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Dioximes of 1,6-heptanediones from acetylene and ketones: only three atom-economic steps

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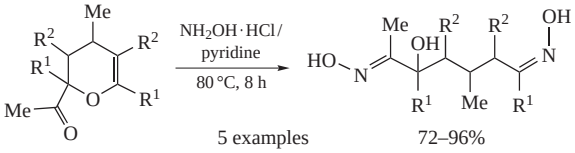
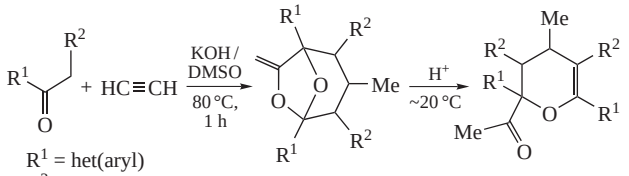
2-Acetyl-3,4-dihydropyrans, synthesized from acetylene and ketones in two steps, react with hydroxylamine to afford 5-hydroxy-1,6-heptanedione dioximes (*E*,*E*-isomers) in 72–96% yields.



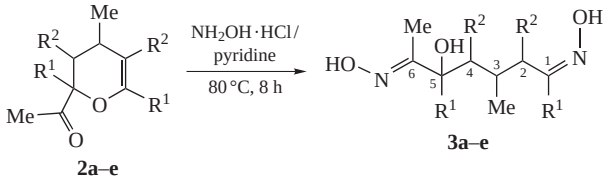
Over the last decade, the investigations devoted to application of acetylene in the superbasic media as the initiating and organizing molecule for one-pot assemblies of the complex molecular systems are gathering momentum.[1–10] In the presence of strong bases, acetylene demonstrates its dual ability to act both as an electrophile (addition of nucleophilic reagents at the triple bond) and a nucleophile (addition of acetylenide ions to the electrophilic molecules).[2] Consequently, several molecules of acetylene and ambifunctional carbonyl compounds are often involved into the self-organization. For example, 7-methylidene-6,8-dioxabicyclo-[3.2.1]octanes **1** (Scheme 1),[11] analogues of insect pheromones[12] and mammal hormones,[13] are diastereoselectively assembled from two molecules of acetylene and two molecules of ketone in the KOH/DMSO superbasic system in a one preparative step.[11] Thus obtained bicyclooctanes **1** in the presence of trace acids at room temperature isomerize instantly and quantitatively into dihydropyrans **2**.[14]



Scheme 1

Herein, we report that dihydropyrans **2a**–**e** upon treatment with two equivalents of hydroxylamine hydrochloride in pyridine are stereoselectively transformed (the configuration is established according to ^{13}C NMR spectra)[15] into dioximes of 5-hydroxy-1,6-diketones **3a**–**e** (Scheme 2) with the configuration of both formed oxime groups being *E*.†

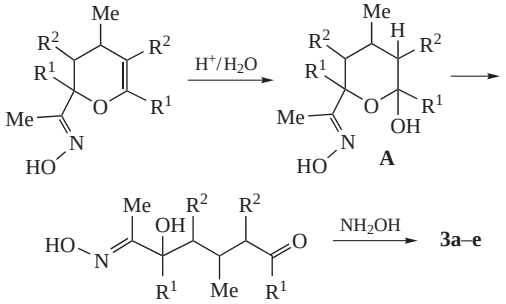
A likely way to dioximes **3a**–**e** lies *via* the acid-catalyzed addition of water, released from oximation of the acetyl function, to the enol moiety of dihydropyrans **2a**–**e** to afford hemiacetal **A**. The latter expectedly undergoes ring-opening to give monoximes of 5-hydroxy-1,6-diketones **B**, whose further oximation leads to final dioximes **3a**–**e** (Scheme 3).



a R^1 = Ph, R^2 = H (94%)
b R^1 = Ph, R^2 = Me (72%)
c R^1 = 4-MeC_6H_4, R^2 = H (96%)
d R^1 = 3-$MeOC_6H_4$, R^2 = H (91%)
e R^1 = 4-PhC_6H_4, R^2 = H (90%)

