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Acetylene as driving and organizing molecule in the assembling reactions with chalcones in the $NaOBu^t/DMSO$ superbase system

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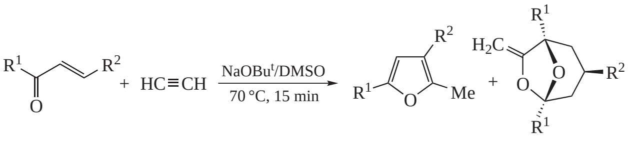
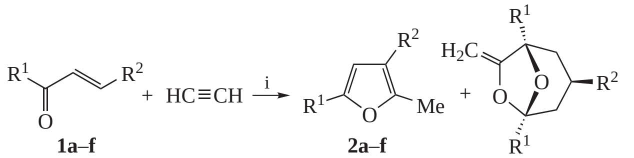
Acetylene reacts with chalcones in the $NaOBu^t/DMSO$ superbase system (3–12 atm, 70 °C, 15 min) to give, along with substituted furans, functionalized 3-*exo*-aryl-7-methylidene-6,8-dioxabicyclo[3.2.1]octanes, novel frontalin congeners, which are diastereoselectively assembled from two molecules of chalcones and one molecule of acetylene.



In last decades, acetylenes have attracted a growing interest as initiators and propagators in the self-organization of complex molecules.[1] Commonly, these processes involve several molecules of acetylene and proceed in superbase media where dual nature of acetylene,[2–4] ability of behaving simultaneously as electrophile and nucleophile, is best expressed. Among these reactions are, for instance, hydrative trimerization of acetylene to 2-vinyloxybuta-1,3-diene,[5] assembling of frontalin[6] derivatives from two molecules of acetylene and two molecules of ketones,[2] synthesis of azulenones,[7] acylcyclopentenols,[8] furans.[4] In the course of these cascades of additions and cyclizations, a number of new C–C and C–heteroatom bonds are usually formed in one synthetic operation, thereby corresponding to modern PASE (pot, atom and step economy) paradigm.[9]

Here we report another example of similar self-organization of complex molecular structures driven by acetylene, namely its reaction with chalcones.

When chalcones **1a–f** are allowed to contact with acetylene under pressure (3–12 atm) in the $NaOBu^t/DMSO$ superbase system at 70 °C for 15 min, along with substituted furans **2a–f**, 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes **3a–f** are formed (Scheme 1).[†] As far as furans **2a–f** are predictable products,[10] this communication is mainly focused on bicyclooctanes **3a–f**.



1a–f **2a–f** **3a–f**

1–3	R^1	R^2	Isolated yield (%)	
			2	**3**
a	Ph	Ph	42 (27 in KOH/DMSO)	~1 (12 in KOH/DMSO)
b	4-FC_6H_4	Ph	61	10
c	4-ClC_6H_4	Ph	34	19
d	Ph	2-furyl	28	11
e	2-furyl	2-furyl	29	12
f	Bu^t	2-furyl	62	10

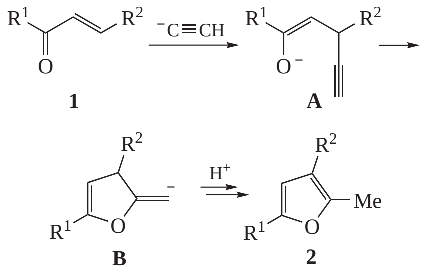
Scheme 1 *Reagents and conditions*: i, chalcone **1** (5 mmol), $NaOBu^t$ (5 mmol, 0.48 g), DMSO (50 ml), 70 °C, 15 min, initial pressure of acetylene at ambient temperature was ~10 atm (stirred reactor).

Mechanism of furan formation is shown in Scheme 2. Addition of acetylide to the double bond of chalcones **1** (acetylene acts here as a nucleophile) leads to enolate **A**, which further undergoes intramolecular cyclization *via* nucleophilic addition of oxygen-centered site of enolate **A** to the triple bond (this time acetylene molecule behaves as electrophile). Intermediate **B** thus formed would prototropically aromatize to furan **2**.

