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Synthesis of Enynic and Allenic Orthoesters via Defluoromethoxylation of 2-Trifluoromethyl-1,3-enynes

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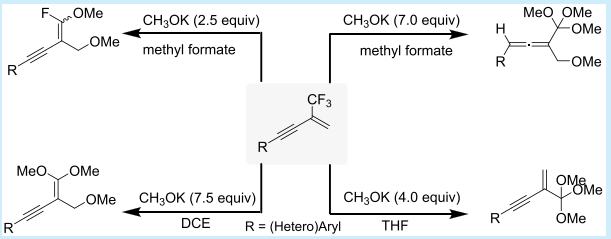
ABSTRACT: In this protocol, the chemoselective defluoromethoxylation reactions of 2-trifluoromethyl-1,3-enynes were developed. The enynic and allenic orthoesters were selectively produced in good to excellent yields via multiple substitution processes under mild reaction conditions, respectively. The enynic orthoester products were proved capable of acting as efficient "platform molecules" to access various functionalized allenyl compounds.



Orthoester skeletons have been widely found in many natural products such as dahuribirins, resiniferatoxins, trigocherrins, and medicinal compounds like tetrodotoxin, orthosomycines, and so on.[1] Recently, the application of orthoesters in material science and supramolecular chemistry has also attracted considerable attention from chemists.[2] Importantly, because of their highly reactive properties, they have been extensively applied as acylating agents,[3] coupling partners,[4] and protecting groups in organic synthesis.[5] Therefore, many efforts have been made to discover practical and efficient methodologies to access functionalized orthoesters. Unfortunately, the need for specific starting materials and harsh reaction conditions in the traditional methods still largely restricts the compatibility of different functional groups in the reactions and the types of products.[6] For example, in the literature previously reported on the synthesis of orthoesters by imidates, the preparation of imidates requires the reaction of a cyanide group in the action of hydrogen chloride gas and methanol, and the conditions are still relatively harsh.[6e] Recently, few to no examples of the electrosynthesis of orthoesters have emerged as efficient alternatives, as they allowed more general and easily available compounds to be used as starting materials.[7] However, to date, all cases reported are limited to only the synthesis of relatively simple aliphatic and aryl-substituted orthoesters. To enlarge the substrate scope and the skeleton diversity of orthoesters, the development of new and reliable methods to install different functionalities in the molecules is highly desirable. It is well known that both the enynic and the allenic fragments are very important building blocks in organic synthesis due to their flexible transformation abilities.[8] It is worth noting that so far, the preparation of functionalized enynic and allenic orthoesters has remained challenging, possibly due to the lack of compatible starting materials and the potential instability of products according to the traditionally synthetic methods.[9] Trifluoromethylvinyl compounds are well known as highly reactive species. When a double bond containing the CF_3 group reacts with a nucleophile, the fluorine atom of the allyl group may leave as the leaving group. When the trifluoromethylalkenes are subjected to nucleophilic attack at the γ-position carbon atom with respect to the fluorine substituent, the formation of 1,1-difluoro-1-alkenes (S_N2'-type reaction) can be accessed (Scheme 1a). On the contrary, the nucleophilic substitution can happen in the 1,1-difluoro-1-alkenes at the vinylic CF_2 carbon atom (Scheme 1b),[10] which will provide the monofluoro-substituted alkenes through an addition−elimination process (S_NV reaction). Therefore, combined with these two defluorination pathways,[11] the 2-trifluoromethyl-1,3-enynes

Scheme 1. Defluorinative Substitution via the S_N2' or S_NV Process

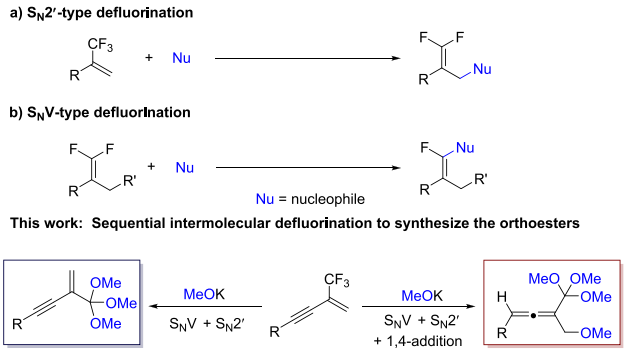


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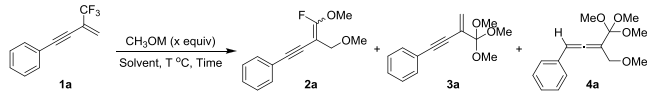
Table 1. Optimization of Reaction Conditions[a]



