EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Visible-Light-Induced Alkynylation of α-C–H Bonds of Ethers with Alkynyl Bromides without External Photocatalyst

Authors: Xiao Fei Xie, Jie Liu, Lei Wang, and Min Wang

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201900872

Link to VoR: http://dx.doi.org/10.1002/ejoc.201900872

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

FULL PAPER

WILEY-VCH

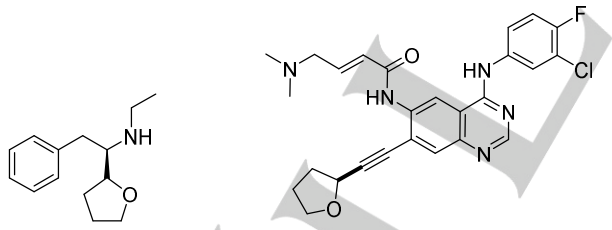
Visible-Light-Induced Alkynylation of α-C–H Bonds of Ethers with Alkynyl Bromides without External Photocatalyst

Xiaofei Xie,[a] Jie Liu,*[a] Lei Wang,[a,b] and Min Wang*[a]

Abstract: A direct alkynylation of C(sp^3)–H bonds adjacent to an oxygen atom of ethers under visible light irradiation was developed in the absence of an external photocatalyst. The reaction of ethers and alkynyl bromides underwent smoothly to generate the corresponding products in good yields with excellent functional-group tolerance. Initial mechanistic experimental results indicated that the reaction may involve a free radical pathway.

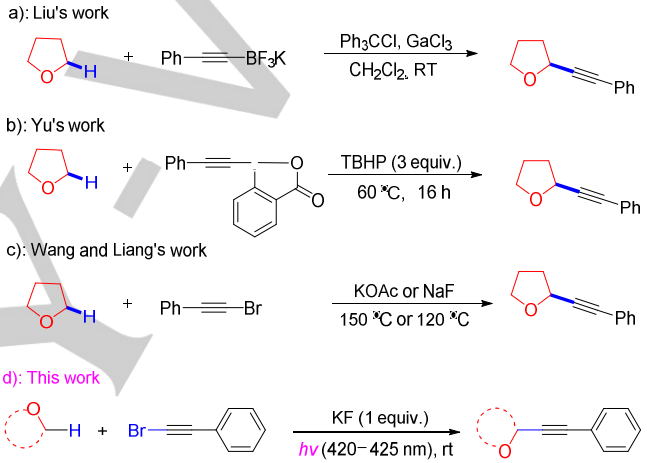
Introduction

α-Substituted ethers are not only useful building blocks in organic synthesis but also one of the most common structural motifs spread across synthetic pharmaceuticals (Scheme 1),[1] more than 20% of the top 200 small-molecule pharmaceuticals containing at least one α-substituted ether moiety.[1a] Traditional methods for the functionalization of ethers require multi-steps.[2] Selective and direct C(sp^3)–H functionalization of ethers, which can eliminate the pre-functionalization step, has attracted tremendous interest since the pioneering studies by Li,[3] and provided a straightforward approach to access multiple α-substituted ether analogues, such as α-arylated ethers,[4] α-tetrahydrofuranyl ethers,[5] α-alkynyl ethers,[6] and so on. In particular, direct C(sp^3)–H alkynylation of ethers receives considerable attention, as α-alkynyl ethers are potential structural motifs of bioactive molecules.[1c] In 2014, Liu developed a synthetic strategy to produce diverse α-alkynyl ethers using readily available trityl ion (Scheme 2a).[7] Yu developed an efficient direct alkynylation of ethers with ethynylbenziodoxolones (Scheme 2b).[8] Wang and Liang almost at the same time reported the functionalization of the C(sp^3)–H bond adjacent to an oxygen atom of ethers with various alkynyl bromides (Scheme 2c).[6] However, harsh reaction conditions, the use of metal, overstoichiometric amounts of oxidants or high reaction temperature are required in the most cases. It is desirable to achieve alkynylation of ethers under mild reaction conditions.



Zylofuramine stimulant drug Irreversible ErbB kinase inhibitor

Scheme 1 Representative bioactive molecules with α-functionalized ethers.



Scheme 2 Direct α-C(sp^3)–H alkynylation of ethers.

Visible-light-mediated reaction, which is associated with mild conditions, has been extensively studied and has become a powerful tool in organic synthesis, especially since MacMillan and coworker's an elegant work had been reported.[9] All achievements in photoreactions demonstrated the combined effectiveness of employing visible light to facilitate organic reactions. Recently, visible-light-induced C−H functionalization has emerged as one of the most active research topics in sustainable organic synthesis.[10] These processes are associated with low energy consumption, concise route and mild conditions. Along this line, C–H fluorinations,[11] arylations,[12] and allylations[13] have been reported recently. Some photoreactions require photosensitizers,[14] such as organic dyes or metal complexes while others can proceed without additional photosensitizers.[15] Being inspired by these work and with our previous experience of visible-light-induced organic transformations in the absence of an external photosensitizer,[16] we herein report a visible-light-induced α-position C–H activation and alkynylation of ethers with alkynyl bromides to generate the corresponding α-alkynyl ethers in good yields at room temperature with broad substrate scope in the absence of any external photocatalyst (Scheme 2d).

