Hydrogenolysis of the C—O bond of hydroxylactams as a convenient method for the synthesis of substituted isoindolin-1-ones

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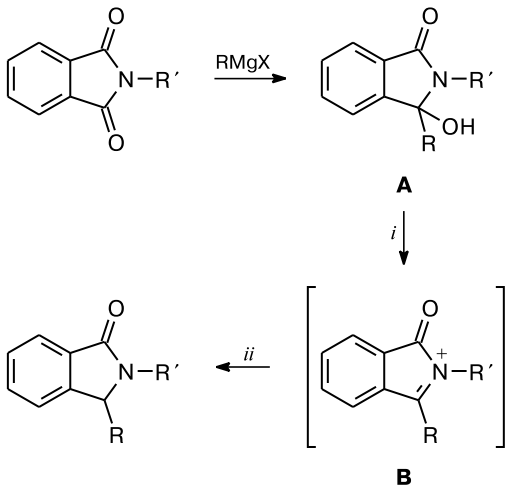
A simple and efficient method for the synthesis of isoindolin-1-ones containing alkyl or aryl substituents at positions 2 and (or) 3 was suggested. The method is based on the earlier unknown Pd^0-catalyzed hydrogenolysis of hydroxylactams.

Key words: hydroxylactams, mono- and disubstituted isoindolin-1-ones, C—O-hydrogenolysis, palladium catalyst.

Alkyl- and aryl-substituted isoindolin-1-ones are structural fragments of a number of natural alkaloids.[1—4] They are also of interest as synthons for the preparation of new potential neuroleptics,[5,6] enzyme inhibitors,[7—9] and other pharmacologically active compounds.[10,11] Relatively readily available hydroxylactams (**A**) commonly obtained by the addition of Grignard reagents to one of the carbonyl groups of phthalimide can be used as the intermediates in the synthesis of substituted isoindolin-1-ones (Scheme 1).

Scheme 1



i. HX or Lewis acid; *ii*. Hydride reduction.

Treatment of hydroxylactams **A** with protonic or Lewis acid leads to the intermediate acyliminium ions **B**, hydride reduction of which gives the target 3-alkyl- or 3-aryl-substituted isoindolin-1-ones. To accomplish these transformations, two- or three-component systems such as BF_3—Et_3SiH,[12,13] TsOH—$TiCl_4$—Et_3SiH,[14] CF_3COOH—Et_3SiH,[15—17] CF_3COOH—$NaCNBH_3$,[18] or HCl—$NaCNBH_3$ were used.[18] A disadvantage of this two-step reduction is the need to use a considerable (up to fivefold) excess of the hydride agent with respect to hydroxylactam **A**. Besides, a high acidity of the reaction medium can cause undesired side processes.

Recently, a possibility of the palladium-catalyzed hydrogenolysis of benzyl alcohols or their esters using triethylsilane[19] or polymethylhydrosiloxane as the hydride donors was shown.[20] In the present work, we report the first examples of the palladium-catalyzed hydrogenolysis of the C—O bond of hydroxylactams of the type **A** with molecular hydrogen, which, to the best of our knowledge, are not described in the literature.

Results and Discussion

Amidation of methyl 2-acetylbenzoate with ammonia or lower amines $R'NH_2$ (R′ = Me, Et) or amidation of ketoacids **1** by the mixed anhydride method (Scheme 2) gave hydroxylactams **2**.

Hydroxylactams **2** are a cyclic form of amides derived from 2-acetyl- and 2-benzoylbenzoic acid (**1a,b**). For the most substrates obtained, the cyclic form **2** is considerably more stable than the open-chain form of the corresponding amides. Hydroxylactam **2b** was synthesized by the addition of PhMgBr to phthalimide.[21]

In our earlier work[22] dealt with hydrogenation of 3-methyleneisoindolin-1-ones, Pd^0 supported on the highly porous carbon support sibunit was used as the catalyst.[23] In the present work, we used the same catalyst for the