entry	CH_3OM (*x* equiv)	solvent	*T* (°C)	time (h)	**2a** (%)[b] (Z/E)[c]	**3a** (%)[b]	**4a** (%)[b]
1	CH_3OK (2.5)	1,2-dimethoxyethane	70	22	53 (58/42)	11	2
2	**CH_3OK (2.5)**	**methyl formate**	**0**	**22**	**93** (57/43)	**6**	**0**
3	CH_3OK (2.5)	methyl formate	70	22	88 (57/43)	8	2
4	CH_3OK (2.5)	chlorobenzene	70	22	0	0	0
5	CH_3OK (2.5)	benzotrifluoride	70	22	trace	25	7
6	CH_3OK (2.5)	tetrahydrofuran	70	22	35 (58/42)	6	trace
7	CH_3OK (3.0)	tetrahydrofuran	70	18	29 (60/40)	8	11
8	CH_3OK (3.5)	tetrahydrofuran	70	18	0	88	0
9	CH_3OK (4.0)	tetrahydrofuran	70	18	0	99	0
10	CH_3OK (4.0)	tetrahydrofuran	50	18	0	99	0
11	**CH_3OK (4.0)**	**tetrahydrofuran**	**30**	**18**	0	**98**	**0**
12	CH_3OLi (4.0)	tetrahydrofuran	30	18	0	0	0
13	CH_3ONa (4.0)	tetrahydrofuran	30	18	0	0	0
14	CH_3OK (5.5)	tetrahydrofuran	30	18	0	96	0
15	CH_3OK (5.5)	methyl formate	30	22	0	trace	39
16	CH_3OK (6.5)	methyl formate	30	22	0	trace	40
17	**CH_3OK (7.0)**	**methyl formate**	**30**	**22**	**0**	**22**	**62**
18	CH_3OLi (7.0)	methyl formate	30	22	0	0	0
19	CH_3ONa (7.0)	methyl formate	30	22	0	0	0
20	CH_3OK (7.5)	methyl formate	25	22	0	13	57
21	CH_3OK (7.5)	methyl formate	30	22	0	17	59
22	CH_3OK (7.5)	methyl formate	40	22	0	53	45
23	CH_3OK (7.5)	methyl formate	50	22	0	60	37
24	CH_3OK (7.5)	methyl formate	60	22	0	65	34
25	CH_3OK (7.5)	methanol	30	22	0	3	51
26	CH_3OK (7.5)	chlorobenzene	30	22	trace	32	5
27	CH_3OK (7.5)	benzotrifluoride	30	22	trace	38	4
28	CH_3OK (7.5)	1,2-dichloroethane	30	22	0	0	0

[a]Unless noted otherwise, the reaction was conducted according to the following conditions: **1** (0.2 mmol) and CH_3OK in anhydrous solvent (1.0 mL) were stirred for the indicated time at the indicated temperature (oil bath) under an argon atmosphere. [b]Yield was determined by ^1H NMR using mesitylene as the internal standard. [c]Z/E ratio was determined by ^1H NMR of the crude product.

were chosen to react with the potassium methoxide. The enynic and allenyl orthoesters are hypothesized to form via multiple S_N2' and S_NV substitution processes, respectively. It was found that the solvents and the amount of potassium methoxide used in reaction are crucial for selectively forming the different orthoester products (Scheme 1).

The study was initiated by investigating the methoxylation of 2-trifluoromethyl-1,3-enyne **1a** with CH_3OK in dimethoxyethane (DME) at 70 °C under an argon atmosphere (Table 1, entry 1). It was found that the major product **2a** (Z/E configuration was determined by measuring the nuclear Overhauser effect (NOE) of compound **2b**; **2b** and **2a** have the same structure, and the only difference is that the methyl group on the *para*-benzene ring) was generated via S_N2' and S_NV processes along with the formation of a trace amount of orthoester products **3a** and **4a** (determined by ^1H NMR). Triggered by this result, a variety of solvents, temperatures, and reaction times were carefully examined. It was found that up to a 93% yield of **2a** was obtained when methyl formate was used as the solvent at 0 °C (Table 1, entry 2). Furthermore, to improve the yields of orthoester products, other solvents and CH_3OM (M = Li, Na) were also tested in the reaction. Unfortunately, no obvious effect was observed for improving the yields. Surprisingly, when the amount of CH_3OK used in the reaction was increased to 4 equiv, product **3a** was formed in excellent yield, but the influence of temperature was not noticeable (Table 1, entries 7−11) (determined by ^1H NMR). When the loading of CH_3OK was further increased to 7 equiv and the solvent was changed to methyl formate, a higher yield of allenic orthoester **4a** was obtained (entry 17). Methyl formate was used as a solvent because it was decomposed into CH_3OH and CO under the action of CH_3OK, and CH_3OH acted as a proton source to participate in the reaction;[14] however, when we tried to promote the conversion of **1a** to **4a** product via tuning the temperatures, the solvents, and CH_3OM (M = Li, Na), no better result was observed. (Table 1, entries 18−28).

