DOI: 10.1002/chem.201001539

Ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX): An Exceptional Reagent for the Ethynylation of Keto, Cyano, and Nitro Esters

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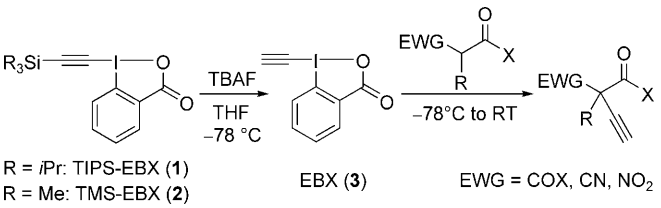
The chemistry of acetylenes has been extensively used in organic synthesis.[1] In recent decades, the functionalization of the triple bond by using metal catalysis has complemented classical acetylene chemistry, providing numerous addition, cyclization, and cycloaddition reactions for the construction of organic molecules.[2] The exceptional properties of acetylenes have also found widespread application in neighboring fields, such as materials science and biochemistry.[1] To respond to this ever increasing demand for structurally diverse acetylenes, the development of new methods for their synthesis is an important task for organic chemists.[3]

Acetylene transfer reactions constitute an efficient method for the introduction of the triple bond. The sp hybridization increases the acidity of the alkyne C–H bond, allowing the easy generation of acetylide anions or metal intermediates, which have been used extensively in addition reactions to carbonyls or imines[4] and in cross-coupling (Sonogashira) reactions.[5] In contrast, electrophilic alkynyl synthons have been much less well developed,[6–8] and disconnections based on this umpolung reactivity are not usually considered when planning syntheses. This constitutes a serious limitation in the syntheses with acetylenes, as, for example, all-carbon quaternary centers containing a triple bond cannot be easily accessed by using acetylide nucleophiles.

Reported methods for the generation of electrophilic acetylene synthons are based on the use of halogen acetylenes,[6] lead acetylide reagents,[7] or alkynyliodonium salts.[8] Although recent progress has been made for the functionalization of aromatic C–H bonds,[9] the methods for the conceptually simple α-alkynylation of carbonyl groups are still limited. In particular, ethynylation reactions would be highly desirable, as they would allow further direct functionalization of the alkyne C–H bond without the need for the removal of protecting groups. To our knowledge, the one-step α-ethynylation of carbonyl groups has been realized in only a few examples that use lead reagents[7a] or alkynyliodonium salts,[8b,e] and the scope reported for these reactions was limited. As a result, these methods have not been broadly adopted by the organic chemistry community and reported applications are scarce.

Recently, we discovered the exceptional reactivity of 1-[(triisopropylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TIPS–EBX, **1**) for the metal-catalyzed alkynylation of C–H bonds and olefins.[10] Herein, we report the in situ generation of the parent reagent, ethynyl-1,2-benziodoxol-3(1*H*)-one (EBX, **3**) from the corresponding trimethylsilyl-protected benziodoxolone **2** (TMS–EBX) and its exceptional acetylene-transfer ability with soft enolates (Scheme 1). The simple procedure and mild reaction conditions, which use tetrabutylammonium fluoride (TBAF) both as an activating agent and a base, allowed high yields and a broad substrate scope, including cyano and nitro esters, two classes of compounds that have never been reported before. Finally, a proof of concept for asymmetric induction has been achieved.



Scheme 1. Alkynylation of soft enolates with EBX (**3**).

