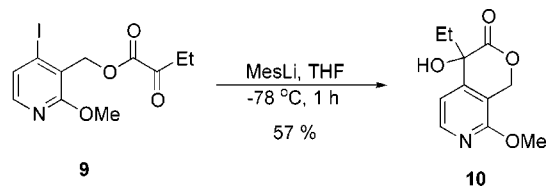
thecin has been well established by Comins, and is considered to be straightforward.[5b]

In summary, a chemoselective lithiation of functionalized haloaromatics could be achieved using mesityllithium, allowing the preparation of an important precursor for the synthesis of camptothecin. Further applications of the present method to the synthesis of biologically active aromatic and heteroaromatic compounds are in progress.