[†] The IR spectra were recorded on a Bruker IFS25 spectrophotometer. NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^1H and 100.6 MHz for ^{13}C) in $CDCl_3$ using HMDSO as internal standard. The assignment of signals in the ^1H NMR spectra was made using COSY and NOESY experiments. Resonance signals of carbon atoms were assigned based on ^1H-^{13}C HSQC and ^1H-^{13}C HMBC experiments.

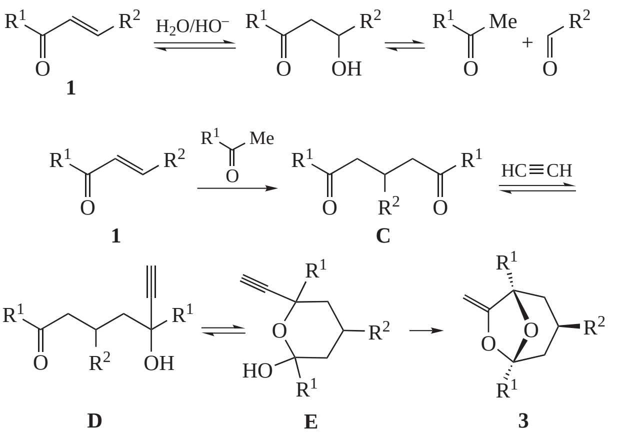
The reaction of chalcones **1** *with acetylene in the $NaOBu^t/DMSO$ system (typical procedure)*. A mixture of chalcone **1** (5 mmol) and $NaOBu^t$ (5 mmol, 0.48 g) in DMSO with water content ~0.10–0.15% (50 ml) was placed into a 0.25 dm^3 stirred reactor. The reactor was fed with acetylene under pressure (initial pressure at ambient temperature was ~10 atm) and then decompressed to atmospheric pressure to remove air. The reactor was fed with acetylene again and heated (70 °C) for 15 min. Maximal pressure of acetylene at the reaction temperature was ~12 atm and then dropped to ~3 atm as the reaction progressed. The mixture after cooling to room temperature was diluted with cold (7–10 °C) water (100 ml) and brine (20 ml) and extracted with Et_2O (7×30 ml). The combined organic extracts were washed with H_2O (3×50 ml) and dried (K_2CO_3) for 3 h. Diethyl ether was evaporated *in vacuo*. Column chromatography (SiO_2, eluent *n*-hexane/AcOEt, 50 : 1) gave pure furan **2** and bicyclooctane **3**.

5-(4-Fluorophenyl)-2-methyl-3-phenylfuran **2b**. Yield 0.769 g (61%); light yellow crystals; mp 87 °C. IR (film, ν/cm^{-1}): 3054, 2955, 2921, 2856, 1648, 1603, 1561, 1499, 1450, 1396, 1310, 1228, 1136, 1061, 838, 810, 762, 697. ^1H NMR, δ: 7.61–7.53 (m, 2H, *o*′-H), 7.39–7.31 (m, 4H, *o*-H, *m*-H), 7.25–7.19 (m, 1H, *p*-H), 7.05–6.94 (m, 2H, *m*′-H), 6.64 (s, 1H, 4-H), 2.45 (s, 3H, Me). ^{13}C NMR, δ: 162.1 (d, *p*′-C, ^1J 246.7 Hz), 151.0 (C^5), 147.7 (C^2), 134.1 (*i*-C), 128.8 (*m*-C), 127.7 (*o*-C), 127.4 (d, *i*′-C, ^4J 2.8 Hz), 126.7 (*p*-C), 125.3 (d, *o*′-C, ^3J 7.9 Hz), 123.2 (C^3), 115.8 (d, *m*′-C, ^2J 21.9 Hz), 106.3 (C^4), 13.3 (Me). Found (%): C, 80.82; H, 5.28; F, 7.46. Calc. for $C_{17}H_{13}FO$ (252.283) (%): C, 80.93; H, 5.19; F, 7.53.



