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Features of Catalyzed Hydration of 2-(Dichloromethyl)-*N*-[(1*R*)-1-phenylethyl)]cyclopent-3-ene-1-carboxamides

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Abstract—The hydration of *gem*-dichloromethyl group in 2-(dichloromethyl)-*N*-[(1*R*)-1-phenylethyl)]cyclopent-3-ene-1-carboxamides in aqueous acetonitrile catalyzed by $AgNO_3$, $FeCl_3 \cdot 6H_2O$, $PdCl_2$, and BaO was investigated. The optimum results were obtained at the use of BaO. It was demonstrated, that Pd-catalyzed reactions initiated intermolecular ether formation from the primary hydration products, bicyclic amides.

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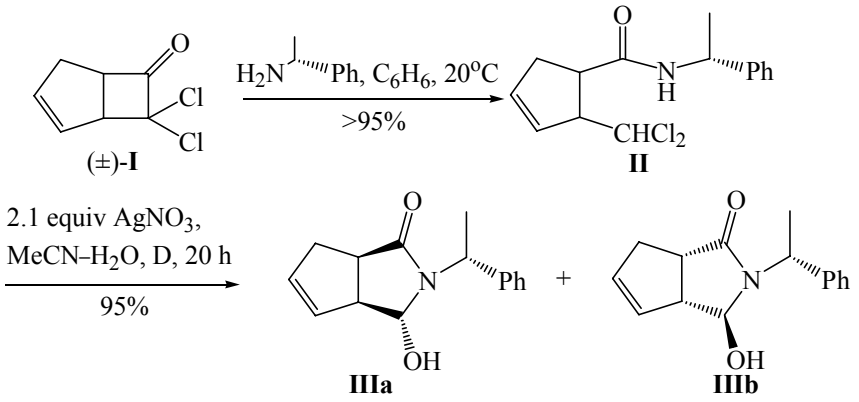
The *gem*-dichlorocyclobutanone ring of bicycle **I** is known to readily undergo opening under the action of heteronucleophiles [1–3]. In continuation of the research on the synthesis of chiral cyclopentenes we carried out a reaction of α,α-dichlorobicyclobutanone (I) with (+)-α-methylbenzylamine in benzene solution at room temperature and obtained in a high yield vicinally disubstituted *gem*-dichloromethyl derivative of cyclopentene **II** that by boiling in aqueous MeCN containing 2.1 equiv of $AgNO_3$ was converted into a diastereomeric mixture of bicyclic amides **IIIa** and **IIIb** separated by column chromatography on SiO_2. In contrast to amides **III** diastereomeric amides **II** failed to be separated on silica gel (Scheme 1).

To replace the expensive silver nitrate we attempted a search for cheaper hydrolysis method of the *gem*-dichloromethyl group in compound **II**. For conversion of the dihalo-substituted compounds **II** into aldehydes it was possible to apply an inexpensive reagent $FeCl_3 \cdot 6H_2O$. In this case the hydrolysis of compound **II** also resulted in the expected compounds **III**, and the yield and the duration of the process were comparable to those in the experiments with $AgNO_3$. At the use in the hydrolysis of catalytic amounts of $PdCl_2$ alongside with the expected compounds **III** quickly formed a product of intermolecular self-condensation **IV**. The ether formation was also found at evaporation of solutions of individual compounds **IIIa** and **IIIb** under reduced pressure and heating to 60°C.

Scheme 1.



We further demonstrated that the most practical and efficient reagent for the hydrolysis of amide **II** was the barium oxide. The employment of the latter both led to the formation of exclusively compound **III** in a high yield and reduced the reaction time 2.5-fold. In the course of further experiments we established that the reverse conversion **IV**→**III** occurred quantitatively at boiling ether **IV** in aqueous THF in the presence of catalytic amount of $FeCl_3 \cdot 6H_2O$. Apparently the iron salt played here the role of a Lewis acid (Scheme 2).

