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Synthesis of Functionalized 3,4-Dihydropyrans via Rearrangement of the Products of a One-Pot Diastereoselective Assembly of Ketones and Acetylene

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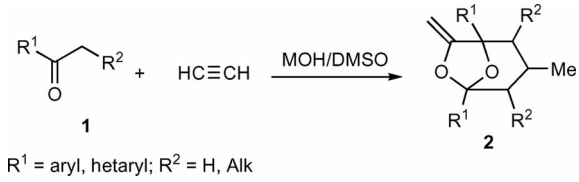
The products of the one-pot assembly of ketones and acetylene, 7-methylene-6,8-dioxabicyclo[3.2.1]octanes, congeners of an insect pheromone frontalin, undergo an acid-catalyzed rearrangement to diastereomerically pure 2-acetyl-3,4-dihydropyrans in excellent yields. The synthesis is realizable in a one-pot manner procedure directly from ketones and acetylene.

Introduction

The polyfunctionalized hydropyran scaffold is known to be a subunit of important natural products such as carbohydrates, alkaloids, polyether antibiotics and pheromones.[1] As a rule, functionalized dihydropyrans are synthesized by multi-step protocols via anionic,[2] cationic[3] or radical[4] cyclization, hetero-Diels–Alder cycloaddition,[5] dioxanone Claisen rearrangement,[6] and ring-closing metathesis of enol ethers.[7] Unlike the above approaches, in this work, we have assembled the functionalized 3,4-dihydropyrans essentially in a one-pot procedure from cheap and available starting materials (ketones and acetylene) in excellent yields.

Recently, we have found[8] that the reaction of alkyl aryl ketones **1** with acetylene in the superbase systems MOH/DMSO (M = K, Cs, 80 °C, 1 h, initial acetylene pressure 12–14 atm) affords, instead of the expected acetylenic alcohols (classic Favorsky reaction),[9] 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **2**, close congeners of well-known insect pheromone frontalin,[10] as the only products in up to 86% isolated yields (Scheme 1).

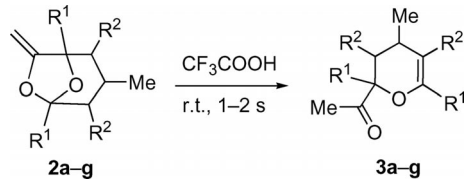


Scheme 1. One-pot assembly of 7-methylene-6,8-dioxabicyclo-[3.2.1]octanes from ketones and acetylene.

The highly reactive double bond present in bicyclooctanes **2a**–**g** promises particular synthetic benefits in term of the rearrangements and addition reactions.

Results and Discussion

Herein we report that in the presence of acids (e.g. CF_3COOH, HCl, H_2SO_4) at room temperature, bicyclooctanes **2a**–**g** rearrange instantly and completely to substituted 2-acetyl-3,4-dihydropyrans **3a**–**g** (Scheme 2).



Scheme 2. Rearrangement of 7-methylene-6,8-dioxabicyclo[3.2.1]-octanes to 2-acetyl-3,4-dihydropyrans.

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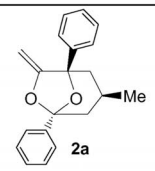
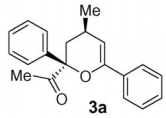
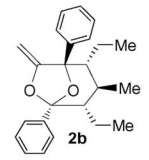
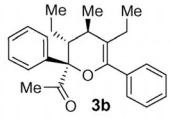
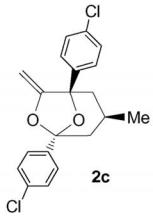
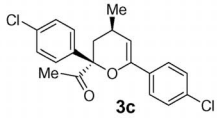
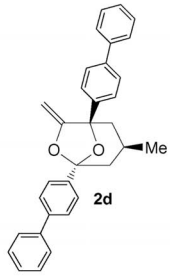
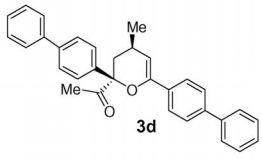
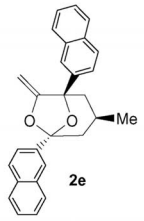
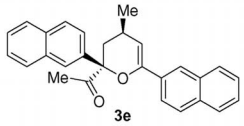
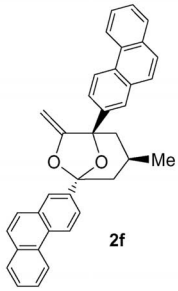
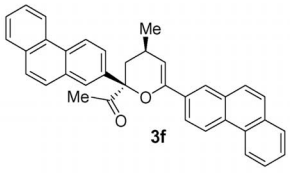
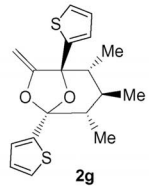
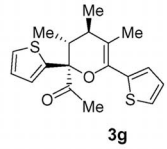
Table 1. 2-Acetyl-3,4-dihydropyrans **3a**–**g**, the products of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes **2a**–**g** rearrangement.