Scheme 2

As for bicyclooctanes **3** (Scheme 3), apparently, first, the retro-aldol disassembling of chalcone **1** by the action of water traces occurs. Methyl ketone thus released adds at the double bond of the second chalcone molecule to afford 1,5-diketone **C**. The latter reacts with acetylene to furnish bicyclooctane **3** as a single 3-*exo*-isomer according to the proved mechanism.[11] Again, acetylene in this domino assembling plays a driving and organizing role initially participating as nucleophile to form acetylenic alcohols **D** and finally as electrophile to acquire nucleophilic attack of the hydroxyl group of hemiacetal **E**.



Scheme 3

These peculiar disassembling/assembling processes are not specifically catalyzed by the NaOBu^t/DMSO superbase system. For instance, they also took place in the presence of KOH/DMSO pair when the yields of furan **2a** and bicyclooctane **3a** were 27 and 12%, respectively. Notably, in the NaOBu^t/DMSO medium chalcone **1a** produces bicyclooctane **3a** in trace amount only (see Scheme 1).

In spite of low isolated yields (though non-optimized), the one-pot transition metal-free assembling of 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes, novel congeners of pheromones related to frontalin and mammal hormones, may contribute both to the organic synthesis toolkit and fast developing phenomenon of molecular self-organization with participation of acetylene.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.01.015.

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*1,5-Bis(4-fluorophenyl)-7-methylidene-3-*exo*-phenyl-6,8-dioxabicyclo[3.2.1]octane* **3b**. Yield 0.098 g (10%); light yellow oil. IR (film, ν/cm^{-1}): 3030, 2925, 2849, 2808, 1686, 1603, 1513, 1455, 1411, 1380, 1350, 1311, 1273, 1231, 1160, 1143, 1090, 1076, 1033, 1013, 991, 957, 910, 833, 813, 764, 735, 700, 676, 598, 590, 576, 528. ^{1}H NMR, δ: 7.66–7.62 (m, 2H, *o*-H), 7.56–7.51 (m, 2H, *o''*-H), 7.37–7.28 (m, 4H, *o'*-H, *m'*-H), 7.26–7.20 (m, 1H, *p'*-H), 7.13–7.02 (m, 4H, *m*-H, *m''*-H), 4.38 (d, 1H, H$_b$, ^2J 2.4 Hz), 3.62–3.50 (m, 2H, H$_a$, 3-H), 2.53 (dd, 1H, 4-H$_{eq}$, ^2J 12.9 Hz, ^3J 5.1 Hz), 2.46 (dd, 1H, 2-H$_{eq}$, ^2J 13.6 Hz, ^3J 5.4 Hz), 2.25 (dd, 1H, 4-H$_{ax}$, ^2J 12.9 Hz, ^3J 12.4 Hz), 2.14 (dd, 1H, 2-H$_{ax}$, ^2J 13.6 Hz, ^3J 12.1 Hz). ^{13}C NMR, δ: 163.3 (d, *p*-C, ^1J 247.8 Hz), 162.9 (d, *p''*-C, ^1J 247.4 Hz), 162.7 (C^7), 143.6 (*i'*-C), 135.5 (d, ^4J 3.1 Hz), 135.3 (d, ^4J 3.1 Hz) (*i*-C, *i''*-C), 129.0 (*m'*-C), 128.1 (d, *o*-C, ^3J 8.2 Hz), 127.48 (*o'*-C), 127.48 (d, *o''*-C, ^3J 8.2 Hz), 127.1 (*p'*-C), 115.43 (d, *m*-C, ^2J 21.6 Hz), 115.4 (d, *m''*-C, ^2J 21.5 Hz), 108.6 (C^5), 85.5 (C^1), 79.42 (C$^\beta$), 41.5 (C^4), 40.10 (C^2), 37.0 (C^3). Found (%): C, 76.85; H, 5.11; F, 9.80. Calc. for $C_{25}H_{20}F_2O_2$ (390.422) (%): C, 76.91; H, 5.16; F, 9.73.

For characteristics of compounds **2c**–**f** and **3c**–**f**, see Online Supplementary Materials.