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Alkoxide-catalyzed addition of alkyl carbonates across alkynes – stereoselective synthesis of (*E*)-β-alkoxyacrylates†

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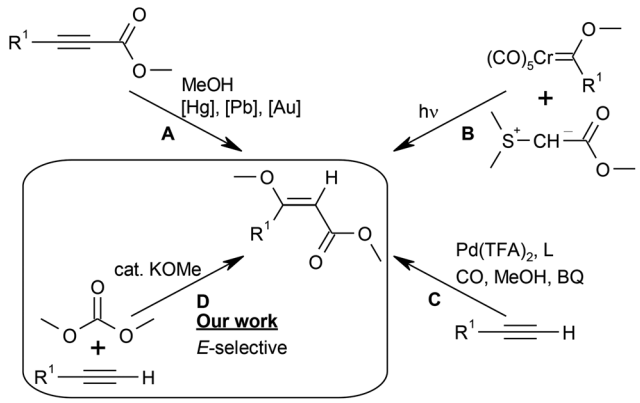
Dialkyl carbonates were found to regio- and stereoselectively add to terminal alkynes in the presence of catalytic amounts of potassium methoxide. Various synthetically meaningful aryl- and heteroaryl-substituted (*E*)-β-alkoxyacrylates were thus obtained in high yields and with near-ideal atom economy.

Introduction

The (*E*)-β-methoxyacrylate subunit is found in various biologically active natural products such as dihydrokawain,[1] tetronic acids,[2] five- and six-membered lactones,[3–10] and β-methoxyacrylate antibiotics,[11–14] including melithiazol[12] and haliangicin[14] (Fig. 1). An *E*-configuration of the methoxyacrylate (MOA) moiety is decisive for biological activity.[15,16]

In view of their tremendous synthetic importance, sustainable, stereoselective synthetic entries to (*E*)-β-MOA are constantly sought. Existing synthetic strategies all have their drawbacks (Scheme 1). The addition of methanol to propargylic esters (**A**) suffers from the poor availability of the starting materials and calls for toxic or expensive catalysts, *e.g.* mercury,[17] lead,[18] or gold complexes, or has poor chemoselectivity.[19] The photochemical coupling of sulfur ylides with chromium Fischer carbene complexes (**B**) gives poor stereoselectivity and produces stoichiometric amounts of sulfoxide and toxic chromium waste.[20–22] Stereoselective syntheses, *e.g. via* Claisen condensation of a lactone with methyl formate, methylation with dimethyl carbonate and subsequent ring opening, require multiple steps.[23] The palladium-catalysed methoxycarbonylation of terminal alkynes reported by Kato and Akita (**C**) is efficient but suffers from the use of toxic carbon monoxide and stoichiometric amounts of benzoquinone (BQ) as the oxidant.[24,25]



Scheme 1 Synthetic routes to β-methoxyacrylates.

From a sustainable chemistry standpoint, the addition of alkyl carbonates across terminal alkynes would represent one of the best conceivable synthetic concepts to access (*E*)-β-MOA.

In the proposed strategy, the alkyl carbonate would act as the source of both the alkyl carboxylate and the alkoxy group, resulting in maximal atom economy, since all atoms of the reagents are incorporated in the desired product (**D**). Scheme 2 shows the proposed mechanism for this transformation. In the first step, the base B^- deprotonates the terminal alkyne to the acetylide (step (I)), which affords the propargylic ester after nucleophilic addition of dimethyl carbonate and elimination of the alkoxide (step (II)). The latter then adds to the C–C triple bond (step (III)), and the (*E*) or (*Z*)-products form upon protonation (IV).

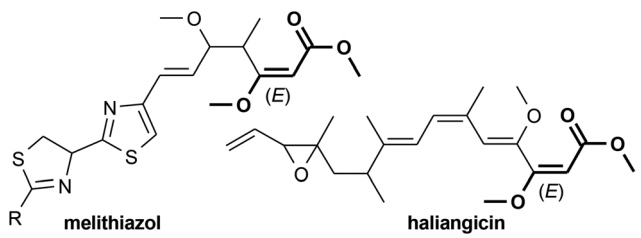


Fig. 1 Bioactive natural compounds bearing a (*E*)-β-methoxyacrylate moiety.

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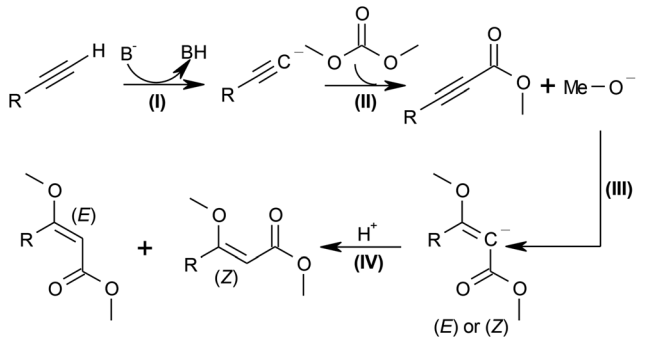


Scheme 2 Mechanism for the β-MOA synthesis from dimethyl carbonate.

