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A surprising double carbon–nitrogen coupling reaction catalyzed by $[H_3Ru_4(C_6H_6)_4(OH)]^{2+}$: synthesis of unusual barbiturate analogues†

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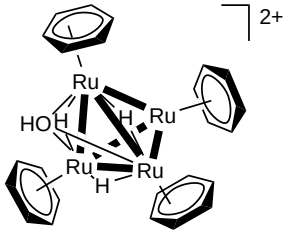
Abstract—Seven- and eight-membered analogues of barbituric acid are easily accessible by insertion of carbodiimides into cyclic anhydrides catalyzed by the cationic hydroxo cluster $[H_3Ru_4(C_6H_6)_4(OH)]^{2+}$.

The last decade has witnessed a considerable interest in the synthesis of medium-size heterocycles, due to the large spectrum of biological activity of these systems.[1] For example, many seven- or eight-membered rings containing one or more heteroatoms are very common in submarine species[2] or in drugs such as taxol,[3] and their preparation still is a challenge in organic synthesis. Barbituric acid derivatives which are six-membered heterocycles are well known for their pharmacological applications,[4] but they are also used in non-linear optics[5] and for molecular recognition.[6] However, seven- or eight-membered analogues of barbituric acid (1,3-diazepine-2,4,7-trione and 1,3-diazocine-2,4,8-trione) are unknown so far, despite a large potential of biological activity to be expected. In this paper, we report a surprisingly simple access to new barbiturate analogues containing seven- or eight-membered ring systems.

We observed that *N*,*N*′-dialkylcarbodiimides react, in the presence of catalytic amounts of $[H_3Ru_4(C_6H_6)_4(OH)]Cl_2$,[7] with succinic anhydride to give, in an unexpected addition process, the seven-membered heterocycles **1a** (R = isopropyl) and **1b** (R = cyclohexyl) (Scheme 1).[8]

The reaction also works with phenylsuccinic anhydride to give the corresponding phenyl derivatives **1c** (R = isopropyl) and **1d** (R = cyclohexyl). With glutaric anhydride, the eight-membered heterocycles **2a** (R = isopropyl) and **2b** (R = cyclohexyl) are obtained. The new heterocycles are isolated as white, air-stable oily solids which melt at around room temperature. All compounds are unambiguously characterized by conclusive MS, IR, ^1H and ^{13}C NMR data; they also give satisfactory microanalytical results (Scheme 2).

The catalytic addition reaction works with acyclic anhydrides, too: propionic anhydride reacts with *N*,*N*′-dicyclohexylcarbodiimide (DCC), in the presence of $[H_3Ru_4(C_6H_6)_4(OH)]Cl_2$, to give (yield: 25%) the known *N*,*N*′-dicyclohexyl-*N*,*N*′-dipropionoylurea, also accessible from the classical reaction between propionic acid and DCC.[9] The new addition reaction, which implies the insertion of the carbodiimide molecule into the anhydride structure by a double carbon–nitrogen coupling sequence, takes place at room temperature in THF solution, giving yields between 15 and 70%. Moreover, no by-products are formed during the condensation, because the resulting mixtures contain only



Scheme 1. Cation $[H_3Ru_4(C_6H_6)_4(OH)]^{2+}$.

Keywords: catalysis; cluster; barbiturates; carbodiimides; acid anhydrides.