Next, with the optimal conditions for the synthesis of enynic orthoester **3a** in hand, the substrate scope of 2-trifluoromethyl-1,3-enynes was investigated (Figure 1). First, different aryl-substituted 2-trifluoromethyl-1,3-enynes were subjected to this reaction. The substrates bearing electron-donating or electron-withdrawing groups on the phenyl ring were well tolerated to give the corresponding products in good to excellent yields. It is worth noting that halides and free amine were also compatible to afford the desired product in moderate to excellent yields, which permitted the products to be further functionalized in the next step. Moreover, the naphthyl-substituted enyne was also smoothly converted to the enynic orthoester **3p**. Finally, when heteroaryls, such as thienyl- and

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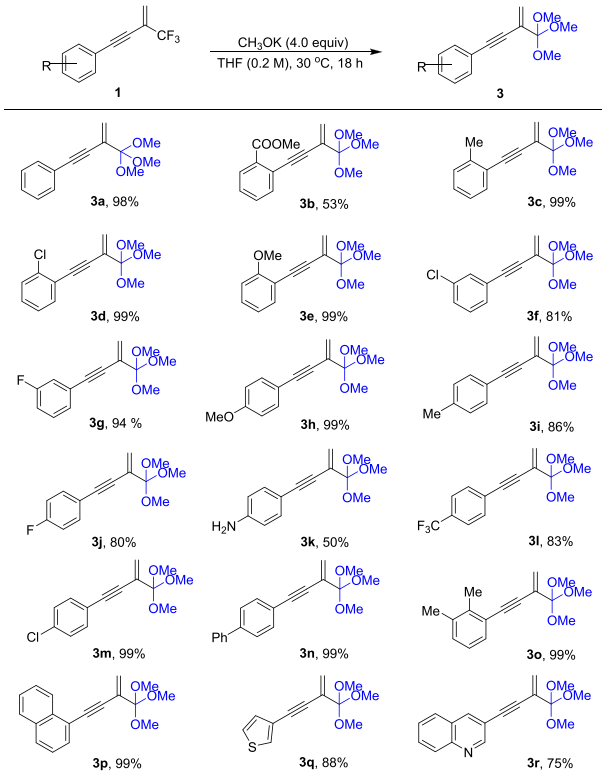


Figure 1. Substrate scope for the synthesis of enynic orthoester **3**. Unless noted otherwise, the reaction was conducted according to the following conditions: The 2-trifluoromethyl-1,3-enyne **1** (0.2 mmol) and CH_3OK in anhydrous tetrahydrofuran (THF) (1.0 mL) were stirred at 30 °C (oil bath) for 18 h under an argon atmosphere. Isolated yield.

quinolinyl-substituted 1,3-enynes, were applied as the substrates, the corresponding products **3q** and **3r** were obtained in 88 and 75% yields, respectively. We tried various ROKs (R = Et, ^{i}Pr, ^{t}Bu), but *gem*-dialkoxy enynes **11**−**13** were produced instead of product **3** (Supporting Information).

After that, the scope of allenic orthoesters **4** was also examined. Similarly, the substrates bearing different functional groups on the phenyl ring such as methoxyl, fluoro, trifluoromethyl, chloro, cyano, and so on were all well tolerated and converted to the corresponding allenic orthoesters in satisfactory yields under the optimized conditions (Figure 2). It should be noted that the thienyl-substituted 1,3-enyne was also converted to compound **4l** in 56% isolated yield. In addition, different ROKs (R = Et, ^{i}Pr, ^{t}Bu) were tried as nucleophiles. However, the corresponding products were not formed because of transesterification.