Dimethyl carbonate is a "green" reagent, because it is a non-toxic, non-irritating liquid (bp. 90.3 °C) which is neither on the list of volatile organic compounds (VOCs), nor does it contribute to tropospheric ozone formation.[26,27] It is used industrially as a solvent, fuel additive, and sustainable alternative to phosgene or harmful methylating agents.[28] Dimethyl carbonate is accessible from methanol and carbon dioxide, potentially contributing to CO_2 sequestration.[28]

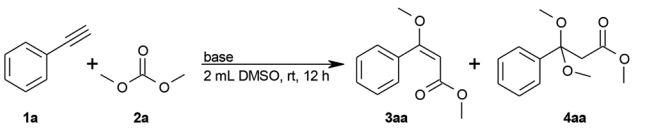
However, the only report on its addition to alkynes dates back to 1949, and states that in the reaction of phenylacetylene with either dimethyl or diethyl carbonate, a hard-to-separate mixture of a β-alkoxyacrylate with unidentified stereochemistry and a ketal was obtained.[29] In order to turn this intriguing concept into an expedient synthetic entry to (*E*)-β-MOA, the chemo- and stereochemistry of the reaction needed to be controlled efficiently.

Results and discussion

Using the reaction of phenylacetylene (**1a**) with dimethyl carbonate (**2a**) as a model, we systematically investigated various reaction conditions. The logical first choice for the base was potassium methoxide, since methoxide ions would be released during the process in any case (step (II)) and are known to deprotonate alkynes. In the presence of stoichiometric amounts of potassium methoxide in 2 mL dimethyl carbonate, the desired (*E*)-methyl 3-methoxy-3-phenylprop-2-enoate (**3aa**) was detected in 54% yield, along with 12% of the ketal by-product **4aa** (Table 1, entry 1). By reducing the amount to 30 or 10 mol% KOMe, the yield increased to 74% or 80%, respectively, with good *E*/*Z* ratios, but 12% of ketal by-product **4aa** were still formed (Table 1, entries 2 and 3).

In order to minimize the amount of **4aa**, which is hard to separate from the desired product **3aa**, we reduced the amount of dimethyl carbonate to 1.2 equivalents and added an external solvent (Table 1, entries 4–7; see also the ESI S1, entries 3–5†). Good yields with low amounts of ketal **4aa** were obtained in polar aprotic solvents (Table 1, entries 4 and 5). DMSO gave the best yield and selectivity (Table 1, entry 7). The yield of product **3aa** was not improved further by increasing neither the temperature nor the amount of dimethyl carbonate (S1, entries 1 and 2†).

Table 1 Optimization of base and the reaction conditions[a]



Entry	Base (mol%)	Solvent	Conv.[b] (%)	Yield[b] (%) 3aa	4aa	*E*/*Z*
1	KOMe (100)	DMC	100	54	12	6 : 1
2	KOMe (30)	DMC	100	74	12	12 : 1
3	KOMe (10)	DMC	100	80	12	10 : 1
4	KOMe (30)	PC	—	—	—	—
5	KOMe (30)	DMF	100	70	2	13 : 1
6	KOMe (30)	NMP	100	76	6	11 : 1
7	KOMe (30)	DMSO	100	80	4	15 : 1
8	KOMe (10)	DMSO	8	5	—	—
9	NaOMe (30)	DMSO	—	—	—	—
10	KO^{t}Bu (30)	DMSO	100	77	3	13 : 1
11	LDA (30)	DMSO	53	9	—	7 : 1
12	Cs_2CO_3 (30)	DMSO	—	—	—	—
13[c]	**KOMe (30)**	**DMSO**	**100**	**89 (75)**[d]	**6**	**15 : 1**

[a] Reaction conditions: 0.50 mmol of **1a**, 0.60 mmol of **2a**, 10–100 mol% base, 2 mL solvent, 12 h, rt. [b] Conversions, yields and *E*/*Z* ratios were determined by GC using *n*-dodecane as internal standard. [c] Dropwise addition of 1.00 mmol of **1a** in 0.5 mL DMSO to 1.20 mmol of **2a** and 0.30 mmol of KOMe in 1 mL DMSO over 45 min, 12 h, rt. [d] Isolated yield. PC = propylene carbonate.

