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A Unique Cascade Reaction between 3-Arylprop-2-inylcarboxylates and Benzaldehydes Leading to the Formation of Morita–Baylis–Hillman Adducts

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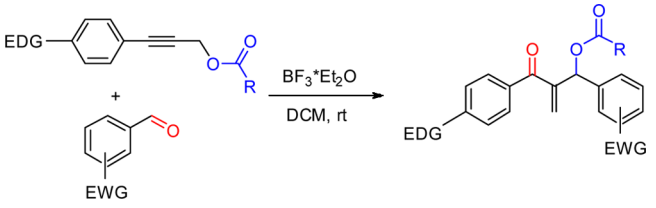
ABSTRACT



During an alkyne-carbonyl metathesis reaction between electron-rich 3-arylprop-2-inylcarboxylates and electron-poor benzaldehydes, a smooth migration of carboxylate groups takes place. This unique cascade reaction allows the formation of Morita–Baylis–Hillman (MBH) adducts unavailable via a traditional MBH reaction.

The Morita–Baylis–Hillman adducts (MBHAs) and their derivatives are useful intermediates in organic synthesis and therefore are widely used in target-oriented synthesis.[1] Various natural products and molecules of biological interest were synthesized from MBHAs.[2] Moreover, some MBHAs showed antiparasitic, antibacterial, antifungal, herbicidal, and in some cases antitumor activities.[3]

Classically MBHAs are synthesized via a highly efficient Morita–Baylis–Hillman reaction which basically involves a reaction between aldehydes and activated alkenes.[4] However the formation of MBHAs from arylvinyl ketones during a classical MBH reaction usually fails due to the high reactivity of starting materials.[5] Therefore, there are only a few examples of a successful synthesis of MBHAs from arylvinyl ketones in the literature.[6] Thus, Trofimov and Gevorgyan utilized a *sila*-MBH reaction using an α-silylated arylvinyl ketone in the presence of a phosphine catalyst.[6a] Some time later, Oh and Li reported a cooperative catalyst system of proline and brucine *N*-oxide.[6b] And very recently, Kim et al. reported on the use of 4-nitrophenol as a proton donor for a successful MBH reaction.[6c]

During investigation of the synthesis of various biologically important unsaturated ketones via alkyne-carbonyl metathesis reactions,[7] we observed the really unique reactivity of some substrates. We noticed that during Lewis acid catalyzed reactions between 3-arylprop-2-inylcarboxylates and aromatic aldehydes, four possible products can

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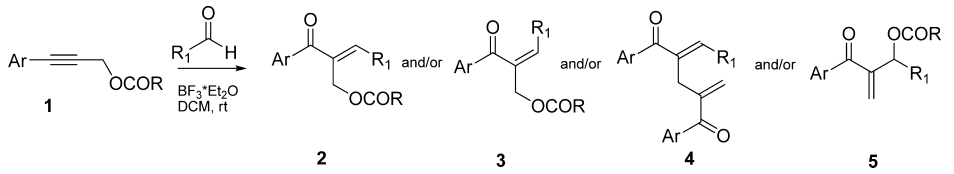
Table 1. Diversity of Products Formed during Reactions between 3-Arylprop-2-inylcarboxylates and Aldehydes