Prior to our work, the few methods describing the ethynylation of carbonyl compounds that use hypervalent iodine reagents were all based on the use of alkynyliodonium salts.[8b,e] In these reports, the enolate was formed in the

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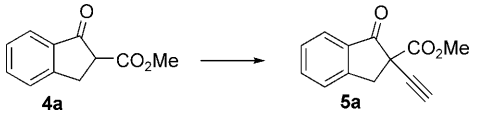
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201001539.

presence of a strong base before the addition of the iodine reagent, probably to prevent its decomposition in presence of the base. Benziodoxolone-based reagents were not used in these works.[11] As TIPS–EBX (**1**) has proven to be very stable to both base and moisture, we first investigated whether milder, one-pot, phase-transfer conditions were possible for the alkynylation of keto ester **4a** (Table 1, entry 1). However, no reaction was observed with this reagent. We then turned to the potentially more reactive TMS–EBX (**2**). In this case, alkynylation was observed, but the deprotected product **5a** was obtained as the major product (Table 1, entry 2). A control experiment showed that this deprotection did not occur at the product stage under these reaction conditions. Consequently, we speculated that EBX (**3**) itself was responsible for the observed ethynylation reaction. Although both TIPS–EBX (**1**) and TMS–EBX (**2**) are bench-stable reagents, we were unable to isolate EBX (**3**), as all attempts towards silyl removal resulted in decomposition. If KF was used as the base, free acetylene product **5a** was obtained exclusively in 87% yield (Table 1, entry 3). Although these reaction conditions worked well for cyclic keto esters, much lower yields were obtained with other classes of substrate (vide infra). We then turned to TBAF as a fluoride source, but extensive decomposition of the reagent was observed at 0°C (Table 1, entry 4). A significantly improved yield was obtained by starting the reaction at −78°C and slowly warming up to 10°C (71%, Table 1, entry 5). Different solvents were then examined (Table 1, entries 5–9) and alkyne **5a** was obtained in 98% yield in only 1.5 h at −78°C in THF (Table 1, entry 9). This result demonstrates the exceptional reactivity of EBX (**3**), which allowed the alkynylation reaction to proceed under mild conditions with use of a simple procedure. When the same reaction was run under previously reported conditions with an alkynyliodonium salt, which reacts via formation of the sodium enolate of **4a**,[8b] alkyne **5a** was isolated in only 69% yield (Table 1, entry 10).

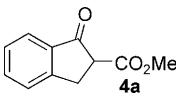
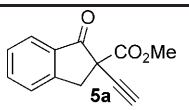
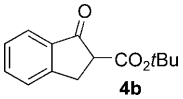
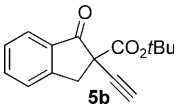
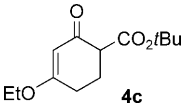
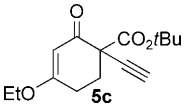
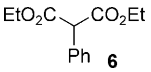
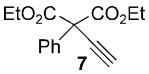
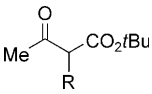
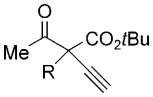
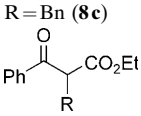
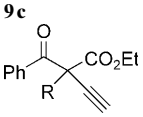
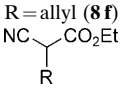
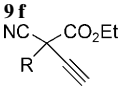
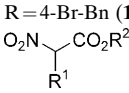
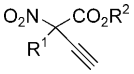
Table 1. Alkynylation of keto ester **4a**.



Entry	Reaction conditions[a]	Solvent	Yield [%]
1	**1**, sat. K_2CO_3, $Me_4N^+Cl^-$, 0°C	toluene	n.r.[b]
2	**2**, sat. K_2CO_3, $Me_4N^+Cl^-$, 0°C	toluene	<80[c]
3	**2**, sat. KF, $Me_4N^+Cl^-$, 0°C	toluene	87
4	**2**, TBAF, 0°C	toluene	decomp[d]
5	**2**, TBAF, −78 to 10°C, 12 h	toluene	71
6	**2**, TBAF, −78 to 10°C, 12 h	Et_2O	49
7	**2**, TBAF, −78 to 10°C, 12 h	*i*PrOH	<90[c]
8	**2**, TBAF, −78°C, 3 h	CH_2Cl_2	78
9	**2**, TBAF, −78°C, 1.5 h	THF	98
10	Ochiai's conditions[8b]	THF	69

[a] Reactions under phase-transfer conditions (entries 1–3): substrate (0.3 mmol), $Me_4N^+Cl^-$ (10 mol%), reagent (**1** or **2**; 1.3 equiv), toluene/saturated base solution (5 mL/1.5 mL). Reactions with TBAF: substrate (0.4 mmol), TBAF (1.3 equiv), **2** (1.3 equiv), solvent (3.3 mL). [b] n.r. = no reaction. [c] Product **5a** could not be separated from unidentified impurities. [d] decomp = decomposition of the starting materials.