Results and Discussion

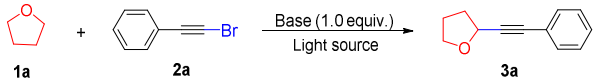
[a] X. Xie, Dr. J. Liu, Prof. M. Wang, Prof. Dr. L. Wang
Department of Chemistry, Huaibei Normal University
Huaibei, Anhui 235000, P. R. China
E-mail: jieliu_1024@163.com, wangmin204@chnu.edu.cn
[b] State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences
Shanghai 200032, P. R. China
Supporting information for this article is given via a link at the end of the document.

10.1002/ejoc.201900872

WILEY-VCH

Our investigations were started with a model reaction of tetrahydrofuran (**1a**) and phenylethynyl bromide (**2a**), and the results were summarized in Table 1. When the model reaction was initially performed with 1.0 equivalent of LiO^tBu under the irradiation of 3 W blue LED (420–425 nm) in air atmosphere at room temperature for 12 h without the addition of any photoredox catalyst, the desired product 2-(phenylethynyl)tetrahydrofuran (**3a**) was obtained in 25% yield (Table 1, entry 1). In the presence of KO^tBu, only trace amount **3a** was observed (Table 1, entry 2). Subsequently, a number of other bases were screened and presented in entries 3–10 of Table 1. Gratifyingly, the use of KF offered the target product **3a** in 83% yield (Table 1, entry 8), making it the most effective base which was utilized for further investigation.

Table 1. Optimization of the reaction conditions[a]

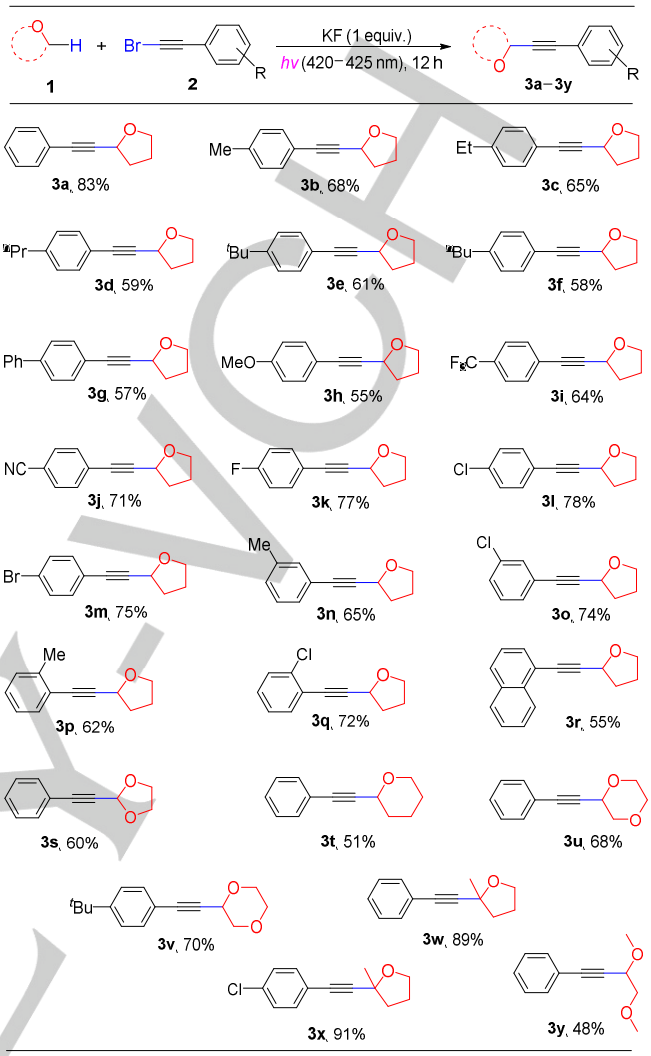


1a 2a 3a

Entry	Base	Light source	Yield (%)[b]
1	LiO^tBu	420–425 nm	25
2	KO^tBu	420–425 nm	Trace
3	K_3PO_4	420–425 nm	63
4	NaOAc	420–425 nm	48
5	KOAc	420–425 nm	67
6	KPF_6	420–425 nm	62
7	NaF	420–425 nm	73
8	*KF*	*420–425 nm*	*83*
9	K_2CO_3	420–425 nm	45
10	$KHCO_3$	420–425 nm	56
11	KF	380–385 nm	51
12	KF	395–405 nm	52
13	KF	410–415 nm	70
14	KF	410–420 nm	73
15	KF	450–455 nm	NR
16	KF	420–425 nm	70[c]
17	KF	420–425 nm	81[d]
18	-	420–425 nm	0
19	KF	-	0

[a] Reaction conditions: phenylethynyl bromide (**2a**, 0.20 mmol), tetrahydrofuran (**1a**, 2.0 mL, as well as solvent), base (1.0 equiv.), under the LED irradiation at room temperature for 12 h. [b] Isolated yield. [c] For 8 h. [d] For 16 h. NR = no reaction.

