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Convenient and efficient synthesis of functionalized unsymmetrical alkynyl sulfides†

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We developed a simple and efficient method for the synthesis of functionalized unsymmetrical alkynyl sulfides under mild conditions in good yields. The designed method is based on the reaction of 5,5-dimethyl-2-thioxo-1,3,2-dioxaphosphorinan-2-disulfanyl derivatives with lithium acetylides. The developed method allows the preparation of unsymmetrical alkynyl sulfides bearing additional hydroxyl, carboxyl, or amino functionalities.

Introduction

The development of practical and versatile methods for introduction of functional groups into molecules to modify their properties is one of the most important task of organic chemistry. The easy to perform reactions that do not require highly specialized synthetic skills have a particularly broad impact to other fields such as medicine, biology, or materials science. From this point of view, among all functional groups in organic chemistry, alkynes occupy a privileged position.[1] Although alkynes contain one of the simplest functional group, two carbon atoms connected with triple bond, the reactivity of that bond makes alkynes exceptionally useful in organic synthesis. They were applied in the stereoselective construction of the carbon backbone of complex natural products,[2] bulk chemical synthesis based on acetylene gas[3] and in the variety of complexity-enhancing metal-catalyzed cyclization reactions to provide carbo- and heterocycles.[4] The electronic properties of alkynes have found also wide applications in preparation of organic materials and dyes.[5] Moreover, their [3 + 2] cycloaddition with azides is recognized as one of the best biorthogonal conjugation method to modify biomolecules and polymers.[6] In this context, the development of new synthetic methods to access alkynes and their derivatives efficiently under user-friendly conditions is highly desirable.

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Driven by the exceptional reactivity of sulfur and its importance in biology, medicine, and materials science,[7] recent research efforts targeted a series of thiol-based transformations including thiol alkylations and the thiol addition to alkenes and alkynes respectively.[8] Unlike the well-established S–Csp^3 bond forming reactions, existing methods to construct S–Csp bonds are rare in number and often lack generality or require harsh conditions.

Alkynyl sulfides can be obtained by methods utilize transition-metal catalysts, such as the copper-catalyzed carbon sulfur coupling between terminal alkynes and disulfides,[9] or as in the elegant study by Yamaguchi, the use of catalytic rhodium to achieve C–S bond formation by C–H and S–S bond metathesis (Scheme 1A).[10] Alternatively, a range of processes utilize alkenyl[11] or alkynyl[12] halides bearing leaving groups that undergo elimination under strongly basic conditions to furnish the desired alkynyl sulfides (Scheme 1B). Consequently, the limited functional group tolerance exhibited by these methods is not surprising as they require harsh conditions, proceed *via* highly reactive intermediates, or involve the use of sensitive catalytic systems. Recently, Waser has developed a thiol-alkynylation procedure utilizing the hypervalent iodine alkyne transfer reagent TIPS-ethynylbenziodoxolone (Scheme 1C).[13] Although the method is highly chemoselective as a vast array of functional groups are tolerated, the problems associated with preparation and stability hypervalent iodine alkyne transfer reagent are the major disadvantages of that transformation. Currently, the most common methods to form alkynyl sulfides require a pre-functionalization of the thiol (Scheme 1D). These methods are generally based on nucleophilic substitutions between highly reactive lithium acetylide intermediates with pre-activated thiols or disulfide species.[14] The major drawback of that approached emerges from availability and long term stability of pre-activated thiols.

We have previously demonstrated the preparation of functionalized unsymmetrical molecules, such as dialkyldisulfanes,[15] alkyl–aryl disulfanes,[16] 'bioresistant' disulfanes,[17] the unsymmetrical disulfanes of L-cysteine and L-cystine,[18] and diaryldisulfanes,[19]