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Application of Hantzsch Ester and Meyer Nitrile in Radical Alkynylation Reactions

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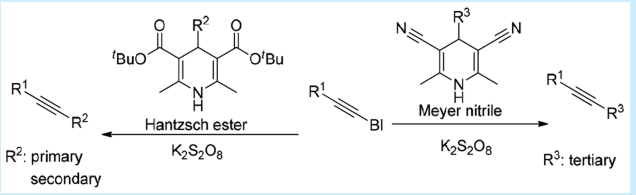
Supporting Information

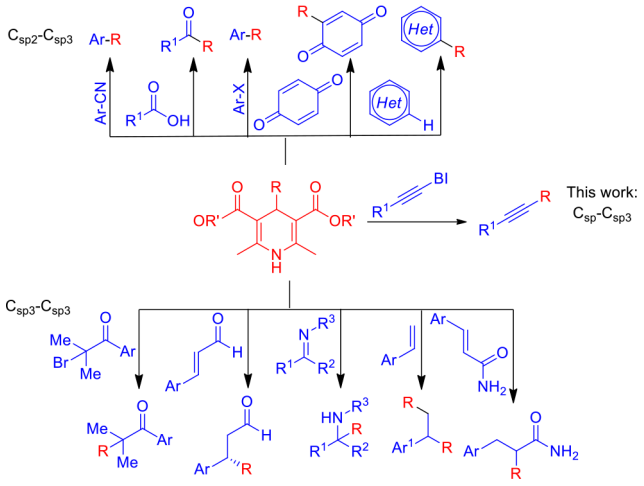
ABSTRACT: The first example of constructing a $C_{sp3}-C_{sp}$ bond with substituted Hantzsch ester and Meyer nitrile is reported. When benziodoxole-activated alkyne was applied as the alkynyl donor, products containing $C_{sp3}-C_{sp}$ bonds involving primary, secondary, and tertiary carbon centers were achieved in up to 97% yields. $K_2S_2O_8$ was the optimum radical initiator in this reaction.



The alkynyl group is a highly reactive functionality that is applied as a precursor in a number of transformations. Introductions of alkynyl groups into molecules have been established via nucleophilic addition,[1] electrophilic addition,[2] and transition-metal-catalyzed coupling reactions.[3] Recently, alkynylation reactions via a radical pathway have been reported with BI (benziodoxolone)-activated acetylenes in combination with radicals from a variety of precursors such as carboxylic acids,[4] alkyl borates,[5] aldehydes,[6] alcohols,[7] and ketones.[8] These radical alkynylation reactions demonstrated complementary reactivity and selectivity to approaches involving ionic species or transitional-metal catalysis.[9]

The synthetic potential of substituted Hantzsch ester (HE) was first exhibited by Tang in Lewis acid catalyzed alkylation reactions (Scheme 1).[10] It was reported as a highly efficient photoredox alkylation reagent in a visible-light-induced reaction first by Nishibayashi.[11] Our group reported an intermolecular construction of a quaternary carbon center fulfilled with substituted HE or Meyer nitrile[12] as radical donors.[13] Substituted HE was successfully applied in the coupling reaction with synergistic catalysis using nickel/photocatalyst by Nishibayashi and Molander's groups.[14] Melchiorre and co-workers revealed the substituted HE could fragment at its excited state in the absence of photocatalyst and gave an alkyl radical that in turn participated in nickel-catalyzed alkylation reactions.[15] Recently, we have disclosed that the substituted HE behaves as a radical reservoir that is able to release a radical without an external electron acceptor in photoredox catalysis.[16] Yu and Zhang presented a photoredox addition of an alkyl radical to imine with substituted HE as radical donor.[17] In addition to the reactivity of substituted HE in the presence of transitional-metal complex, the reaction reported by Molander and co-workers showed HE also works with an organo-radical initiator such as $Na_2S_2O_8$ in the $C_{sp2}-H$ alkylation reaction.[18] An asymmetric radical 1,4-addition was achieved by Melchiorre with visible-light-induced iminium catalysis employing substituted HE as radical precursor.[19] In spite of extensive applications of substituted HE in various alkylation reactions, the alkylation of alkyne giving the $C_{sp}-C_{sp3}$ bond remains elusive. Herein, we report our study of the alkylation reaction with substituted HE and Meyer nitrile and alkyne activated by a BI group to build a $C_{sp}-C_{sp3}$ bond.