entry	starting alkyne	aldehyde	reaction time	**2:3:4:5**	products	overall yield, %
1	**1a**: Ar = Ph; R = Me	R_1 = *c*-Hex	24 h	1:0:0:0	**2aa**	49%
2	**1a**	R_1 = 2,4-$Cl_2C_6H_3$	30 h	2:1:0:0	**2ab**, **3ab**	69%
3	**1a**	R_1 = 2-$NO_2C_6H_4$	72 h	2.8:1:0:0	**2ac**, **3ac**	38%
4	**1a**	R_1 = 4-MeC_6H_4	120 h	0:0:1:0	**4ad**	22%
5	**1a**	R_1 = 4-$MeOC_6H_4$	1.5 h[a]	0:0:1:0	**4ae**	12%
6	**1a**	R_1 = 4-$NO_2C_6H_4$	48 h	5:1.6:0:1	**2af**, **3af**, **5af**[b]	61%
7	**1a**	R_1 = C_6F_5	48 h	0:1:0:3.3	**3ah**, **5ah**[c]	47%
8	**1b:** Ar = Ph; R = Ph	R_1 = *c*-Hex	24 h	1:0:0:0	**2ba**	24%
9	**1b**	R_1 = 2,4-$Cl_2C_6H_3$	48 h	4.5:1:0:0	**2bb**, **3bb**	61%
10	**1b**	R_1 = 2-$NO_2C_6H_4$	24 h	4.8:4:0:1	**2bc**, **3bc**, **5bc**[d]	45%
11	**1b**	R_1 = 2-NO_2-4-$(CF_3)C_6H_3$	48 h	1:2.6:0:1.5	**2bd**, **3bd**, **5bd**[e]	77%
12	**1b**	R_1 = 2,4-$(NO_2)_2C_6H_3$	24 h	0:0:0:1	**5be**	67%
13	**1b**	R_1 = C_6F_5	48 h	0:0:0:1	**5bf**	40%
14	**1c:** Ar = 4-$NO_2C_6H_4$; R = Ph	R_1 = *c*-Hex	n.r.	–	–	–
15	**1c**	R_1 = 2,4-$(NO_2)_2C_6H_3$	n.r.	–	–	–
16	**1c**	R_1 = C_6F_5	n.r.	–	–	–
17	**1d:** Ar = 4-$MeOC_6H_4$; R = Me	R_1 = Me	5 min	1:0:0:0	**2da**	52%
18	**1d**	R_1 = 4-$MeOC_6H_4$	5 min	0:0:1:0	**4db**	38%
19	**1d**	R_1 = 2,4-$Cl_2C_6H_3$	5 min	0:0:0:1	**5dc**	86%
20	**1d**	R_1 = 4-$NO_2C_6H_4$	5 min	0:0:0:1	**5dd**	82%
21	**1e:** Ar = 4-$MeOC_6H_4$; R = Ph	R_1 = 2,4-$Cl_2C_6H_3$	10 min	0:0:0:1	**5ea**	88%
22	**1e**	R_1 = 4-$NO_2C_6H_4$	5 min	0:0:0:1	**5eb**	70%

[a] The reaction mixture was refluxed. [b] **2af** and **5af** were isolated as a mixture due to same R_f's. Their ratio was determined from ^{1}H NMR spectrum. [c] **3ah** and **5ah** were not isolated as individual compounds due to the same R_f's. Their ratio was determined from ^{1}H NMR spectrum. [d] **3bc** and **5bc** were not isolated as individual compounds due to the same R_f's. Their ratio was determined from ^{1}H NMR spectrum. [e] Products were not isolated as individual compounds due to similar R_f's. Their ratio was determined from ^{1}H NMR spectra.

be obtained. We were pleasantly surprised to see that in some cases the derivatives of MBHAs formed as main reaction products. Keeping in mind that 2-aroyl-1-arylallylcarboxylates are privilleged structures and they are not easily synthetically available, we decided to study reactions between 3-arylprop-2-inylcarboxylates and aromatic aldehydes and to determine the factors dictating the outcome of the reactions. So herein, we report the results of our investigations and present a unique cascade reaction comprising the formal alkyne-carbonyl metathesis followed by the sigmatropic [3,3] migration of carboxylate.

First, we prepared the starting 3-arylprop-2-inylcarboxylates **1** by means of the classical Sonogashira coupling[8] between aryliodides and propargyl acetates or benzoates. Then we tested their reactivity toward the Lewis acid catalyzed coupling reaction with aldehydes. Several Lewis acids such as BF_3*Et_2O, $FeCl_3$, $AgSbF_6$, SbF_5, BBr_3, TMSOTf, different solvents (DCM, DCE, CH_3CN, THF, CH_3NO_2), and different reaction temperatures were examined. After this brief search of the most suitable reaction conditions, we came to conclusion that 1 equiv of BF_3*Et_2O in dichloromethane at rt gave the best results. The data for reactions between 3-arylprop-2-inylcarboxylates **1a**–**e** and various aldehydes under the optimal conditions are summarized in Table 1.

It should be noted that the rate of the reactions strongly depends on the substituents on the arene moiety of 3-arylprop-2-inylcarboxylates **1**. Thus, the reaction of unsubstituted 3-phenylprop-2-inylcarboxylates **1a,b** with various aldehydes generally required one to several days for full conversion of the starting materials (Table 1, entries 1–4; 6–13). Unfortunately, introduction of an electron-withdrawing nitro group into the 3-arylprop-2-inylcarboxylate structure (compound **1c**) deactivates the starting material toward coupling with aldehydes (entries 14–16). In these cases the starting material was recovered after the workup of reaction mixtures. On the other hand, the