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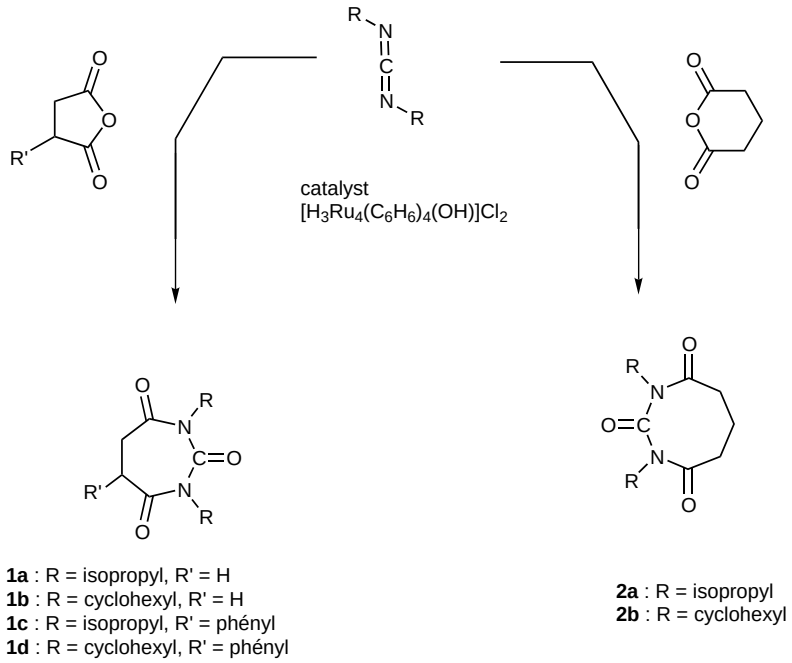

Scheme 2. Synthesis of *N*,*N*′-dialkyl-1,3-diazepine-2,4,7-triones **1** and *N*,*N*′-dialkyl-1,3-diazocine-2,4,8-triones **2**.

the products and unreacted starting materials. Given a catalyst/substrate ratio of 1:1000, the catalytic turnovers vary between 150 and 700. After the catalytic reaction, the catalyst $[H_3Ru_4(C_6H_6)_4(OH)]Cl_2$ can be recovered unchanged and reused for further runs.

The mechanism of the catalytic reaction is not completely clear, but it seems to involve the triply-bridging hydroxo ligand in $[H_3Ru_4(C_6H_6)_4(OH)]^{2+}$, since the reaction is also catalyzed by the tetranuclear rhenium complex $[Re(CO)_3(OH)]_4$[10] containing μ_3-OH ligands as well. However, with $[H_3Ru_4(C_6H_6)_4(OH)]^{2+}$ being almost insoluble in THF, the separation of the (solid) catalyst and the (dissolved) product is very easy. Without catalyst, the carbodiimides do not react at all with succinic or glutaric anhydrides, even under forcing conditions (reflux in THF during one week). Addition of Lewis acids such as $AlCl_3$, $ZnCl_2$, $BF_3{\cdot}OEt_2$ and HBF_4 does not give the heterocyclic products either. Even other ruthenium compounds such as $Ru_2(C_6H_6)_2Cl_4$ and $[H_4Ru_4(C_6H_6)_4]Cl_2$ do not catalyze the addition of DCC to anhydrides.

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8. **General procedures for preparation of heterocycles**: The carbodiimides (1 mmol) and the acid anhydride (1 mmol; succinic anhydride: 1.0 g, glutaric anhydride: 1.14 g or phenylsuccinic anhydride: 1.76 g) are dissolved in 20 ml of THF at room temperature. After addition of $[H_3Ru_4(C_6H_6)_4(OH)]Cl_2$ (1 μmol, 0.8 mg), the mixture is vigorously stirred under N_2 for 12 h at room temperature. The resulting mixture is filtered to remove the solid catalyst (recovery >95%). Then the solution is evaporated to dryness. The product is extracted from the resulting solid by anhydrous ether (two times, 20 ml), the combined extracts are concentrated under reduced pressure to give the pure heterocycle.
   Compound **1a**: *N*,*N*′-diisopropyl-1,3-diazepine-2,4,7-trione (yield 70%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.87 (d, 12H, ^3J(H,H) = 6.6), 2.75 (s, 4H, CH_2), 3.19 (h, 2H, ^3J(H,H) = 6.6); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 25.0, 26.6, 35.1, 56.0, 166.1, 169.9; IR (KBr): ν 1690 cm^{-1} (C=O), 1775 cm^{-1} (C=O); MS (M): 226. Anal. calcd for **1a** ($C_{11}H_{18}N_2O_3$): C, 58.39; H, 8.02; N, 12.38. Found: C, 58.29; H, 8.35; N, 12.17%. Compound **1b**: *N*,*N*′-dicyclohexyl-1,3-diazepine-2,4,7-trione (yield 30%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2–1.9 (m, 20H), 2.90 (s, 4H, CH_2), 3.19 (h, 2H, ^3J(H,H) = 4.2); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 25.0, 26.6, 35.1, 56.0, 166.1, 169.9; IR (KBr): ν 1690 cm^{-1} (C=O), 1775 cm^{-1} (C=O); MS (M): 306. Anal. calcd for **1b** ($C_{17}H_{26}N_2O_3$): C, 66.67; H, 8.55; N, 9.14. Found: C, 66.49; H, 8.61; N, 9.14%. Compound

