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Alkynylthioimidazolium salts: Efficient Reagents for the Synthesis of Alkynyl Sulfides by Electrophilic Thioalkynylation

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Abstract: The efficient synthesis of a series of alkynylthioimidazolium salts by reaction of organozinc compounds with dibromoimidazolium/sulfuranes is reported. Addition of the Grignard reagent caused immediate decomposition (Scheme 1d). The utility of this protocol is showcased by the preparation of alkynyl sulfides which are particularly difficult to obtain, or simply unavailable, through the existing methodologies. In addition, the synthetic method has been extended to the preparation of alkynyl selenides.

The continuously increasing spectrum of applications reached by sulfur containing compounds expands along different fields, from organic synthesis and drug discovery to material science. [1] This demand of organosulfur compounds has stimulated over the past decades the development of new methodologies focused on the efficient introduction of S-based functionalities into organic substrates, and the subsequent chemoselective transformation of these primary products. [2]

Among S-containing building blocks the unique reactivity of 1-alkynylsulfides, constituted by a sulfur atom directly attached to a chemically very versatile alkyne moiety, confers an enormous synthetic potential to these fragments. [3] However, it is also this particular atomic distribution what has surely prevented their broader use. Note that both the alkyne and the sulfide groups are inherently nucleophilic moieties and the umpolung of one of them is necessary for the construction of the thioacetylene. This often implies the use of unselective reagents and/or harsh reaction conditions for their preparation, which are not always compatible with sensitive functional groups (Scheme 1a,b). [4a,b] General routes to alkynylthioethers were reported only recently [4c-d, 5], however, some limitations regarding the scope of products still persist.

To the best of our knowledge, a synthetic strategy based on the electrophilic thioalkynylation of C-based nucleophiles has never been reported, probably due to the absence of an appropriate [R=C-S]+ synthetic equivalent. Herein, we introduce alkynylthioimidazolium salts as a family of air stable reagents depicting this uncommon reactivity, and describe the implementation of a highly modular route to alkynyl sulfides making use of these compounds (Scheme 1d).

In a first attempt to prepare alkynylthioimidazolium salts, we studied the reaction of sulfurane 1 with propionylmagnesium bromide. Addition of the Grignard reagent caused immediate decolorization of the reaction mixture already at -78°C, and precipitation of a bright yellow solid which was probed to be dicaticonic disulfide 2 (Scheme 2; see the Supporting Information).

Conversely, switch of the Grignard by the softer organozinc analogue cleanly provided thiaoalkyne 3a, which was isolated as an air stable light yellow powder after anion exchange with an aqueous solution of NaSbF6. The described reaction conditions proved to be broadly applicable and, as shown in Scheme 2, a complete set of alkynylthioimidazolium salts could be prepared in high yields from the corresponding organozinc reagents following an identical reaction sequence. Importantly, many functional groups including ethers, silyl...
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protected alcohols, carbamates, esters, amides, azides, acetals and halogens were tolerated, opening up numerous opportunities for further transformation. Compounds 3a-e,n were isolated as crystalline materials whereas 3f-m, decorated with longer lateral chains, are amorphous solids or viscous oils. Indistinctly of their aggregation state, they all are air stable salts and can be stored during months at room temperature without evident decomposition. In addition, the synthesis of 3b was scaled up to 10 grams without compromising the yield of the product.

Crystals suitable for X-ray analysis were grown by slow diffusion of diethyl ether into saturated dichloromethane solution of 3b, and thus its connectivity could be unambiguously established (See Figure 1). As expected, 3b adopts and angular geometry, with a C1-S1-C3 angle of 99.6(2)°. Of particular relevance in this structure is the key contact measured between S(1) and one of the fluorine atoms of the hexafluoroantimonate counteranion (S1-F1, 2.965 Å), which is significantly shorter than the sum of the van der Waals radii S-F (3.27 Å). Considering the non-coordinating nature of the SbF₆⁻ anion, this interaction is indicative of high electrophilicity at the sulfur atom in these compounds.