Scheme 2

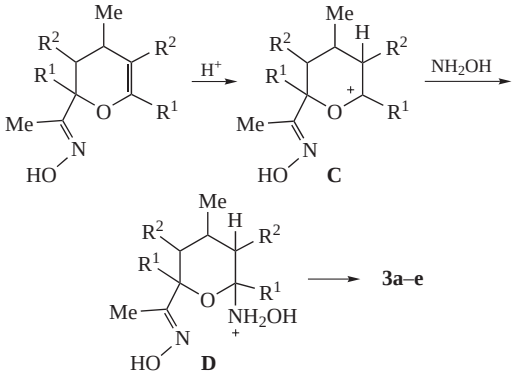
However, because of no monoximes **B** are discernible in the crude products, an alternative route to dioximes **3** seems to be also probable. Actually, the intermediate carbocation **C** may be attacked by a molecule of hydroxylamine to generate hemiacetal **D** that



Scheme 3

† The IR spectra were recorded on a Bruker IFS25 spectrophotometer. The NMR spectra were recorded on Bruker DPX-400 and AV-400 spectrometers (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C and 40.5 MHz for ^{15}N) in DMSO-d_6. The assignment of signals was made using COSY, NOESY, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, and 2D ^{1}H-^{15}N HMBC experiments.

Dioximes **3** *(typical procedure)*. A mixture of dihydropyran **2** (2 mmol) and hydroxylamine hydrochloride (4 mmol, 280 mg) in pyridine (5 ml) was stirred at 80 °C for 8 h. The mixture was poured into water (20 ml), the product was collected by filtration, washed with H_2O and recrystallized from hexane.



Scheme 4

directly delivers (in the course of its decomposition) dioximes **3a**–**e** (Scheme 4).

1,6-Diketones and their derivatives, especially functionally substituted ones, are still hardly accessible, though synthetically and pharmaceutically prospective compounds.[16] All this relates completely to dioximes of 1,6-diketones **3** bearing the additional hydroxyl function. Since the assembly of bicyclooctanes **1** (see Scheme 1) tolerates a wide range of diverse ketones,[11] the first syntheses of 1,6-diketone dioximes from acetylene and ketones described here can be considered as the priority application in development of general atom-economic, base- and acid-catalyzed method for the preparation of new derivatives of 1,6-dicarbonyl compounds.

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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.2018.03.010.

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*(1*E,*6*E*)-5-Hydroxy-3-methyl-1,5-diphenylheptane-1,6-dione dioxime* **3a**: yield 640 mg (94%), white solid, mp 160–161 °C. ^{1}H NMR, δ: 0.80 (d, 3H, C^{3}Me, ^3J 6.5 Hz), 1.47 (s, 3H, C^{6}Me), 1.56 (m, 1H, H-3), 1.93 (m, 1H, H-4′), 2.24 (m, 2H, H-2′, H-4), 2.64 (m, 1H, H-2), 5.37 (s, 1H, C^{5}OH), 7.18–7.31 (m, 10H, Ph), 10.64 (s, 1H, C^{6}NOH), 10.97 (s, 1H, C^{3}NOH). ^{13}C NMR, δ: 10.3 (C^6*Me*), 21.3 (C^3*Me*), 26.5 (C^3), 32.4 (C^2), 45.5 (C^4), 78.0 (C^5), 125.5, 125.8 (*o*-C, *o*′-C), 127.7, 128.1 (*m*-C, *m*′-C), 126.3, 128.2 (*p*-C, *p*′-C), 135.8 (*i*-C), 144.0 (*i*′-C), 155.9 (C^1), 159.8 (C^6). ^{15}N NMR, δ: –28.7 (C^{6}N), –19.6 (C^{1}N). IR (film, ν/cm^{-1}): 3544, 3457, 3320, 3086, 3061, 2959, 2926, 2875, 1958, 1891, 1817, 1640, 1492, 1448, 1373, 1308, 1220, 1182, 1130, 1072, 999, 945, 915, 758, 699, 648, 570, 498. Found (%): C, 70.24; H, 7.05; N, 8.34. Calc. for $C_{20}H_{24}N_2O_3$ (%): C, 70.56; H, 7.11; N, 8.23.

