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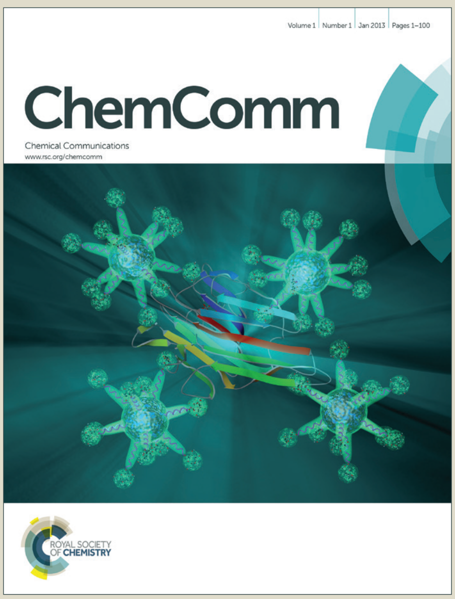
Volume 1 | Number 1 | Jan 2013 | Pages 1–100
ChemComm
Chemical Communications
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Chemical Communications ChemComm

DOI: 10.1039/C4CC00608A

Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Electrophilic Alkynylation of Ketones Using Hypervalent Iodine

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A new method for the electrophilic α-alkynylation of ketones was developed using hypervalent iodine under mild and metal-free conditions. Carbonyl compounds containing an α-acetylene group were obtained in good to excellent yields for several ketones using 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX) as alkynylation agent in the presence of *t*-BuOK and TBAF in THF as solvent. Under the same conditions, an aldehyde was alkynylated.

The α-functionalization of carbonyl compounds, such as alkylation, acylation, arylation, and alkynylation, is one of the most important class of reaction in organic synthesis. Among the aforementioned transformations, the α-alkynylation seems to be the less explored. Acetylenes are versatile functional groups in organic chemistry.[1] Their unique properties and reactivity allow formation of complex molecular structures making them very interesting intermediates in synthetic strategies.[1] Therefore, the development of new methods to add this group in a molecule is a valuable tool for carbon-carbon bond formation and functional group interconversion.

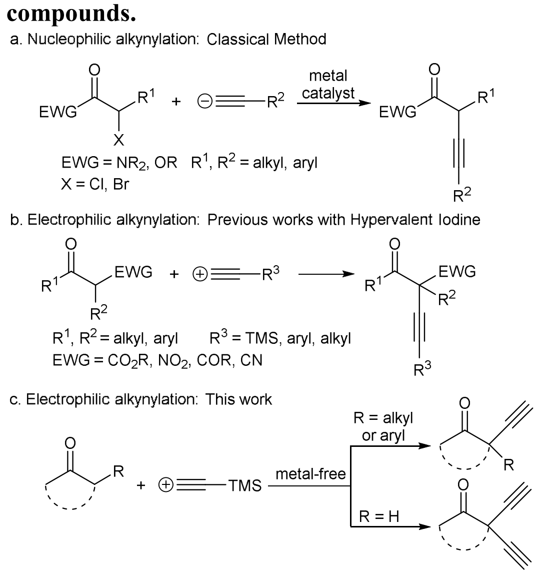
There are two strategies to carry out the α-alkynylation of carbonyl compounds. The most utilized relies on a nucleophilic source of the acetylene component that typically reacts with α-halocarbonyl compounds. Included on this approach are several metal catalyzed reactions where the majority of examples utilizes only esters and amides as the carbonyl partner (Scheme 1, equation a).[2]

An alternative and much less explored route is using an electrophilic source of an alkyne.[3] In this scenario, easy to obtain and user friendly hypervalent iodine reagents[4] are particularly promising.[3a,5] Over the years, numerous strategies for the α-alkynylation of carbonyl compounds have been described using a variety of hypervalent iodine compounds.[6] Nonetheless, the scope of the carbonyl compounds is still restricted to β-keto esters (and related methylene-activated compounds) (Scheme 1, equation b).

There are only two reports regarding the direct α-alkynylation of non-activated carbonyl compounds. Yamaguchi and co-workers described the α-ethynylation of ketones with chlorosilylethyne using trialkylgallium to generate the enolate.[7] Kende and his group reported the reaction of ketones with 1-chloroalkynes in the presence of LDA/HMPA.[8] In the latter method, two steps are necessary to obtain terminal alkynes, using dichloroacetylene as acetylene component. To the best of our knowledge, there are no precedents for the α-alkynylation of aldehydes utilizing either nucleophilic or electrophilic alkynylating reagents. Other research groups have been trying the same type of alkynylation without success. For example, the recent work of Huang and co-workers described the reaction of aldehydes with TMS-EBX. However, only allenes were obtained in the presence of gold and an amine. The alkynation product was a minor component.

