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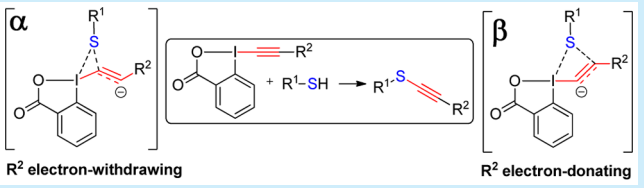
Alkynylation of Thiols with Ethynylbenziodoxolone (EBX) Reagents: α- or β- π-Addition?

Matthew D. Wodrich,* Paola Caramenti, and Jerome Waser*,†

†Laboratory of Catalysis and Organic Synthesis, Ecole Polytechnique Fédérale de Lausanne, EPFL SB ISIC LCSO, BCH 4306, 1015 Lausanne, Switzerland

Supporting Information

ABSTRACT: The alkynylation of thiols with EthynylBenziodoXolone (EBX) reagents is a fast and chemoselective method for the synthesis of thioalkynes. Combined experimental and computational studies are reported, which led to the identification of a new mechanism for this reaction, proceeding via an initial sulfur−iodine interaction followed by β-addition, α-elimination, and a 1,2-shift. Depending on the substituent on the alkyne, this mechanism can be favored over the previously disclosed concerted α-addition pathway.

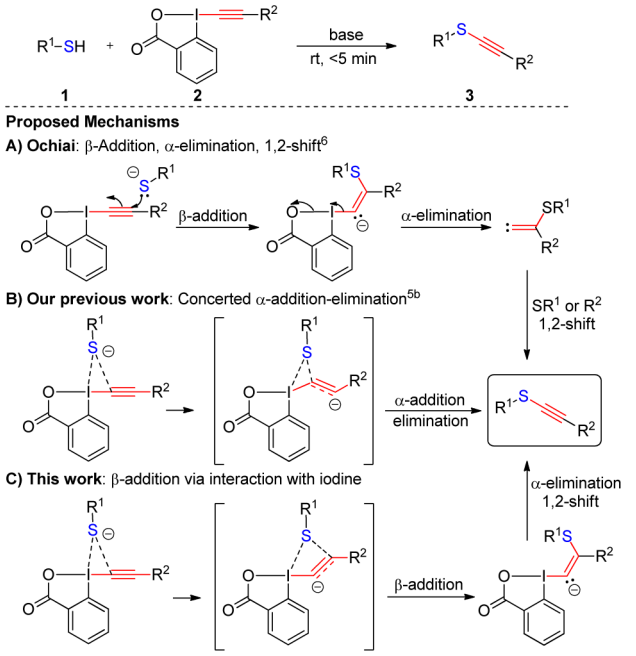


Alkynes are among the most versatile building blocks in synthesis due to their interesting structural properties and the numerous methods available for their transformation.[1] Additionally, they have found a multitude of applications in chemical biology and materials science. Heteroatom-substituted alkynes, such as ynamides and thioalkynes, are particularly interesting owing to their enhanced reactivity.[2] Whereas important breakthroughs have recently been realized in the efficient synthesis of ynamides, most methods for accessing thioalkynes require multiple steps and/or the use of highly reactive intermediates, such as lithium acetylides.[3] Recently, milder metal-catalyzed methods for the alkynylation of thiols have emerged.[4] Our group developed a metal-free alternative approach based on the use of EthynylBenziodoXolone (EBX) hypervalent iodine reagents.[5] Originally limited to the transfer of silyl alkynes, the method was later extended to the synthesis of aryl and alkyl acetylenes and was also applied to the functionalization of cysteines in proteins in the living cell.

Most reactions of nucleophiles with alkynyliodonium salts involve a conjugate addition, α-elimination, and 1,2-shift pathway (Ochiai's mechanism, Scheme 1A).[6] Based on Density Functional Theory (DFT) computations, we proposed in 2014 an unprecedented concerted α-addition mechanism proceeding via a low energy three-atom transition state for the alkynylation of thiols with EBX reagents (Scheme 1B).[5b] Herein, we present further computational results which reveal a third unexpected mechanism, resulting from the shift of a van der Waals complex characterized by a favorable sulfur−iodine interaction directly to a low lying transition state for β-addition (Scheme 1C). Computations predict that either α- or β-addition can be favored depending on the reagent substituents, as supported by a ^{13}C-labeling experiment.

In our previous studies, we demonstrated that thiols could be alkynylated in high yields with both silyl- and alkyl-substituted EBX reagents.[5b] DFT computations led to the discovery of a new concerted α-addition pathway, which was 12.2 kcal/mol lower in energy than β-addition for the alkynylation of benzylthiol **1a** with the commercially available TIPS-EBX reagent **2a** (Scheme 2). However, for Me-EBX **2b** we were able to isolate a side product **4** coming from a β-addition pathway. Computations indeed showed that the difference in energy between the two pathways was smaller for methyl than silyl substituents (4.7 instead of 12.2 kcal/mol). Nevertheless, the α-addition pathway was still significantly lower in energy and the isolation of **4** was therefore intriguing.