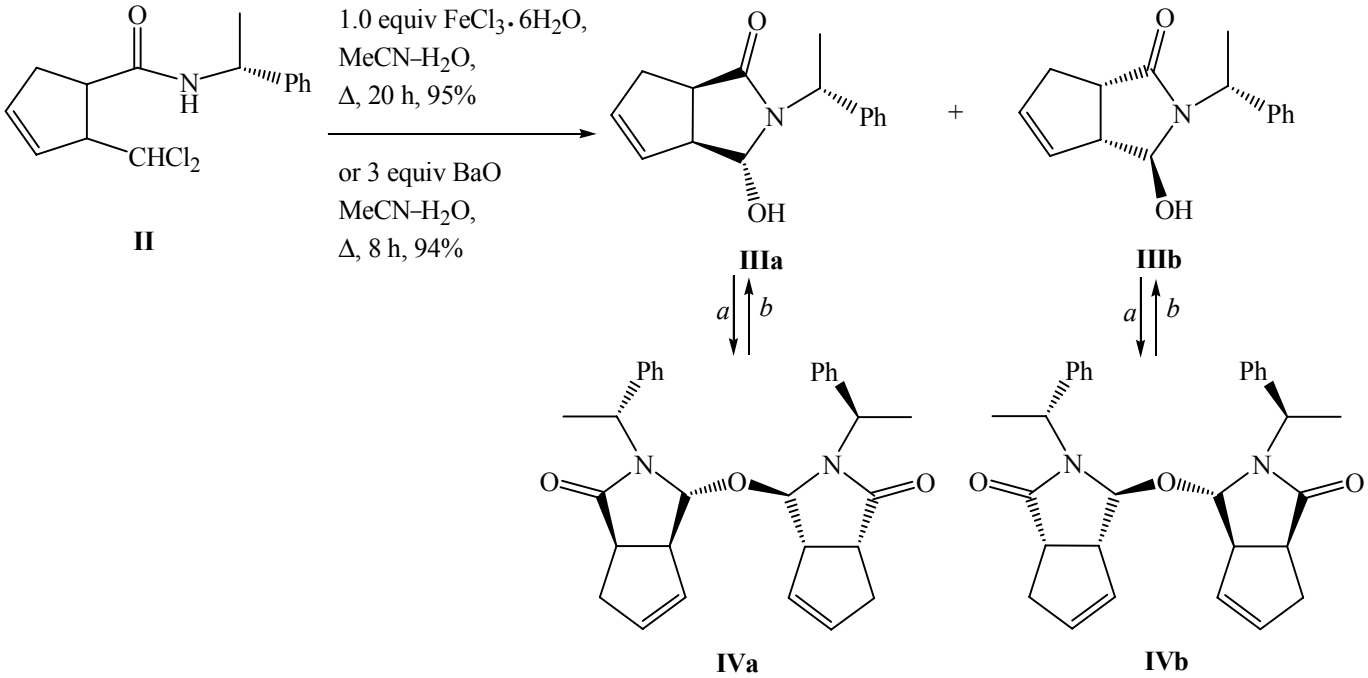
The pair of salts Pd(II)–Fe(III) made it possible to perform effectively the conversions **III**–**IV** although the most well-known examples of the using $FeCl_3 \cdot 6H_2O$ and $PdCl_2$ [4–10] regarded the hydrolysis of the protective groups. The cause of the different final hydrolysis results in the presence on the one hand of $PdCl_2$ (formation of ether **IV**) and $AgNO_3$, $FeCl_3$, and BaO (formation of **III**), on the other hand is as follows. Evidently both the hydrolysis and etherification in the transitions **II**→**III**→**IV** are catalyzed by H^+ and Lewis acids. Under the same conditions (MeCN–H_2O, boiling) only the $PdCl_2$-catalyzed reaction gave ether **IV**. We attribute this fact to the specific feature of the Pd-system where due to the possible N-coordination of Pd(II) the intermolecular ether formation is facilitated, and the acidity of the medium is insufficient for the reverse hydration reaction **IV**→**III**. At the use of $AgNO_3$ and $FeCl_3$ the acidity of the environment apparently is on the optimum level, and compound **IV** does not accumulate due to the preferable hydration (**IV**) → (**III**).

