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Mendeleev Commun., 2018, **28**, 145–146

Mendeleev Communications

2,4,6-Trisubstituted 3,4-dihydropyrans from acetylene and ketones: deacetylation in the KOBu^t/DMSO system

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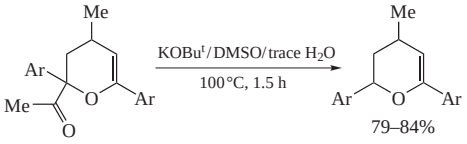
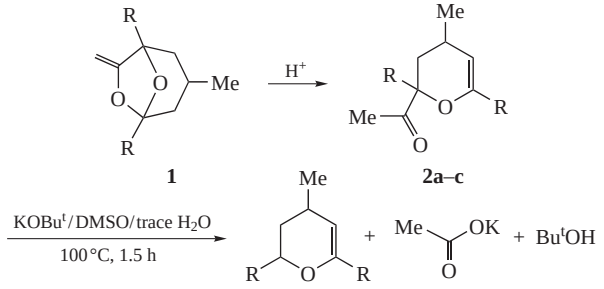
DOI: 10.1016/j.mencom.2018.03.011

2-Acetyl-3,4-dihydropyrans bearing 2-, 4- and 6-positioned aryl and alkyl groups, available from acetylene and ketones, undergo easy deacetylation in the KOBu^t/DMSO system (100 °C, 1.5 h) to give 2,4,6-trisubstituted dihydropyrans.



Synthesis of complex polyfunctional molecules of high synthetic and pharmaceutical potential from available starting materials in a fewest number of steps under simple conditions is among the topical issues of current organic chemistry.[1] In this line, acetylene owing to its dual nature, *i.e.* acting both as electrophile and nucleophile in superbasic surrounding, behaves often as organizing and initiating entity in the multiparticle assemblies of polyfunctionalized molecular systems.[2] In this trend, a one-pot self-organization of 7-methylidene-6,8-dioxabicyclo[3.2.1]-octanes **1**, close congeners of some insect pheromones,[3] from two molecules of ketones and two molecules of acetylene in the KOH/DMSO system has been developed.[4] Expectedly, these compounds proved to be rewarding synthetic intermediates, *e.g.* readily quantitatively rearranging to uniquely substituted 2-acetyl-3,4-dihydropyrans **2** in the presence of trace acids (Scheme 1).[5]

Here we report an unexpected easy deacetylation of dihydropyrans **2a**–**c** under the action KOBu^t/DMSO system in the presence of trace water (see Scheme 1). The reaction proceeds at 100 °C for 1.5 h to afford deacylated dihydropyrans **3a**–**c** in 79–84% yields.† Under these conditions, the conversion of acetyldihydropyrans **2** was close to 100%.

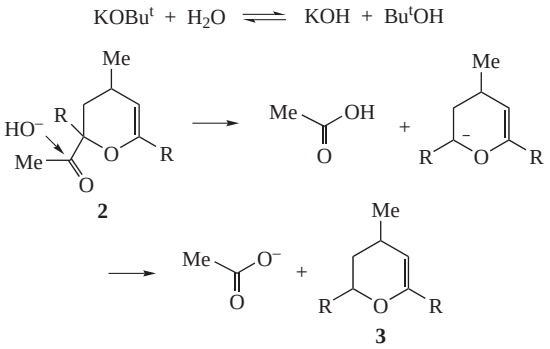


3a R = Ph (79%)
3b R = 4-PhC_6H_4 (84%)
3c R = 2-naphthyl (81%)

Scheme 1

† 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 ^{1}H and 100.6 MHz for ^{13}C) in $CDCl_3$ using HMDSO as internal standard. The assignment of signals was made using COSY, NOESY, ^{1}H-^{13}C HSQC and ^{1}H-^{13}C HMBC experiments.

These results may be rationalized in terms of nucleophilic substitution at the acetyl carbon by hydroxide anion generated from KOBu^t upon its reaction with trace water present in DMSO (Scheme 2).



Scheme 2

*3,4-Dihydro-2*H*-pyrans* **3a**–**c** *(typical procedure)*. A mixture of 2-acetyl-3,4-dihydropyran **2** (2 mmol) and KOBu^t (2 mmol, 224 mg) in DMSO with water content ~0.5% (10 ml) was stirred at 100 °C for 1.5 h. The reaction mixture, after cooling (~20 °C), was diluted with H_2O (15 ml) and extracted with Et_2O (4×10 ml). The organic extract was washed with H_2O (3×5 ml) and dried (K_2CO_3). Diethyl ether was evaporated in vacuum and the residue was purified by column chromatography (SiO_2, eluent hexane).