Scheme 1. Alkynylation of Thiols and Proposed Mechanisms



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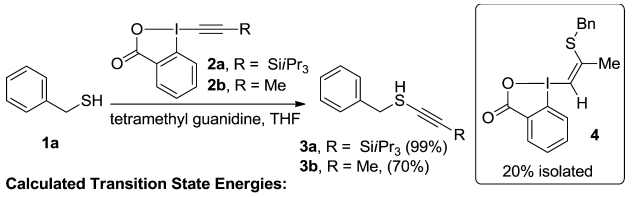
Scheme 2. Alkynylation of Benzyl Thiol 1a and Computed Transition State Energies



Consequently, we conducted additional computations for the alkynylation with EBX reagents (at the PBE0-dDsC/TZ2P//M06-2X/def2-SVP theoretical level; see computational details in the Supporting Information for additional information).[7] Thiophenol **1b** was used as a substrate, rather than the previously employed benzylthiol, to minimize conformational freedom (Figure 1). Lower energy pathways involving direct β-addition of thiophenolate **1b′** on the triple bond could not be identified. In fact, all these attacks involve a nonfavorable van der Waals interaction with the β-position of the alkyne ($\mathbf{b_0}^{old}$). However, when we reinvestigated pathways starting from the more favorable van der Waals interaction complex $\mathbf{a_0}$ between the sulfur and the iodine atom, which was previously identified as the entry point for the concerted α-addition ($\mathbf{a_{TS1}}$), a new low energy pathway proceeding via transition state $\mathbf{b_{TS1}}$ was found. This corresponds to a direct attack of the sulfur atom on the alkyne β-position and is lower in energy than the α-addition pathway (9.3 vs 10.1 kcal/mol). In this new transition state, the sulfur atom attacks at a trajectory 180° to the arene ring, rather than 90° as in the previously identified β-addition pathway.[8] After formation of vinyl intermediate $\mathbf{b_1}$, elimination of iodine occurs readily via transition state $\mathbf{b_{TS2}}$, followed by a barrierless 1,2-silicon shift to give the observed product **5a** and 2-iodobenzoate (**6**).

The new reaction pathway was also computed for Me-EBX **2b** (Figure 2). In this case, β-addition via transition state $\mathbf{b_{TS1}}$ was favored by 5.8 kcal/mol. Furthermore, the obtained vinyl intermediate $\mathbf{b_1}$ was more stable, with a barrier of 12.2 kcal/mol for carbon−iodine bond cleavage. Interestingly, intermediate $\mathbf{b_2}$, corresponding to a vinylidene carbene, could also be identified, as the sulfur shift was significantly slower than the silicon shift. Finally, a relatively facile (8.4 kcal/mol activation energy) 1,2-sulfur shift gives the observed product **5b**.

An important difference between silyl and alkyl reagents in the β-addition pathway is the identity of the migrating group: silicon vs sulfur.[9] In the case of TIPS-EBX **2a**, introducing a ^{13}C label onto the alkyne would unambiguously differentiate the two pathways. Indeed, when thiophenol **1b** was reacted with ^{13}C-labeled reagent **2c**,[10] a 1:1.2 mixture of products labeled in the α- and β-positions to silicon was obtained (products **5a′** and **5a″**; Scheme 3). This result supports the coexistence of the two reactions pathways and agrees well with the small energy difference (0.8 kcal/mol) obtained by computation.

In order to better understand the factors determining the relative energies of the two possible reactions pathways, we computed the reaction of EBX reagents with systematically varied heterocyclic cores (**2**, **7**−**9**) and alkynyl substituents (Figure 3).[11]

From these computations, it appears that the structure of the hypervalent iodine heterocycle has only a marginal effect on the energy of the transition state (Figure 4). In contrast, the substituent on the alkyne had a strong influence on the transition state energy. With an electron-withdrawing substituent, such as an ester, α-addition is favored, as the resulting partial negative charge is stabilized. With silyl and phenyl substituents, both pathways are competitive. Finally, electron-donating groups make the α-pathway less favorable and at the same time lower the energy for the transition state of the β-pathway.[12] Interestingly, alkynes bearing either a highly electron-rich or an electron-withdrawing substituent are expected to react faster with nucleophiles (activation energy around 5 kcal/mol). Unfortunately, to date we have been unable to synthesize reagents bearing a methoxy or an ester group for experimental verification. It is also worth mentioning that alkynyliodonium salts, such as **9**, displayed very similar behavior to EBX reagents, although they cannot be used for the