Encouraged by the results, the reactions were examined with respect to the wavelength of the light source (Table 1, entries 11–15). It was found that the desired product **3a** was obtained in comparable yields with the irradiation of LED at 380–385 and 395–405 nm (Table 1, entries 11 and 12). Other light sources including blue LED 410–415 nm and 410–420 nm was also examined, the desired product **3a** were obtained with slightly less efficiency (Table 1, entries 13 and 14). No product



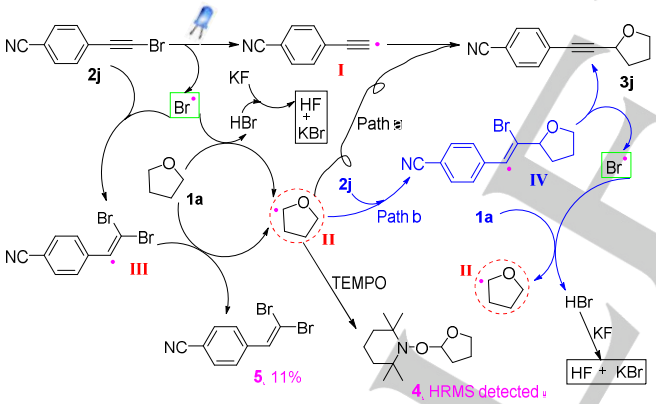
Scheme 3 The scope of substrates [*reaction conditions:* alkynyl bromide (**2**, 0.20 mmol), ether (**1**, 2.0 mL), KF (1.0 equiv), blue LED (420–425 nm, 3 W) at room temperature for 12 h under air atmosphere; isolated yield of the product after column chromatography].

was observed under blue LED irradiation with the wavelength of 450–455 nm (Table 1, entry 15). Extensive screening other parameters revealed that the reaction time affected the reaction, and the product yield was decreased for either 8 h or 16 h (Table 1, entries 16 and 17). Finally, control experiments conducted under the absence of either a base or LED (entries 18 and 19) pointed to complete inhibition of the reactivity.

After establishment of the optimal reaction condition, the generality and limitation of this method were examined, as shown in Scheme 3. In the beginning, reactions of tetrahydrofuran (**1a**) with various alkynyl bromides **2** were investigated. Different electron-donating groups and electron-withdrawing groups on the *para*-position of the phenyl rings in alkynyl bromides **2** were well tolerated, and the corresponding products (α-alkynyl ethers, **3b**–**3g**) were obtained in 57–68% yields. It should be noted that substrate **2h** with a stronger

electron-donating substituent (MeO), and substrates **2i** and **2g** with a stronger electron-withdrawing substituent (CF_3 and CN) on the phenyl rings, proved to be suitable substrates for the present reactions, generating the corresponding products in 55%, 64%, and 71% yield, respectively. Halogens including F, Cl, and Br attached on the substrates **2** reacted well with THF, giving the anticipated products (**3k**–**3m**) in 75–78% yields. The substrates **2n** and **2o** with a substituted group (Me and Cl) on the *meta*-position of the phenyl rings underwent the reactions with THF smoothly to afford the corresponding products **3n** and **3o** in 65% and 74% yields, respectively. No significant steric effect was observed during the reaction between **2p**–**2r** with a group on the *ortho*-position of the phenyl rings and THF, and the alkynylated products **3p**–**3r** were isolated in 62%, 72% and 55% yields, respectively. However, the reactions of 2-(bromoethynyl)pyridine and 2-(bromoethynyl)thiophene with THF failed under the standard reaction conditions.

We next turned our attention to investigate the scope of ethers. Various ethers, including 1,3-dioxolane, tetrahydro-2*H*-pyran and 1,4-dioxane, participated in the alkynylation with a slightly less activity as compared with the reaction of THF. It should be noted that 2-methyltetrahydrofuran was an excellent candidate, delivering the expected products (**3w** and **3x**) in high yields (89%, and 91% yields, respectively). An open-chain aliphatic ether 1,2-dimethoxyethane reacted with phenylethynyl bromide to furnish the desired product **3y** in 48% yield.



Scheme 4 Plausible mechanism for the reaction.

