Tandem Reaction of Enynyl Acetate: Precursor of Allenyl Ketones

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Deacetylation of enynyl acetates under basic conditions allows convenient access to reactive allenyl ketones, which can then undergo 1,4-addition of nucleophiles to furnish β,γ-unsaturated ketones. Benzofuran and indole derivatives have also been obtained from enynyl acetates with an o-hetero-atom-substituted aryl group via intramolecular 1,4-addition.

Key words alkyn; allenyl ketone; tandem reaction; enynyl acetate; furan; indole

Reactions of functionalized allenes have been investigated in the past two decades.1–8 Among them, α-allenyl carbonyl compounds are important building blocks for a variety of organic transformations. Cycloisomerization of allenyl ketones (Chart 1) in the presence of a transition metal catalyst is an efficient way to build substituted furans.9–16 It was first reported by Marshall and Robinson9) and later by Hashmi.11) In 2003, Gevorgyan and colleagues reported copper-catalyzed cycloisomerization of thioallenyl ketones via 1,2-migration of the thiogroup17) and later developed a series of metal-catalyzed 1,2-migration/cycloisomerization methodology toward multisubstituted 3-seleno,18) acyloxy,19) halo,20) aryl, and alkyl-furans.21) In some of those studies, alkynyl ketones or propargyl ketones were used as precursors of allenyl ketones, involving propargyl-allenyl isomerization prior to 1,2-migration/cycloisomerization.13,15,16

During the course of our study on exploration of a new tandem reaction triggered by the reactivity of an alkyne triple-bond, we reported multisubstituted furan formation from (E)- or (Z)-enynyl acetates,22 which were prepared regio- and stereoselectively by Sonogashira coupling reaction of (E)- or (Z)-iodoenyl acetates, obtained from the reaction of alkyne with N-iodosuccinimide (NIS) and acetic acid23) (Chart 2). Treatment of (E)-enynyl acetates 2 and (Z)-enynyl acetates 3 with NIS afforded multisubstituted furans 5 via the common iodoallenyl ketones 4 regardless of the double-bond geometry of starting enynyl acetate.24) The proposed reaction pathway involves the formation of iodoallenyl ketone 4 by electrophilic addition of NIS to the triple-bond of enynyl acetate followed by 1,2-halogen migration25) of the resulting iodoallenyl ketone and cycloisomerization.

This result encouraged us to explore the possibility of enynyl acetates as precursors of allenyl ketones and application for a new tandem reaction. Hammond and colleagues reported regioselective reactions of alkynyl enolate25,26) in which alkynyl enolates were generated by deprotonation of allenyl ketone or propargyl ketone. We hypothesized that
deacetylation of enynyl acetate and subsequent trapping with an electrophile at \( \gamma \)-carbon would afford allenyl ketone via an alkynyl enolate intermediate (Chart 3). This resulting allenyl ketone is too electron-deficient, and successive 1,4-addition of a nucleophile would give \( \beta,\gamma \)-unsaturated ketone. In the case with enynyl acetates possessing a nucleophilic moiety on the alkynyl substituent, cyclic compounds could be obtained via intramolecular 1,4-addition. Herein we report the reactions of enynyl acetate via an alkynyl enolate intermediate.

First, deacetylation of enynyl acetate was carried out under basic conditions (Table 1). Treatment of enynyl acetate 6 with potassium carbonate (K\(_2\)CO\(_3\)) in a primary alcohol such as methanol, ethanol, or allyl alcohol afforded 1,4-addition product 7 together with a small amount of 9\(_a\). The reaction in 2-propanol did not lead to the desired product after 24h at 60°C, but gave allenyl ketone 8 to carbonyl-conjugated alkene 11 occurred under the basic reaction conditions (Table 2, entry 1). As shown in Fig. 1, the geometry of olefinic double bond of (Z)-12 was confirmed as cis by NOESY experiment between two methylene groups (vide supra). Mixed solvent systems (MeOH/tetrahydrofuran (THF)), MeOH/MeCN, and MeOH/1,2-dichloroethane (DCE)) resulted in poorer E/Z selectivity to give a 1:1 ratio of 12 (entries 2–4). Use of lithium hydroxide instead of K\(_2\)CO\(_3\) slightly improved the E/Z selectivity (entry 5). When a 1:0.5 mixture of (E)- and (Z)-12 was subjected to LiOH/MeOH conditions, E/Z ratio of 12 was 1:0.15 after 24h, suggesting that (E)- and (Z)-12 may be in equilibrium via enol intermediate. In contrast, isomerization of compound 8\(_a\) was not observed after 24h. The length of the tether of 9 affected the product distribution. The major products from 9\(_b\) were methanol adducts 13\(_a\) together with a small amount of 11 (entry 6). Enynyl acetate 9\(_c\) exclusively gave 13\(_b\) probably due to the difficulty of intramolecular cyclization (entry 7).