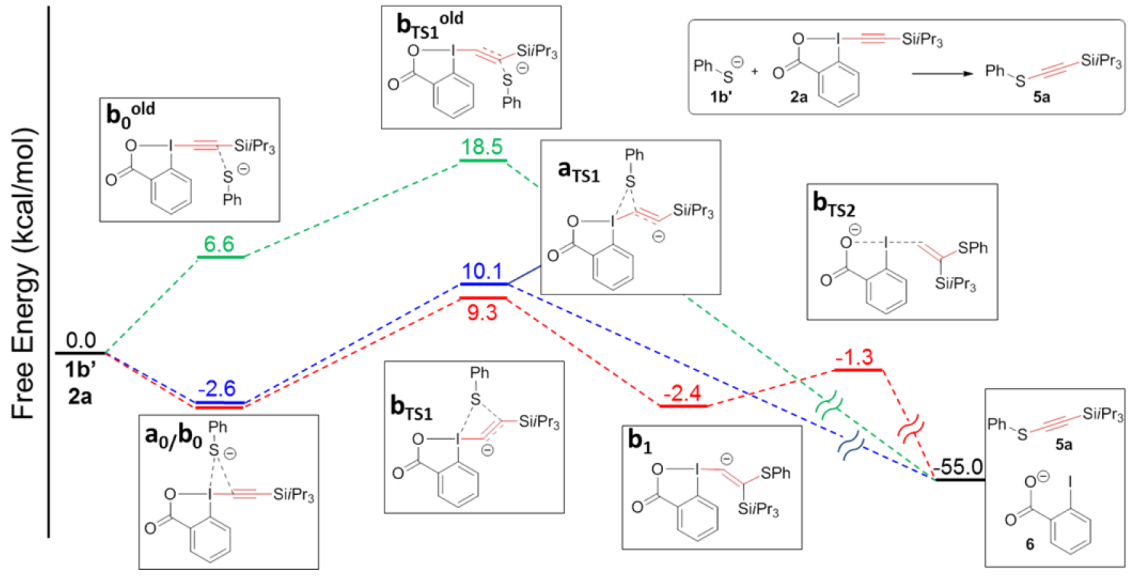


Figure 1. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the three possible mechanistic pathways **a** (blue), $\mathbf{b}^{old}$ (green), and **b** (red) for the reaction of TIPS-EBX **2a** with thiolate **1b′**.

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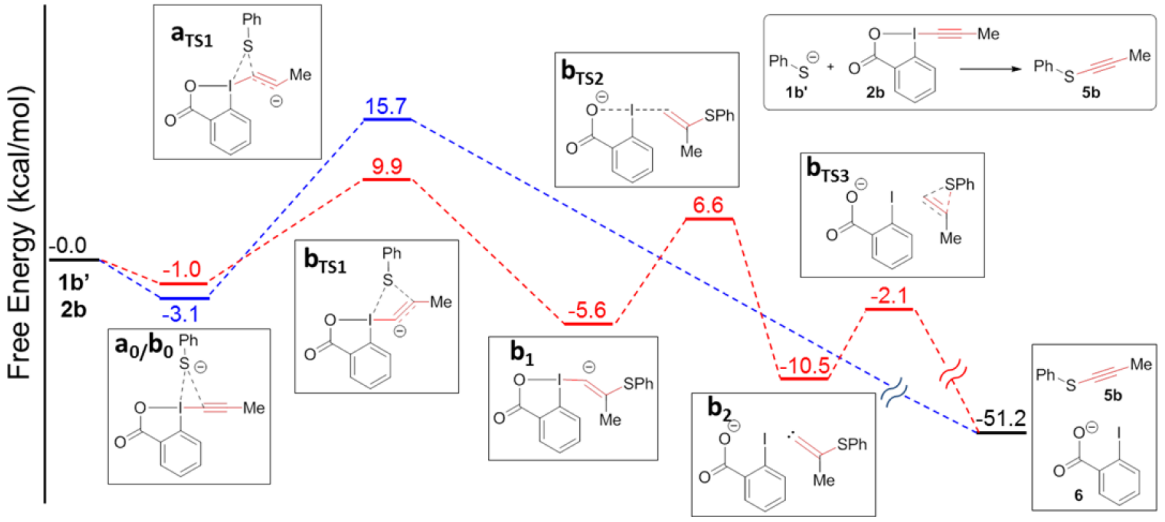
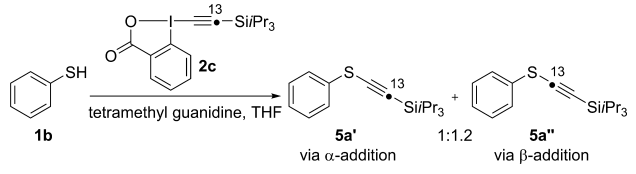
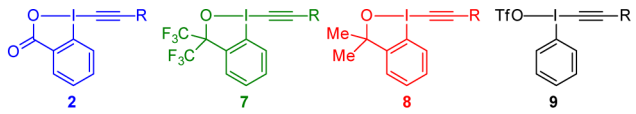


Figure 2. Reaction free energy profile [PBE0-dDsC/TZ2P//M06-2X/def2-SVP level in implicit THF solvent (COSMO-RS)] for the two possible mechanistic pathways **a** (blue) and **b** (red) for the reaction of Me-EBX **2b** with thiolate **1b**′.