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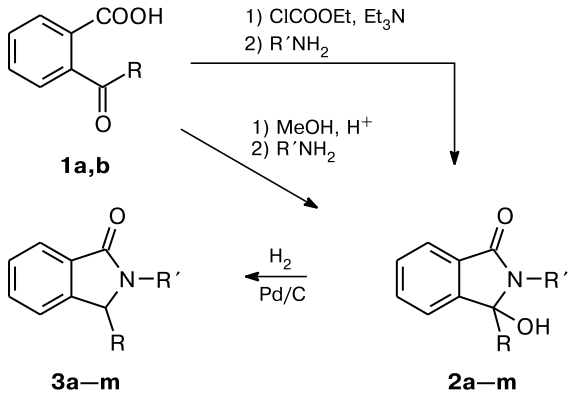
Scheme 2



R = Me (**a**), Ph (**b**)

studies of hydrogenolysis of hydroxylactams **2** (see Scheme 2). We found that hydrogenolysis readily occurred in MeOH at room temperature. For the most substrates under study, the complete conversion in this solvent was reached within 2 h with the formation of isoindolinones **3** as the only reaction products (Table 1). Hydrogenolysis in the non-polar solvent toluene proceeded considerably slower than in MeOH.

Table 1 shows that the efficiency of hydrogenolysis depends on the nature of substituents at positions 2 and 3.

Table 1. Synthesis of substituted isoindolin-1-ones **3** by catalytic hydrogenolysis of hydroxylactams[a]

Entry	Substrate (**S**)	Substituents		τ/h	Conversion of **S** (%)
		R	R´		
1	**2a**	Me	H	2	7
2[b]	**2a**	Me	H	2	100
3	**2b**	Ph	H	2	100
4	**2c**	Me	Me	2	4
5	**2c**	Me	Me	20	10
6[b]	**2c**	Me	Me	2	100
7	**2d**	Me	Et	2	100
8	**2e**	Ph	Et	20	100
9	**2f**	Me	Bn	2	100
10	**2g**	Ph	Bn	20	100
11	**2h**	Me	*p*-MeO-Bn	2	100
12	**2i**[c]	Me	(*S*)-CH(Me)Ph	2	100
13	**4**	Ph	Bu^t	20	52
14	**2l**	Me	*p*-MeO-C_6H_4	2	100
15	**2m**	Ph	*p*-MeO-C_6H_4	20	50

[a] Reaction conditions: the substrate (**S**) (0.37 mmol), Pd(1%)/C, the molar ratio **S**/Pd = 100, the solvent MeOH (3 mL), 20 atm (H_2), 22 °C.

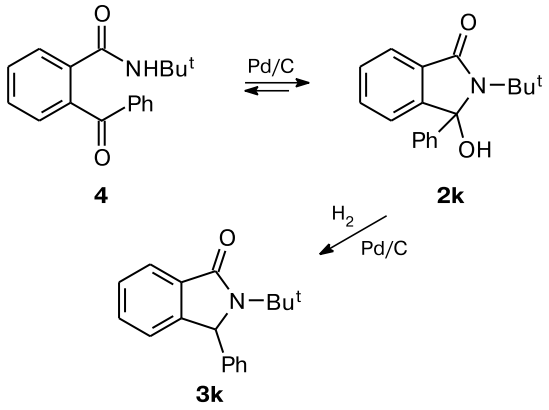
[b] A 1.38 *M* solution of HCl in dioxane (20 mol.% calculated on the substrate) was added as a cocatalyst.

[c] Hydrogenolysis gave a mixture of two diastereoisomers **3i** in the ratio 1 : 1.

The most reactive substrates are the 2,3-disubstituted hydroxylactams with bulky substituents at the nitrogen atom. At the same time, under the standard conditions 3-methyl- and 2,3-dimethyl-substituted hydroxylactams **2a** and **2c** (R´ = H, CH_3, respectively) showed a lower reactivity as compared to the majority of substrates tested (entries *1* and *4*). However, the addition of the acid cocatalyst (HCl) made it possible to achieve a complete conversion of these reagents at room temperature within 2 h (entries *2* and *6*). The reactivity of 3-methyl-substituted hydroxylactams **2** was much higher as compared to that of 3-phenyl-substituted substrates containing the same amide fragments (*cf.* entries *7* and *8*, *9* and *10*, *14* and *15*).