Table 2. Scope of the alkynylation of activated carbonyls.

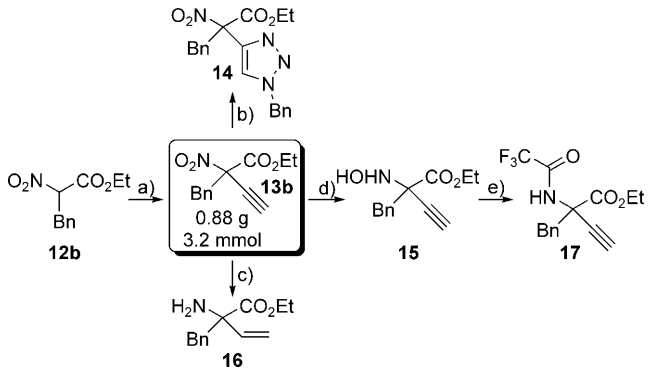
Entry	Substrate	Product	Isolated yield [%][a]
1	 **4a**	 **5a**	98
2	 **4b**	 **5b**	94
3	 **4c**	 **5c**	50[b]
4	 **6**	 **7**	95[c]
			
5	R = Me (**8a**)	**9a**	90
6	R = Et (**8b**)	**9b**	63[b]
7	R = Bn (**8c**)	**9c**	77
			
8	R = Me (**8d**)	**9d**	83
9	R = Bn (**8e**)	**9e**	93[b,c]
10	R = allyl (**8f**)	**9f**	88[b]
			
11	R = Bn (**10a**)	**11a**	90
12	R = 4-Br-Bn (**10b**)	**11b**	75
			
13	R^1 = Me, R^2 = Et (**12a**)	**13a**	75
14	R^1 = Bn, R^2 = Et (**12b**)	**13b**	93
15	R^1 = Ph, R^2 = Me (**12c**)	**13c**	80
16	R^1 = Ph, R^2 = *t*Bu (**12d**)	**13d**	85

[a] Reaction conditions: substrate (0.4 mmol), TBAF (1.3 equiv), **2** (1.3 equiv), at −78°C or from −78°C to 10°C, 1–20 h, THF (3.3 mL; see Supporting Information for the exact reaction time and temperature) [b] The reagent was slowly added as a solution (THF/CH_2Cl_2; 5:1) over 10 h. [c] The reaction was run with 1.8 equiv of **2**.

The scope of the reaction was examined next (Table 2). Cyclic keto esters **4a–c** and diethyl phenylmalonate (**6**) gave moderate to excellent yields in the alkynylation reaction (Table 2, entries 1–4). In contrast to cyclic keto esters and malonates, only the alkynylation of acyclic keto esters by lead reagents has been reported,[7a,c] and there are no examples of the ethynylation of these more challenging substrates. Gratifyingly, the desired acetylene products were obtained in 63–93% yield for keto esters **8a–f**, giving quater-

nary centers with four different carbon substituents (Table 2, entries 5–10). Both methyl and phenyl ketones (Table 2, entries 5–10) with several different α-alkyl substituents, including an allyl group, could be used, which provided access to the versatile 1,5-enyne product **9 f** (Table 2, entry 10). Cyano and nitro esters (Table 2, entries 11–16) were also good substrates for the reaction. Importantly, the alkynylation of theses two classes of compounds has never been reported before. The nitro substrates in particular are very sensitive compounds and the mild conditions developed were crucial to obtaining good yields.[12] A practical issue with the ethynylation reaction is caused by the similar polarity of the starting materials and products, which makes their separation by thin layer or column chromatography nearly impossible. Consequently, complete conversion was required to allow purification of the products. For slow reacting substrates, a better conversion was achieved if reagent **2** was added slowly at −78 °C by using a syringe pump.