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20 from thin films or mulls in mineral oil. ^1H and ^{13}C NMR spectra were registered on a spectrometer Bruker AM-300 (at 300 and 75.47 MHz respectively) from solutions in $CDCl_3$, internal reference TMS. Mass spectra were taken in ethanol on a Shimadzu LCMS-2010 instrument, ionizing electrons energy 70 eV. TLC was performed on Sorbfil plates. The optical rotation was measured on a polarimeter Perkin-Elmer 241 MC. The purity of the initial compounds was checked by GLC on a chromatograph Chrom 5.

(±)-7,7-Dichlorobicyclo[3.2.0]hept-2-en-6-one (I). To a stirred solution of 53 g (0.8 mol) of a freshly distilled cyclopentadiene and 60 g (0.4 mol) of dichloroacetyl chloride in 400 ml of hexane was added dropwise within 1.5 h 59 ml of triethylamine in 300 ml of anhydrous hexane. The reaction mixture was stirred for

Scheme 2.



a: 0.1 equiv of $PdCl_2$, MeCN–H_2O, Δ, 2 h, 98% or 60°C, 20 mm Hg; b: 0.1 equiv $FeCl_3 \cdot 6H_2O$, THF–H_2O, Δ, 5 h, >95%.

15 h under argon, the mixture obtained was filtered, the precipitate was washed on the filter with hexane (300 ml). The solution was evaporated on a rotary evaporator, the residue was distilled in a vacuum collecting the fraction boiling at 49–50°C (0.3 mm Hg). Yield 59.48 g (84%). Yellow oily fluid. IR spectrum, ν, cm^{-1}: 1805, 1028, 887, 814, 797, 754, 731, 631. ^1H NMR spectrum, δ, ppm: 2.48–2.88 m (2H, C^4H), 4.04–4.22 m (1H, C^5H), 4.32–4.42 m (1H, C^1H), 5.78–5.90 m (1H, C^3H), 6.03–6.17 m (1H, C^2H). ^{13}C NMR spectrum, δ, ppm: 35.21 (C^4), 58.60 (C^1), 59.53 (C^5), 88.18 (C^7), 128.41, 136.88 (C^2, C^3), 197.79 (C^6). Mass spectrum (APCI), m/z (I_{rel}, %): 177 (100) $[MH, {}^{35}Cl]^+$, 149 (13.3) $[MH - CO]^+$. Found, %: C 47.23; H 3.09; Cl 39.96. $C_7H_6OCl_2$. Calculated, %: C 47.46; H 3.38; Cl 40.11.

2-(Dichloromethyl)-*N*-[(1R)-1-phenylethyl)]-cyclopent-3-ene-1-carboxamide (II). To a solution of 1.5 g (8.5 mmol) of dichloroketone **I** in 40 ml of benzene was added a solution of 1.09 g (9 mmol) of (+)-α-methylbenzylamine in 10 ml of benzene, and the mixture was stirred at room temperature for 4 h (TLC monitoring). The solution was evaporated, the separated precipitate was washed with hexane to obtain 2.4 g (95%) of a mixture of diastereomers of compound **II** as yellow crystals. IR spectrum, ν, cm^{-1}: 3311, 2953, 2852, 1633, 1548, 1446, 1375, 1240, 709, 698. ^1H NMR spectrum, δ, ppm: 1.52 d (3H, CH_3, J 6.8 Hz), 2.53–2.73 m (2H, C^5H), 3.17 q (1H, C^1H, J 7.8, 8.0 Hz), 3.62–3.74 m (1H, C^2H), 5.13 quintet (1H, CH–Ph, J 6.7, 6.4 Hz), 5.81–5.93 m (2H, NH and C^4H), 5.96–6.08 m (1H, C^3H), 6.33 m (1H, $CHCl_2$), 7.35–7.55 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 21.29 (CH_3), 36.49 and 36.22 (C^5), 46.64 and 46.78 (CH–Ph), 48.70 and 48.86 (C^2), 58.95 and 58.49 (C^1), 74.34 ($CHCl_2$), 126.3 and 126.13, 127.40 and 127.51, 128.66 and 128.73 (Ph), 128.88 (C^4), 133.40 (C^3), 142.57 and 142.8 (Ph), 171.07 and 171.02 (C=O). Mass spectrum (APCI), m/z (I_{rel}, %): 298 (100) $[MH, {}^{35}Cl]^+$, 149 (12.5). Found, %: C 60.05; H 5.42; Cl 23.15; N 4.64. $C_{15}H_{17}Cl_2NO$. Calculated, %: C 60.40; H 5.70; Cl 23.83; N 4.70.