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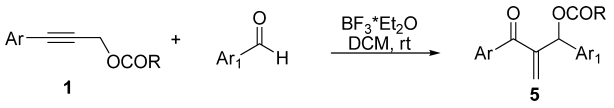
Table 2. Synthesis of MBHA Carboxylates by the Presented Method



entry	starting alkyne	aldehyde; Ar_1:	reaction time	product	yield, %
1	**1b:** Ar = Ph; R = Ph	$2,4\text{-}(NO_2)_2C_6H_3$	24 h	**5be**	67%
2	**1b**	C_6F_5	48 h	**5bf**	40%
3	**1d**: Ar = $4\text{-}MeOC_6H_4$; R = Me	$2,4\text{-}Cl_2C_6H_3$	5 min	**5dc**	86%
4	**1d**	$4\text{-}NO_2C_6H_4$	5 min	**5dd**	82%
5	**1d**	C_6F_5	1 h	**5de**	60%
6	**1d**	$3\text{-}NO_2C_6H_4$	5 min	**5df**	54%
7	**1d**	$2,4\text{-}(NO_2)_2C_6H_3$	5 min	**5dg**	68%
8	**1d**	$2\text{-}NO_2\text{-}4\text{-}(CF_3)C_6H_3$	5 min	**5dh**	87%
9	**1e**: Ar = $4\text{-}MeOC_6H_4$; R = Ph	$2,4\text{-}Cl_2C_6H_3$	10 min	**5ea**[a]	88%
10	**1e**	$4\text{-}NO_2C_6H_4$	10 min	**5eb**[a]	70%
11	**1e**	$2,4\text{-}(NO_2)_2C_6H_3$	10 min	**5ec**[a]	90%
12	**1e**	$2\text{-}ClC_6H_4$	5 min	**5ed**[a]	59%
13	**1e**	C_6F_5	30 min	**5ee**[a]	66%
14	**1f**: Ar = $2,4\text{-}(MeO)_2C_6H_3$; R = Me	$2\text{-}NO_2C_6H_4$	5 min	**5fa**[a]	52%
15	**1f**	$4\text{-}NO_2C_6H_4$	3 min	**5fb**[a]	51%
16	**1g**: Ar = $2,3,4\text{-}(MeO)_3C_6H_2$; R = Ph	$2,4\text{-}Cl_2C_6H_3$	10 min	**5ga**[a]	79%
17	**1g**	$4\text{-}NO_2C_6H_4$	5 min	**5gb**[a]	85%

[a] Formation of hydrolyzed product together with benzoylated MBHAs is possible in the case of nonabsolute solvent.

presence of an electron-donating methoxy group in 3-arylprop-2-inylcarboxylates (**1d**, **1e**) shortened the reaction time to up to 10 min (entries 17−22).

Next, we found the general dependence between the product formed and the structure of the aldehyde. In all cases where aliphatic carbaldehydes were used (entries 1, 8, 17) the selective formation of *E*-configurated alkyne-carbonyl metathesis products **2** took place in low or moderate yields.[9] However, the mixtures of *E* (**2**) and *Z* (**3**) isomers of the corresponding α,β-unsaturated ketones were formed during reaction of **1a,b** with aromatic aldehydes, especially those having an *ortho*-substituent (Table 1, entries 2, 3, 9). The reactions of **1a,d** with benzaldehydes bearing an electron-donating group in the *para*-position (entries 4, 5, 18) were complicated[10] and required a longer reaction time (entry 4) or heating (entry 5) for full conversion of the alkyne. After workup of the reaction mixtures, 2:1 adducts **4ad**, **4ae**, **4db** were isolated in poor yields as sole reaction products.

The reaction of **1a** with 4-nitrobenzaldehyde led to the formation of three products: the major one, **2af**, which had the same R_f as its impurity, resulting in unsuccessful purification, and the *Z*-isomer **3af** (entry 6). After careful study of the spectral data for impure compound **2af**, we came to the conclusion that the impurity could be acetylated MBHA **5af**.[11] During the reaction of **1a** with 2,3,4,5,6-pentafluorobenzaldehyde, the mixture of two products (*Z* isomer **3ah** and the major product acetylated MBHA **5ah**) was formed (entry 7). We became deeply intrigued by these results and decided to investigate the scope and the reasons for formation of MBHAs. It is obvious that the formation of **5af** and **5ah** occurs during migration of the acetoxy group. We envisioned that the migration of the benzoyloxy group could be more favored due to stabilization of the intermediate carbocation by the neighboring phenyl group. Indeed, while the reaction of **1b** with 2-nitrobenzaldehyde or 2-nitro-4-trifluoromethylbenzaldehyde led to the formation of three compounds (*E* isomer **2**, *Z* isomer **3**, and MBHA **5**) (entries 10, 11), the use of more electron-poor 2,4-dinitrobenzaldehyde or pentafluorobenzaldehyde (entries 12, 13) gave the desired benzoylated MBHAs **5be**, **5bf** as sole reaction products. And finally, we were pleasantly intrigued in finding that the reactions between starting 3-(4-methoxyphenyl)prop-2-inylcarboxylates (**1d**, **1e**) and dichloro- or nitrosubstituted benzaldehydes were smooth and selective, leading to good-yielding formation of MBHAs **5dc**, **5dd**, **5ea**, and **5eb** (entries 19−22).

