SYNLETT
Spotlight 108

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Mesityllithium

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Santosh Mhaske obtained his B.Sc. (C. T. Bora College, Shirur) and M.Sc. (Abasaheb Garware College, Pune) degrees from University of Pune, India. After qualifying in the CSIR-National Eligibility Test (NET) for a research fellowship, he joined the research group of Dr. N. P. Argade for a Ph. D. at National Chemical Laboratory. In 2002, he received the NCL Research Foundation 'Best Research Scholar Award'. His research interests include total synthesis of bioactive natural products, development of new synthetic methods for building blocks of natural products and drugs, synthesis of natural product hybrids, and generation of combinatorial libraries.

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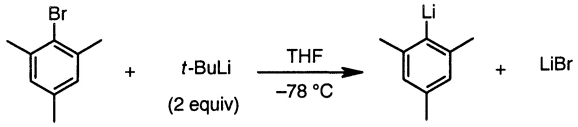
Dedicated to my research supervisor Dr. N. P. Argade for his support and encouragement.

Introduction

The use of lithium reagents in organic synthesis is well documented in the literature.[1–3] Amongst the other reagents, mesityllithium has occupied an important place[4–24] because of its non-nucleophilicity, strongly basic nature, clean selective reactivity and easy preparative methods. 2-Bromomesitylene is treated with *tert*-butyllithium in THF solution, a method that leads to a 1:1 mixture of the reagent and lithium bromide (Scheme 1).[4,11,12] For large scale reactions, it may be more convenient to prepare mesityllithium from bromomesitylene and lithium metal.[13–15]

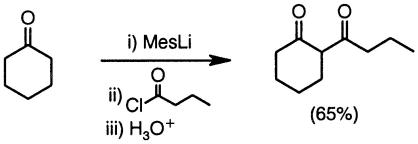


Scheme 1 Preparation of mesityllithium reagent

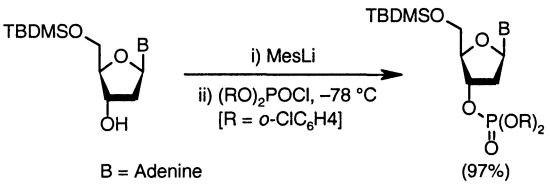
The highly hindered mesityllithium reagent is monomeric[16] i.e. not aggregated as are most other lithium derivatives. Freshly prepared mesityllithium is normally used, but mesityllithium may be stored, refrigerated, in solution with Et_2O/THF under Ar or N_2.

Abstracts

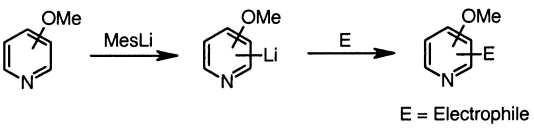
(A) A simple procedure[17] using mesityllithium provides high yields of 1,3-dicarbonyl compounds from 1:1 reactions of amine-free lithium enolates and acid chlorides. It is also a convenient method for generating amine-free enolates directly from ketones.[17]



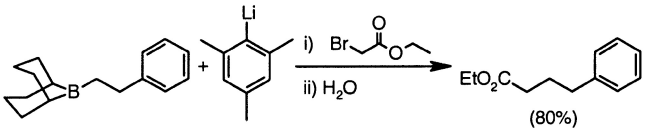
(B) A key process in oligonucleotide synthesis is the condensation of a nucleoside hydroxyl group and a phosphoric acid derivative. A rapid preparation of nucleoside phosphates under very mild conditions using mesityllithium with quantitative yields is possible.[18]



(C) After considerable study, mesityllithium was determined[19] to be the base of choice for effective lithiation of the methoxypyridine ring without undergoing nucleophilic addition to the pyridine nucleus. Using mesityllithium, 2-, 3-, and 4-methoxypyridines were lithiated and treated with various electrophiles to give substituted methoxypyridines in good yields.[19]



(D) Reaction of α-chloro and α-bromo esters with B-alkyl-9-borabicyclo[3.3.1]nonanes in the presence of mesityllithium furnishes the corresponding esters in good yields.[20] Use of mesityllithium in this α-alkylation reaction permitted trapping of the intermediate boron ester enolate using benzaldehyde. However, the aldol product thus obtained was a mixture of *syn* and *anti* isomers.[20]