3-Hydroxy-2-[(1*R*)-phenylethyl]-3,3a,6,6a-tetrahydrocyclopenta[*c*]pyrrol-1(2*H*)-ones (IIIa) and (IIIb). (a) To a solution of 2.7 g (9 mmol) of amide **II** in 40 ml of MeCN was added a solution of 3.21 g (19 mmol) of $AgNO_3$ in 14 ml of H_2O, and the mixture obtained was stirred at boiling for 20 h (TLC monitoring). After evaporation of acetonitrile the water phase was extracted with EtOAc (3 × 40 ml). The combined organic extracts were dried with $MgSO_4$, the solvent was evaporated under a reduced pressure. The residue was subjected to chromatography on SiO_2, eluent petroleum ether–ethyl acetate, 7:3. We obtained 1.04 g (47%) of yellowish crystals of compound **IIIa** and 1.06 g (48%) of colorless crystals of compound **IIIb**.

(b) To a solution of 2.3 g (7.7 mmol) of amide **II** in 35 ml of MeCN was added a solution of 2.1 g (7.7 mmol) of $FeCl_3 \cdot 6H_20$ in 11 ml of H_2O, and the mixture obtained was stirred at boiling for 20 h (TLC monitoring). After evaporation of acetonitrile the water phase was extracted with EtOAc (3 × 35 ml). The combined organic extracts were dried with $MgSO_4$, the solvent was evaporated under a reduced pressure. The residue was subjected to chromatography on SiO_2, eluent petroleum ether–ethyl acetate, 7:3. We obtained 0.88 g (47%) of compound **IIIa** and 0.9 g (48%) of compound **IIIb**.

(c) To a solution of 1.0 g (3.33 mmol) of the equimolar mixture of amides **II** in 20 ml of MeCN was added a solution of 1.54 g (10 mmol) of BaO in 5 ml of H_2O, and the mixture obtained was stirred at boiling for 20 h (TLC monitoring). After evaporation of acetonitrile the water phase was extracted with EtOAc (3×15 ml). The residue was subjected to chromatography on SiO_2, eluent petroleum ether–ethyl acetate, 7:3. We obtained 377 mg (46%) of compound **IIIa** and 385 mg (47%) of compound **IIIb**.).

(3aS,6aR)-3-Hydroxy-2-[(1*R*)-phenylethyl]-3,3a,6,6a-tetrahydrocyclopenta[c]pyrrol-1(2*H*)-one (IIIa), mp 105–107°C, $[\alpha]_D^{20}$ +142.4° (C 0.65, MeOH). IR spectrum, ν, cm^{-1}: 3232, 2922, 2852, 1647, 1456, 1327, 1290, 1215, 1058, 802, 702. ^1H NMR spectrum, δ, ppm: 1.68 d (3H, CH_3, J 6.8 Hz), 2.54–2.84 m (2H, C^6H), 3.21–3.33 m (1H, $C^{3a}H$), 3.39 t (1H, $C^{6a}H$, J 9.08 Hz), 3.73–4.03 br.s (1H, OH), 4.63–4.73 br.s (1H, CH–OH), 5.34 q (1H, CH–Ph, J 7.05 Hz), 5.33–5.49 m (1H, C^5H), 5.72–5.84 m (1H, C^4H), 7.13–7.35 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 18.66 (CH_3), 35.70 (C^6), 42.83 (C^{6a}), 49.96 (CH–Ph), 54.17 (C^{3a}), 84.83 (C^3), 127.32, 127.43, 128.40 (Ph), 128.61 (C^5), 132.30 (C^4), 139.79 (Ph), 177.27 (C=O). Mass spectrum (APCI), m/z (I_{rel}, %): 244 (100) $[MH]^+$, 226 (39), 198 (35.3), 177 (13.7), 161 (18.1), 121 (12.8), 93 (13.2), 65 (9.3). Found, %: C 73.28; H 6.36; N 5.25. $C_{15}H_{17}NO_2$. Calculated, %: C 74.07; H 6.70; N 5.76.

