JOC Note

TBAF-Mediated Aldol Reaction of β-Allenoates: Regio- and Stereoselective Synthesis of (2*E*,4*E*)-4-Carbinol Alkadienoates

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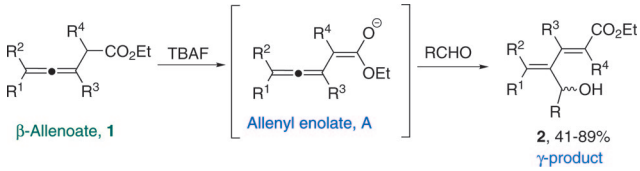
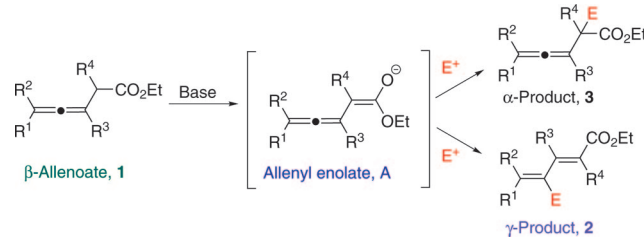


The aldol reaction of β-allenoate with use of a commercial THF solution of tetrabutylammonium fluoride (TBAF) yielded polyfunctionalized (2*E*,4*E*)-4-carbinol alkadienoate—a valuable building block—in highly regio- and stereoselective fashion.

Functionalized 2,4-alkadienoates are important building blocks in organic chemistry; they are widely used in synthesis and a frequent motif in natural products.[1,2] In this vein, carbinol alkadienoates would be expected to enhance the synthetic value of 2,4-alkadienoates; indeed carbinol alkadienoates have been intermediates in natural product syntheses, but their preparation needed multiple steps or showed low stereoselectivity.[3] We were intrigued by the synthesis of the 4-regioisomer, where the carbinol substituent is strategically placed in the diene moiety (i.e., **2**). Although an obvious disconnection for the synthesis of **2** is the aldol reaction of an extended enolate **A** with an aldehyde (E^+ = RCHO) (Scheme 1), this reaction is hitherto unknown. Herein we report a new role of allenyl enolate **A** as intermediate in the regio- and stereoselective synthesis of (2*E*,4*E*)-4-carbinol alkadienoate **2**, starting from a readily available β-allenoate **1**, under very mild conditions. To the best of our knowledge, this is the first report where β-allenoate **1** has been functionalized through trapping of an allenyl enolate with a carbon electrophile.

SCHEME 1. Regio- and Stereoselective Considerations in the Base-Mediated Reactions of β-Allenoate 1



One advantage of using β-allenoate **1** as the starting material is that it is readily synthesized by a Claisen rearrangement of a propargylic alcohol and an ortho ester.[4] If a strong enough base is present, the deprotonation of **1** would produce allenyl enolate **A**, which, in turn, could either isomerize to the corresponding diene **4** (structure in Table 1 footnote) and react further, or it could react with an electrophile E^+, like an aldehyde or an imine, to give α- or γ-products **2** or **3** (Scheme 1). Although some reactions of allenyl enolates have been studied, most of these derived from 1,6-additions of copper reagents to alkenynones or alkenynoates.[5] Reactions of these allenyl copper enolates with aldehydes generally favor α-products.[5,6]

The reactions of dienolates are important synthetic tools.[7] But our recent focus has been the chemistry of alkynyl enolates,

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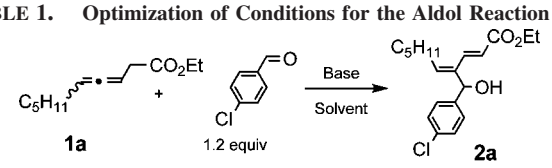
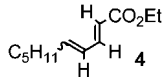
TABLE 1. Optimization of Conditions for the Aldol Reaction of 1