The obtained propargylic nitro and cyano products containing an ester group are new structures that have never before been synthesized. In particular, propargylic nitro compounds with a free acetylene are a very rare class of compounds and their properties have never been studied in detail. Consequently, we decided to examine the synthetic potential of product **13b** more intensively (Scheme 2).

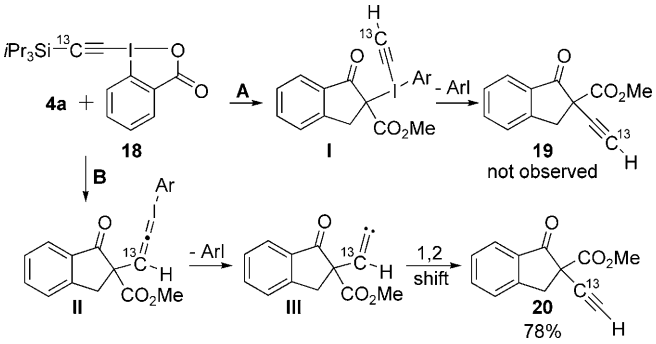


Scheme 2. Scaled-up synthesis and functionalization of **13b**. Reaction conditions: a) **2** (1.3 equiv), TBAF (1.3 equiv), THF, −78 °C, 77 %; b) BnN_3 (1 equiv), $CuSO_4$ (5 mol %), sodium ascorbate (10 mol %), *t*BuOH/H_2O (1:1), 60 °C, 65 %; c) Zn, HCl/AcOH (1 N), 0 °C, 57 %; d) Zn, NH_4Cl, EtOH/H_2O (1:1), 0 °C, 94 %; e) SmI_2, THF, *t*BuOH, then TFAA, 67 %.

The ethynylation of **12b** proceeded with a yield of 77 % on a 4.7 mmol scale to give **13b**. The Cu-catalyzed [3+2] cycloaddition of **13b** with BnN_3 gave the corresponding triazole (**14**) in 65 % yield.[13] This constitutes the first example of a [3+2] cycloaddition reaction of a propargyl nitro compound. Reduction of the nitro group to the amine was attempted next. To the best of our knowledge, there is only one report of the reduction of a propargylic nitro compound to the amine, which proceeds through the corresponding hydroxylamine.[14] Although reduction to hydroxylamine **15** with Zn dust worked well, it was not possible to use the reported conditions for the reduction of the N–O bond.[14,15] If Zn dust was used under more forcing conditions, allyl amine **16** was obtained in 57 % yield.[16] Gratifyingly, we found that selective reduction of the N–O bond in **15** was possible by using SmI_2 in THF/*t*BuOH.[17] Purification of the free amine was difficult, but quenching the reaction with trifluoroacetic anhydride (TFAA) allowed the isolation of the corresponding trifluoro amide (**17**) in good yield and purity. The obtained protected alkynyl amino acids display interesting biological activities and few methods have been reported for their synthesis.[18]

During optimization of the reaction, we speculated that EBX (**3**) was the alkynylating agent. As it was not possible to isolate this reagent, we decided to monitor its formation by ^1H and ^{13}C NMR at low temperature. Treating TMS–EBX (**2**) with TBAF at −78 °C led to immediate conversion to a new compound, the spectrum of which was in full agreement with the structure of EBX (**3**).[19] The ^1H NMR spectrum remained unchanged when the solution was heated up to −20 °C. At this point, EBX (**3**) gradually decomposed to generate several as yet unidentified products. If a substrate was added to the EBX (**3**) solution, the only signals observed belonged to EBX (**3**), 2-iodobenzoic acid, the substrate and the ethynylation product; no other intermediates were observed.[20]

In principle, two reaction pathways can be envisaged for this reaction (Scheme 3): addition of the enolate to the iodine atom followed by reductive elimination (pathway **A**)