With that selection of alkynylthioimidazolium salts in hand, we set up to preliminary explore their reactivity towards nucleophiles. Interestingly, all organomagnesium reagents tested were found to smoothly attack salts 3a-j,l at the sulfur atom providing the corresponding alkynylthioethers in good to excellent yields (Scheme 3). This reactivity contrast with the one we observed for imidazolium thyocyanates or excellent yields (Scheme 3). This reactivity contrast with the one we set up to preliminary explore their reactivity towards nucleophiles. Interestingly, all organomagnesium reagents tested were found to smoothly attack salts 3a-j,l at the sulfur atom providing the corresponding alkynylthioethers in good to excellent yields (Scheme 3). This reactivity contrast with the one we observed for imidazolium thyocyanates or excellent yields (Scheme 3). This reactivity contrast with the one we observed for imidazolium thyocyanates or excellent yields (Scheme 3). This reactivity contrast with the one we observed for imidazolium thyocyanates or excellent yields (Scheme 3). This reactivity contrast with the one we observed for imidazolium thyocyanates or excellent yields (Scheme 3). This reactivity contrast with the one we observed for imidazolium thyocyanates or excellent yields (Scheme 3).

The robustness and applicability of the protocol developed is specifically highlighted by the successful preparation of a number of structurally differentiated thiocetylenes incorporating alkyl- 4-9, aryl- 10-14, vinyl- 15-19 or even a second alkynyl- unit 20-23 directly attached to the central sulfur atom. The preparation of the last two groups of products is remarkable since their synthesis is not obvious through other routes.[9] Although the functional group tolerance is limited by the non-discriminating reactivity of Grignard reagents, this reaction still allows the accommodation of valuable functionalities such as ethers, silanes, silyl ethers, acetal, azides and halogens substituents on both termini of the thioacetylene. Alkynylsulfides decorated with carbamates 9, 22 are more efficiently prepared by reaction of the corresponding alkynyl thioimidazolium salt with organozinc reagents; however, even under these softer reaction conditions, untreated product mixtures were obtained when using precursors 3k and 3n as electrophiles.

![Molecular structure of compound 3b in the solid state.](image)

Figure 1. Molecular structure of compound 3b in the solid state. Anisotropic displacement parameter shown at 50% probability level and hydrogens omitted for clarity. Selected bond lengths [Å] and angles [deg]: C1-S1, 1.695(5); C3-S1, 1.744(5); C1-C2, 1.188(7); S1-F1, 2.965(5); C3-S1-C1, 99.6(2).[7]

No drop in the yield of product 4 was observed when the thioalkynylation is carried out in the presence of TEMPO (50 mol%). Moreover, quenching of the reaction mixtures with powder Se (2 equiv.) generates selenourea 24 in good isolated yields (80-85%). Based on this, and considering the electrophilic character of sulfur in 3, we tentatively propose a substitution...
mechanism in which the Grignard transfers its negatively charged R group to the sulfur atom followed by concomitant elimination of the N-heterocyclic carbene either free or, more probably, as a Mg complex.

Next, we turned our attention to study the extension of this method to the preparation of selenoacetylenes \[\text{[10]}\]. Hence, known selenourea \[\text{24} \] \[\text{11}\] was submitted to bromination conditions obtaining the corresponding hypervalent selenium compound \[\text{25}\] as a bright orange solid in high yield and analytical purity (Scheme 4; for the X-ray structure of this compounds see the Supplementary Information). \[\text{1}\] \[\text{12}\] 

Subsequent addition of the desired zinc acetylide caused the slow disappearance of the color and the formation of the corresponding imidazolium seleno urea \[\text{26} \] \[\text{a}\]. These were isolated as slightly pale yellow solids that can be stored at room temperature and handle in air for short times without evident decomposition.