Herein, we report a practical, metal-free and efficient electrophilic α-alkynylation of non-activated cyclic ketones using hypervalent iodine reagent. The protocol was also applied to an aldehyde. Additionally, this procedure is an important tool to broaden the scope of available methods to afford quaternary carbon centers (Scheme 1, equation c).

Scheme 1. Strategies for the α-alkynylation of carbonyl compounds.



We began the optimization of the reaction conditions for the α-alkynylation of non-activated ketones using ketone **1a** as model substrate. Previous work have shown the superior properties of 1-[(trimethylsilyl)ethynyl]-1,2-benziodoxol-3(1*H*)-one (TMS-EBX, **2a**) over other alkynylating agents[6g,6h,9] and, consequently, all optimization was made utilizing this electrophilic compound.. First, the protocol developed by Waser and co-workers for activated carbonyl compounds was applied.[6g,6h] Unfortunately, the combination of TMS-EBX as alkynylating reagent and tetrabutylammonium fluoride (TBAF) as base in THF at -78 ºC was not efficient to provide the desired α-acetylene product and only starting material was recovered (Table 1, entry 1). Considering the difference in pK_a between β-keto esters and ketones, other bases were tested. No desired product was observed when K_2CO_3 and CsF were utilized (entries 2 and 3). The use of stronger base, such as NaH afforded **3a** in only 41% along with undesired side products formation (entry 4). Very good yields were achieved using LiHMDS and *t*-BuOK (entries 5 and 6). Using inexpensive and readily available *t*-BuOK, other solvents were tested. The reaction in Et_2O or in CH_2Cl_2 provided

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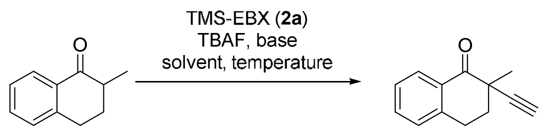
lower yields when compared to THF (entries 7-8). Finally, when the reaction was performed at higher temperatures, undesired side product formation was observed diminishing the efficacy of the method (entries 9 and 10). In summary, the best result (89% yield) was obtained utilizing *t*-BuOK at -78 °C in THF (entry 6). To avoid any decomposition of TMS-EBX in the reaction medium,[6g] this electrophilic reagent is added after the formation of the enolate from ketone and base. This is another difference when compared to the procedure described by Waser and co-workers.[6g,6h]

Table 1. Optimization of the α-alkynylation reaction[a].



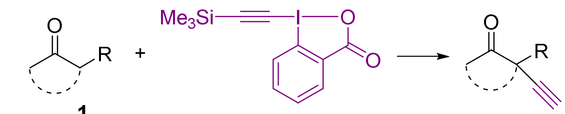
Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1	----	THF	-78	0[c]
2	K_2CO_3	THF	-78	0[c]
3	CsF	THF	-78	0[c]
4	NaH	THF	-78	41[d]
5	LiHMDS	THF	-78	79
6	t-BuOK	THF	-78	89
7	t-BuOK	Et_2O	-78	73
8	t-BuOK	CH_2Cl_2	-78	50[d]
9	t-BuOK	THF	0	68[d]
10	t-BuOK	THF	rt	30[d]

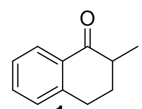
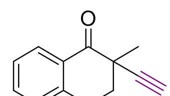
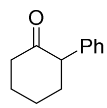
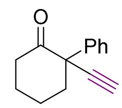
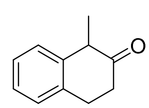
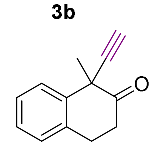
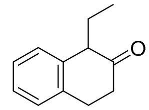
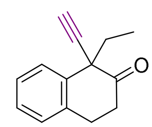
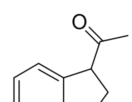
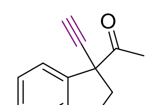
[a] Reaction conditions: 0.100 mmol of **1a**, 0.125 mmol of base, 0.130 mmol of TMS-EBX (**2**), 0.130 mmol of TBAF, solvent 0.100 M, 6 h. [b] Yield determined by GC using dodecane as internal standard. [c] Starting material recovered. [d] Other products were formed.

The scope of the α-alkynylation reaction for diverse ketones was then examined, starting with α-substituted substrates. On a 1 mmol scale, **3a** was obtained in 93 % yield after 3 h (Table 2, entry 1). Similar yield was observed using 2-phenylcyclohexanone (**1b**), as substrate (entry 2). Good results were obtained with 2-tetralones **1c-d** that bear methyl and ethyl substituents, respectively (entries 3-4). Indane derivative **1e** led to the alkynylated product **3e** in 85% yield.