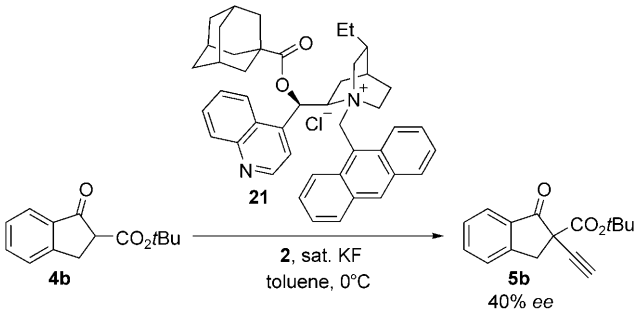


Scheme 3. Possible mechanisms for the ethynylation reaction and labeling experiment (Ar = phenyl-2-carboxylate).

or conjugate addition to the alkyne, followed by an elimination and 1,2-hydride shift (pathway **B**). For both pathways, initial interaction with the carbonyl oxygen could also be envisaged. The use of ^{13}C-labeled reagent **18**[21] led to product **20**, which is only consistent with the 1,2-hydride-shift pathway. This mechanism has also been proposed in the case of alkynyliodonium salts.[8b] Interestingly, the opposite result was obtained in the case of metal-catalyzed alkynylation reactions that used TIPS–EBX (**1**).[10]

The use of benziodoxolone-based reagents for the ethynylation reaction allowed us to increase the scope and efficiency of the reaction. Nevertheless, the obtained products are racemic and an asymmetric method would be highly de-

sirable. The only reported enantioselective method for the alkynylation of enolates is limited to carbonyl substituted acetylenes.[6i] Preliminary investigations by using the phase-transfer conditions developed by Jørgensen[6i] led to moderate asymmetric induction (Scheme 4). Interestingly, the use



Scheme 4. An asymmetric ethynylation reaction.

of alkynyliodonium salts led to the formation of racemic products in this case, highlighting a further advantage of EBX (**3**) as an electrophilic ethynylation reagent.

In conclusion, we have reported the first use of benziodoxolone-based hypervalent iodine reagents for the ethynylation of activated carbonyl compounds. The reactive EBX (**3**) was generated from bench-stable TMS–EBX (**2**) in the presence of TBAF under mild conditions. The high acetylene transfer ability of **3** resulted in good yields for ethynylation reactions. For the first time, acetylene transfer to acyclic keto and cyano esters was achieved, which gave access to quaternary centers with four different carbon substituents, a synthetically challenging class of compounds in organic chemistry. Unprecedented alkyne substituted nitro esters were synthesized and methods for their transformation to the corresponding protected amino acids were developed. The reaction was shown to proceed through a 1,2-hydride-shift mechanism similar to the one proposed for alkynyliodonium salts. Finally, we demonstrated that asymmetric induction was possible under phase-transfer conditions. The simplicity of the reported method, as well as its broad scope, greatly enhance the usability of electrophilic alkyne synthons in organic chemistry and is expected to stimulate chemists to more routinely use an umpolung approach for the synthesis of acetylenes. The application of benziodoxolone reagents for the alkynylation of other nucleophiles, as well as the improvement of the asymmetric induction are currently under investigation in our laboratory.

Acknowledgements

EPFL and SNF (grant number: 200021_119810) are acknowledged for financial support. Raha Sedigh-Zadeh (EPFL) is acknowledged for the preparation of starting materials.

Keywords: alkynylation · hypervalent compounds · iodine · quaternary carbon atoms · umpolung

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[20] In the case of slower-reacting substrates, partial decomposition of EBX was also observed.

[21] For reasons of synthetic accessibility, the labeled TIPS–EBX reagent **18** was used. Generally, TIPS–EBX (**1**) was as efficient as TMS–EBX (**2**) as the reagent precursor, although the silyl-group removal was slightly slower.

Received: May 6, 2010
Published online: July 19, 2010