Scheme 1. Application of Substituted Hantzsch Ester in C−C Bond Formation Reactions



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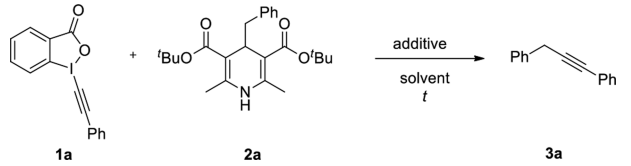
On the outset of our study, we chose phenylacetylene BI derivative **1a** and benzyl-substituted Hantzsch ester **2a** as starting materials in the presence of different catalysts or reagents (Table 1). At room temperature, 1 mol % of *fac*-

Table 1. Optimization of Alkylation of BI-Activated Alkyne[a]



1a 2a 3a

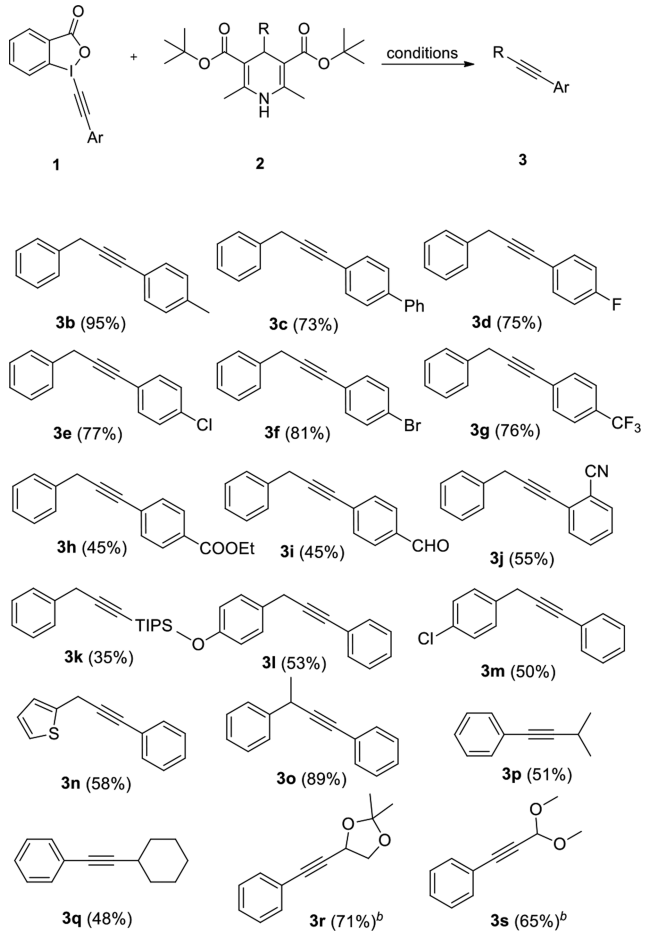
entry	photocatalyst[b] (1 mol %)	oxidant[c] (equiv)	yield[d] (%)
1	*fac*-Ir(ppy)$_3$		12
2	Ru(bpy)$_3$Cl$_2$		8
3	Safranine		42
4		$K_2S_2O_8$ (1.5)	88 (84)[e]
5[f]		$K_2S_2O_8$ (1.5)	trace
6		$Na_2S_2O_8$ (1.5)	84
7		TBHP (1.5)	48
8		BPO (1.5)	15
9		30% H_2O_2 (1.5)	19
10		PhI(OAc)$_2$ (1.5)	10
11		*m*-CPBA (1.5)	23
12		$K_2S_2O_8$ (1)	71

[a]Reaction conditions: **1** (0.1 mmol), **2** (0.2 mmol), Ar atmosphere, 18 h. [b]Cs_2CO_3 (0.1 mmol), DCE (1 mL), 24 W blue LEDs, rt. [c]MeCN/H_2O (v/v = 1:1, 1 mL), 50 °C. [d]NMR yield using diphenylmethane as the internal standard. [e]Isolated yield in parentheses. [f]Room temperature.

Ir(ppy)$_3$ was used as the photoredox catalyst, and phenyl benzyl acetylene **3a** was generated with only 12% NMR yield (entry 1). Another widely applied complex, Ru(bpy)$_3$Cl$_2$, gave an even poorer result (entry 2). Further evaluation of other photocatalysts showed safranine gave a moderate yield of 42% (entry 3). We then turned to thermal radical initiators and found that with 1.5 equiv of $K_2S_2O_8$ **3a** could be obtained in 84% isolated yield at 50 °C (entry 4, 75% yield at 1 mmol scale). It was also confirmed that heating was necessary to achieve the conversion as the reaction run at room temperature could not offer the desired product (entry 5). If $Na_2S_2O_8$ was applied, a marginal loss of yield of **3a** was observed (entry 6). Other oxidative reagents did not give competitive results in comparison to $K_2S_2O_8$ (entries 7−11). In a reaction employing 1.0 equiv of $K_2S_2O_8$, an inferior yield of 71% was obtained.

