

Rearrangements of Propargylic Esters Can Be Induced by Some Electrophiles

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(5) Supporting Information

ABSTRACT: An electrophile-induced rearrangement of propargylic esters without need of transition catalysis is possible. In particular, this observation provides a mild, economic, and effective method for the introduction of benzyl ether derivatives to access functionalized α,β -unsaturated ketones. Preliminary mechanistic studies suggest that this rearrangement undergoes an intramolecular 1,3-acyloxy shift.



Propargylic esters are a specific class of alkynes with interesting chemical behavior. It is known that these substrates are able to undergo a transition-metal-catalyzed 1,2or 1,3-acyloxy shift leading to the formation of metal vinyl carbenoid species or metal allenic intermediates, poised for subsequent functionalization to give a huge variety of important products (Scheme 1).¹ Thus, 1,2-migration opens possibilities

Scheme 1. Metal-Mediated 1,2- and 1,3-Acyloxy Shifts of Propargylic Esters



for "carbene-type" reactivity; for example, cyclopropanation reactions or C–H insertions.² On the other hand, 1,3-acyloxy shift results in formation of nucleophilic allenes easily trapped by electrophilic reagents by intra- or intermolecular processes.³

It was envisioned, that propargylic esters being representative of nucleophilic alkynes could be able to react with electrophilic reagents forming ionic intermediates. Then an ester carbonyl group could participate in stabilization of vinylic carbocations by forming 6- or 5-membered ionic intermediates. This reactivity mode would give a precedent for electrophile initiated 1,3- or 1,2acyloxy shifts and therefore would considerably extend the synthetic utility of propargylic esters.

This hypothesis was verified by choosing 3-(4methoxyphenyl)prop-2-ynyl acetate **1a** as a model substrate and investigation of its reactivity toward various electrophiles. It should be noted that in all successful cases formation of 2-substituted 1-(4-methoxyphenyl)prop-2-en-1-ones 2 was detected (Scheme 2). The results obtained are summarized in Table 1.

Scheme 2. Reaction between 3-(4-Methoxyphenyl)prop-2ynyl Acetate 1a and Electrophiles



First, molecular iodine was chosen as an electrophilic reagent. After stirring of the reaction mixture in DCM at room temperature and full conversion of the starting material, two products were isolated. The major one was the result of simple electrophilic addition to the triple bond; however, some small amount of 2-iodo-1-(4-methoxyphenyl)prop-2-en-1-one **2a** was also isolated (entry 1). While use of iodine monochloride gave a slightly higher yield of desired product (entry 2), other sources of electrophilic iodine, such as the Barluenga reagent or NIS, were not successful. Phenylselenyl chloride underwent electrophilic addition reaction to the triple bond of the starting material and did not induce the desired rearrangement (entry 3).

After these not very exciting starting experiments, attention was switched to ethers as potential sources of oxocarbenium ions. Entry 4 represents the only one more or less successful example of tetrahydrofuran modification. Although there are a number of literature reports about tetrahydrofuran C–H modification via a

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entry	E-X	conditions	time	product (yield, %)
1	I ₂	DCM, rt	2 h	2a (15%) ^[a]
2	ICl	DCM, rt	2 h	2a (36) ^[a]
3	PhSeCl	DCM, rt	2h	_[b]
4	Гон	<i>t</i> -Bu ₂ O ₂ (3 equiv), FeBr ₃ (20 mol %), DCE, MW, 125 °C	6h	2b (10%) ^[C]
5		DDQ (1 equiv), DCM, rt	24 h	2c (traces) ^[c]
6	Стро Н	DDQ (1 equiv), DCE, reflux	24 h	2c (51)
7	Стро Н	DDQ (1 equiv), DCE, MW, 130 °C	30 min	2c (69)
8	Стро Н	DDQ (1 equiv), DCM, Cu(OTf)2 (10 mol %), rt	24 h	2c (63)
9	Стро Н	DDQ (1 equiv), DCM, AgOTf (10 mol %), rt	24 h	2c (70)
10	Стро Н	DDQ (1 equiv), DCM, AgNO3 (10 mol %), rt	24 h	n.r.
11	C H	DDQ (1 equiv), DCM, AuCl ₃ (10 mol %), rt	24 h	n.r.
12	C C C C C C C C C C C C C C C C C C C	DDQ (1 equiv), DCM, CuI (10 mol %), rt	24 h	n.r.
13		DDQ (1 equiv), DCM, AgOTf (10 mol %), rt	24 h	2d (11) ^[c]
14	L H	DDQ (1 equiv), DCE, MW, 130 °C	20 min	2d (62)
15	L H	DDQ (1 equiv), DCE, MW, 130 °C, AgOTf (10 mol %)	10 min	2d (78)
16		TMSOTf (1 equiv), DCM, rt	5 min.	2c (90)