To further demonstrate the utility of the orthoesters, the synthetic applications of product **3a** were investigated. First, the gram-scale synthesis of **3a** was realized under the standard reaction conditions. Next, the cyanation of orthoester **3a** with cyanoamine and $SiCl_3OTf$ furnished the corresponding cyanoacetal **5** in high yield (Scheme 2, (2)).[12] Enynic esters are known as one kind of active and useful enyne in organic synthesis. However, aryl-substituted enynic esters were not stable enough for isolation. Therefore, a common method to use this kind of active compound is preparing its dilute solutions.[13] Herein the enynic ester (**3a**) can easily be handled with concentrated HCl to provide the enynic ester product in high yield. Therefore, the aryl-substituted enynic esters

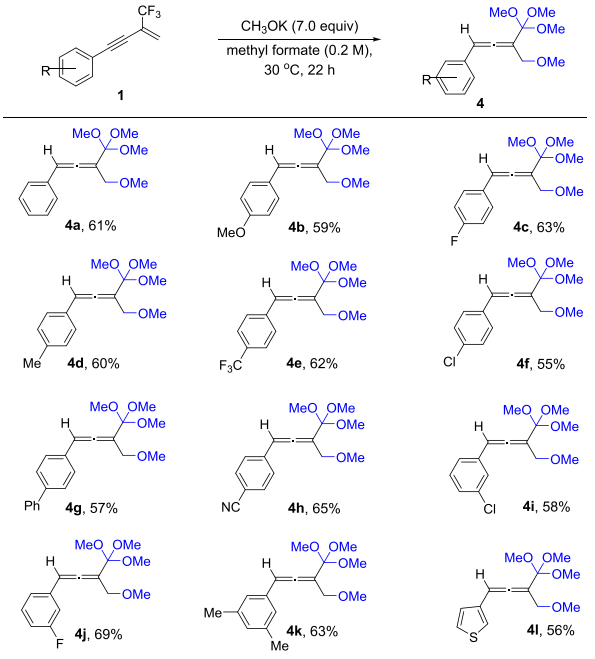
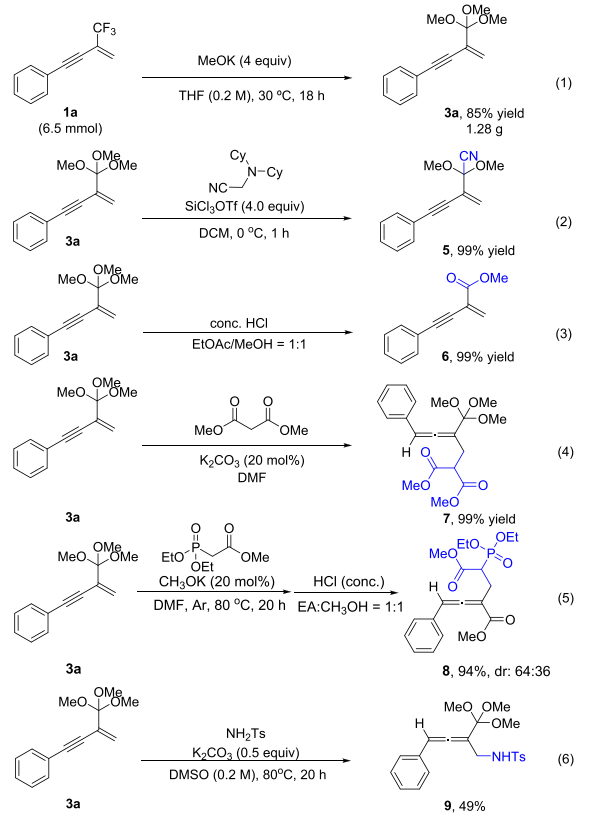


Figure 2. Substrate scope for the synthesis of allenic orthoester **4**. Unless noted otherwise, the reaction was conducted according to the following conditions: **1** (0.2 mmol) and CH_3OK in anhydrous methyl formate (1.0 mL) were stirred at 30 °C (oil bath) for 22 h under an argon atmosphere. Isolated yield.

Scheme 2. Transformation of Enynic Orthoester 3a to Different Functionalized Allenes



obtained here can be used as good candidate precursors of the enynic esters. Furthermore, when **3a** was treated with dimethyl malonate in dimethylformamide (DMF), the