Subsequently, we explored the substrate scope of this formation process of the C_{sp}−C_{sp3} bond (Scheme 2). At first, a variety of BI-derived aryl acetylenes **1** were used as alkynyl donors in reactions with **2a**. Compound **3b** with a methyl group at the *para* position was produced in 95% yield. Biphenyl benzyl acetylene **3c** was achieved in 73% yield. Compounds **3d**, **3e**, and **3f** bearing halogen atoms were obtained in good yields. Further increasing the electron-withdrawing ability in substrate **1g** did not decrease the yield of **3g**. On the other hand, a conjugative electron-withdrawing group such as an ester, aldehyde, or nitrile group, impacted the transformation. Corresponding products **3h**, **3i**, and **3j** were prepared in only moderate yields. Next, BI-activated acetylene **1k** substituted with a silyl group was evaluated, and **3k** was isolated in 35% yield. Consequently, Hantzsch esters **2** bearing varied substituents were screened. 4-Methoxybenzyl and 4-

Scheme 2. Reaction of Substituted HEs and BI-alkynes[a]



[a]Conditions: (a) **1** (0.2 mmol), **2** (0.4 mmol), $K_2S_2O_8$ (0.3 mmol), MeCN/H_2O = 1:1 (v/v), 2 mL, 50 °C, 18 h, isolated yields; (b) **1** (0.1 mmol), **2** (0.2 mmol), Ar atmosphere, 18 h. [b]Safranine (1 mol %), Cs_2CO_3 (0.1 mmol), DCE (2 mL), 24 W blue LEDs, rt.

chlorobenzyl groups could be introduced into molecules **3l** and **3m** in moderate yields. Alkyne **3n** with a thiophene moiety was generated in 58% yield. Hantzsch esters with secondary alkyl side chains were also reactive, and desired molecules **3o**, **3p** and **3q** were isolated in moderate to good yields. Two compounds **3r** and **3s** were prepared using photoredox (Table 1, entry 3) instead of persulfate to avoid acidic decomposition.

In comparison to the Hantzsch ester, the backbone of the Meyer nitrile was less bulky and able to accommodate more hindering side chains such as tertiary alkyl groups. Next, we investigated the transformation involving substituted Meyer nitriles **4** and BI-derived alkynes **1** (Scheme 3). We were glad to find that the target product **3t** bearing a quaternary carbon center was produced in 75% yield. Compound **3u** was achieved in almost quantitative yield with the same approach. When halogen atoms or CF_3 groups were present on the side chains in the Meyer nitrile, corresponding alkynes **3v−x** were obtained in moderate to acceptable yields. Meyer nitrile bearing thiophene was examined, and **3y** was prepared in 61% yield. Consequently, more combinations of BI-derived aryl acetylene **1** and Meyer nitrile **4** were subjected to this coupling protocol. Compound **3z** was isolated in good yield. Products **3aa** and **3ab** containing four-membered ring moieties were acquired in 85% and 97% yields, respectively. In addition,

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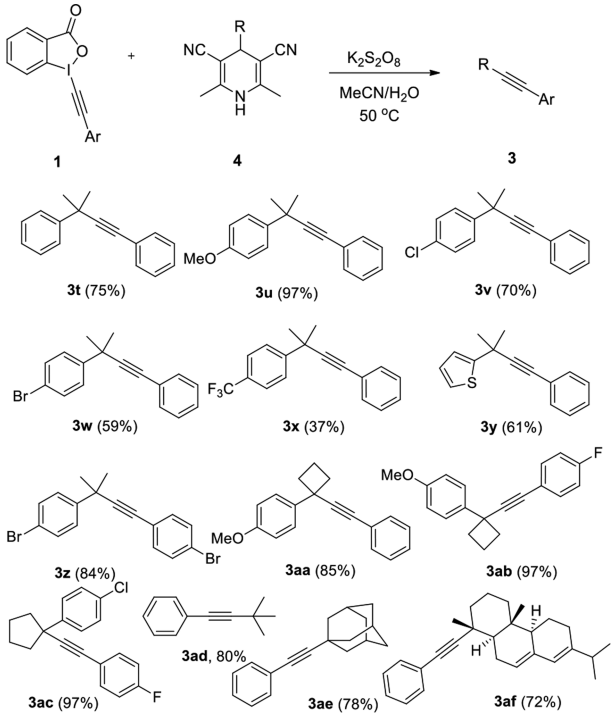
Scheme 3. Reaction of Substituted Meyer Nitrile and BI-alkyne[a]

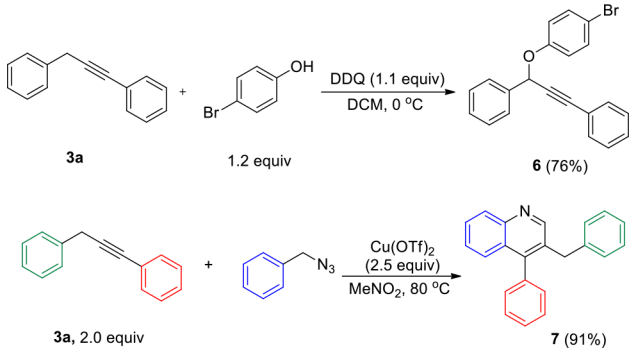


[a]Conditions: **1** (0.2 mmol), **2** (0.4 mmol), $K_2S_2O_8$ (0.3 mmol), MeCN/H_2O = 1:1 (v/v), 2 mL, 50 °C, 18 h, isolated yield.