In order to facilitate intramolecular cyclization, enynyl acetates 14 with an \( \omega \)-heteroatom-substituted aryl group were prepared (Table 3). As expected, enynyl acetate with \( \omega \)-ace- toxyphenyl group 14\(_a\) underwent deacetylation at two acetyl groups followed by intramolecular cyclization to give the de-
The NMR data are described as follows: chemical shift, multiplet \([\delta (ppm)]\), coupling constant \([J (Hz)]\), relative integration value. Infrared spectra were obtained with an FT spectrometer. Mass spectroscopy experiments were performed on a double-focusing mass spectrometer by using electron ionization (EI) as the ionization mode. Analytical thin layer chromatography was performed on Merck silica gel 60 F254 TLC plates.

General Procedure for Deacetylation To a solution of enynyl acetate 6 (0.15 mmol) in alcohol (1.5 mL) was added \(\text{K}_2\text{CO}_3\) (0.45 mmol), and the mixture was stirred at room temperature until completion. Water was added to the reaction mixture and extracted with EtOAc (two times). The combined organic solution was washed with brine, dried over anhydrous \(\text{Na}_2\text{SO}_4\), and concentrated at reduced pressure. Column chromatography on silica gel using hexane/ethyl acetate as an eluent afforded \(\beta\gamma\)-unsaturated ketones 8.

\(1-(4\text{-Methoxyphenyl})-2-(2\text{-phenyl}-1\text{H}-2\text{H})\text{-vinylidene}6\text{-unsaturated ketones}\). 

**Experimental**

**General** The \(^1\text{H}\) - and \(^13\text{C}\)-NMR spectroscopic data were recorded with a 600 MHz spectrometer. Chemical Shifts [\(\delta\) (ppm)] are reported in ppm relative to an internal tetramethylsilane standard (\(\delta 0.00\) ppm) for \(^1\text{H}\)-NMR spectra and to the solvent signals (\(\delta 77.16\) ppm for \(\text{CDCl}_3\)) for \(^13\text{C}\)-NMR spectra. The NMR data are described as follows: chemical shift, multiplicity [s (singlet), d (doublet), t (triplet), q (quartet), br (broad), and m (multiplet)], coupling constant \([J (Hz)]\), relative integration value. Infrared spectra were obtained with an FT spectrometer. Mass spectroscopy experiments were performed on a double-focusing mass spectrometer by using electron ionization (EI) as the ionization mode.
(E)-2-Butyl-3-methoxy-1-(4-methoxyphenyl)cycloct-3-en-1-one (8c) Pale yellow oil. 1H-NMR (600 MHz, CDCl3): δ: 7.60 (d, J = 7.7 Hz, 2H), 6.80 (d, J = 8.9 Hz, 2H), 4.36 (s, 3H), 3.80 (s, 3H), 2.21–2.14 (m, 2H), 1.78 (br, 1H), 1.58–1.50 (m, 2H), 1.41–1.32 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H). 13C-NMR (150 MHz, CDCl3): 168.8, 159.9, 145.8, 128.9, 127.7, 113.3, 112.6, 94.3, 75.9, 61.7, 55.3, 31.3, 31.3, 30.1, 22.5, 20.9, 16.3, 14.0. IR (CHCl3, cm⁻¹) 3624, 2960, 2873, 1755, 1608, 1511, 1465, 1370, 1297, 1252, 1177, 1087, 1034. MS (EI): m/z = 316 (M⁺). HR-MS (EI): m/z Calcd for C₂₀H₂₄O₄: 316.1675. Found: 316.1679.

(2)-2-(1-Ethoxy-2-phenylvinyl)-1-(4-methoxyphenyl)hex-1-en-1-one (8d) Orange oil. 1H-NMR (600 MHz, CDCl3): δ: 7.65 (d, J = 7.3 Hz, 3H), 7.60 (d, J = 7.5 Hz, 2H), 7.29–7.24 (m, 1H), 6.72 (d, J = 7.8 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 4.36 (s, 3H), 3.70 (t, J = 5.9, 5.9 Hz, 2H), 2.45 (t, J = 6.9 Hz, 2H), 2.21 (s, 3H), 1.84–1.71 (m, 2H), 1.45–1.42 (m, 1H), 1.17–1.14 (m, 3H), 0.93 (t, J = 7.3 Hz, 3H). 13C-NMR (150 MHz, CDCl3): 168.9, 159.6, 145.9, 128.9, 127.7, 113.3, 112.6, 94.3, 75.9, 61.7, 55.3, 31.3, 31.3, 30.1, 22.4, 20.9, 16.3, 14.0. IR (CHCl3, cm⁻¹) 3624, 2960, 2873, 1755, 1608, 1511, 1465, 1370, 1297, 1252, 1177, 1087, 1034. MS (EI): m/z = 330 (M⁺). HR-MS (EI): m/z Calcd for C₂₀H₂₂O₃: 330.1681. Found: 330.1625.
(E)-2-Butyl-7-hydroxy-3-methoxy-1-(4-methoxyphenyl)-hept-3-en-1-one (13a) Colorless oil. H-NMR (600 MHz, CDCl3) δ: 7.95 (d, J = 8.9 Hz, 2H), 6.90 (d, J = 8.91 Hz, 2H), 4.41 (t, J = 7.3 Hz, 1H), 4.14 (t, J = 7.1 Hz, 1H), 3.85 (s, 3H), 3.68 (t, J = 6.3 Hz, 2H), 3.40 (s, 3H), 2.32–2.19 (m, 2H), 2.05–1.96 (m, 1H), 1.77–1.60 (m, 3H), 1.46 (br, 1H), 1.42–1.44 (m, 4H), 0.90 (t, J = 7.1 Hz, 3H). 13C-NMR (150 MHz, CDCl3) δ: 177.7, 163.3, 155.3, 130.1, 113.6, 98.4, 62.5, 55.5, 54.8, 49.7, 33.7, 30.0, 29.2, 23.0, 14.2. IR (CHCl3, cm−1): 2985, 1675, 1659, 1601, 1576, 1465, 1256, 1240, 1171, 1033. MS (EI): m/z = 320 (M+). HR-MS (EI): m/z c Alcal for C28H36NO2: 463.2359. Found: 463.2361.