(3aR,6aS)-3-Hydroxy-2-[(1*R*)-phenylethyl]-3,3a,6,6a-tetrahydrocyclopenta[*c*]pyrrol-1(2*H*)-one (IIIb), mp 120–121°C, $[\alpha]_D^{20}$ +37.8° (C 0.8, MeOH). IR spectrum, ν, cm^{-1}: 3244 (O–H), 2922 (CH_3), 2852 (CH_3), 1651 (C=O), 1616, 1456 (CH_3), 1336 (CH_3), 1303, 1273, 1222, 1058, 805, 698. ^1H NMR spectrum, δ, ppm: 1.56 d

(3H, CH_3, J 5.7 Hz), 2.15–2.35 br.s (1H, OH), 2.54–2.84 m (2H, C^6H), 3.13–3.24 m (1H, $C^{3a}H$), 3.23 t (1H, $C^{6a}H$, J 7.08 Hz), 5.06–5.17 br.s (1H, CH–OH), 5.35 q (1H, CH–Ph, J 7.05 Hz), 5.59–5.67 m (1H, C^5H), 5.75–5.85 m (1H, C^4H), 7.20–7.54 m (5H, Ph). ^{13}C NMR spectrum, δ, ppm: 17.05 (CH_3), 35.64 (C^6), 42.85 (C^{6a}), 49.94 (CH–Ph), 53.32 (C^{3a}), 84.38 (C^3), 126.96, 127.23, 128.07 (Ph), 128.73 (C^5), 132.65 (C^4), 141.21 (Ph), 177.35 (C=O). Mass spectrum (APCI), m/z (I_{rel}, %): 244 (100) $[MH]^+$, 226 (43), 198 (33.3), 177 (16.7), 161 (15), 121 (11.7), 93 (16.7), 65 (8.3). Found, %: C 73.97; H 6.63; N 5.35. $C_{15}H_{17}NO_2$. Calculated, %: C 74.07; H 6.70; N 5.76.

(3a*S*,6a*R*,3a'*S*,6a'*R*)-3,3'-Oxybis{2-[(1*R*)-1-phenylethyl]-3,3a,6,6a-tetrahydrocyclopenta[*c*]-pyrrol-1(2*H*)-one} (IVa). To a solution of 1.5 g (5 mmol) of amide **IIIa** in 20 ml of MeCN was added a solution of 89 mg (0.5 mmol) of $PdCl_2$ in 7 ml of H_2O, and the mixture obtained was stirred at boiling for 2 h (TLC monitoring). The organic solvent was evaporated, the water phase was extracted with EtOAc (3 × 20 ml). The combined organic extracts were dried with $MgSO_4$, the solvent was evaporated under a reduced pressure. The residue was subjected to chromatography on SiO_2, eluent petroleum ether–ethyl acetate, 1:1. Yield 1.42 g (98%). Orange oily fluid, $[\alpha]_D^{20}$ +98.4° (C 1.25, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2933, 2922, 2852, 1685, 1418, 1375, 1344, 1288, 1261, 1078. ^1H NMR spectrum, δ, ppm: 1.60 d (3H, CH_3 and $C'H_3$, J 6.8 Hz), 2.54–2.84 m (3H, C^6H and $C^{3a}H$, $C^{6'}H$ and $C^{3a'}H$), 3.17 t (1H, $C^{6a}H$ and $C^{6a'}H$, J 7.08 Hz), 4.23 s (1H, CH–O and C'H–O), 5.16–5.23 m (1H, C^5H and $C^{5'}H$), 5.32 q (1H, CH–Ph and C'H–Ph, J 7.05 Hz), 5.74–5.81 m (1H, C^4H and $C^{4'}H$), 7.13–7.35 m (5H, Ph and Ph'). ^{13}C NMR spectrum, δ, ppm: 17.90 ($C'H_3$), 18.66 (CH_3), 35.51 ($C^{6'}$), 35.73 (C^6), 42.80 ($C^{6a'}$), 42.98 (C^{6a}), 48.78 (CH–Ph), 49.82 (C'H–Ph), 54.18 ($C^{3a'}$ and C^{3a}), 84.78 (C^3), 86.79 ($C^{3'}$), 127.35, 127.64, 128.01 (Ph and Ph'), 128.38 (C^5), 128.82 ($C^{5'}$), 132.33 (C^4), 133.12 ($C^{4'}$), 139.28 (Ph'), 139.81 (Ph), 177.20 (C'=O), 177.27 (C=O). Mass spectrum (APCI), m/z (I_{rel}, %): 469 (68) $[MH]^+$, 246 (31.6), 244 (32), 226 (100), 198 (28). Found, %: C 76.48; H 4.36; N 5.55. $C_{30}H_{32}N_2O_3$. Calculated, %: C 76.92; H 4.71; N 5.98.