With less base, the conversion dropped to only 8% (Table 1, entry 8). No conversion at all was observed when sodium methoxide was used instead of the potassium salt (Table 1, entry 9). Potassium *tert*-butoxide afforded 77% yield of **3aa** (Table 1, entry 10), whereas all other bases were ineffective (Table 1, entries 11 and 12). The amount of solvent could be reduced to 1 mL without negatively affecting the yield (S1, entry 6†). The best procedure consisted of adding the alkyne dropwise to a stirred solution of dimethyl carbonate and 30 mol% potassium methoxide in DMSO (Table 1, entry 13).

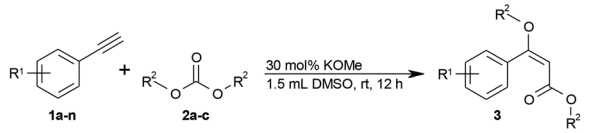
In the presence of 50 μl of water, no conversion was observed, presumably due to deactivation of the catalytic methoxide base (S1, entry 7†). The yield is also slightly decreased when the reaction is performed under air instead of a nitrogen atmosphere (S1, entry 8†).

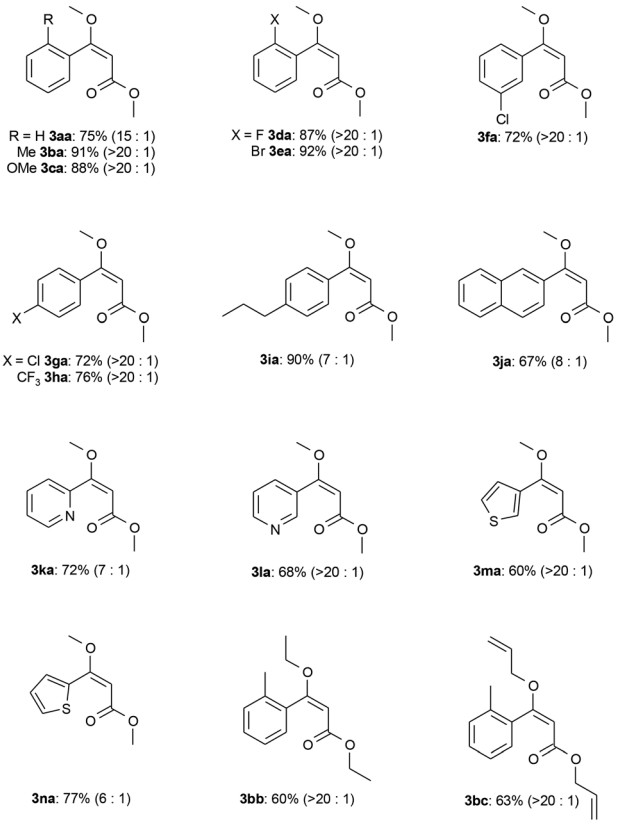
With an efficient reaction protocol in hand, we next investigated its scope using various alkynes (**1**) and carbonates (**2**). As shown in Table 2, both electron-rich and electron-deficient aromatic alkynes were selectively converted to the (*E*)-β-MOA (**3**) in good to excellent yields and high chemo- and regioselectivity.

Common functionalities including methoxy, fluoro, bromo, chloro, and trifluoromethyl groups are tolerated. Heteroaromatic alkynes, such as pyridine or thiophene derivatives, also gave the desired products in good yields (Table 2, **3ka–3na**).

The protocol also extends to other carbonates, as was shown by the addition of diethyl and diallyl carbonate (**2b** and **2c**) to 2-ethynyltoluene (**1b**). Only trace amounts of methoxy-

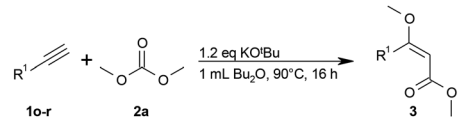
Table 2 Scope for the synthesis of β-alkyloxyacrylates from aromatic alkynes and dialkyl carbonates[a]

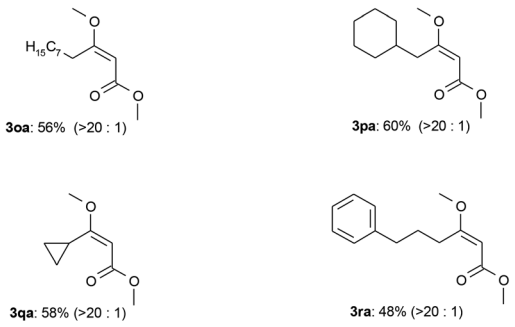




[a] Reaction conditions: Dropwise addition of 1.00 mmol of **1** in 0.5 mL DMSO to 1.20 mmol of **2** and 0.30 mmol of KOMe in 1 mL DMSO over 45 min, 12 h, rt. Isolated yield. *E*/*Z* values are given in parentheses.