Unlike the most substrates obtained in the highly stable cyclic form **2**, the amidation of γ-ketoacid **1b** with sterically hindered *tert*-bulylamine initially led to the formation of the open-chain form of benzamide **4** as the only initial product (Scheme 3).

Scheme 3

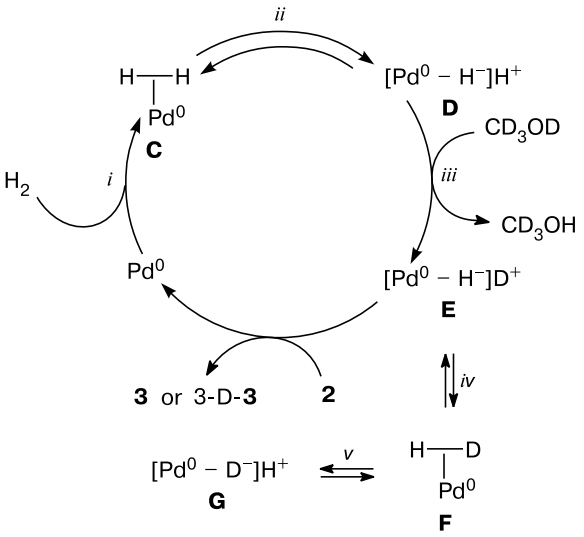


Nonetheless, it could be suggested that under conditions of Pd-catalyzed reduction it would be possible for the open-chain form of amide **4** to close the ring to yield the cyclic form (lactam **2k**) with subsequent hydrogenolysis of the C—O bond of the latter. This suggestion was confirmed experimentally (entry *13*). The ^{1}H NMR-monitoring of the process of reduction of amide **4** in the presence of Pd/C catalyst shows that in the reaction mixture amide **4** and hydroxylactam **2k** are at equilibrium. In this case both the conversion of the open-chain form of amide to the cyclic configuration and subsequent hydrogenolysis of **2k** are slow processes. After the reaction mixture was reduced for 20 h, it contained the intermediate **2k** and isoindolinone **3k** in the molar ratio 1 : 1.

By analogy with the reduction of hydroxylactams of the type **A** by the systems acid—hydride agent that involves the intermediate acyliminium ion **B** (see Scheme 1),[12–17] it can be assumed that hydrogenolysis of substrates **2** in MeOH also follows the ionic mechanism, including a Pd-catalyzed heterolysis of molecular

hydrogen and the formation of the ionic intermediate **D** (Scheme 4).

Scheme 4



To confirm this suggestion, we carried out a Pd-catalyzed hydrogenolysis of hydroxylactam **2f** in CD_3OD and determined the isotopic composition of the reaction product **3f**. As we have shown[24] earlier for the Ru-catalyzed reduction of methyl levulinate with molecular hydrogen in MeOD, a rapid H/D-exchange between the H_2 and the deuterated solvent was observed in the course of this reaction, most likely proceeding through the step of heterolysis of H_2 on the metal complex. This exchange, in turn, led to the isotopic enrichment of the reduction product, resulting from the involvement of the active particles Ru—D generated in MeOD by the H/D-exchange in the catalytic cycle. In the present work, a similar result was obtained in the hydrogenolysis of substrate **2f** in CD_3OD under conditions given in the note to the Table 1. In this experiment, isoindolinone **3f** isolated from the reaction mixture contained (according to the ^1H NMR data) 75% of deuterium at position C(3). It is obvious that the hydrogenolysis process includes the heterolysis of the H_2 molecules on Pd^0 atoms (see Scheme 4, steps *ii*, *iii*) with the formation of ionic intermediates **D** and **E**, which are involved in subsequent H/D-exchange with deuteromethanol due to the rapid steps (*iii*—*v*) of the catalytic cycle involving intermediates **E—G**. More recently, both the experimental[25—31] and the theoretical[32] studies indicated an important role of transition metal anionic complexes, including Pd^0 complexes, in the organic reactions catalyzed by metal complexes.

