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TBAF-catalyzed cyclization of 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates

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Abstract

Tetrabutyl ammonium fluoride (TBAF) was found to be capable of catalyzing the intramolecular hydroalkoxylation of 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates. The reaction could be used to prepare 2,5-substituted THF rings and 2,6-substituted THP rings.

Keywords: Tetrabutyl ammonium fluoride; Et_3SiH; Tetrahydrofuran; Tetrahydropyran

The saturated five-membered and six-membered oxygenated heterocycles are important structural motifs which are found ubiquitously in natural products. Great efforts have been made to develop efficient methods for the synthesis of these ring structures [1]. The tetrahydrofuran (THF) and tetrahydropyran (THP) rings can be constructed by the intramolecular Michael-type addition of oxygen nucleophiles to α,β-unsaturated ketones or esters [1e]. This methodology has been applied to the oxo-Michael addition to electron-deficient carbon–carbon triple bonds [2], and the intramolecular hydroalkoxylation of 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates can be used to prepare the synthetically useful 2-tetrahydrofurylideneacetates [3–5], and β-pyranoacetal esters [5], respectively. Recently we found that tetrabutyl ammonium fluoride (TBAF) could catalyze the hydroalkoxylation of 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates. Herein we wish to report our results.

The TBAF-catalyzed cyclization of 6-hydroxyhex-2-ynoates was carried out by treating 6-hydroxyhex-2-ynoates (**1**) with TBAF in THF at refluxing temperature. The reaction was complete in 15 minutes [6], and products **2** were obtained in good yields with high stereoselectivity. Only the *E*-enol ethers were obtained (Fig. 1). Similarly, 7-hydroxyhept-2-ynoates **3** were transformed to the corresponding six-membered 2-tetrahydropyrylideneacetates **4** under the same reaction conditions (Fig. 2). This result is noteworthy in that the transformation from **3** to **4** did not take place under basic conditions [3]. Compounds **4** were generated as mixtures of *E*-and *Z*-enol ethers, with the *Z*-enol ethers being the major products [7,8]. Since the *E*-isomers were thermodynamically more stable than the *Z*-isomers for compounds **2** [5], these results suggest that for compounds **4**, the *Z*-configuration might be thermodynamically more favored.

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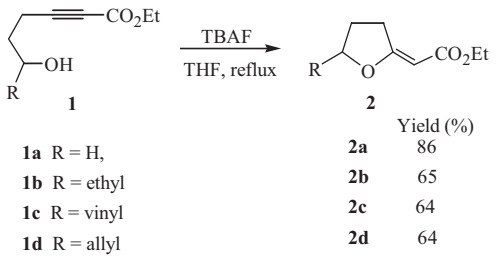


Fig. 1. TBAF-catalyzed cyclization of 6-hydroxyhex-2-ynoates.

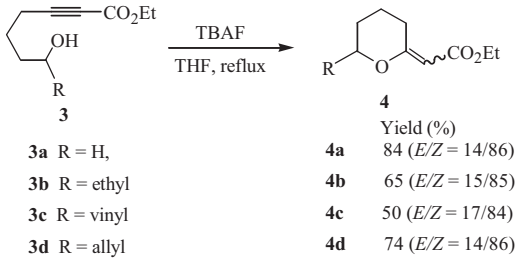


Fig. 2. TBAF-catalyzed cyclization of 7-hydroxyhex-2-ynoates.

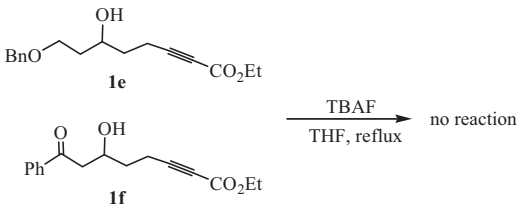
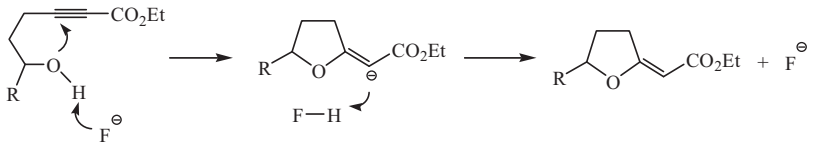


Fig. 3. The result with substrates **1e** and **1f**.