To investigate the reaction mechanism, the control experiments were conducted. Under the optimal conditions, when a radical-trapping reagent TEMPO (2,2,6,6-tetramethyl-1-oxylpiperidine) was added to the reaction, no desired product was detected, along with the formation of TEMPO−THF adduct (**4**), which was detected by HRMS (high resolution mass spectroscopy, SI for detail). This result suggested that the reaction may proceed by a free radical pathway and a carbon-centred radical of THF is probably involved. Based on the above experimental results and the previous reports,[17] a plausible reaction pathway was proposed with tetrahydrofuran (**1a**) and 4-(bromoethynyl)benzonitrile (**2j**), as shown in Scheme 4. First, a homolytic cleavage of alkynyl bromide was triggered by visible-light (blue LED, 420−425 nm) irradiation to generate alkynyl radical (**I**) and Br radical, which was further confirmed by the formation of a by-product 4-(2,2-dibromovinyl)benzonitrile (**5**) from the intermediate (**III**), which was derived from the addition reaction of Br radical to **2j**. Subsequently, the formed Br radical reacted with tetrahydrofuran (**1a**) via a α-position C(sp^3)−H bond cleavage of **1a** to generate the tetrahydrofuran radical (**II**), which underwent a cross-coupling with alkynyl radical (**I**) to afford the final product **3j** along with the generation of HBr, which reacted with KF to generate a week acid HF (Path a). On the other hand, tetrahydrofuran radical (**II**) reacted with **2j** to form a radical (**IV**), followed by Br radical elimination to produce the final product **3j** (Path b). However, the exact reaction mechanism remained unclearuntil now, and further effort on the reaction mechanism is underway in our laboratory.

Conclusions

An efficient and eco-friendly methodology for the synthesis of α-alkynyl ethers was developed in moderate to good yields under photo-induced alkynylation of α-C–H bonds of ethers with alkynyl bromides without external photocatalyst. The value of this strategy has been highlighted via the ability to perform the reaction at room temperature by visible light irradiation protocol. More detailed investigation of the reaction mechanism and application of this kind of strategy are underway in our laboratory.

Experimental Section

General methods: All ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker FT-NMR spectrometer (400 MHz or 100 MHz, respectively). All chemical shifts are given as δ value (ppm) with reference to tetramethylsilane (TMS) as an internal standard. The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, *J*, are reported in Hertz (Hz). High resolution mass spectroscopy data of the products were collected on an Agilent Technologies 6540 UHD Accurate-Mass Q-TOF LC/MS (ESI). All reactions were set up in air. All chemicals were purchased commercially and used without further purification. Products were purified by flash chromatography on 200–300 mesh silica gels, SiO_2.

Typical procedure for the visible-light-induced alkynylation of α-C–H bonds of ethers with alkynyl bromides without external photocatalyst: A 5 mL oven-dried reaction vessel equipped with a magnetic stirrer bar was charged with tetrahydrofuran (THF, **1a**, 2.0 mL) and phenylethynyl bromide (**2a**). The reaction vessel was exposed to blue LED (420−425 nm, 3 W) irradiation at room temperature in air with stirring for 12 h. After completion of the reaction, the mixture was concentrated to yield the crude product, which was further purified by flash chromatography (silica gel, petroleum ether/ethyl acetate = 100:1) to give the desired product **3a**.

2-(Phenylethynyl)tetrahydrofuran (3a):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.44–7.41 (m, 2H), 7.29–7.27 (m, 3H), 4.82–4.78 (m, 1H), 4.03–3.97 (m, 1H), 3.87–3.81 (m, 1H), 2.24–2.17 (m, 1H), 2.13–2.02 (m, 2H), 1.97–1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.6, 128.12, 128.09, 122.7, 89.0, 84.4, 68.5, 67.8, 33.3, 25.4.

2-(*p*-Tolylethynyl)tetrahydrofuran (3b):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 4.81–4.78 (m, 1H), 4.03–3.98 (m, 1H), 3.87–3.82 (m, 1H), 2.33 (s, 3H), 2.24–2.18 (m, 1H), 2.14–2.02 (m, 2H), 1.97–1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.3, 131.6, 128.9, 119.7, 88.3, 84.6, 68.6, 67.8, 33.4, 25.4, 21.4.

2-((4-Ethylphenyl)ethynyl)tetrahydrofuran (3c): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.82-4.78 (m, 1H), 4.03–3.98 (m, 1H), 3.87–3.82 (m, 1H), 2.62 (q, *J* = 7.6 Hz, 2H), 2.25–2.17 (m, 1H), 2.13–2.02 (m, 2H), 1.97–1.89 (m, 1H), 1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.5, 131.6, 127.7, 119.9, 88.2, 84.5, 68.6, 67.81, 33.4, 28.7, 25.4, 15.2. IR (KBr): 2966, 2874, 2200, 1414, 1112, 1052, 835 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd. for $[C_{14}H_{17}O]^+$: 201.1274, found: 201.1274.