Bicyclooctane **2**	Dihydropyran **3**	Yield of **3** [%]
 **2a**	 **3a**	88
 **2b**	 **3b**	87
 **2c**	 **3c**	86
 **2d**	 **3d**	90
 **2e**	 **3e**	91
 **2f**	 **3f**	90
 **2g**	 **3g**	93

For example, when 10 mol-% of CF_3COOH is added to the solution of bicyclooctanes **2a**–**g** (0.2 mmol in 2 mL Et_2O, $CHCl_3$, benzene or *n*-hexane), the rearrangement takes seconds, the isolated yields of 3,4-dihydropyrans **3a**–**g** (after column chromatography) reaching 93% (Table 1).

The structure of dihydropyrans **3a**–**g** unambiguously follows from the single-crystal X-ray diffraction of their typical representative, compound **3g** (Figure 1). The dihedral angle between two thiophene cycles equals 115.0°. Maximal deviation of non-hydrogen atoms from O(1)C(4)C(5)C(6) plane is 0.04 Å [C(6) atom]. C(2) and C(3) atoms deviate from this plane at –0.54 and +0.29 Å, respectively.

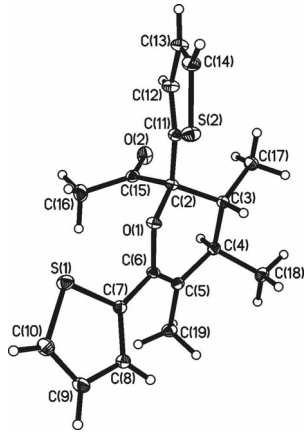


Figure 1. X-ray structure of 3,4-dihydropyran **3g**.

^1H and ^{13}C NMR spectra of compounds **3a**–**g** are in full agreement with the structure of **3g**. In the ^1H NMR spectra of **3a**, **3c**–**f**, the singlet of olefinic proton H-5 (5.35–5.65 ppm) is present. The position of the acetyl moiety of compounds **3a**–**g** has been determined using 2D HBMC spectra, where the correlation of Me-group protons with carbon atom C-2 resonance (86.4–88.8 ppm) is observed.

The important feature of the sequence **2** → **3** is its diastereoselectivity predetermined by diastereoselectivity of the preceding assembly of bicyclooctanes **2** (Scheme 1). Indeed, these compounds are assembled as one diastereomer only.[8] Consequently, dihydropyrans **3a**–**g** retain the stereochemistry of the precursors **2**: in their NMR spectra, ^1H and ^{13}C signals of only one diastereomer are discernible (no signals doubling).

The rearrangement vs. acid-addition reaction implies that after initial protonation, the fragmentation proceeds faster than possible addition of a counterion to the protonated species, i.e. allowing no addition of acid anion to the emerging carbocation (Scheme 3).

The concerted character of the rearrangement is also supported by the inability of bicyclooctanes **2a**–**g** to add carboxylic acids, hydrogen halides, water and alcohols to their double bond. Commonly, these electrophilic additions are most typical for the enol ethers chemistry.[11] In contrast, when gaseous hydrogen chloride is passed (0.6 mL/min, 30 sec) through the solution of bicyclooctanes **2a**–**g** in $CHCl_3$ (0.2 mmol in 2 mL) at room temperature, the Scheme 2 rearrangement occurs within seconds, no the ex-

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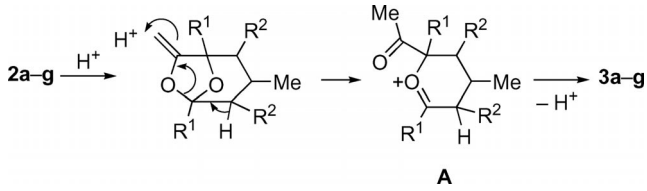
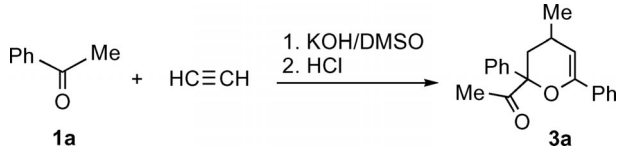