entry	base	base equiv	temp (°C)	time (h)	yield of **2a**[e] (%)
1	*t*-BuOK	0.2	0	4	complex mixture[b]
2	phosphazene (P_1-*t*-Bu)	0.2	0	4	complex mixture[b]
3	phosphazene (P_2-Et)	0.2	0	4	complex mixture[b]
4	LDA	1.0	−79	4	complex mixture[b]
5	TBAOH	0.2	0	4	25.0[a,b]
6	K_2CO_3	0.2	rt	4	31.5[a,d]
7	K_2CO_3	2.0	rt	4	43.9[a,d]
8	K_2CO_3	2.0	rt	16	52.3[a,d]
9	DBU	0.2	0	4	no reaction[b]
10	TEA	0.2	0	4	no reaction[b]
11	KF	0.2	0	4	no reaction[b]
12	CsF	0.2	0	4	no reaction[b]
13	TBAF	0.2	0	2	28.6[a,b]
14	TBAF	0.5	0	2	55.5[a,b]
15	TBAF	1.0	0	2	68.1[a,b]
16	TBAF	1.5	0	2	70.0[a,b]
17	TBAF	2.0	0	2	84.6[a,b]
18	TBAF	2.0	0	2	64.0
19	TBAF	2.0	0	2	70.9[c]

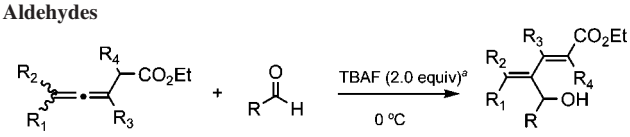
[a] ^{1}H NMR yield. [b] Reaction ran with 1.5 mL of THF as solvent. [c] With 1.0 equiv of aldehyde and 1.2 equiv of allene. [d] Reaction ran on DMF as solvent. [e] In most cases, **4** was also isolated as byproduct.



starting from α-allenyl- or propargyl-ester precursors.[8a−e] This research led to regioselective syntheses of carbinol allenoates,[8a] α,α-disubstituted α-alkynyl esters,[8b] 2-alkynyl-substituted glutaric acid derivatives,[8c] and α-fluoro propargyl esters or γ-iodoallenoates.[8d] In these syntheses, the Lewis acidity and size of the base counterion played a critical role on the regioselectivity. With this experience in mind, we screened various inorganic and organic bases at different temperatures to find the best conditions for the aldol reaction of β-allenoate **1a** (Table. 1). Employing strong bases gave rise to a complex mixture of products (entries 1−4, Table. 1), while weak bases produced no reaction, or low yields (entries 5−12, Table. 1). TBAF (commercially available as a 1 M solution in THF) at 0 °C gave the best results in the synthesis of carbinol alkadienoate **2a** (entry 17, Table. 1). The main competition was the base-promoted isomerization to 2,4-alkadienoate, **4**. The isomeric byproduct **4** has been prepared by sequential allenyl enolate formation−protonation (EtONa in EtOH) or alumina-catalyzed isomerization.[9] Different solvents were also screened (data not shown), showing that polar solvents, such as ethanol and acetonitrile, promoted the unwanted 2,4-alkadienoate isomerization, while in nonpolar solvents, such as toluene and DCM, there was no reaction.

With optimized experimental conditions in hand, we investigated the scope of the aldol reaction using various aldehydes and β-allenoates **1** with different substitution patterns (Table 2). The yields of aldol condensation were affected by the substitution pattern of the β-allenoate. Monosubstitution at the α-carbon (such as in **1a**, **1b**; **1d**, **1e**; and **1h**, **1i**) give good yields (entries 1, 2; 4, 5; and 8, 9, Table 2). Terminal β-allenoates **1c** only give moderate yield (entry 3, Table 2). This may be due to the fact that **1c** was less stable and polymerized under the basic conditions utilized. A β-allenoate disubstituted on the δ-carbon (**1g**, entry 9, Table 2) appeared to be less reactive, giving rise to the formation of its corresponding 2,4-alkadienoates, due to the steric hindrance of the γ-carbon in this molecule.[2b] Under similar conditions, the reaction of an aliphatic aldehyde (hexanal) gave the 2,4-allenoate isomer product **4** exclusively.

