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Domino assembly of functionalized cyclopentenols from 1,5-diphenylpentane-1,5-dione and phenylacetylene in the KOH/DMSO suspension

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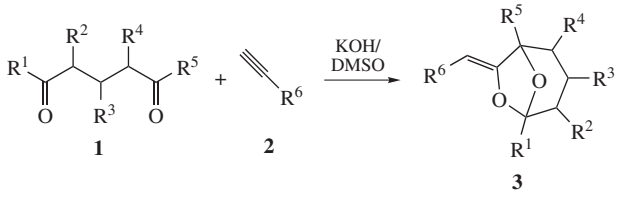
1,5-Diphenylpentane-1,5-dione reacts (50 mol% KOH in DMSO, 70 °C, 3 h) with phenylacetylene in a domino manner to afford 3-benzoyl-2-benzyl-1-phenylcyclopenten-1-ol and its debenzoylated derivative in 66 and 25% yields, respectively.

Recently, we have published the one-pot stereoselective assembly of 7-methylidene-6,8-dioxabicyclo[3.2.1]octanes **3** from 1,5-diketones **1** and acetylenes **2** in the KOH/DMSO suspension (100–200 mol% KOH, 70 °C, 0.5–4 h), the yields reaching 92% (Scheme 1).[1]



1 **2** **3**

R^1, R^5 = Ar, Het
R^2, R^3, R^4 = H, Me, Ph
$R^1 + R^2$, $R^4 + R^5 = (CH_2)_4$
R^6 = H, Ar, Het

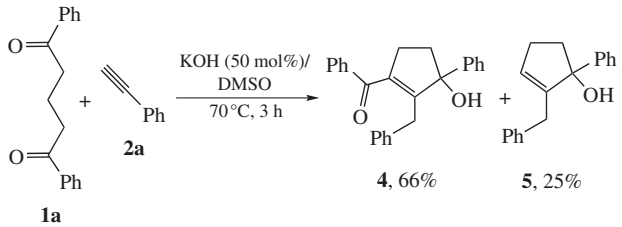
Scheme 1

These bicyclic acetals **3** belong to the frontalin family of aggregate pheromones[2] and mammal hormones.[3] Since 1,5-diketones are easily prepared by aldehyde–ketone condensation,[4] further development of such a chemistry seems promising.

Although seven 1,5-diketones **1** tolerated the reaction,[1] we here report that one of them, 1,5-diphenylpentane-1,5-dione **1a** combined with phenylacetylene **2a** appeared to be surprisingly sensitive towards the change of the process conditions.

Indeed, when the KOH : **1a** ratio has been decreased from 2:1 to 0.5:1, the reaction takes absolutely other direction: instead of the expected 7-methylidene-6,8-dioxabicyclo[3.2.1]octane **3a** ($R^1 = R^5 = Ph$, $R^2 = R^3 = R^4 = H$, $R^6 = Ph$), functionalized cyclopentenes **4** and **5** were obtained in 66 and 25% yields, respectively (Scheme 2).†

Obviously, both the syntheses of bicyclooctanes **3** and cyclopentenes **4**, **5** are triggered by the Favorsky reaction onto a one of carbonyl groups to give the common intermediate, acetylenic alcoholate **A** (Scheme 3).[1] Then, instead of normal Favorsky ethynylation of the second carbonyl group, domino type intramolecular competitive O- *vs.* C-vinylation occurs. As shown in previous publication,[1] the O-vinylation leading to bicyclooctanes



