SYNLETT Spotlight 393

n-Butyllithium

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

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Dedicated to my research supervisor Dr. Pinaki S. Bhadury

Introduction

n-Butyllithium (*n*-BuLi) is one of the most prominent organolithium reagents in the whole of synthetic chemistry,^{1–3} and available as solutions in alkanes such as pentane, hexane, or heptane, which is usually encountered as a pale yellow solution. It is unstable towards air or moisture but stable in an atmosphere of nitrogen. It has been widely used in organic reactions, such as regioselective lithiation reaction,⁴ reversible metathesis reaction,⁵ Claisen rearrangement,⁶ phospho-Fries rearrangement,⁷

coupling reaction,⁸ asymmetric deprotonation–electrophilic trapping reaction,⁹ enantioselective hydroxyalkylation,¹⁰ etc. In general, *n*-butyllithium is commercially available and can also be prepared readily by the reaction of 1-bromobutane or 1-chlorobutane with Li metal (Scheme 1).¹¹ An overview of the usage of *n*-BuLi in organic synthesis is presented below.

Scheme 1

(A) Fort and co-workers described an efficient method for the synthesis of polysubstituted furo[2,3-*c*]pyridines via successive regioselective lithiations, using *n*-BuLi or [*n*-BuLi/LiDMAE] as base. For each step the products were obtained in moderate to excellent yields.⁴

(B) Bailey et al. reported mild and highly efficient experimental conditions for the reversible metathesis reaction known as the lithium–halogen exchange. The reaction products of 1-bromo-4-*tert*-butylbenzene with *n*-BuLi at 0 °C are obtained quantitative in heptane containing a small quantity of THF. Particularly, nettlesome side reactions, including coupling of aryllithium with the co-generated alkyl halide and formation of a benzyne intermediate via ortho-metalation of the aryl halide, are effectively avoided.⁵

(C) Upon treatment with *n*-BuLi, a variety of allyl 1,1-dichlorovinyl ethers undergo rearrangement to furnish high yields of γ,δ -unsaturated esters after alcohol addition. A potential advantage of this method over other variants of the Claisen rearrangement is the ability to add a variety of alcohol nucleophiles to the proposed ketene intermediate, allowing the one-pot preparation of diverse esters of γ,δ -unsaturated carboxylic acids with high stereoselectivity.⁶

(D) *n*-BuLi together with *i*-Pr₂NH has been used in the preparation of bifunctional BINOL ligands bearing phosphine oxides [P(=O)R₂], phosphonates [P(=O)(OR)₂], or phosphoramides [P(=O)(NR₂)₂] at the 3,3'-positions via a phospho-Fries rearrangement as key step. This method has an advantage with regard to yield and purification in comparison with a coupling method that uses halide compounds, expensive diphenylphosphine oxide [Ph₂P(=O)H], and palladium or nickel catalysts.⁷

(E) Tarselli and Micalizio described a successful procedure for the coupling of aliphatic imines with allylic and allenic alkoxides enabled by a unique reactivity profile of Ti(IV) isopropoxide/*n*-BuLi compared to well-known Ti(IV) isopropoxide/RMgX systems. This coupling proceeds with moderate to excellent yields.⁸

(F) An enantioselective hydroxyalkylation of *o*-tolualdehyde and 3-aminotetrahydrofurans (or 3-aminopyrrolidines, 3-aminotetrahydrothiophenes) in the presence of *n*-BuLi and lithium amides gives the target product 1-*o*-tolylpentan-1-ol in good yield and moderate ee.¹⁰

(G) The highly pyramidalized alkene pentacyclo-[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]non-4-ene was successfully synthesized with *n*-BuLi via dehalogenation of vicinal dihalides. The method has proven to be reliable for the synthesis of a variety of strained alkenes.¹²

(H) Luliński et al. found that lithiated benzonitriles can be generated in high yields from reactions of bromobenzonitriles with *n*-BuLi in THF under standard cryogenic conditions (ca. -70 °C, even up to -60 °C). The reverse addition mode is employed to reduce significantly side reactions.¹³

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