(3a*R*,6a*S*,3a'*R*,6a'*S*)-3,3'-Oxybis{2-[(1*R*)-1-phenylethyl]-3,3a,6,6a-tetrahydrocyclopenta[*c*]-pyrrol-1(2*H*)-one} (IVb) was similarly prepared from 1.0 g (3.3 mmol) of amide **IIIb** and 60 mg (0.3 mmol) of $PdCl_2$. Yield 0.95 g (98%). Orange oily fluid, $[\alpha]_D^{20}$ +69.7° (C 1.15, $CHCl_3$). IR spectrum, ν, cm^{-1}: 2935, 2922, 2852, 1688, 1418, 1375, 1348, 1292, 1267, 1078. ^1H NMR spectrum, δ, ppm: 1.55 d (3H, CH_3 and $C'H_3$, J 6.0 Hz), 2.45–2.9 m (4H, C^6H, $C^{3a}H$, $C^{6'}H$, $C^{3a'}H$, $C^{6a}H$ and $C^{6a'}H$), 4.66 C (1H, CH–O and C'H–O), 5.18 q (1H, CH–Ph and C'H–Ph, J 7.05 Hz), 5.37–5.43 m (1H, C^5H and $C^{5'}H$), 5.78–5.85 m (1H, C^4H and $C^{4'}H$), 7.22–7.50 m (5H, Ph and Ph'). ^{13}C NMR spectrum, δ, ppm: 17.01 ($C'H_3$), 17.55 (CH_3), 35.43 ($C^{6'}$), 35.66 (C^6), 42.55 ($C^{6a'}$), 42.82 (C^{6a}), 50.06 (CH–Ph), 50.52 (C'H–Ph), 53.30 ($C^{3a'}$ and C^{3a}), 84.33 (C^3), 86.76 ($C^{3'}$), 127.00, 127.14, 127.23 (Ph and Ph'), 128.04 (C^5), 128.73 ($C^{5'}$), 132.66 (C^4), 133.60 ($C^{4'}$), 140.87 (Ph'), 141.24 (Ph), 177.26 (C'=O), 177.86 (C=O). Mass spectrum (APCI), m/z (I_{rel}, %): 469 (73) $[MH]^+$, 246 (37.6), 244 (35.2), 226 (100), 198 (22.3). Found, %: C 76.55; H 4.43; N 5.64. $C_{30}H_{32}N_2O_3$. Calculated, %: C 76.92; H 4.71; N 5.98.

Hydrolysis of compound IVa. To a solution of 1.0 g (2.1 mmol) of compound **IVa** in 15 ml of THF was added a solution of 57 mg (0.21 mmol) of $FeCl_3 \cdot 6H_2O$ in 5 ml of H_2O, and the mixture obtained was stirred at boiling for 2 h (TLC monitoring). The organic solvent was evaporated, the water phase was extracted with EtOAc (3 × 15 ml). The combined organic extracts were dried with $MgSO_4$, the solvent was evaporated under a reduced pressure. The residue was subjected to chromatography on SiO_2, eluent petroleum ether–ethyl acetate, 1:1. We obtained 0.99 g (95%) of compound **IIIa**.

Hydrolysis of compound IVb. Likewise from 1.2 g (2.5 mmol) of ether **IVb** and 68 mg (0.25 mmol) of $FeCl_3 \cdot 6H_2O$ we obtained 1.18 g (95%) of compound **IIIb**.

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