The optimized conditions were applied toward a series of non-substituted cyclic ketones, where two alkynyl groups would be introduced. Indanone (**4a**) gave the desired compound **5a** in 69% yield (Table 3, entry 1). Higher yields were observed for 1-tetralone (**4b**) and benzosuberone (**4c**) (entries 2-3). The reaction with 2-tetralone (**4d**) gave the desired product in only 42% yield, probably due to the fast decomposition of the substrate (entry 4). The reaction of methyl and methoxy substituted aromatic rings with hypervalent iodine reagents can be problematic.[10] Fortunately, these groups are well tolerated in the alkynylation. The methyl substituted tetralone **4e** led to **5e** in excellent yield (entry 5). *Bis*-acetylenic compounds **5f-g** were formed in 60 and 75% yield, respectively from the methoxy ketones **4f-g** (entries 6-7). Lower yield (43%) was obtained when the substrate bears a bromine atom in the aromatic ring (entry 8). The behavior of heterocyclic aromatic rings was also investigated. Furan derivative **4i** gave the alkynylated product in only 30% yield, whereas the corresponding thiophene compound **4j** led to the desired product in very good yield (entries 9-10). As expected, alkynylation on the aromatic ring was not observed. This transformation only takes place in the presence of a metal catalyst.[11] The reaction condition was also efficient to alkynylate non-cyclic ketone **4k**, affording the desired product in 74% yield (entry 11). Unfortunately, under the developed set of conditions, non-aromatic ketones such as 4-phenylcyclohexanone did not yield the desired alkynylated product and only starting material was recovered. Other bases were tried (e.g. NaH, BuLi, LiHMDS, LDA), however in all cases the α-ethynylated product was not observed.

Table 2. Scope of the α-alkynylation of ketones: monoalkynylation.[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **1a**	 **3a**	93
2	 **1b**	 **3b**	85
3	 **1c**	 **3c**	60
4	 **1d**	 **3d**	78
5	 **1e**	 **3e**	85

[a] Reaction conditions: 1.00 mmol of **1**, 1.25 mmol of base, 1.30 mmol of TMS-EBX (**2**), 1.30 mmol of TBAF, THF, -78 °C, 2-10 h. [b] Isolated yield after purification by column chromatography.

The reactivity of other alkynylating compounds was tested, using 2-phenylcyclohexanone (**1b**) as substrate and TIPS-EBX (**2b**)[6h] and Ochiai´s reagent (**2c**)[6c] as electrophilic component. Product **3b** was obtained using these reagents, albeit lower yields and longer reaction time was observed, comparing to the reaction using TMS-EBX, which afford the product in only 2 h (Scheme 2 and Table 2, entry 2).

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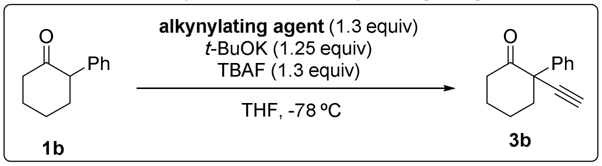
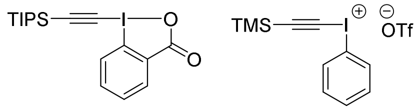
Scheme 2. Reactivity of different alkynating reagents



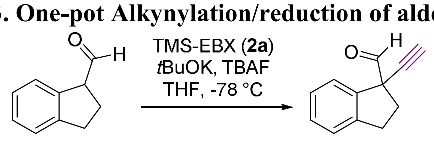


TIPS-EBX (**2b**)
4 h, 80%

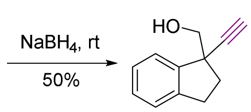
Ochiai´s reagent (**2c**)
12 h, 67%

The α-alkynylation of aldehyde **6a** was also investigated. To our delight, this transformation took place smoothly under the same conditions used for the ketones, as verified by TLC, GC-MS, and NMR analysis. However, all attempts to purify the crude product by column chromatography were unsuccessful. Based on our previous experience on related aldehydes,[12] we decided to reduce the aldehyde *in situ* using $NaBH_4$. Indeed, the corresponding alkynylated alcohol **7a** could be isolated in pure form (Scheme 3). Although the purification of the alkynylated aldehyde was difficult, the crude material can certainly be used on other transformations, as reported for similar compounds.[13] The non-aromatic cyclohexanecarboxaldehyde did not afford the desired alkynylated product under the developed set of conditions.