compound **3ac** incorporating a five-membered ring was also available in 97% yield. A *tert*-butyl group was also introduced into product **3ad** in 80% yield. Product **3ae** bearing an admantyl group was synthesized in 78% yield. Abietyl phenyl acetylene **3af** was also prepared in good yield.

To explore the applications of this transformation, we subjected compound **3a** to further derivations (Scheme 4). At

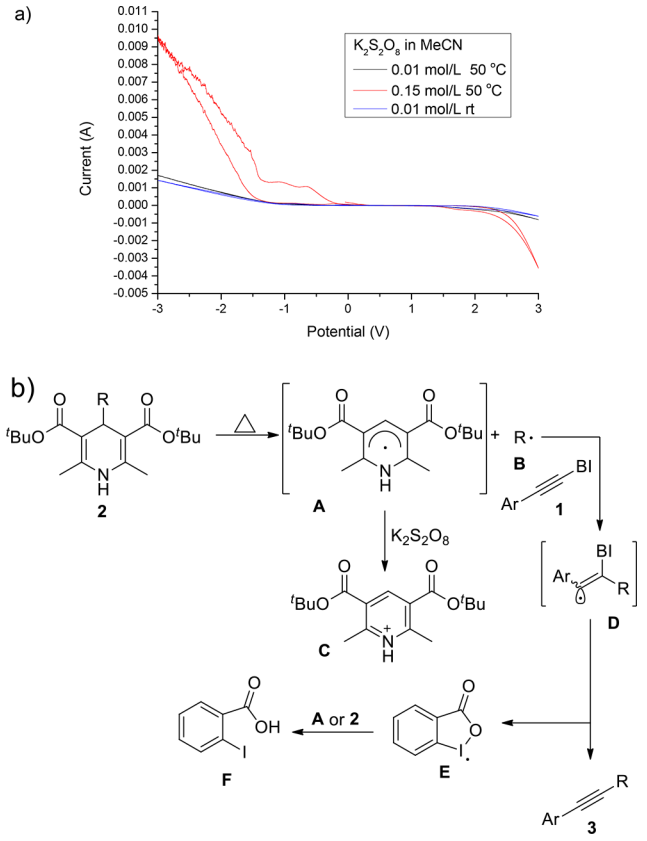
Scheme 4. Transformations of Compound 3a



first, with stoichiometric DDQ as oxidant, the propargylic C–H was converted to phenol ether **6** in 76% yield.[20] Mediated with 2.5 equiv of copper(II) triflate, alkyne **3a** reacted with benzyl azide, forming quinoline **7** substituted with benzyl and phenyl groups.[21]

Next, we turned our attention to the role of excess $K_2S_2O_8$ in this reaction. As reported by Molander and co-workers, the oxidation potential of persulfate was not in direct relation with the reactivity with HE.[17] We carried out a cyclic voltammetry experiment of $K_2S_2O_8$ in MeCN/H_2O and found that a concentration 0.15 mol/L, a peak at −0.6 V (vs SCE) was present. This species was not detected in the same experiment carried out with a 0.01 mol/L solution of $K_2S_2O_8$ (Scheme 5a).

Scheme 5. Plausible Reaction Pathway



Recently, we found that the substituted HE can cleave to dihydropyridine radical **A** and alkyl radical **B**.[15] The excess persulfate might provide a species that could undergo faster electron transfer from highly reductive dihydropridine radical **A**;[22] this process might lead to accelerated generation of alkyl radical **B** (Scheme 5b). Then, species **B** would add to the BI derived aryl acetylene **1**, giving intermediate **D**. Then the BI group could leave as an iodo radical **E** that could react with HE **2** or radical **A** in a chain manner. Meanwhile, the desired molecule **3** is furnished as a terminal product.

In summary, we report the first application of substituted Hantzsch ester and Meyer nitrile in the formation of C_{sp}–C_{sp3} bonds. With $K_2S_2O_8$ as initiator, substituted dihydropyridine released an alkyl radical to react with BI-activated alkyne. The corresponding 1,2-disubsituted acetylene was obtained in up to 97% yield. By applying Meyer nitrile as an alkyl radical donor, intermolecular construction of a quaternary carbon center was fulfilled.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03050.

Detailed procedures of this C_{sp}–C_{sp3} bond formation reaction and derivatization of product **3a**; character-

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ization of new compounds NMR spectra of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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