2-((4-Propylphenyl)ethynyl)tetrahydrofuran (3d):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 4.82–4.79 (m, 1H), 4.04–3.98 (m, 1H), 3.88-3.83 (m, 1H), 2.57 (t, *J* = 7.6 Hz, 2H), 2.25–2.18 (m, 1H), 2.14-2.03 (m, 2H), 1.98–1.89 (m, 1H), 1.62 (q, *J* = 7.6 Hz, 2H), 0.92 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.1, 131.6, 128.4, 120.0, 88.3, 84.6, 68.7, 67.9, 37.9, 33.5, 25.5, 24.3, 13.7.

2-((4-(*tert*-Butyl)phenyl)ethynyl)tetrahydrofuran (3e):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.4 Hz, 2H), 4.82–4.79 (m, 1H), 4.03–3.98 (m, 1H), 3.87–3.82 (m, 1H), 2.24–2.18 (m, 1H), 2.14–2.03 (m, 2H), 1.97–1.88 (m, 1H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 151.4, 131.4, 125.1, 119.8, 88.3, 84.5, 68.6, 67.8, 34.7, 33.4, 31.1, 25.4.

2-((4-Butylphenyl)ethynyl)tetrahydrofuran (3f): Light yellow oil. ^{1}H NMR (400 MHz, CDCl3) δ: 7.34 (d, *J* = 8.0 Hz, 2H), 7.10 (d, *J* = 8.0 Hz, 2H), 4.82–4.79 (m, 1H), 4.03–3.98 (m, 1H), 3.88–3.82 (m, 1H), 2.58 (t, *J* = 8.0 Hz, 2H), 2.25–2.18 (m, 1H), 2.14–2.03 (m, 2H), 1.98–1.91 (m, 1H), 1.61–1.53 (m, 2H), 1.38–1.28 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ:143.3, 131.6, 128.3, 119.9, 88.3, 84.6, 68.6, 67.8, 35.5, 33.4, 33.3, 25.4, 22.2, 13.9. IR (KBr): 2931, 2360, 2191, 1549, 1052, 845 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd. for $[C_{16}H_{21}O]^+$: 229.1587, found: 229.1585.

2-([1,1'-Biphenyl]-4-ylethynyl)tetrahydrofuran (3g):[6b] Light yellow oil ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57–7.55 (m, 2H), 7.53–7.48 (m, 4H), 7.43–7.39 (m, 2H), 7.35–7.31 (m, 1H), 4.84–4.81 (m, 1H), 4.04–3.99 (m, 1H), 3.88–3.83 (m, 1H), 2.25–2.19 (m, 1H), 2.14–2.02 (m, 2H), 1.97–1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.9, 140.3, 132.1, 128.8, 127.5, 126.9, 126.8, 121.7, 89.7, 84.3, 68.6, 67.9, 33.4, 25.4.

2-((4-Methoxyphenyl)ethynyl)tetrahydrofuran (3h):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.81–4.78 (m, 1H), 4.03–3.98 (m,1H), 3.87–3.82 (m, 1H), 3.79 (s, 3H), 2.25–2.18 (m, 1H), 2.14–2.02 (m, 2H), 1.98–1.88 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 159.6, 133.1, 115.0, 113.8, 87.6, 84.4, 68.7, 67.8, 55.2, 33.4, 25.5.

2-((4-(Trifluoromethyl)phenyl)ethynyl)tetrahydrofuran (3i):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57–7.51 (m, 4H), 4.84–4.80 (m, 1H), 4.04–3.99 (m, 1H), 3.90–3.85 (m, 1H), 2.29–2.21 (m, 1H), 2.14–2.06 (m, 2H), 2.00–1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.9, 130.0 (q, J_{CF} = 32.4 Hz), 126.6, 125.1 (q, J_{CF} = 3.7 Hz), 123.9 (q, J_{CF} = 270.3 Hz), 91.6, 83.1, 68.4, 68.0, 33.3, 25.5.

4-((Tetrahydrofuran-2-yl)ethynyl)benzonitrile (3j): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.59 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H), 4.84–4.80 (m, 1H), 4.03–3.98 (m, 1H), 3.90–3.85 (m, 1H), 2.29–2.22 (m, 1H), 2.15–2.04 (m, 2H), 2.01–1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 132.1, 131.8, 127.7, 118.3, 111.6, 93.7, 82.8, 68.3, 68.0, 33.2, 25.4. IR (KBr): 2954, 2343, 1677, 1407, 1054, 846, 669 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd. for $[C_{13}H_{12}NO]^+$: 198.0913, found: 198.0914.

2-((4-Fluorophenyl)ethynyl)tetrahydrofuran (3k):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.41–7.38 (m, 2H), 7.00–6.95 (m, 2H), 4.80–4.77 (m, 1H), 4.02–3.96 (m, 1H), 3.86–3.81 (m, 1H), 2.23–2.17 (m, 1H), 2.12–2.01 (m,2H), 1.96–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 162.3 (d, J_{CF} = 247.8 Hz), 133.4 (d, J_{CF} = 8.4 Hz), 118.8 (d, J_{CF} = 3.6 Hz), 115.3 (d, J_{CF} = 21.9 Hz), 88. 7, 83.2, 68.3, 67.7, 33.2, 25.3.