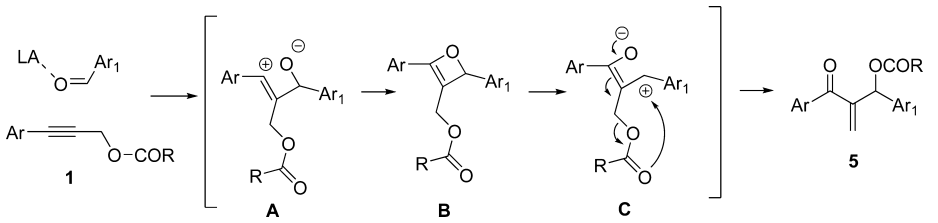
So it can be summarized that the outcome of the reaction is dictated by the structures of both starting 3-arylprop-2-inylcarboxylates and aldehydes. While the use of aliphatic aldehydes always leads to the *E* isomer of an α,β-unsaturated ketone, the reaction with aromatic aldehydes gives

(9) Aliphatic aldehydes undergo a self-condensation reaction in the presence of Lewis acids; therefore the yields of alkyne-carbonyl metathesis products are not satisfactory.

(10) The reactions with electron-rich aldehydes usually led to the formation of big amounts of tars.

(11) In the ^1H NMR spectrum of the **2af** and **5af** mixture there were two doublets at 5.94 ppm (1H, d, J = 0.9 Hz) and 6.18 ppm (1H, d, J = 1.5 Hz) together with broad singlet at 2.18 ppm (2H, br.s.). The ^{13}C NMR of the same mixture showed the presence of a tertiary *CH*−O carbon (signal at 73.07 ppm).

Scheme 1. Possible Mechanism of the Formation of MBHA Carboxylates



mixtures of *E* and *Z* isomers. The presence of an electron-donating group on benzaldehydes diminishes the reaction rates and stimulates the formation of a 2:1 adduct.[12] An electron-withdrawing group on benzaldehydes is crucial for the formation of MBHAs. And the combination of an electron-donating group onto starting 3-arylprop-2-inylcarboxylates with an electron-withdrawing group on benzaldehydes afforded a very smooth and selective formation of the acetylated or benzoylated Morita–Baylis–Hillman adducts.

Therefore, we have prepared various 2-aroyl-1-arylallylcarboxylates **5** by the presented method. The results are summarized in Table 2.

Mechanistically, we believe that the formation of MBHA carboxylates proceeds *via* coordination of carbonyl oxygen to the Lewis acid, followed by stepwise ionic formation of the intermediates **A** and **B** (Scheme 1).[13] This initial step is consistent with the good results obtained with electron-rich Ar moieties. Then, the subsequent electrocyclic oxete ring opening followed by [3,3]-sigmatropic rearrangement leads to the desired 3-aroyl-1-arylallylcarboxylates **5**.

Propargylic esters are able to undergo a gold catalyzed 1,2- or 1,3-acyl shift leading to the formation of gold carbene intermediates, poised for subsequent functionalization.[14] Herein we have shown that [3,3] rearrangement can be initiated during intermolecular reactions between propargylic esters and benzaldehydes. Our mechanistic considerations offer support for the migration of a carboxylate during an alkyne-carbonyl metathesis stage. First, the starting alkynes did not undergo an acyl shift in the presence of $BF_3 \cdot Et_2O$. Second, the addition of $BF_3 \cdot Et_2O$ to the mixture of **2af**, **3af**, and **5af** in DCM did not lead to either an increase in **5af** amount or a change in the **2af**, **3af**, and **5af** ratio after 24 h of stirring at rt. These facts confirmed that the formation of MBHA carboxylates proceeded neither from unsaturated ketones **2**, **3** nor via rearranged 3-arylprop-2-inylcarboxylates **1**.

In conclusion, we have developed a simple, highly efficient approach to 3-aroyl-1-arylallylcarboxylates via a reaction between 3-arylprop-2-inylcarboxylates and aromatic aldehydes. This protocol proceeds via a new formal alkyne-carbonyl metathesis/[3,3] sigmatropic rearrangement cascade and allows the mild and efficient synthesis of structural units unavailable via a traditional MBH reaction. Further studies of these transformations are underway in our laboratory, and the results will be published in due course.

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Supporting Information Available. A complete description of experimental details, products characterization, possible mechanism of formation of products **4**, copies of ^1H, ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(12) For the structural elucidation and possible mechanism, see the Supporting Information.

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The authors declare no competing financial interest.