It was reported previously that HF-pyridine could promote the intramolecular addition of silyl group-protected oxygen to α,β-unsaturated ketones [9]. But we have not found any example in literature for the F^--catalyzed nucleophilic addition of hydroxyl group to electron deficient carbon–carbon multiple bonds. Our results show that this type of reactions could happen to 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates. However, when compound **1e** or **1f** was used as the substrate, the reaction failed to take place (Fig. 3). On the basis of these results, a tentative mechanism was proposed to rationalize the TBAF-catalyzed cyclization (Scheme 1). We speculate that the unreactiveness of **1e** or **1f** might be due to the reason that the incorporation of another oxygen-containing group near the hydroxy group would lead to the formation of intramolecular hydrogen bond, and thus obstruct the action of F^- on the OH hydrogen.

Compounds **2** and **4** incorporate an exocyclic double bond, which could be reduced to generate the corresponding 2,5-substituted THF rings and 2,6-substituted THP rings. The nucleophilic addition of hydride to cyclic oxocarbenium ions provides an efficient method to fulfill this task. It has been reported that oxygenated heterocycles could be prepared via the reductive-cyclization of hydroxyketones or diketones by using Et_3SiH as reducing agent and a Lewis acid as catalyst [1a,10−12]. We employed this protocol to effect the reduction of **2** and **4** [13]. The results are shown in



Scheme 1. Proposed mechanism for TBAF catalysis.

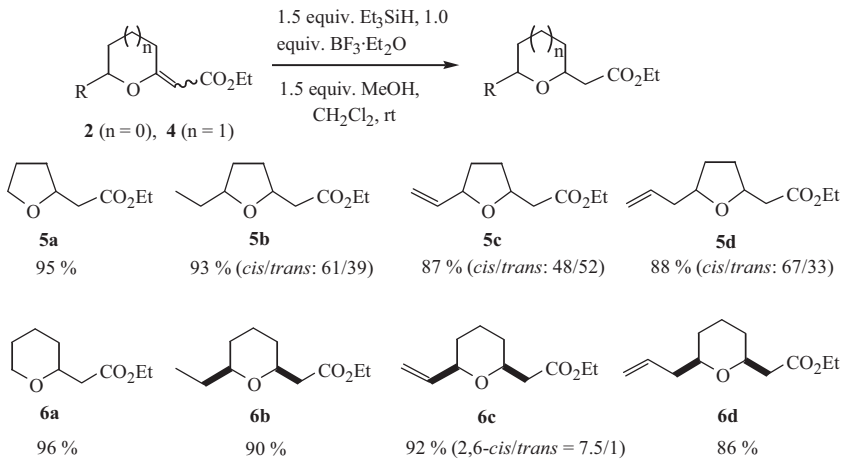


Fig. 4. Reduction of **2** and **4**.

Fig. 4. The reactions proceeded very well with $BF_3{\cdot}Et_2O$ as catalyst, and the reduction products were obtained in good to excellent yields. For the transformations from **2** to **5,** both the 2,5-*cis* and 2,5-*trans* diastereoisomers were generated, but the stereoselectivity was low [14]. On the other hand, the reactions of **4b–4d** led to the formation of **6** with high stereoselectivity. **6b** and **6d** were only obtained as the *cis*-isomers after silica-gel chromatography. The stereoselectivity was somewhat lower for the formation of **6c**, but still the *cis*-**6** was largely favored over its *trans*-counterpart. These results, the high selectivity for THP rings and low selectivity for THF rings, were consistent with those reported in literatures [1a,10,12]. Besides the high efficiency, employing Et_3SiH as the reducing agent has the advantage of leaving the isolated C=C bond intact. As such, synthetically useful intermediates **6c** [15] and **6d** [16] were conveniently prepared from **3** in two steps.

In summary, a new method for the intramolecular hydroalkoxylation of 6-hydroxyhex-2-ynoates and 7-hydroxyhept-2-ynoates was developed by using TBAF as catalyst. This method might find application for the synthesis of THF and THP rings.