2-((4-Chlorophenyl)ethynyl)tetrahydrofuran (3l):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.4 Hz, 2H), 4.80–4.76 (m, 1H), 4.01–3.96 (m, 1H), 3.86–3.81 (m, 1H), 2.23–2.17 (m, 1H), 2.11–2.01 (m, 2H), 1.96–1.87 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.1, 132.7, 128.4, 121.2, 90.0, 83.1, 68.3, 67.8, 33.2, 25.3.

2-((4-Bromophenyl)ethynyl)tetrahydrofuran (3m):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 8.8 Hz, 2H), 7.28 (d, *J* = 8.8 Hz, 2H), 4.80–4.77 (m, 1H), 4.03–3.97 (m, 1H), 3.88–3.83 (m, 1H), 2.26–2.19 (m, 1H), 2.14–2.02 (m, 2H), 1.99–1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.1, 131.4, 122.5, 121.8, 90.3, 83.4, 68.5, 67.9, 33.3, 25.5.

2-(*m*-Tolylethynyl)tetrahydrofuran (3n):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.25–7.22 (m, 2H), 7.18–7.14 (m, 1H), 7.09–7.08 (m, 1H), 4.80–4.77 (m, 1H), 4.02–3.96 (m, 1H), 3.86–3.80 (m, 1H), 2.29 (s, 3H), 2.22–2.16 (m, 1H), 2.12–2.01 (m, 2H),

1.95–1.86 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.7, 132.1, 128.9, 128.6, 127.9, 122.5, 88.6, 84.4, 68.4, 67.7, 33.3, 25.3, 21.0.

2-((3-Chlorophenyl)ethynyl)tetrahydrofuran (3o): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.42–7.41 (m, 1H), 7.32–7.22 (m, 3H), 4.81–4.78 (m, 1H), 4.03–3.97 (m, 1H), 3.89–3.83 (m, 1H), 2.26–2.19 (m, 1H), 2.14–2.03 (m, 2H), 2.00–1.90 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.0, 131.5, 129.8, 129.4, 128.5, 124.5, 90.4, 83.0, 68.4, 68.0, 33.3, 25.4. IR (KBr): 2959, 2343, 1433, 1131, 810, 757 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd. for $[C_{12}H_{12}ClO]^+$: 207.0571, found: 207.0574.

2-(*o*-Tolylethynyl)tetrahydrofuran (3p):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (d, *J* = 7.6 Hz, 2H), 7.12–7.09 (m, 2H), 7.05–7.01 (m, 1H), 4.80–4.77 (m, 1H), 3.97–3.92 (m, 1H), 3.82–3.77 (m, 1H), 2.34 (s, 3H), 2.19–2.12 (m, 1H), 2.08–1.97 (m, 2H), 1.92–1.82 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.2, 132.0, 129.3, 128.2, 125.4, 122.6, 93.1, 83.3, 68.7, 67.8, 33.6, 25.4, 20.6.

2-((2-Chlorophenyl)ethynyl)tetrahydrofuran (3q): Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.44 (m, 1H), 7.37–7.35 (m, 1H), 7.23–7.15 (m, 2H), 4.87–4.84 (m, 1H), 4.04–3.99 (m, 1H), 3.89–3.83 (m, 1H), 2.26–2.18 (m, 1H), 2.16–2.07 (m, 2H), 1.98–1.89 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.8, 133.2, 129.1, 129.0, 126.2, 122.5, 94.4, 81.0, 68.4, 67.7, 33.2, 25.2. IR (KBr): 2960, 2360, 1709, 1473, 1190, 1051, 754 cm^{-1}; HRMS (ESI) $[M + H]^+$ Calcd. for $[C_{12}H_{12}ClO]^+$: 207.0571, found: 207.0573.

2-(Naphthalen-1-ylethynyl)tetrahydrofuran (3r):[6b] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (d, *J* = 8.4 Hz, 1H), 7.80 (t, *J* = 9.2 Hz, 2H), 7.67–7.65 (m, 1H), 7.57–7.47 (m, 2H), 7.41–7.37 (m, 1H), 4.98–4.95 (m, 1H), 4.12–4.05 (m, 1H), 3.93–3.88 (m, 1H), 2.34–2.25 (m, 1H), 2.23–2.11 (m, 2H), 2.03–1.92 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.3, 133.1, 130.5, 128.7, 128.2, 126.7, 126.3, 126.1, 125.1, 120.4, 94.1, 82.5, 68.8, 67.9, 33.6, 25.5.

