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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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 place⁴⁻²⁴ 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 monomeric¹⁶ 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 Et₂O/THF under Ar or N₂.

Abstracts

(A) A simple procedure¹⁷ 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 determined¹⁹ 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

(E) Mesityllithium was found to be an excellent selective lithiating agent in the preparation of aryllithium compounds having alkoxy-carbonyl 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

References

- (1) Rappoport, Z.; Marek, I., Eds.; *The Chemistry of Organolithium Compounds*; Wiley: New York, **2004**.
- (2) Clayden, J. In *Organolithiums: Selectivity for Synthesis*, *Tetrahedron Organic Chemistry Series*; Baldwin, J. E.; Williams, R. M., Eds.; Pergamon: Oxford, **2002**, Vol. 23.
- (3) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
- (4) Rathman, T. L.; Woltermann, C. J. *PharmaChem* **2003**, *2*, 6.
- (5) Zadel, G.; Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1035.
- (6) Tobita, H.; Habazaki, H.; Ogino, H. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 797.
- (7) Powell, S. A.; Tenenbaum, J. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 12648.
- (8) Turck, A.; Plé, N.; Trohay, D.; Ndzi, B.; Quéguiner, G. J. *Heterocycl. Chem.* **1992**, *29*, 699.
- (9) Pelter, A.; Peverall, S.; Pitchford, A. *Tetrahedron* **1996**, *52*, 1085.
- (10) Yamada, K.; Miyaura, N.; Itoh, M.; Suzuki, A. *Synthesis* **1977**, 679.
- (11) Seebach, D.; Neumann, H. *Chem. Ber.* **1974**, *107*, 847.
- (12) Yoshifuji, M.; Nakamura, T.; Inamoto, N. *Tetrahedron Lett.* **1987**, *28*, 6325.
- (13) Fuson, R. C.; Speranza, G. P.; Gaertner, R. *J. Org. Chem.* **1950**, *15*, 1155.
- (14) Rosenberg, S. D. *J. Am. Chem. Soc.* **1954**, *76*, 4389.
- (15) Rausch, M. D.; Tibbetts, F. E. *Inorg. Chem.* **1970**, *9*, 512.
- (16) Ruhlandt-Senge, K.; Ellison, J. J.; Wehmschulte, R. J.; Pauer, F.; Power, P. P. *J. Am. Chem. Soc.* **1993**, *115*, 11353.
- (17) Beck, A. K.; Hoekstra, M. S.; Seebach, D. *Tetrahedron Lett.* **1977**, 1187.
- (18) Hayakawa, Y.; Aso, Y.; Uchiyama, M.; Noyori, R. *Tetrahedron Lett.* **1983**, *24*, 1165.
- (19) Comins, D. L.; LaMunyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
- (20) Juarez-Brambila, J. J.; Singaram, B. *J. Indian Inst. Sci.* **1994**, *74*, 7.
- (21) Kondo, Y.; Asai, M.; Miura, T.; Uchiyama, M.; Sakamoto, T. *Org. Lett.* **2001**, *3*, 13.
- (22) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255.
- (23) Yamamoto, Y.; Maeda, K.; Tomimoto, K.; Mase, T. *Synlett* **2002**, 561.
- (24) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563.