*4-Methyl-2,6-diphenyl-3,4-dihydro-2*H*-pyran* **3a** (mixture of two diastereomers in a 1.5:1 molar ratio): yield 396 mg (79%), cream oil. *cis*-**3a** (major isomer). ^{1}H NMR, δ: 1.18 (d, 3H, Me, J 7.0 Hz), 1.64 (m, 1H, H-3), 2.21 (m, 1H, H-3′), 2.78 (m, 1H, H-4), 5.07 (d, 1H, H-2, J 11.7 Hz), 5.35 (s, 1H, H-5), 7.30–7.52 (m, 8H, Ph), 7.68 (m, 2H, *o*-H). ^{13}C NMR, δ: 21.6 (Me), 28.4 (C^4), 40.0 (C^3), 78.2 (C^2), 103.8 (C^5), 124.7 (*o*-C), 126.8 (*o*′-C), 127.7 (*p*′-C), 127.9 (*p*-C), 128.2 (*m*′-C), 128.8 (*m*-C), 135.9 (*i*-C), 142.2 (*i*′-C), 151.0 (C^6). *trans*-**3a** (minor isomer). ^{1}H NMR, δ: 1.23 (d, 3H, Me, J 7.1 Hz), 1.87 (m, 1H, H-3), 2.13 (m, 1H, H-3′), 2.46 (m, 1H, H-4), 5.11 (d, 1H, H-2, J 10.1 Hz), 5.47 (d, 1H, H-5, J 4.0 Hz), 7.33–7.52 (m, 8H, Ph), 7.70 (m, 2H, *o*-H). ^{13}C NMR, δ: 22.8 (Me), 25.5 (C^4), 37.3 (C^3), 74.2 (C^2), 103.6 (C^5), 124.7 (*o*-C), 125.9 (*o*′-C), 127.5 (*p*′-C), 127.9 (*p*-C), 128.2 (*m*′-C), 128.5 (*m*-C), 136.0 (*i*-C), 142.3 (*i*′-C), 150.8 (C^6). IR (film, ν/cm^{-1}): 3286, 3058, 3036, 2954, 2923, 2866, 1951, 1885, 1804, 1648, 1602, 1542, 1495, 1450, 1360, 1330, 1281, 1183, 1142, 1070, 1028, 911, 844, 792, 757, 696, 646, 551, 452. Found (%): C, 86.45; H, 7.18. Calc. for $C_{18}H_{18}O$ (%): C, 86.36; H, 7.25.

Surprisingly, when using commercial KOH·0.5H_2O, deacetylation does not take place. Probably in the presence of water, even in small concentration, the hydroxide ion becomes insufficiently active for this reaction. Apparently, KOBu^t behaves here as a scavenger of water thereby increasing basicity of the medium and hence deeper desolvating the hydroxide ion. This makes possible the above nucleophilic substitution. The attack of *tert*-butoxide ion at the carbonyl group, though expectable, will not lead to deacylation since in this case no proton is available to quench the leaving carbanionic species.

Thus, the observed deacylation of available uniquely substituted acetyl dihydropyrans substantially extends possible areas of their synthetic applications.

This work was supported by the Russian Science Foundation (grant no. 14-13-00588).

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2018.03.011.

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Received: 5th July 2017; Com. 17/5296