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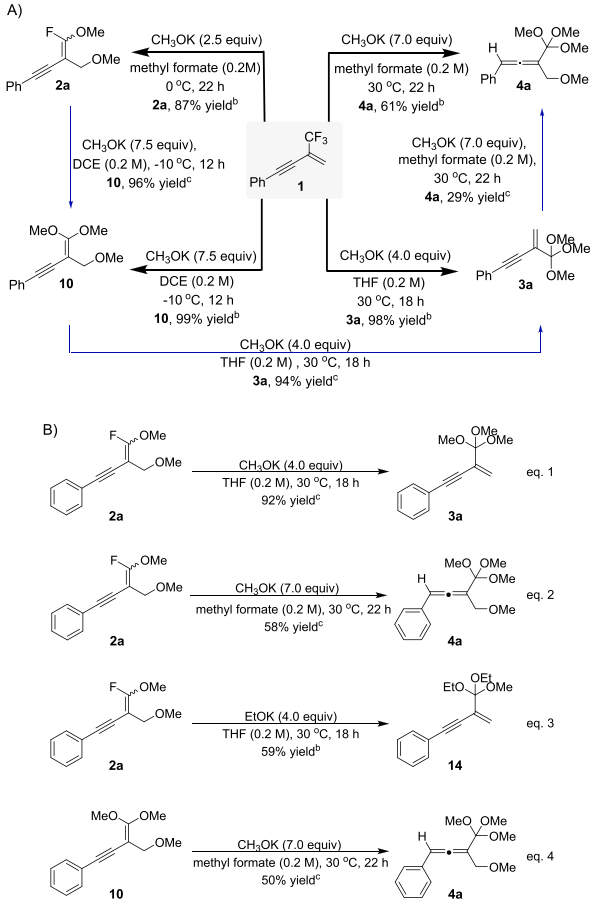
corresponding allenic orthoester product **7** was formed in 99% yield (Scheme 2, (4)). Similarly, when the nucleophile was changed to methyl 2-(diethoxyphosphoryl)acetate, the corresponding byproduct could be generated and further converted to functionalized allenic ester **8** in 94% yield in the presence of concentrated HCl (aq). Finally, the enynic ester (**3a**) reacted with *p*-toluenesulfamide under basic conditions to furnish **9** in 49% yield. The above examples show that the enynic orthoester is a very flexible building block to construct various functionalized allenes.

To disclose the possible mechanisms from the 2-trifluoromethyl-1,3-enyne to the enynic and allenic orthoesters, the controlled experiments were carried out, and the results are shown in Scheme 3. Mono-fluoro-substituted enyne **2a** (Scheme 3A) was formed in 87% yield via the treatment of **1a** with 2.5 equiv of CH_3OK in methyl formate at 0 °C. On the contrary, the defluoromethoxylation product *gem*-dimethoxy enyne **10** (Scheme 3A) was obtained in excellent yield using 7.5 equiv of CH_3OK in 1,2-dichloroethane (DCE) at −10 °C from compound **1**. The controlled experiment proved that **10** (Scheme 3A) could also be generated from the mono-fluoro-substituted enyne compound **2a** under the same reaction conditions. Similarly, from the *gem*-dimethoxy enyne **10**, the enynic orthoester **3a** (Scheme 3A) was smoothly formed under the standard reaction conditions (Table 1, entry 11). From the enynic orthoester **3a**, the allenic orthoester **4a** (Scheme 3A) was also obtained in 29% yield under the developed reaction conditions (Table 1, entry 17). To better validate the conclusion, some additional control experiments were administered. First, under the standard reaction conditions (Table 1, entry 11), a 92% yield of enynic orthoester **3a** (Scheme 3B, eq 1) was achieved from mono-fluoro-substituted enyne **2a**, and a 59% yield of **14** (Scheme 3B, eq 3) could be formed by changing MeOK to EtOK. In addition, mono-fluoro-substituted enyne **2a** could convert to allenic orthoester **4a** (Scheme 3B, eq 2) in 58% yield under the developed reaction conditions (Table 1, entry 17). We found that a 50% yield of allenic orthoester **4a** (Scheme 3B, eq 4) could be achieved from *gem*-dimethoxy enyne **10** under the developed reaction conditions.

Scheme 3. Mechanistic Study of the 2-Trifluoromethyl-1,3-enyne to Form the Enynic and Allenyl Orthoesters[a]



[a]Unless noted otherwise, the reaction was conducted according to the following conditions: **1** (0.2 mmol) and CH_3OK in anhydrous solvent (1.0 mL) were stirred for the indicated time at the indicated temperature under an argon atmosphere. [b]Isolated yield. [c]Yield was determined by ^1H NMR using mesitylene as the internal standard.

In summary, we have developed selective and diverse defluoromethoxylation reactions of trifluoromethyl-substituted 1,3-enynes. Under mild reaction conditions, the enynic and allenyl orthoesters were obtained in good to excellent yields. In addition, the transformations of enynic orthoesters were also studied, which proved this class of compounds to be efficient and flexible "platform molecules" for the synthesis of various functionalized allenes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00311.

Experimental details, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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