TABLE 2. TBAF-Mediated Reaction of β-Allenoates with Aldehydes



entry	R_1	R_2	R_3	R_4	R	time (h)	yield (%)[b]
1	H	C_5H_{11}	H	H (**1a**)	*p*-ClC_6H_4	2	70 (**2a**)
2	H	C_5H_{11}	H	CH_3 (**1b**)	*p*-ClC_6H_4	2	66 (**2b**)
3	H	H	CH_3	H (**1c**)	*p*-ClC_6H_4	2	41 (**2c**)
4	H	$CH(CH_3)_2$	H	H (**1d**)	*p*-ClC_6H_4	2	84 (**2d**)
5	H	$CH(CH_3)_2$	H	CH_3 (**1e**)	*p*-ClC_6H_4	2	82 (**2e**)
6	H	CH_2CH_3	CH_3	H (**1f**)	*p*-ClC_6H_4	5	49 (**2f**)
7		$(CH_2)_5$	H	H (**1g**)	*p*-ClC_6H_4	2	41 (**2g**)
8	H	CH_3	H	H (**1h**)	*p*-ClC_6H_4	2	89 (**2h**)
9	H	CH_3	H	CH_3 (**1i**)	*p*-ClC_6H_4	2	87 (**2i**)
10	H	CH_3	H	CH_3 (**1i**)	C_6H_5	3	68 (**2j**)
11	H	CH_3	H	CH_3 (**1i**)	*p*-BrC_6H_4	2	80 (**2k**)
12	H	CH_3	H	CH_3 (**1i**)	*p*-FC_6H_4	2	44 (**2l**)
13	H	CH_3	H	CH_3 (**1i**)	*p*-$CF_3C_6H_4$	1	81 (**2m**)
14	H	CH_3	H	CH_3 (**1i**)	*p*-$NO_2C_6H_4$	3	36 (**2n**)
15	H	CH_3	H	CH_3 (**1i**)	*p*-CNC_6H_4	3	65 (**2o**)
16	H	CH_3	H	CH_3 (**1i**)	*p*-$OCH_3C_6H_4$	6	37 (**2p**)

[a] TBAF, 1 M in THF. The reaction was conducted in the absence of additional solvent. [b] Isolated yields.

It should be noted that all the reactions in Table 2 were highly regio- and stereoselective. We did not detect either the formation of the 4-carbinol alkadienoate sterereoisomer, the product **2** with a (2*Z*)- and/or (4*Z*)-configuration, or other products arising from the lactonization of (2*Z*)-**2** in basic media.

The olefin stereochemistry of all products (**2a**−**p**) was (2*E*,4*E*); this was confirmed by an inspection of their *J* coupling constants, as well as NOESY NMR experiments. This selectivity could be explained by invoking the argument of Ma and coworkers[2b] that the steric repulsion between the bulky ester and γ-vinyl groups favors a trans stereoselective orientation of the alkadienoate. We monitored the reaction of **1a** with *p*-chlorobenzaldehyde using in situ IR spectroscopy.[10] The reaction proceeded very fast, and reached its maximum conversion after only 10 min.

To further expand the scope of this protocol, we examined the reaction of β-allenoate **1h** with an imine electrophile, *p*-toluenesulfonamide (*p*-TSA) (eq 1). Using a commercial 1 M THF solution of TBAF, we obtained only (2*E*,4*E*)-4-carbinol alkadienoate **2h**, probably because the sulfonamide hydrolyzed

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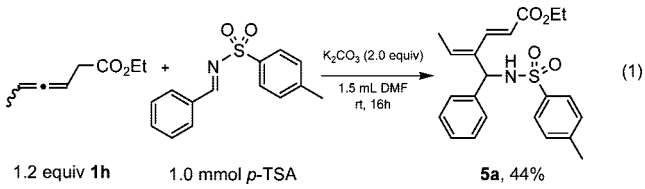
(10) The reaction was conducted with the conditions in Table 2 and was monitored by the changes in the aldehyde and alkadienoate **2a** characteristic absorption bands at 1743 and 1611 cm^{-1} (see the figure in the Supporting Information).

to the corresponding aldehyde in the presence of the water present in commercial TBAF (~3−5% H_2O content). Dryer conditions (K_2CO_3 in DMF) prevented the sulfonamide hydrolysis, and led to the synthesis of (2*E*,4*E*)-4-sulfonamidomethly alkadienoate (**5a**), albeit in moderate yield.

(1)



(1)

In summary, the regio- and stereoselective synthesis of a functionalized 2,4-alkadienoate has been achieved through an aldol reaction of β-allenoate. This simple base-mediated reaction can yield hitherto unknown intermediates that could be further utilized in a variety of transformations, such as oxidations, reductions, and olefin cross-metathesis.