Table 3 Scope for the synthesis of β-methoxyacrylates from aliphatic alkynes[a]



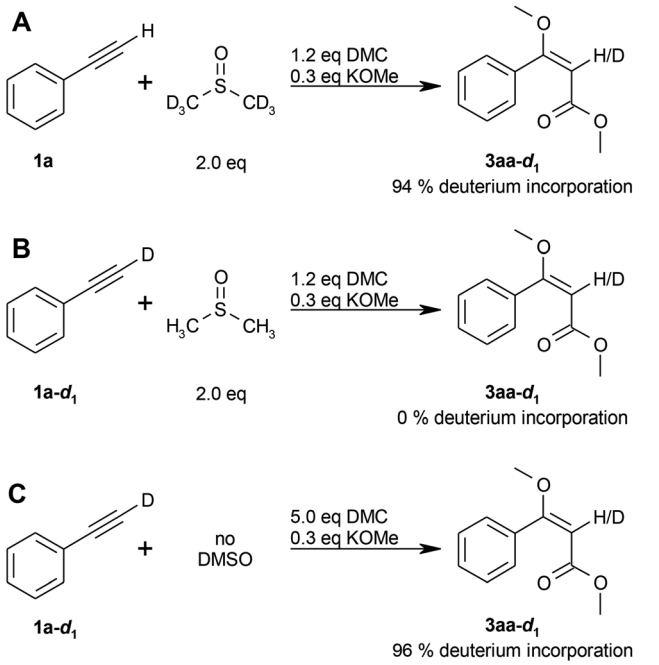


[a] Reaction conditions: 1.00 mmol of **1**, 3.00 mmol of **2a**, 1.20 mmol of KO^{t}Bu, 1 mL Bu_2O, 16 h, 90 °C. Isolated yield. *E*/*Z* values are given in parentheses.

substituted by-products were observed resulting from transesterification with the methoxide base. Diphenyl carbonate gave no conversion. Instead, the methoxide undergoes quantitative transesterification with diphenyl carbonate and the resulting phenolate is not sufficiently basic to deprotonate a terminal alkyne (see step (I) in the proposed mechanism; Scheme 2).

The less acidic aliphatic alkynes could not be converted under these exceptionally mild conditions. Additional screening (see ESI S2†) showed that aliphatic alkynes were converted to the desired aliphatic (*E*)-β-methoxyacrylates (**3**) in moderate yields using stoichiometric amounts of *tert*-butoxide in dibutyl ether at 90 °C (Table 3).

The scalability of the reaction was demonstrated on 15 mmol scale by the synthesis of *ortho*-bromophenyl (*E*)-β-MOA **3ea**, which is a useful synthetic intermediate towards a variety of compounds with fungicidal activity.[30] Simple distillation of the crude reaction mixture yielded **3ea** in pure form and 80% yield. The *E*-factor (total kg waste per kg product) for the large scale synthesis of **3ea** of 5.2 demonstrates the sustainability of this process (see S9† for the calculations). This is an excellent value in comparison to *E*-factors in chemical industry for the production of fine chemicals, which are typically in the range of 5–50.[31] By recycling the solvent, the *E*-factor may further be reduced, ideally down to 1.5.



Scheme 3 Deuterium labeling experiments.

To elucidate the origin of the high stereoselectivity, we subjected an *E*/*Z*-mixture of **3aa** to the reaction conditions. Within 12 h, the *E*/*Z* ratio changed to 15 : 1 in favor of the *E*-isomer. This points to interconversion between isomers and indicates that the *E*-isomer is thermodynamically more stable. The high *E*/*Z* ratio is a consequence of the unprecedentedly low reaction temperature.

Deuterium labelling experiments were performed for further insight into the reaction mechanism, as well as to clarify the origin of the olefinic proton (see step (IV) in the proposed mechanism; Scheme 2). The reaction of phenylacetylene (**1a**) with dimethyl carbonate (**2a**) in DMSO-d_6 resulted in a deuterium incorporation of 94% (Scheme 3**A**), whereas the reaction of d_1-phenylacetylene (**1a-*d*$_1$**) in non-deuterated DMSO showed no deuterium incorporation (Scheme 3**B**), thus indicating that the olefinic proton originates from the solvent.

In contrast, the deuterium incorporation was 96% for the reaction of d_1-phenylacetylene (**1a-*d*$_1$**) in the absence of DMSO (Scheme 3**C**), indicating that the alkyne proton is transferred to the product in case no other proton source is available.

Conclusions

The alkoxide-catalyzed addition of alkyl carbonates to terminal alkynes represents an efficient approach for the stereoselective synthesis of synthetically valuable (*E*)-β-methoxyacrylates. The protocol offers a broad substrate scope covering a broad range of functionalized arenes and heteroarenes. Due to its remarkably high atom economy and low *E*-factor, this synthetic route is highly sustainable and interesting also for industrial applications.

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