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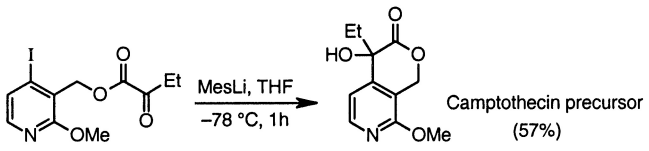
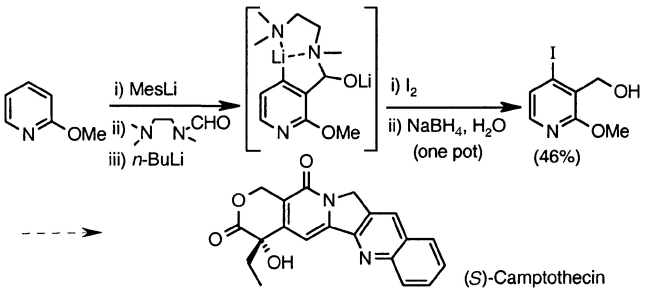
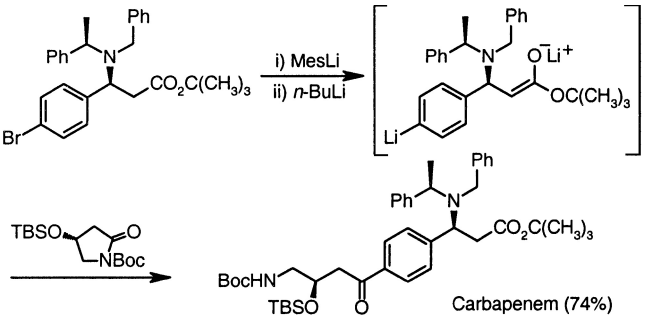
(E) Mesityllithium was found to be an excellent selective lithiating agent in the preparation of aryllithium compounds having alkoxycarbonyl groups. In an extension of the studies on chemoselective lithiation, an important precursor in the synthesis of camptothecin was prepared using a halogen–lithium exchange reaction followed by an intramolecular 1,2-addition.[21]



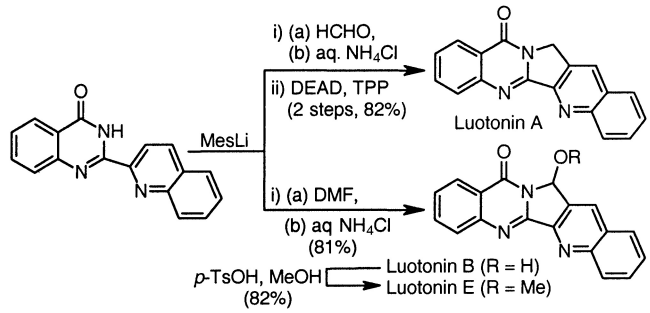
(F) Ortho-directed lithiation on methoxypyridine was carried out using mesityllithium and *n*-BuLi to effect hydroxymethylation and iodination at desired positions. This one-pot process is a key step in a practical, asymmetric, six-step synthesis of (*S*)-camptothecin.[22]



(G) A new methodology has been developed for the metalation of aryl bromide functionalized with an active methylene adjacent to a carbonyl group.[23] In order to avoid self-quenching, selective deprotonation was necessary prior to the halogen–metal exchange reaction. For this purpose, mesityllithium was found to be the best choice. Subsequent treatment with *n*-BuLi resulted in lithium–bromine exchange to generate the dianion, which was successfully trapped with electrophiles in good yield. This method was applied to the efficient synthesis of carbapenem.[23]



(H) A regioselective quinazolinone-directed ortho lithiation on an adjacent quinoline moiety using mesityllithium has been used as a key step in a short, efficient and practical synthesis of the human DNA topoisomerase I poison luotonin A and luotonins B and E. It is important to note that several attempts with other lithiating agents met with failure, whereas mesityllithium served the purpose with good yields.[24]



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