Acknowledgments

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[6] General procedure for the cyclization of **1** and **3**: To a 2 mL THF solution of **1** (or **3**) (0.5 mmol) was added 0.1 mL of TBAF (1 mol/L). The mixture was stirred at refluxing temperature for 15 min. Then the reaction mixture was poured into 5 mL H_2O, and the product was extracted with Et_2O (3 × 15 mL). The combined organic phase was dried with anhydrous Na_2SO_4, and after filtration was concentrated under reduced pressure. The residual was treated with silica gel chromatography to give the product. Selective spectroscopic data of the products: **2d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81–5.74 (m, 1H), 5.27 (s, 1H), 5.17–5.11 (m, 2H), 4.46–4.43 (m, 1H), 4.12 (q, 2H, *J* = 7.2 Hz), 3.30–3.23 (m, 1H), 3.00–2.90 (m, 1H), 2.47–2.32 (m, 2H), 2.19–2.14 (m, 1H), 1.77–1.72 (m, 1H), 1.25 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.3, 168.7, 132.9, 118.3, 89.4, 83.1, 59.2, 39.1, 30.4, 28.5, 14.5. EI-MS *m/z* (rel. int., %): 196 (M^+, 14), 155 (37), 127(26), 69 (100), 41 (78). *Z*-**4d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88–5.78 (m, 1H), 5.11–5.04 (m, 2H), 4.63–4.65 (m, 1H), 4.16 (q, 2H, *J* = 7.2 Hz), 3.91–3.85 (m, 1H), 3.00 (s, 2H), 2.45–2.30 (m, 1H), 2.28–2.23 (m, 1H), 2.09–1.96 (m, 2H), 1.83–1.78 (m, 1H), 1.61–1.48 (m, 1H), 1.26 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 147.6, 134.3, 117.0, 98.7, 75.1, 60.7, 40.4, 39.1, 26.3, 20.0, 14.2. EI-MS *m/z* (rel. int., %): 210 (M^+, 30), 167 (27), 95 (68), 80 (100), 55 (72), 40 (98).

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[13] General procedure for the reduction of **2** and **4**: To a 2 mL CH_2Cl_2 solution of 0.5 mmol **2** (or **4**) were added consecutively 0.75 mmol of CH_3OH, 0.75 mmol of Et_3SiH and 0.5 mmol of $BF_3{\cdot}Et_2O$. The mixture was stirred at room temperature for about 30 min. After the reaction finished as indicated by TLC, the solvent was removed under reduced pressure, and the residual was subjected to silica gel chromatography to give the product. Selective spectroscopic data of the products: 2,5-*cis*-**5d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83–5.76 (m, 1H), 5.10–5.03 (m, 2H), 4.26–4.23 (m, 1H), 4.15 (q, 2H, *J* = 7.2 Hz), 3.94–3.91 (m, 1H), 2.65–2.59 (m, 1H), 2.47–1.94 (m, 5H), 1.63–1.56 (m, 2H), 1.26 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 134.7, 116.9, 78.8, 75.4, 60.3, 41.1, 40.2, 30.9, 30.1, 14.1. 2,5-*trans*-**5d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.83–5.76 (m, 1H), 5.10–5.03 (m, 2H), 4.38–4.34 (m, 1H), 4.15 (q, 2H, *J* = 7.2 Hz), 4.11–4.03 (m, 1H), 2.65–2.59 (m, 1H), 2.47–1.94 (m, 5H), 1.63–1.56 (m, 2H), 1.26 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 134.7, 116.9, 77.3, 75.0, 60.3, 40.8, 40.1, 31.7, 31.0, 14.1. EI-MS *m/z* for **5d** (rel. int., %): 199 (M + 1, 2), 157 (43), 111 (64), 83 (44), 55(59), 41 (100). HRMS (ESI): calcd. for $C_{11}H_{18}O_3$ + H = 199.1329, found: 199.1333. **6d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.84–5.75 (m, 1H), 5.07–4.98 (m, 2H), 4.14 (q, 2H, *J* = 7.2 Hz), 3.78–3.74 (m, 1H), 3.38–3.34 (m, 1H), 2.52 (dd, 1H, J_1 = 14.8 Hz, J_2 = 7.6 Hz), 2.37 (dd, 1H, J_1 = 14.8 Hz, J_2 = 7.6 Hz), 2.30–2.25 (m, 1H), 2.16–2.11 (m, 1H), 1.85–1.81 (m, 1H), 1.65–1.50 (m, 3H) 1.22 (t, 3H, *J* = 7.2 Hz), 1.21–1.15 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 135.1, 116.3, 77.5, 74.5, 60.3, 41.8, 40.7, 31.1, 30.7, 23.3, 14.2. EI-MS *m/z* (rel. int., %): 212 (M^+, 2), 171 (16), 125 (52), 97 (28), 55 (43), 41 (100).

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