2-(Phenylethynyl)-1,3-dioxolane (3s):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48–7.45 (m, 2H), 7.34–7.30 (m, 3H), 5.89 (s, 1H), 4.15–4.11 (m, 2H), 3.99–3.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.9, 128.9, 128.2, 121.6, 93.4, 85.2, 84.5, 64.5.

2-(Phenylethynyl)tetrahydro-2H-pyran (3t):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.44 (m, 2H), 7.31–7.29 (m, 3H), 4.51 (dd, J_1 = 2.8 Hz, J_2 = 7.6 Hz, 1H), 4.08–4.03 (m, 1H), 3.62–3.56 (m, 1H), 1.96–1.88 (m, 2H), 1.83–1.75 (m, 1H), 1.66–1.56 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.7, 128.24, 128.17, 122.7, 88.1, 85.2, 67.4, 66.6, 32.2, 25.6, 21.8.

2-(Phenylethynyl)-1,4-dioxane (3u):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.44 (m, 2H), 7.33–7.30 (m, 3H), 4.57 (dd, J_1 = 2.8 H, J_2 = 8.4 Hz, 1H), 3.96–3.91 (m, 2H), 3.78–3.67 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.8, 128.6, 128.2, 122.0, 86.5, 84.2, 70.3, 66.4, 66.3, 65.7.

2-((4-(*tert*-Butyl)phenyl)ethynyl)-1,4-dioxane (3v):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 4.56 (dd, J_1 = 2.8 Hz, J_2 = 8.4 Hz, 1H), 3.95–3.90 (m, 2H), 3.77–3.65 (m, 4H), 1.30 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 152.0, 131.6, 125.2, 119.0, 86.7, 83.6, 70.5, 66.5, 66.3, 65.8, 34.7, 31.1.

2-Methyl-2-(phenylethynyl)tetrahydrofuran (3w):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.43–7.40 (m, 2H), 7.29–7.27 (m, 3H), 4.05–3.94 (m, 2H), 2.33–2.27 (m, 1H), 2.21–2.10 (m, 1H), 2.04–1.95 (m, 1H), 1.89–1.82 (m, 1H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.6, 128.1, 128.0, 123.0, 92.3, 82.7, 76.4, 67.6, 40.1, 27.7, 25.7.

2-((4-Chlorophenyl)ethynyl)-2-methyltetrahydrofuran (3x):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 4.03–3.93 (m, 2H), 2.31–2.25 (m, 1H), 2.19–2.09 (m, 1H), 2.04–1.95 (m, 1H), 1.89–1.82 (m, 1H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 134.1, 132.9, 128.5, 121.5, 93.4, 81.6, 76.3, 67.7, 40.1, 27.6, 25.7.

(3,4-Dimethoxybut-1-yn-1-yl)benzene (3y):[6a] Light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.44 (m, 2H), 7.33–7.30 (m, 3H), 4.42–4.39 (m, 1H), 3.69–3.62 (m, 2H), 3.53 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 131.8, 128.5, 128.2, 122.3, 86.8, 84.9, 74.9, 71.0, 59.3, 56.8.

Conflict of Interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the National Natural Science Foundation of China (21772062, 21602072) and Excellent Youth Talents Fund Program of Higer Education Institutions of Anhui Province, China (gxyq2019167) for financial support of this work.

Keywords: Alkynylation• C–H Functionalization • Visible-light irradiation • Alkynyl bromides • Ethers

[1] a) S. D. Roughley, A. M. Jordan, *J. Med. Chem*. **2011**, *54*, 3451–3479; b) E. J. Kang, E. Lee, *Chem. Rev*. **2005**, *105*, 4348–4378;c) Y. S. Tsantrizos, M. D. Bailey, F. Bilodeau, R. J. Carson, L. Fader, T. Halmos, S. Kawai, S. Landry, S. Laplante, B. Simoneau, Inhibitors of human immunodeficiency virus replication and their preparation and use as inhibitors of HIV replication, WO Patent 2009062289A1, 2009.

[2] a) P. A. Wender, V. A. Verma, T. J. Paxton, T. H. Pillow, *Acc. Chem. Res*. **2008**, *41*, 40–49;b) G. Wang, J. Wan, Y. Hu, X. Wu, M. Prhavc, N. Dyatkina, V. K. Rajwanshi, D. B. Smith, A. Jekle, A. Kinkade, J. A. Symons, Z. Jin, J. Deval, Q. Zhang, Y. Tam, S. Chanda, L. Blatt, L. Beigelman, *J. Med. Chem.* **2016**, *59*, 4611–4624.

[3] a) Y. Zhang, C.-J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 4242–4243; b) Y. Zhang, C.-J. Li, *Angew. Chem. Int. Ed*. **2006**, *45*, 1949–1952.

[4] D. Liu, C. Liu, H. Li, A. Lei, *Angew. Chem. Int. Ed.* **2013**, *52*, 4453–4456.

[5] R. Baati, A. Valleix, C. Mioskowski, D. K. Barma, J. R. Falck, *Org. Lett.* **2000**, *2*, 485–487.