Table 1. Data on the Reaction between 3-(4-Methoxyphenyl)prop-2-ynyl Acetate 1a and Electrophilic Reagents

^{*a*}An electrophilic addition reaction to the triple bond occurred concurrently. ^{*b*}Only electrophilic addition reaction took place. ^{*c*}Low conversion of the starting material was reached.

single-electron-transfer process,⁴ in the present case most of these methodologies (radical initiator together with transitionmetal salt as SET oxidant) did not give any satisfactory results. It is also known that 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) is able to promote a single-electron transfer followed by H-abstraction from benzylic ethers, thus causing formation of aryloxycations, stabilized by stereoelectronic effects.⁵ Indeed,

when a solution of the starting material with isochromane and an equivalent of DDQ was stirred in dichloromethane at room temperature, a trace formation of product was observed by TLC after 24 h (entry 5).

Increasing the reaction temperature improved conversion and led to 51% and 69% yields of **2c** during reflux or irradiation of dichloroethane solutions in a microwave oven (entries 6 and 7). Moreover, on one hand, it was found that catalytic amounts of copper or silver triflates initiated reaction between starting alkyne and isochromane effectively even at room temperatures (entries 8 and 9), and on the other hand silver nitrate, gold(III) chloride, and copper iodide were proven to be totally ineffective (entries 10-12). Benzyl methyl ether was less reactive than isochromane but also underwent DDQ- and triflate-promoted C(sp³)–C(sp²) forming reaction (entries 13-15).

The role of copper and silver triflate was checked by TLC and ¹³C NMR monitoring of starting 3-(4-methoxyphenyl)prop-2ynyl acetate **1a** solution in dichloromethane- d_2 during prolonged (48–72 h) interaction with catalyst. Any changes of the starting alkyne were not observed by TLC, and any sufficient complexation between 3-(4-methoxyphenyl)prop-2-ynyl acetate **1a** and silver triflate was not observed by ¹³C NMR spectroscopy. Therefore, it was presumed that the crucial role of copper and silver triflate for the promotion of the reaction is in formation of the carboxonium triflate ion pair.⁶ This hypothesis was undoubtedly supported by reaction between 3-(4-methoxyphenyl)prop-2-ynyl acetate **1a** and 1-methoxyisochromane in the presence of 1 equiv of trimethylsilyl triflate.⁷ To our pleasant surprise, the reaction was efficiently accomplished just in 5 min, resulting 90% yield of **2c** (entry 16).

Optimized reaction conditions (entries 15 and 16) were applied for the synthesis of 2-substituted 1-arylprop-2-en-1-ones 2. The results are summarized in Figure 1. It should be noted that



Figure 1. Compounds prepared via electrophile induced rearrangement of 3-arylprop-2-ynyl acetates.

reaction rate is affected by the substituent next to the triple bond. Thus, electron-donating groups on aromatic rings shortened reaction times up to 3-5 min, while in the case of 3-phenylprop-2-ynyl acetate **1b** or 3-(4-chlorophenyl)prop-2-ynyl acetate **1c** 1-1.5 h is required for full conversion of the starting materials. 4-Arylbut-3-yn-2-yl acetates **1e**,**g** and 1,3-diphenylprop-2-ynyl acetate **1f** after the trimethylsilyl triflate promoted treatment with 1-methoxychroman formed mixtures of *E*- and *Z*-isomers **2j–l**. However, aliphatic pent-2-ynyl acetate did not participate in electrophilic rearrangements. This fact supports ionic

mechanism of the rearrangement, where 3-aryl moiety is crucial for the stabilization of charge deficiency.