\[\text{Scheme 4. Synthesis of alkynylseleno imidazolium salts. Reagents and conditions (yields): (a) Br}_2, \text{CH}_2\text{Cl}_2, \text{0 °C} \rightarrow \text{RT}, \text{78 °C} \rightarrow \text{RT}, \text{then NaSbF}_6; \text{26a (98%), 26b, (94%); 26c (58%).}\]

Figure 2 depicts the X-ray structure of \[\text{26b}\]. If compared with that of \[\text{3b}\], it features the structural changes expected when descending along a group; namely, longer bond lengths between the central chalcogen and the flanking carbon atoms (Se1-C1, 1.839(4) Å; Se1-C3, 1.895(4) Å) and an acuter angle around Se (C1-Se1-C3; 96.38(18)°), which is consequence of the decreased tendency to hybridization typical for the heavier atoms in a group. Shorter contacts than the sum of the Se-F van der Waals radii (3.37 Å) were again measured between the chalcogenide and F1 from the hexafluoroantimonate anion (Se1-F1, 3.177(4) Å) (Figure 2).

Reactions of \[\text{26a-c} \] with Grignards proceeds in an identical fashion to that observed for their lighter isosteres, allowing the isolation of a series of alkyl-alkynyl \[\text{27}\], aryalkynyl \[\text{28, 29}\], vinylalkynyl \[\text{30, 31}\] and even asymmetric dialkynyl selenoalkynes \[\text{32}\] in good to excellent yields (Scheme 5). \[\text{13}\]

The functionalities present in the products obtained could be involved into further transformations. Illustrative examples are described in Scheme 6 taking \[\text{17}\] and \[\text{21}\] as model substrates. Following standard oxidation procedures, \[\text{17}\] can be selectively transformed either into sulfoxide \[\text{33}\] or sulphonylacetylene \[\text{34}\]. \[\text{14}\] This last compound is an efficient double Michael acceptor and reacts with butyl amine, or Na\text{2S} to afford dihydrothiazine or dihydridithione derivatives \[\text{35}\] and \[\text{36}\] respectively. \[\text{15}\] Thiophene \[\text{37}\] was also obtained after extensive heating from \[\text{17}\] in the presence of Na\text{2S}. Further studies are still necessary to determine the complete mechanistic pathway of this transformation; however, the substitution pattern in \[\text{37}\] supports a mechanism in which migration of a propenyl cation between the two sulphur centers takes place after a first hydrothiolation of the C-C triple bond. Finally 1,4-dithiane \[\text{39}\], which depicts an asymmetric substitution pattern, was prepared by reaction of Na\text{2S} with di(alkynyl)sulfide \[\text{21}\] (Scheme 6). \[\text{16}\]

\[\text{Scheme 5: Substrate scope for the reaction of 26 with Grignard reagents.}\]

In conclusion, we describe herein a new synthetic strategy for the preparation of a broad spectrum of alkynylsulfides and selenides based on an unprecedented electrophilic thio- or selenoalkynylation. The method developed is operationally simple, scalable, high yielding, and uses inexpensive starting materials. In addition, a broad range of functionalities were well tolerated and the products could be further transformed into useful building blocks. Considering the continuously increasing number of applications reached by sulphur containing compounds, we expect our method to find a wide range of application, particularly in the synthesis of organic functional materials. Efforts along these lines are currently underway in our laboratory.
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Keywords: electrophilic thioalkynylation • Grignard reagents • alkynylthiomiazolium salts • alkynylthioethers • alkynylselenoethers


[7] CCDC 1505415-1505418 contain the supplementary crystallographic data for this paper.


[12] The synthesis of 2S has been previously reported albeit a different procedure was used: Dutton, J.; Tabshi, R.; Jennings, M. C.; Lough, A. J.; Ragopasa, P. J. Inorg. Chem. 2007, 46, 8594-8602.


Novel Thioalkynylation reagents: Alkynylthioimidazolium salts are easy to prepare, air stable compounds that react with Grignards affording alkynylthioethers of diverse architecture. Thus, they are very convenient synthetic equivalents of the $[\text{R-C≡C-S}]^+$ cation.