1c: *N*,*N*′-diisopropyl-5-phenyl-1,3-diazepine-2,4,7-trione (yield 60%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, 12H, ^3J(H,H) = 6.6), 3.05 (dd, 1H, ^3J(H,H) = 6.6 Hz, ^2J(H,H) = 19.04), 3.21 (h, 2H, ^3J(H,H) = 6.6), 3.45 (dd, 1H, ^3J(H,H) = 10.25, ^2J(H,H) = 19.04), 3.05 (dd, 1H, ^3J(H,H) = 6.6, ^3J(H,H) = 10.25); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 28.0, 36.9, 46.8, 61.3, 127.6, 128.9, 129.8, 170.6, 172.3; IR (KBr): ν 1697 cm^{-1} (C=O), 1782 cm^{-1} (C=O); MS (M): 302. Anal. calcd for **1c** ($C_{17}H_{22}N_2O_3$): C, 67.53; H, 7.33; N, 9.26. Found: C, 66.85; H, 7.51; N, 9.66%. Compound **1d**: *N*,*N*′-dicyclohexyl-5-phenyl-1,3-diazepine-2,4,7-trione (yield 25%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2–1.9 (m, 20H, CH_2), 3.05 (dd, 1H, ^3J(H,H) = 6.6, ^2J(H,H) = 19.04), 3.21 (h, 2H, ^3J(H,H) = 4.2), 3.45 (dd, 1H, ^3J(H,H) = 10.25, ^2J(H,H) = 19.04), 3.05 (dd, 1H, ^3J(H,H) = 6.6, ^3J(H,H) = 10.25); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 28.0, 36.9, 46.8, 61.3, 127.6, 128.9, 129.8, 170.6, 172.3; IR (KBr): ν 1697 cm^{-1} (C=O), 1782 cm^{-1} (C=O); MS (M): 382. Anal. calcd for **1d** ($C_{23}H_{30}N_2O_3$): C, 72.22; H, 7.91; N, 7.32. Found: C, 72.26; H, 7.97; N, 7.23%. Compound **2a**: *N*,*N*′-diisopropyl-1,3-diazocine-2,4,8-trione (yield 28%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.89 (d, 12H, ^3J(H,H) = 6.6), 2.02 (q, 2H, ^3J(H,H) = 6.6), 2.76 (t, 4H, ^3J(H,H) = 6.6), 3.19 (h, 2H, ^3J(H,H) = 6.6); ^{13}C NMR (200 MHz, $CDCl_3$,): δ 16.5, 25.0, 26.6, 30.2, 35.1, 56.0, 165.1, 166.9; IR (KBr): ν 1695 cm^{-1} (C=O), 1780 cm^{-1} (C=O); MS (M): 240. Anal. calcd for **2a** ($C_{12}H_{20}N_2O_3$): C, 59.98; H, 8.39; N, 11.66. Found: C, 60.12; H, 8.53; N, 11.54%. Compound **2b**: *N*,*N*′-dicyclohexyl-1,3-diazocine-2,4,8-trione (yield 15%). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.2–1.9 (m, 20H), 2.02 (q, 2H, ^3J(H,H) = 6.6), 2.76 (t, 4H, ^3J(H,H) = 6.6), 3.19 (h, 2H, ^3J(H,H) = 4.2); ^{13}C NMR (200 MHz, $CDCl_3$): δ 16.5, 25.0, 26.6, 30.2, 35.1, 56.0, 165.1, 166.9; IR (KBr): ν 1695 cm^{-1} (C=O), 1780 cm^{-1} (C=O); MS (M): 320. Anal. calcd for **2b** ($C_{18}H_{28}N_2O_3$): C, 67.47; H, 8.81; N, 8.74. Found: C, 67.42; H, 8.64; N, 9.08%.

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