A plausible mechanism of an electrophile-induced transformation of 3-arylprop-2-ynyl acetates is presented in Scheme 3.





Oxocarbenium ions formed either from benzylic ethers during 2,3-dichloro-5,6-dicyanobenzoquinone-mediated single electron transfer or trimethylsilyl triflate initiated cleavage of isochromane acetal are easily trapped by the triple bond of the starting 3-arylprop-2-ynyl acetates 1. After formation of ionic intermediates I, a subsequent nucleophilic attack of the ester carbonyl occurs leading to 6-membered carbocations II. Cleavage of the 6-membered intermediates takes place together with loss of acetyl group, promoted by a nucleophilic particle (i.e., water from the atmosphere or methoxygroup from isochromane acetal).

Very recently, Hashmi et al. reported on a gold-initiated intermolecular $C(sp^3)-C(sp^2)$ bond-forming reaction involving rearrangement of propargylic esters to nucleophilic allenes and a subsequent reaction with electrophilic oxocarbenium ions (Scheme 4).⁸ In contrast to the observation of Hashmi et al.,

Scheme 4. Gold-Catalyzed Protocol for the Preparation of Isochromane Derivatives, Proposed Recently by Hashmi et al.



4-phenylbut-3-yn-2-yl acetate **1e** under reaction conditions formed major *E*-isomer **2j**. However, other 1-substituted 3arylprop-2-ynyl acetates **1f**,**g** underwent unselective rearrangement to *E*- and *Z*-isomers. This fact supports that in the present case 1,3-acyloxy shift occurs by different mechanism, excluding formation of intermediate allenes. Although the electrophilic rearrangement of 1-substituted 3-arylprop-2-ynyl acetates is not a diastereoselective process, for the linear substrates this methodology represents a very mild, economic, and efficient process for preparation of ethers of Morita–Baylis–Hillman

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adducts (compounds 2c-i) since it does not require use of expensive gold and silver complexes.

For the confirmation of the proposed mechanistic scenario, an isotopic labeling experiment was designed and conducted. Labeled 3-(4-methoxyphenyl)prop-2-ynyl acetate 1a-¹⁸O was synthesized by the Steglich esterification⁹ between the corresponding 3-(4-methoxyphenyl)prop-2-ynyl alcohol and ¹⁸O-labeled acetic acid. With substrate 1a-¹⁸O in hand, the trimethylsilyl triflate catalyzed reaction with isochromane acetal was conducted and the product 2c-¹⁸O was obtained in 89% yield without any loss of ¹⁸O, as it was determined by the HRMS spectrum. Moreover, an observed $\delta = 0.05$ ppm (5 Hz) upfield chemical shift was found for ketone carbonyl carbon in the ¹³C NMR spectrum of 2c-¹⁸O, thus undoubtedly confirming¹⁰ an 1,3-acyloxy shift (Figure 2).



Figure 2. Isotopic labeling experiment and fragment of $^{13}\mathrm{C}$ NMR spectra of $2c\text{-}^{18}\mathrm{O}.$

In summary, it was shown that 1,3-acyloxy shift in propargylic esters can be induced by some electrophiles. It is the first example of electrophilic isomerization of propargylic esters without need of gold catalysis,¹¹ and this reactivity mode points toward a broad and divergent applicability of the propargylic substrates for the synthesis of synthetically and biologically useful α , β -unsaturated ketones. Further experimental and theoretical investigations of these methodologies are underway in our laboratory and will be published in due course.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, product characterization and copies of ¹H and ¹³C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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