Radical Alkynylation with EthynylBenziodioXolones: From Photocatalysis to Direct Excitation

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Abstract: Ethynylbenziodoxolones (EBXs) have recently emerged as potent reagents for the alkynylation of radicals. Their combination with photocatalysis allows the synthesis of valuable alkynes at room temperature. Herein, we discuss two photomediated strategies for the synthesis of internal alkynes. The first transformation is a 1,2-oxalkynylation of N- and O-alkenes using 4GICzIPN as a photocatalyst. The second strategy makes use of EBXs as strong photooxidants allowing the oxidation of a variety of substrates with no need for a photocatalyst.

Keywords: Alkyne · Deoxygenation · Difunctionalization · Photochemistry

Introduction

1.1 Alkynes and their Synthesis

From the synthetic chemist’s perspective, alkynes are versatile intermediates. They can undergo selective Lewis acid or transition metal activation allowing the construction of complex (poly)cyclic scaffolds or the conversion into diverse functional groups such as ketones or allenes. They can be reduced to Z and E alkenes and used in metathesis reactions. Their intrinsic rigidity is valuable in medicinal chemistry and materials science. They can also be used in chemical biology for stapling and click reactions. Traditionally, alkyne synthesis proceeds through the construction of an alkyne from aldehydes with the Ohira-Bestmann or the Corey-Fuchs reactions. These reactions often require the presence of a strong base and can be limited by the presence of slightly acidic functional groups on the desired scaffold. In this regard, alkyne transfer appears as an attractive alternative. Internal alkynes can be accessed by the nucleophilic addition of acetylenes to electrophilic centers. Since the development of transition metal catalysis, the Sonogashira alkyne coupling reaction has enabled the coupling of C(sp)-C(sp²) centers. More recently, the use of EthynylBenziodioXolones (EBXs) as an electrophilic alkyne source has allowed the alkynylation of nucleophilic centers. Finally, alkyne transfer can also proceed through the alkynylation of free radicals using alkynyl radical traps such as alkynyl sulfones, free alkynes with a transition metal or EBXs.

1.2 Photomediated Alkynylation with EBXs

Over the past decade, EBXs have emerged as highly efficient radical traps, be it under thermal or photochemical activation. Upon addition of radical I to the EBX reagent, the desired alkyne is formed releasing the iodanyl radical. The high energy associated to free radical intermediates helps to overcome the energy barriers associated to the construction of sterically demanding scaffolds, such as quaternary centers. In this regard, the development of radical alkynylation strategies is of utmost interest.

1. Photocatalysis to Direct Excitation

Stephanie G. E. Amos was born in Exeter (UK) and moved to France aged 11. She has a BSc and MSc in chemistry from the University Claude Bernard Lyon 1 (UCBL, France). In 2016, she joined the CASYEN group (UCBL, France) with Prof. Bruno Andrioletti working on biomass valorization. She then joined the group of Prof. Jerome Waser at the École Polytechnique Fédérale de Lausanne (EPFL, Switzerland) as an intern, developing a sulfenate alkylation strategy. Stephanie is now studying photomediated alkylnylations with hypervalent iodine reagents as a PhD student in the same group.
We found that blue LED irradiation (2 × 40 W, \(\lambda_{\text{max}} = 440\) nm) of the ArEBX (1) in presence of the cesium oxalate (6) provided the desired deoxyalkynylated products (7, Scheme 5). These conditions allowed us to access quaternary alkynes 7a–c in up to 70% yield.

From a mechanistic standpoint, the absorption, fluorescence, and fluorescence excitation spectra of PhEBX (1),

3. From Photoredox Catalysis to the Direct Excitation of ArEBXs: Deoxygenation and other Transformations

Refunctionalization strategies have gained importance over the past few decades. Indeed, the revalorization of biomass entails the transition from poorly functionalized to highly functionalized starting materials.[20] Earlier this year, we reported the direct photooxidation of EBXs for the activation of a variety of redox active groups (RAGs) while developing a deoxyalkynylation of cesium oxalates (Scheme 4).[21] First, the direct excitation was explored and used to activate multiple redox active groups (RAGs) in absence of a photocatalyst (A). Second, we explored photocatalytic conditions to enable a broader scope for the deoxyalkynylation of tertiary alcohols (B).

We found that blue LED irradiation (2 × 40 W, \(\lambda_{\text{max}} = 440\) nm) of the ArEBX (1) in presence of the cesium oxalate (6) provided the desired deoxyalkynylated products (7, Scheme 5). These conditions allowed us to access quaternary alkynes 7a–c in up to 70% yield.

From a mechanistic standpoint, the absorption, fluorescence, and fluorescence excitation spectra of PhEBX (1)
all confirmed the possible excitation of 1 in the visible region (400–460 nm). Cyclic voltammetry experiments allowed the estimation of the redox potential $E_{1/2}(1^*/1^-)$ to be approximately +1.8 V vs SCE, suggesting the strong oxidative character of $1^*$. In addition to the deoxyalkynylation, it was also possible to activate other RAGs by simply using 2.5 equiv of PhEBX (1, Scheme 5). Decarboxylation afforded 9a and 9b (B, 81% and 41%) and enabled the fragmentation of oximes (10) to give alkynyl nitriles 11a and 11b (C, 74% and 69%). Deboronative alkyynylation yielded 13a and 13b (D, 72% and 69%). THF could be readily alkynylated affording 15 in 81% yield (E) and enamide difunctionalization could also be achieved (17, 35% yield). Finally, an unprecedented deaminative alkyynylation was performed via the formation of imine 18 delivering 19 in 57% (G).

Although the scope of applications of the excited state PhEBX (1) was broad, the major drawback of this approach was that only Ph- and pTol-EBXs afforded the desired deoxyalkynyalted products in synthetically relevant yields (Scheme 5). To circumvent this limitation, we found that the deoxyalkynylation reaction could be performed with 4CzIPN (2b) as a photocatalyst with a lower loading of EBX reagent (1.5 equiv, Scheme 7). These photocatalytic conditions allowed us to access 21 different alkynyalted quaternary centers in up to 82% yield allowing greater functional group tolerance either by varying the EBX or the alcohol 7c–7h (55–78% yield).

4. Conclusions

When combined with radicals, EBXs are an attractive source of alkynes. Under photocatalytic conditions, their applications have been extended to atom economical difunctionalization and deoxyalkynylation. Under irradiation at 440 nm (2 × 40 W), they
can undergo direct excitation to a highly oxidizing species unlocking the way to photocatalyst-free photomediated alkynylations. On the one hand, the fine tuning of a photocatalyst enables efficient alkynylations with greater tolerance. On the other hand, the direct excitation approach can enable facile reaction discovery and simplified reaction set-up. For the alkynylation of radicals with EBXs, both photocatalyzed and direct approaches appear as complementary and valuable and promise further developments in this field.

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