[6] a) J. Zhang, P. Li, L. Wang, *Org. Biomol. Chem.* **2014**, *12*, 2969–2978; b) Y. Yang, H. Huang, X. Zhang, W. Zeng, Y. Liang, *Synthesis* **2013**, *45*, 3137–3146.

[7] M. Wan, Z. Meng, H. Lou, L. Liu, *Angew. Chem. Int. Ed.* **2014**, *53*, 13845–13849.

[8] R. Zhang, L. Xi, L. Zhang, S. Liang, S.-Y. Chen, X.-Q. Yu, *RSC Adv.* **2014**, *4*, 54349–54353.

[9] G. A. Nicewicz, D. W. C. MacMillan, *Science* **2008**, *322*, 77–80.

[10] a) I. Ghosh, L. Marzo, A. Das, R. Shaikh, B. König, *Acc. Chem. Res.* **2016**, *49*, 1566–1577; b) D. Ravelli, M. Fagnoni, A. Albini, *Chem. Soc. Rev.* **2013**, *42*, 97–113.

[11] J.-B. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494–17500.

[12] D. R. Heitz, J. C. Tellis, G. A. Molander, *J. Am. Chem. Soc.* **2016**, *138*, 12715–12718.

[13] S. Paul, J. Guin, *Green Chem.* **2017**, *19*, 2530–2534.

[14] a) N. A. Romero, D. A. Nicewicz, *Chem. Rev.* **2016**, *116*, 10075–10166; b) C. K. Prier, D. A. Rankic, D. W. C. MacMillan, *Chem. Rev.* **2013**, *113*, 5322–5363.

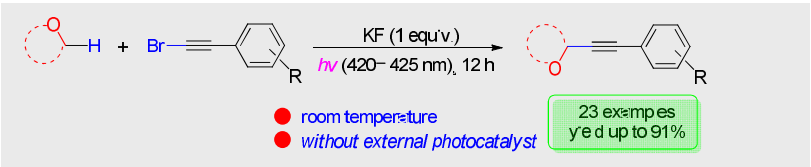
[15] a) Y. Zhao, B. Huang, C. Yang, W. Xia, *Org. Lett.* **2016**, *18*, 3326–3329; b) J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, L. E. A. Berlouis, T. McGuire,T. Tuttle, J. A. Murphy, *J. Am. Chem. Soc.* **2016**, *138*, 7402–7410; c) J. J. Murphy, D. Bastida, S. Paria, M. Fagnoni, P. Melchiorre, *Nature* **2016**, *532*, 218–222.

[16] a) H. Tan, H. Li, W. Ji, L. Wang, *Angew. Chem.Int. Ed.* **2015**, *54*, 8374–8377; b) X. Zhu, P. Li, Q. Shi, L. Wang, *Green Chem.* **2016**, *18*, 6373–6379; c) S. Yang, P. Li, L. Wang, *Org. Lett.* **2017**, *19*, 3386–3389; d) W. Ji, H. Tan, M. Wang, P. Li, L. Wang, *Chem. Commun.* **2016**, *52*, 1462–1465; e) S. Yang, H. Tan, W. Ji, X. Zhang, P. Li, L. Wang, *Adv. Synth. Catal.* **2017**, *359*, 443–453; f) W. Ji, P. Li, S. Yang, L. Wang, *Chem. Commun.* **2017**, *53*, 8482–8485; g) L. Zhao, P. Li, X. Xie, L. Wang, *Org. Chem. Front.* **2018**, *5*, 1689–1697; h) Y. Li, F. Ma, P. Li, T. Miao, L. Wang, *Adv. Synth. Catal.* **2019**, *361*, 1606–1616; i) L. Zhao, P. Li, X. Xie, L. Wang, *Org. Chem. Front.* **2019**, *6*, 87–93.

[17] a) K. Ni, L.-G. Meng, K. Wang, L. Wang, *Org. Lett.* **2018**, *20*, 2245–2248. b) K. Ni, L.-G. Meng, H. Ruan, L. Wang, *Chem. Commun.* **2019**, *55*, 8438–8441; c) G. Bogonda, D. V. Patil, H. Y. Kim, K. Oh, *Org. Lett.* **2019**, *21*, 3774–3779; d) S.-R. Guo, Y.-Q. Yuan, J.-N. Xiang. *Org. Lett.* **2013**, *15*, 4654–4657.

Table of Contents

FULL PAPER



A direct alkynylation of α-C(sp^3)–H of ethers with alkynyl bromides under visible-light irradiation at room temperature without external photocatalyst was developed.

Alkynylation via Alkynyl Bromides

Xiaofei Xie, Jie Liu, Lei Wang and Min Wang**

Page No. – Page No.

Visible-Light-Induced Alkynylation of α-C–H Bonds of Ethers with Alkynyl Bromides without External Photocatalyst