*2,6-Di(biphenyl-4-yl)-4-methyl-3,4-dihydro-2*H-*pyran* **3b** (mixture of two diastereomers in a 1.3:1 molar ratio): yield 676 mg (84%), white solid, mp 108–110 °C. *cis*-**3b** (minor isomer). ^{1}H NMR, δ: 1.14 (d, 3H, Me, *J* 7.0 Hz), 1.63 (m, 1H, H-3), 2.21 (m, 1H, H-3′), 2.76 (m, 1H, H-4), 5.08 (d, 1H, H-2, *J* 11.7 Hz), 5.35 (s, 1H, H-5), 7.30–7.62 (m, 16H, Ph), 7.71 (m, 2H, *o*-H). ^{13}C NMR, δ: 21.6 (Me), 28.5 (C^4), 40.0 (C^3), 78.1 (C^2), 104.1 (C^5), 125.1 (*o*-C), 126.6 (*o*′-C), 126.9–128.9 (14C_{Ar}), 134.9 (*i*-C), 140.5–141.0 (4C_{Ar}), 141.3 (*i*′-C), 150.8 (C^6). *trans*-**3b** (major isomer). ^{1}H NMR, δ: 1.20 (d, 3H, Me, *J* 7.1 Hz), 1.85 (m, 1H, H-3), 2.14 (m, 1H, H-3′), 2.46 (m, 1H, H-4), 5.11 (d, 1H, H-2, *J* 9.8 Hz), 5.48 (d, 1H, H-5, *J* 4.4 Hz), 7.30–7.62 (m, 16H, Ph), 7.72 (m, 2H, *o*-H). ^{13}C NMR, δ: 22.8 (Me), 25.5 (C^4), 37.3 (C^3), 74.1 (C^2), 103.8 (C^5), 125.1 (*o*-C), 126.4 (*o*′-C), 126.9–128.9 (14C_{Ar}), 135.0 (*i*-C), 140.5–141.0 (4C_{Ar}), 141.4 (*i*′-C), 150.5 (C^6). IR (film, ν/cm^{-1}): 3055, 3032, 2954, 2922, 2866, 1949, 1913, 1801, 1714, 1676, 1647, 1602, 1519, 1486, 1451, 1404, 1358, 1328, 1285, 1189, 1109, 1073, 1008, 909, 841, 794, 762, 732, 697, 647, 568, 513. Found (%): C, 89.75; H, 6.46. Calc. for $C_{30}H_{26}O$ (%): C, 89.51; H, 6.51.

*4-Methyl-2,6-di(2-naphthyl)-3,4-dihydro-2*H-*pyran* **3c** (mixture of two diastereomers in a 1.6:1 molar ratio): yield 568 mg (81%), white solid, mp 81–83 °C. *cis*-**3c** (minor isomer). ^{1}H NMR, δ: 1.17 (d, 3H, Me, *J* 6.9 Hz), 1.73 (m, 1H, H-3), 2.25 (m, 1H, H-3′), 2.79 (m, 1H, H-4), 5.21 (d, 1H, H-2, *J* 11.1 Hz), 5.46 (s, 1H, H-5), 7.39–7.94 (m, 10H, H_{naph}), 7.59 (m, 1H, H-3″$_{naph}$), 7.72 (m, 1H, H-3′$_{naph}$), 7.94 (s, 1H, H-1″$_{naph}$), 8.11 (s, 1H, H-1′$_{naph}$). ^{13}C NMR, δ: 21.5 (Me), 28.6 (C^4), 39.9 (C^3), 78.4 (C^2), 104.7 (C^5), 122.8 ($C^{3'}_{naph}$), 123.5 ($C^{1'}_{naph}$), 124.4 ($C^{3''}_{naph}$), 124.9 ($C^{1''}_{naph}$), 125.8–128.4, 133.1–133.4 (14C_{naph}), 133.0 ($C^{2'}_{naph}$), 139.6 ($C^{2''}_{naph}$), 151.0 (C^6). *trans*-**3c** (major isomer). ^{1}H NMR, δ: 1.22 (d, 3H, Me, *J* 7.1 Hz), 1.91 (m, 1H, H-3), 2.20 (m, 1H, H-3′), 2.47 (m, 1H, H-4), 5.27 (d, 1H, H-2, *J* 9.8 Hz), 5.58 (d, 1H, H-5, *J* 4.2 Hz), 7.39–7.94 (m, 10H, H_{naph}), 7.55 (m, 1H, H-3″$_{naph}$), 7.74 (m, 1H, H-3′$_{naph}$), 7.90 (s, 1H, H-1″$_{naph}$), 8.15 (s, 1H, H-1′$_{naph}$). ^{13}C NMR, δ: 22.8 (Me), 25.6 (C^4), 37.3 (C^3), 74.5 (C^2), 104.5 (C^5), 122.8 ($C^{3'}_{naph}$), 123.4 ($C^{1'}_{naph}$), 124.2 ($C^{3''}_{naph}$), 124.6 ($C^{1''}_{naph}$), 125.8–128.4, 133.1–133.4 (14C_{naph}), 132.9 ($C^{2'}_{naph}$), 139.7 ($C^{2''}_{naph}$), 150.7 (C^6). IR (film, ν/cm^{-1}): 3055, 2954, 2922, 2866, 1919, 1644, 1600, 1506, 1450, 1359, 1319, 1286, 1231, 1194, 1130, 1071, 1023, 951, 903, 857, 815, 744, 650, 477. Found (%): C, 89.21; H, 6.28. Calc. for $C_{26}H_{22}O$ (%): C, 89.11; H, 6.33.