1a **2a** **4**, 66% **5**, 25%

Scheme 2

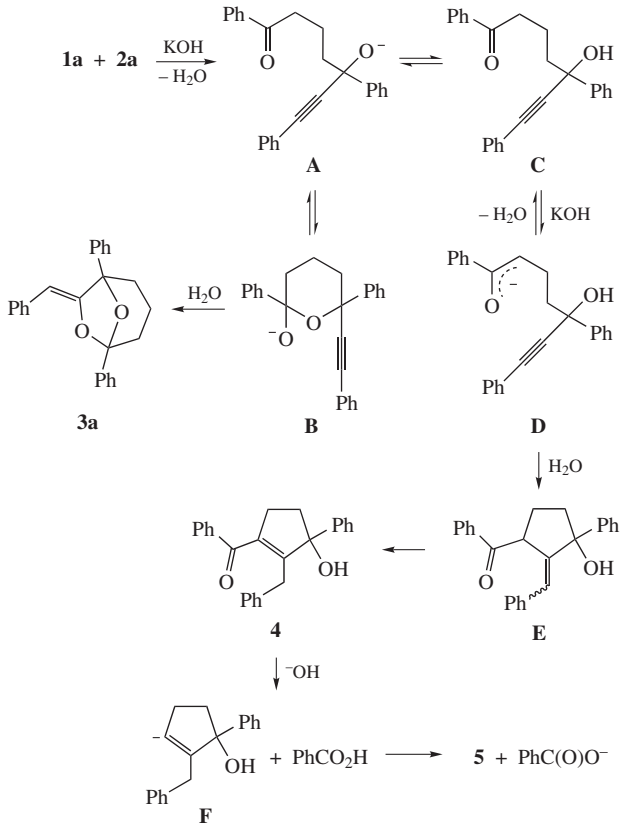
3 is preceded by the formation of hemiacetal alcoholate **B** *via* the attack of oxygen-centered anion **A** at the carbonyl group. When the content of KOH is reduced to 50 mol%, alcoholate **A**

† ^{1}H and ^{13}C NMR spectra were recorded at 400.13 and 100.61 MHz, respectively, on an instrument equipped with an inverse gradient 5 mm probe with HMDS as an internal standard. All 2D NMR spectra were recorded using a standard gradient Bruker pulse program. IR spectra were taken with FT-IR. The 1,5-diketone **1a** was synthesized using published procedures.[7] KOH (water content 15%), DMSO (water content 0.2–0.3%) and all other chemicals and solvents are commercially available and were used without further purification. The elaborated procedure does not require degassing of DMSO and use of inert atmosphere.

Cyclopentenols **4**, **5**. A suspension of 1,5-diphenylpentane-1,5-dione **1a** (1.50 g, 6 mmol) and KOH (water content 15%, 0.20 g, 3 mmol) in DMSO (40 ml) was heated (70 °C) with stirring. Then phenylacetylene **2a** (0.79 g, 7.7 mmol) in DMSO (10 ml) was added for 20 min. The mixture was heated for 3 h and, after cooling to room temperature, was diluted with H_2O (100 ml) and extracted with Et_2O (7×20 ml). The extract was washed with water (3×20 ml) and dried (K_2CO_3) for 3 h. Column chromatography (basic Al_2O_3, eluent hexane–chloroform with gradient from 1:0 to 0:1) of a crude residue after removal of the solvent (1.87 g) gave pure products **4**, **5**.

3-Benzoyl-2-benzyl-1-phenylcyclopent-2-en-1-ol **4**: yield 1.39 g (66%), colorless crystals, mp 102–105 °C. ^{1}H NMR (C_6D_6) δ: 7.83–7.81 (m, 2H, *o*-H_{Ph1}), 7.41–7.39 (m, 2H, *o*-H_{Ph2}), 7.16–6.97 and 6.87–6.78 (m, 11H, H_{Ph}), 3.49 (d, 1H, CH_2Ph, ^2J 14.8 Hz), 3.08 (d, 1H, CH_2Ph, ^2J 14.8 Hz), 2.78–2.73 (m, 1H, 5-H), 2.48–2.43 (m, 1H, 5-H′), 2.17–2.10 (m, 1H, 4-H), 2.06–1.99 (m, 1H, 4-H′), 1.53 (s, 1H, OH). ^{13}C NMR (C_6D_6) δ: 196.7 (C=O), 149.1 (1-C), 146.2 (*i*-C_{Ph3}), 141.3 (2-C), 139.0 (*i*-C_{Ph2}), 137.8 (*i*-C_{Ph1}), 133.0 (*p*-C_{Ph1}), 129.6 (*o*-C_{Ph2}), 129.2 (*o*-C_{Ph1}), 128.7 (*m*-C_{Ph1}), 128.5 (*m*-$C_{Ph2,3}$), 127.1 (*p*-C_{Ph3}), 126.4 (*p*-C_{Ph2}), 125.7 (*o*-C_{Ph3}), 89.7 (3-C), 42.8 (4-C), 33.5 (CH_2Ph), 33.0 (5-C). IR (film, ν_{max}/cm^{-1}): 3331, 3083, 3060, 3026, 2963, 2918, 2850, 1662, 1629, 1595, 1493, 1447, 1385, 1273, 1174, 1135, 1069, 1022, 923, 885, 770, 717, 703, 689. Found (%): C, 84.68; H, 6.14. Calc. for $C_{25}H_{22}O_2$ (%): C, 84.72; H, 6.26.