(2-Benzononyl-2-y1)-(4-methoxyphenyl)hexan-1-one (15a) Pale yellow oil. H-NMR (600 MHz, CDCl3) δ: 8.03 (d, J = 8.9 Hz, 2H), 7.47 (d, J = 7.6 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.21 (dd, J = 8.1, 7.4 Hz, 1H), 7.17 (dd, J = 7.6, 7.4 Hz, 1H), 6.92 (d, J = 8.9 Hz, 2H), 6.54 (s, 1H), 4.76 (t, J = 7.3 Hz, 1H), 3.85 (s, 3H), 2.24–2.16 (m, 1H), 2.10–2.01 (m, 1H), 1.39–1.30 (m, 4H), 0.88 (t, J = 6.6 Hz, 3H). 13C-NMR (150 MHz, CDCl3) δ: 195.9, 163.7, 156.8, 154.8, 131.1, 129.6, 128.8, 123.8, 122.8, 110.4, 111.2, 103.8, 55.6, 47.0, 31.3, 29.9, 22.8, 14.1. IR (CHCl3, cm−1): 2960, 1676, 1601, 1576, 1512, 1454, 1420, 1315, 1260, 1173, 1032. MS (EI): m/z = 322 (M+). HR-MS (EI): m/z calcd for C26H29NO2: 322.1569. Found: 322.1564.

(2-(1H-Indol-2-yl)-1-(4-methoxyphenyl)hexan-1-one (15b) Red oil. H-NMR (600 MHz, CDCl3) δ: 8.67 (s, 1H), 8.03 (d, J = 8.6 Hz, 2H), 7.53 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.12 (dd, J = 8.1, 7.1 Hz, 1H), 7.05 (dd, J = 7.8, 7.1 Hz, 1H), 6.92 (d, J = 8.6 Hz, 2H), 6.40 (s, 1H), 4.83 (t, J = 7.4 Hz, 1H), 3.85 (s, 3H), 2.15–2.06 (m, 1H), 1.98–1.89 (m, 1H), 1.39–1.25 (m, 4H), 0.84 (t, J = 6.6 Hz, 3H). 13C-NMR (150 MHz, CDCl3) δ: 199.4, 164.0, 136.5, 136.5, 131.1, 129.5, 128.3, 121.7, 120.1, 119.8, 114.1, 110.1, 105.5, 55.7, 46.1, 33.9, 29.9, 22.7, 14.0. IR (CHCl3, cm−1): 3452, 2960, 1663, 1601, 1576, 1512, 1456, 1491, 1262, 1170, 1032. MS (EI): m/z = 321 (M+). HR-MS (EI): m/z calcd for C26H29NO2: 321.1729. Found: 321.1735.

tert-Butyl 2-(1-(4-Methoxyphenyl)-1-oxohexan-2-yl)-1H-indole-1-carboxylate (15c) Colorless oil. H-NMR (600 MHz, CDCl3) δ: 8.02 (dd, J = 8.9, 1.2 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.22 (dd, J = 8.4, 7.3 Hz, 1H), 7.16 (dd, J = 7.6, 7.3 Hz, 1H), 6.89 (d, J = 8.9, 1.1 Hz, 2H), 6.43 (d, 1H), 5.64 (t, J = 6.8 Hz, 1H), 3.83 (s, 3H), 2.17–2.08 (m, 1H), 1.95–1.85 (m, 1H), 1.70 (s, 9H), 1.47–1.29 (m, 4H), 0.88 (t, J = 7.1 Hz, 3H). 13C-NMR (150 MHz, CDCl3) δ: 197.6, 163.3, 150.9, 140.3, 136.4, 131.1, 130.0, 129.3, 123.8, 122.8, 120.5, 115.7, 113.8, 108.9, 84.4, 55.4, 46.1, 33.0, 30.3, 28.4, 23.0, 14.1. IR (CHCl3, cm−1): 2960, 1730, 1675, 1601, 1511, 1452, 1371, 1328, 1254, 1171, 1119, 1082, 1033. MS (EI): m/z = 421 (M+). HR-MS (EI): m/z calcd for C28H34NO2: 421.2253. Found: 421.2255.

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Conflict of Interest The authors declare no conflict of interest.

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