*(1*E,*6*E*)-5-Hydroxy-2,3,4-trimethyl-1,5-diphenylheptane-1,6-dione dioxime* **3b**: yield 531 mg (72%), white solid, mp 196–197 °C. ^{1}H NMR, δ: 0.66 (d, 3H, C^{3}Me, ^3J 7.0 Hz), 0.89 (d, 3H, C^{4}Me, ^4J 6.9 Hz), 0.95 (d, 3H, C^{2}Me, ^2J 7.0 Hz), 1.33 (m, 1H, H-3), 1.49 (s, 3H, C^{6}Me), 2.54 (m, 1H, H-2), 2.75 (m, 1H, H-4), 5.00 (br. s, 1H, C^{5}OH), 7.02–7.26 (m, 10H, Ph), 10.47 (br. s, 2H, NOH). ^{13}C NMR, δ: 10.0 (C^4*Me*), 10.4 (C^6*Me*), 11.2 (C^3*Me*), 15.0 (C^2*Me*), 33.7 (C^3), 39.1 (C^4), 43.9 (C^2), 81.9 (C^5), 125.8, 126.2, 127.4, 127.5, 127.8 (10C, Ph), 134.0 (*i*-C), 143.3 (*i*′-C), 158.6 (C^6), 158.8 (C^1). IR (film, ν/cm^{-1}): 3503, 3457, 3288, 3246, 3107, 3066, 2986, 2931, 2881, 1743, 1686, 1647, 1536, 1497, 1444, 1377, 1342, 1223, 1191, 1151, 1112, 1067, 1009, 941, 895, 763, 702, 654, 580, 542. Found (%): C, 71.94; H, 7.60; N, 7.51. Calc. for $C_{22}H_{28}N_2O_3$ (%): C, 71.71; H, 7.66; N, 7.60.

*(1*E,*6*E*)-5-Hydroxy-3-methyl-1,5-di*-p-*tolylheptane-1,6-dione dioxime* **3c**: yield 707 mg (96%), white solid, mp 153–155 °C. ^{1}H NMR, δ: 0.78 (d, 3H, C^{3}Me, ^3J 6.6 Hz), 1.45 (s, 3H, C^{6}Me), 1.53 (m, 1H, H-3), 1.87 (m, 1H, H-4′), 2.21 (m, 2H, H-2′, H-4), 2.25 (s, 3H, *Me*C$_6$H$_4$), 2.27 (s, 3H, *Me*C$_6$H$_4$), 2.57 (m, 1H, H-2), 5.26 (s, 1H, C^{5}OH), 7.03 (m, 4H, *m*-H, *m*′-H), 7.14 (m, 4H, *o*-H, *o*′-H), 10.58 (s, 1H, C^{6}NOH), 10.82 (s, 1H, C^{3}NOH). ^{13}C NMR, δ: 10.3 (C^6*Me*), 20.6, 20.7 (2*Me*C$_6$H$_4$), 21.3 (C^3*Me*), 26.5 (C^3), 32.4 (C^2), 45.4 (C^4), 77.8 (C^5), 125.4, 126.7 (*o*-C, *o*′-C), 128.3, 128.6 (*m*-C, *m*′-C), 132.9, 135.1 (*p*-C, *p*′-C), 137.5 (*i*-C), 141.0 (*i*′-C), 155.8 (C^1), 159.9 (C^6). ^{15}N NMR, δ: –28.3 (C^{6}N), –20.1 (C^{1}N). IR (film, ν/cm^{-1}): 3544, 3297, 3090, 3059, 3030, 2955, 2923, 2870, 1910, 1641, 1619, 1511, 1455, 1411, 1369, 1307, 1237, 1184, 1104, 1041, 1020, 987, 939, 879, 814, 736, 671, 637, 585, 508, 422. Found (%): C, 71.74; H, 7.64; N, 7.58. Calc. for $C_{22}H_{28}N_2O_3$ (%): C, 71.71; H, 7.66; N, 7.60.