2-Benzyl-1-phenylcyclopent-2-en-1-ol **5**: yield 0.37 g (25%), yellow oil. ^{1}H NMR ($CDCl_3$) δ: 7.40–7.38 (m, 2H, *o*-H_{Ph1}), 7.35–7.32 (m, 2H, *m*-H_{Ph1}), 7.25–7.24 (m, 2H, *m*-H_{Ph2}), 7.23–7.22 (m, 1H, *p*-H_{Ph1}), 7.19–7.17 (m, 1H, *p*-H_{Ph2}), 7.07–7.05 (m, 2H, *o*-H_{Ph2}), 5.45–5.44 (m, 1H, 3-H), 3.19–3.15 (m, 1H, CH_2Ph), 3.10–3.06 (m, 1H, CH_2Ph), 2.47–2.43 (m, 1H, 4-H), 2.32–2.30 (m, 1H, 5-H), 2.25–2.21 (m, 1H, 4-H′), 2.20–2.19 (m, 1H, 5-H′), 1.82 (s, 1H, OH). ^{13}C NMR ($CDCl_3$) δ: 148.5 (2-C), 146.2 (*i*-C_{Ph1}), 139.9 (*i*-C_{Ph2}), 129.9 (3-C), 129.3 (*o*-C_{Ph2}), 128.5 (*m*-C_{Ph2}), 128.4 (*m*-C_{Ph1}), 126.7 (*p*-C_{Ph1}), 126.2 (*p*-C_{Ph2}), 125.2 (*o*-C_{Ph1}), 88.2 (1-C), 44.0 (5-C), 33.6 (CH_2Ph), 29.6 (4-C). IR (film, ν_{max}/cm^{-1}): 3566, 3448, 3084, 3059, 3027, 2964, 2930, 2905, 2853, 1951, 1881, 1811, 1751, 1681, 1600, 1581, 1497, 1448, 1361, 1334, 1298, 1281, 1222, 1176, 1089, 1059, 1028, 1002, 982, 942, 912, 846, 766, 701. Found (%): C, 86.12; H, 7.10. Calc. for $C_{18}H_{18}O$ (%): C, 86.36; H, 7.25.



Scheme 3

would equilibrate with the neutral acetylenic keto alcohol **C**. The latter gives then enolate **D**, which is cyclized to benzylidenecyclopentanol **E**, expectedly isomerizing to the final cyclopentenol **4**. Similar enolization of alcoholate **A** is virtually forbidden due to the electrostatic repulsion of two negative charges.

Debenzoylation of cyclopentenol **4** likely results from the nucleophilic attack of hydroxide anion at the carbonyl carbon atom of the benzoyl group leading to the cleavage of the C^1–C(O) bond to form benzoic acid and to release cyclopentene carbanion **F**. Such a scheme is supported by the detection of benzoic acid in the reaction mixture after its acidification.

Substituted functionalized cyclopentenes are frequent motifs in ribose-derived natural compounds[5] and some modern important drugs.[6] Therefore, the one-pot domino assembly of a novel family of these pharmaceutically promising compounds from available materials under simple transition metal-free conditions deserves further in-depth study.

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