Scheme 3. Tentative concerted mode of the rearrangement of bicyclooctanes **2a**–**g** to dihydropyrans **3a**–**g**.

pected adduct (α-Cl-ether) being formed. Likewise, water and methanol in $CHCl_3$ or benzene in the presence of 10 mol-% CF_3COOH do not add to the enol ether moiety of bicyclooctanes **2a**–**g** and the same rearrangement (Scheme 2) takes place, again instantly and quantitatively.

In contrast to the chemistry of common enol ethers, which quantitatively add carboxylic acids, hydrogen halides and alcohols, the reaction found unveils a new basic facet of the reactivity of the double bond adjacent to oxygen.

Most important is that the diastereoselective straightforward synthesis of 2-acetyl-3,4-dihydropyrans **3a**–**g** can be accomplished from ketones **1a**–**g** and acetylene (without isolation and purification of bicyclooctanes **2a**–**g**) by the treatment of the ketone-acetylene crude product ($CHCl_3$ extracts) with HCl. For example, by such a way, dihydropyran **3a** has been prepared from acetophenone **1a** and acetylene in 63% isolated yield, and what is particularly synthetically valuable on a larger scale (about 40-fold scaling up) (Scheme 4).



Scheme 4. Direct synthesis of 3,4-dihydropyrans from ketones and acetylene (an example).

Conclusions

In summary, the diastereoselective synthesis of 2,6-diaryl(hetaryl)-2-acetyl-3,4-dihydropyrans via acid-catalyzed rearrangement of 7-methylene-6,8-dioxabicyclo[3.2.1]octanes, readily accessible in a pure diastereomeric form from ketones and acetylene, has been discovered. The synthesis can be realized as a one-pot procedure starting directly from ketones and acetylene. The rearrangement contributes to the chemistry of dihydropyrans, frontalin family pheromones and other regulators of insects and mammals behaviour.

Experimental Section

General Procedure for the Synthesis of 3,4-Dihydropyrans 3a–g: To the stirred solution of 6,8-dioxabicyclo[3.2.1]octane **2a**–**g** (0.2 mmol in 2 mL $CHCl_3$), 10 mol-% of CF_3COOH was added at room temperature. The reaction mixture was poured on basic (pH = 8.25) Al_2O_3 (3.0 g) and the solvent was evaporated. Pure dihydropyrans **3a**–**g** were eluted with hexane from the Al_2O_3-packed column.

2-Acetyl-2,6-diphenyl-4-methyl-3,4-dihydropyran (3a): Yellow oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 7.76 (d, J = 7.44 Hz, 2 H, H_o), 7.61 (d, J = 7.72 Hz, 2 H, $H_{o'}$), 7.42–7.29 (m, 6 H, H_{phen}), 5.37 (s, 1 H, H^5), 2.92–2.87 (m, 1 H, H^3), 2.55–2.52 (m, 1 H, H^4), 2.08 (s, 3 H, COMe), 1.44–1.38 (m, 1 H, $H^{3'}$), 1.07 (d, ^3J = 6.96 Hz, 3 H, CHMe) ppm. ^{13}C NMR (101.61 MHz, $CDCl_3$): δ = 210.0 (C=O), 148.8 (C^6), 139.6 (C_i), 135.2 ($C_{i'}$), 128.6, 138.3 (C_m, $C_{m'}$), 128.2, 127.9 (C_p, $C_{p'}$), 124.8, 124.4 ($C_{o'}$, $C_{o'}$), 105.3 (C^5), 87.1 (C^2), 39.2 (C^3), 25.0 (C^4), 24.8 (COMe), 21.1 (CHMe) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3087, 2959, 2926, 1717, 1652, 1600, 1494, 1448, 1352, 1283, 1198, 1125, 761, 699, 559 cm^{-1}. $C_{20}H_{20}O_2$ (292.37): calcd. C 82.16, H 6.89; found C 82.26, H 6.71.

CCDC-777831 (for **3g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and characterization of all compounds.

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