*(1*E,*6*E*)-5-Hydroxy-1,5-bis(3-methoxyphenyl)-3-methylheptane-1,6-dione dioxime* **3d**: yield 729 mg (91%), white solid, mp 107–110 °C. ^{1}H NMR, δ: 0.81 (d, 3H, C^{3}Me, ^3J 6.5 Hz), 1.48 (s, 3H, C^{6}Me), 1.63 (m, 1H, H^3), 1.93 (m, 1H, H-4′), 2.23 (m, 2H, H-2′, H-4), 2.57 (m, 1H, H-2), 3.69 (s, 3H, MeO), 3.72 (s, 3H, MeO), 5.37 (s, 1H, C^{5}OH), 6.72–7.16 (m, 8H, Ph), 10.61 (s, 1H, C^{6}NOH), 10.98 (s, 1H, C^{3}NOH). ^{13}C NMR, δ: 10.3 (C^6*Me*), 21.4 (C^3*Me*), 26.7 (C^3), 32.4 (C^2), 45.5 (C^4), 54.8, 54.9 (2MeO), 77.9 (C^5), 110.9, 111.4, 111.6, 114.1, 117.8, 118.3, 128.8, 129.1 (8C, Ph), 137.3 (*i*-C), 145.9 (*i*′-C), 155.9 (C^1), 158.9, 159.0 (*m*-CO, *m*′-CO), 159.8 (C^6). IR (film, ν/cm^{-1}): 3327, 3081, 2950, 2840, 2083, 1928, 1646, 1593, 1483, 1455, 1434, 1375, 1312, 1293, 1243, 1175, 1138, 1044, 957, 866, 782, 710, 645, 567, 448. Found (%): C, 65.74; H, 7.09; N, 6.94. Calc. for $C_{22}H_{28}N_2O_5$ (%): C, 65.98; H, 7.05; N, 7.00.

*(1*E,*6*E*)-1,5-Di(biphenyl-4-yl)-5-hydroxy-3-methylheptane-1,6-dione dioxime* **3e**: yield 887 mg (90%), white solid, mp 216–217 °C. ^{1}H NMR, δ: 0.89 (d, 3H, C^{3}Me, ^3J 6.2 Hz), 1.51 (s, 4H, C^{6}Me, H-3), 1.90 (m, 1H, H-4′), 2.37 (m, 2H, H-2′, H-4), 2.70 (m, 1H, H-2), 5.45 (s, 1H, C^{5}OH), 7.27–7.59 (m, 18H, Ph), 10.70 (s, 1H, C^{6}NOH), 11.06 (s, 1H, C^{3}NOH). ^{13}C NMR, δ: 10.4 (C^6*Me*), 21.6 (C^3*Me*), 26.9 (C^3), 32.7 (C^2), 45.1 (C^4), 78.3 (C^5), 126.0, 126.2, 126.3, 126.4, 126.5, 127.3, 127.5, 128.9, 129.0, 134.7, 139.4, 139.8 (22C, Ph), 138.0 (*i*-C), 143.3 (*i*′-C), 155.6 (C^1), 159.9 (C^6). ^{15}N NMR, δ: –27.6 (C^{6}N), –17.9 (C^{1}N). IR (film, ν/cm^{-1}): 3480, 3310, 3083, 3060, 3033, 2959, 2923, 2872, 1953, 1910, 1803, 1643, 1484, 1452, 1383, 1333, 1306, 1193, 1131, 1097, 1052, 1014, 940, 903, 833, 765, 734, 700, 647, 551. Found (%): C, 77.88; H, 6.65; N, 5.78. Calc. for $C_{32}H_{32}N_2O_3$ (%): C, 78.02; H, 6.55; N, 5.69.