Experimental Section

Typical Procedure for the Preparation of (2*E*,4*E*)-4-Carbinol Dienoates: Synthesis of 2a. *p*-Chlorobenzaldehyde (70.4 mg, 0.5 mmol) was dissolved in 1.0 mL of TBAF (1 M in THF, 2 equiv, 1 mmol). The mixture was stirred in an ice bath for 3 min before compound **1a** was added dropwise. The reddish solution was stirred for 2 h. Then, saturated NH_4Cl solution (10 mL) was used to quench the reaction. After being stirred for 5 min at room temperature, the mixture was extracted with ether (2 × 20 mL). The organic layer was dried over $MgSO_4$ and the filtrate was concentrated in vacuo. The residue was purified by flash silica gel column chromatography (9:1, 8:1, 6:1, 4:1, 2:1 hexanes: ethyl acetate) to give **2a** (119.4 mg, 0.35 mmol, 70%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (3H, t, J = 7.0 Hz), 1.26 (3H, t, J = 7.0 Hz), 1.31−1.34 (4H, m), 1.46 (2H, m), 2.35 (2H, q, J = 7.5 Hz), 2.61 (1H, br s), 4.16 (2H, q, J = 7.0 Hz), 5.42 (1H, s), 5.85 (1H, d, J = 16.0 Hz), 6.14 (1H, t, J = 7.5 Hz), 7.29 (4H, m), 7.58 (1H, d, J = 16.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 14.6, 22.7, 28.2, 29.4, 31.7, 60.7, 74.3, 119.8, 128.3, 128.3, 128.9, 128.9, 133.7, 136.3, 138.2, 140.8, 140.8, 167.5; MS (EI) *m*/*z* 336 (M^+), 320, 291, 274, 263; IR (neat) ν 3435, 2956, 2857, 1709, 1691, 1489, 1282 cm^{-1}. Anal. Calcd for $C_{19}H_{25}ClO_3$: C, 67.75; H, 7.48. Found: C, 67.96; H, 7.44.

Preparation of (2*E*,4*E*)-4-Sulfonamidomethyl Dienoate, 5a. After K_2CO_3 (276.6 mg, 2.0 mmol) in 1.0 mL of DMF was stirred for 3 h at room temperature, *p*-toluenesulfonamide (*p*-TSA, 259.4 mg, 1.0 mmol) was added together with an extra 0.5 mL of DMF. Compound **1h** (169.2 mg, 1.2 equiv) was added dropwise, then the mixture was stirred at room temperature for 16 h. Saturated NH_4Cl solution (10 mL) was added to the resulting reddish mixture and after 5 min of stirring, the solution was extracted with ether (3 × 20 mL). The organic layer was extracted with distilled H_2O (3 × 20 mL) to remove the DMF and then dried over $MgSO_4$. The solvent was removed by reduced pressure and the crude product was purified by flash silica gel column chromatography (9:1, 8:1, 6:1, 4:1, 2:1 hexanes:ethyl acetate) to give **5a** (181.8 mg, 0.44 mmol, 44%) as a white solid (mp 111−113 °C). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.26 (3H, t, J = 7.0 Hz), 1.77 (3H, d, J = 7.5 Hz), 2.42 (3H, s), 4.16 (2H, q, J = 7.0 Hz), 5.04 (1H, d, J = 7.5 Hz), 5.22 (1H, d, J = 8.0 Hz), 5.64 (1H, d, J = 16.0 Hz), 5.97 (1H, q, J = 7.5 Hz), 7.09 (2H, m), 7.24 (4H, m), 7.49 (1H, d, J = 16.0 Hz), 7.63 (2H, d, J = 16.0 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 14.2, 14.5, 21.7, 59.6, 60.7, 119.6, 127.3, 127.3, 127.5, 127.5, 128.1, 129.0, 129.0, 129.7, 129.7, 134.1, 136.5, 137.6, 137.9, 139.2, 143.6, 167.2; MS (EI) *m*/*z* 398 (M^+), 353, 324, 260, 229; IR (neat) ν 3275, 2981, 2926, 1710, 1281, 1160 cm^{-1}. Anal. Calcd. for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31. Found: C, 65.91; H, 6.29.

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Supporting Information Available: Experimental procedures, characterization, spectroscopic spectra for **2** and **5**, and in situ IR spectroscopy (Figure SI1). This material is available free of charge via the Internet at http://pubs.acs.org.

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