Scheme 3. Reaction of thiophenol 1b with ^{13}C-labelled reagent 2c





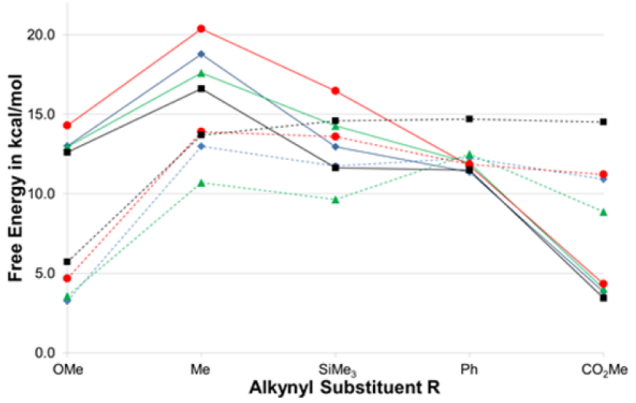


Figure 3. Transition state energies for α (full lines) and β (dotted lines) pathways for EBX reagents depending on the R group and heterocyclic core **2** (blue diamond), **7** (green triangle), **8** (red circle), and **9** (black square).

alkynylation of thiols due to the formation of disulfides as major products.[5a] The superiority of EBX reagents, therefore, can be assigned not to a faster alkynylation of thiols, but to a slower oxidation to disulfides.

In conclusion, further in-depth computational studies prompted discovery of a new mechanism for the alkynylation of thiols with EBX reagents proceeding via an initial sulfur–iodine interaction followed by a concerted β-addition. This mechanism is favored in the presence of electron-donating

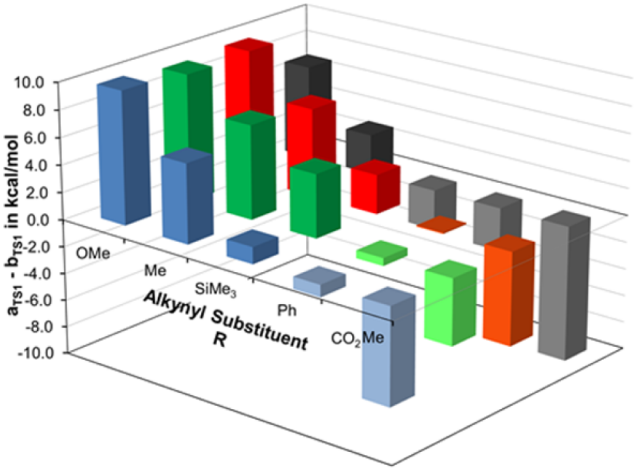


Figure 4. Energy difference $a_{TS1}-b_{TS1}$ depending on the R group and heterocyclic core **2** (blue), **7** (green), **8** (red), and **9** (black).

groups on the alkyne, whereas the previously reported α-addition pathway dominates in the presence of electron-withdrawing groups. With the commercially available reagent TIPS-EBX **2a**, both pathways are accessible, as supported by a labeling experiment. With this study, a more complete picture of the mechanism of the alkynylation of thiols has emerged, which will be highly useful for the design of new transformations using the versatile EBX reagents.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b03241.

Experimental procedures and analytical data for the labeling experiments and computational details (energies) (PDF)

Cartesian coordinate .xyz files (ZIP)

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AUTHOR INFORMATION

Corresponding Authors

*E-mail: matthew.wodrich@epfl.ch.
*E-mail: jerome.waser@epfl.ch.

Notes

The authors declare no competing financial interest.

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(8) See Figure S1 in Supporting Information for the computed structures.

(9) A methyl shift is much higher in energy and was not observed by computation.

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(11) Preliminary computations were also performed with phenolate and tolyl anions as nucleophiles. For the case of the oxygen nucleophile, pathways corresponding to α and β addition could also be identified and were close in energy. For the carbon nucleophile, the β addition pathway via preliminary interaction with the iodine atom could not be easily located and requires further study.

(12) The fact that the transition state energy of the α pathway is lower for methoxy than methyl could be tentatively explained by the inductive effect of the oxygen atom.

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