Scheme 3. One-pot Alkynylation/reduction of aldehyde 6a.

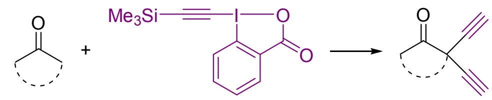


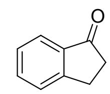
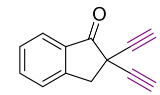
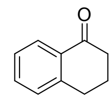
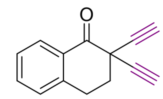
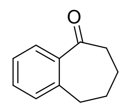
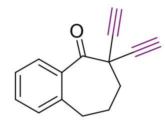
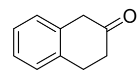
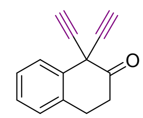
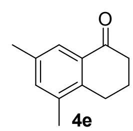
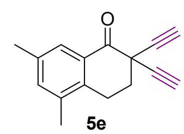
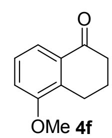
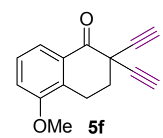
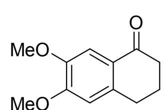
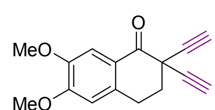
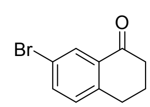
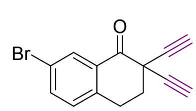
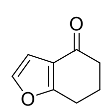
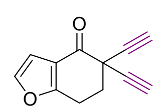
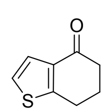
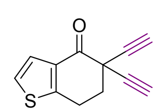
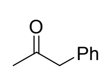
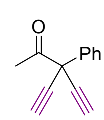
6a



7a

Table 3. Scope of the α-alkynylation of ketones: dialkynylation.[a]



Entry	Substrate	Product	Yield (%)[b]
1	 **4a**	 **5a**	69
2	 **4b**	 **5b**	80
3	 **4c**	 **5c**	81
4	 **4d**	 **5d**	42
5	 **4e**	 **5e**	92[c]
6	 **4f**	 **5f**	60
7	 **4g**	 **5g**	75[c]
8	 **4h**	 **5h**	43[d]
9	 **4i**	 **5i**	30
10	 **4j**	 **5j**	74
11	 **4k**	 **5k**	74

[a] Reaction conditions: 1.0 mmol of **4**, 2.5 mmol of *t*-BuOK, 2.6 mmol of TMS-EBX **(2)**, 2.6 mmol of TBAF, THF, -78 °C, 1-10 h. [b] Isolated

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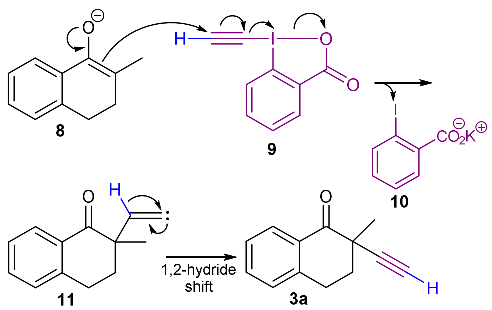
yield after purification by column chromatography. [c] 3.0 mmol *t*-BuOK. [d] 0.3 mmol of **4h**.

The proposed mechanism for α-alkynylation is shown in Scheme 3 using **1a** as example.[6g,6h] In presence of base, this ketone gives enolate **8**. EBX (**9**) is originated by reaction of TMS-EBX (**2**) with TBAF. Nucleophilic attack of enolate **8** into the electrophilic α-carbon of **9** furnishes carbene **11**.[6b] Rearrangement of this carbene leads to the isolated product **3a**.[6c]

Scheme 3. Mechanism for the α-alkynylation of carbonyl compounds.



In conclusion, a new method for the electrophilic α-alkynylation of ketones and aldehydes was developed using TMS-EBX under mild and metal-free conditions. Carbonyl compounds bearing an α-acetylene group were obtained in good to excellent yields. The pKa values of the substrates are in the range from at least 17.6 (2-tetralone) to 24.7 (1-tetralone). To the best of our knowledge the examples presented here represent the only effective electrophilic α-alkynylation of ketones and aldehydes employing hypervalent iodine reagent. Additional studies are ongoing on our group to increase the scope of the methodology to non-cyclic aromatic and aliphatic ketones as well as an asymmetric version of the reaction.

Notes and references

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[*] *Corresponding Author: luizfsjr@iq.usp.br.*
† Electronic Supplementary Information (ESI) available: [Experimental procedures and characterization data]. See DOI: 10.1039/b000000x/

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