In conclusion, we developed a simple and convenient method for the synthesis of 3-substituted and 2,3-disubstituted isoindolin-1-ones based on the earlier unknown reaction of hydrogenolysis of hydroxylactams. An ionic mechanism of hydrogenolysis is considered to be the most probable.

Experimental

Commercially available 2-acetylbenzoic acid, 2-benzoylbenzoic acid, phthalimide, ethyl chloroformate, ammonia, methylamine, ethylamine, benzylamine, *p*-methoxybenzylamine, anisidine, *tert*-bulylamine, bromobenzene (Aldrich), (*S*)-(–)-1-ethyl-1-phenylamine (Zeeland chemicals, INC), metallic sodium, magnesium turnings, Pd(1%)/sibunit were used without preliminary purification. Methyl 2-acetylbenzoate **1a** was synthesized according to the procedure published earlier.[33]

Methanol, ethanol, THF, diethyl ether, and triethylamine were dried and distilled under argon.

Melting points were determined on a Kofler heating stage. Flash-chromatography was performed on a column with silica gel 60 (Fluka), using the system ethyl acetate—light petroleum (2 : 1) as the eluent. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer. High resolution mass spectra (ESI) were recorded on a Bruker maXis instrument.[34]

3-Hydroxy-3-methylisoindolin-1-one (2a). A solution of methyl 2-acetylbenzoate (10 g, 0.06 mol) in methanol (150 mL) was saturated with ammonia (9.5 g, 0.56 mol). The reaction mixture was stirred for three weeks at ~20 °C. The solvent was evaporated, a solid residue was crystallized from ethyl acetate. Light yellow crystals. The yield was 8.5 g (93%), m.p. 111—113 °C (*cf.* Ref. 35: m.p. 139—140 °C). Found (%): C, 66.38; H, 5.59; N, 8.65. $C_9H_9NO_2$. Calculated (%): C, 66.25; H, 5.56; N, 8.58. ^1H NMR (DMSO-d_6), δ: 1.79 (s, 3 H, CH_3); 3.98 (s, 1 H, OH); 7.18 (s, 1 H, NH); 7.31—7.45 (m, 1 H, Ph); 7.52 (d, 1 H, Ph, J = 7.4 Hz); 7.58 (s, 2 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 26.6; 84.8; 121.8; 122.3; 128.8; 131.0; 132.0; 150.5; 167.4. Found: m/z 186.0533 $[M]^+$. Calculated: M = 186.1631.

3-Hydroxy-3-phenylisoindolin-1-one (2b). Magnesium turnings (0.7 g, 0.029 mol) were placed in a glass flask (100 mL), a crystal of iodine was added, and the mixture was heated for 1 h at 100 °C under argon. After cooling, anhydrous diethyl ether (30 mL) and one tenth of the required amount of PhBr (0.43 g, 0.003 mol) were added. After the reaction was initiated, the rest of the solution of PhBr (3.87 g, 0.024 mol) in diethyl ether (10 mL) was added dropwise, then the reaction mixture was refluxed for 1 h with stirring. A solution of phthalimide (2 g, 0.014 mol) in anhydrous THF (20 mL) was added dropwise to the cooled (ice bath) Grignard reagent, and the mixture was stirred for 3 h at ~20 °C. After the solvent was evaporated, the residue was dissolved in CH_2Cl_2, sequentially washed with saturated aqueous NH_4Cl, $NaHCO_3$, and NaCl, then dried with $MgSO_4$. The solvent was evaporated, the residue was purified by column chromatography (silica gel), eluent ethyl acetate—light petroleum (2 : 1). R_f = 0.73. White crystals. The yield was 0.9 g (30%), m.p. 160—162 °C (*cf.* Ref. 36: m.p. 164—165 °C). Found (%): C, 74.43; H, 4.95; N, 6.24. $C_{14}H_{11}NO_2$. Calculated (%): C, 74.65; H, 4.92; N, 6.22. ^1H NMR (DMSO-d_6), δ: 7.26—7.41 (m, 4 H, Ph); 7.41—7.56 (m, 4 H, Ph); 7.65 (d, 1 H, Ph, J = 7.1 Hz); 9.23 (s, 1 H, OH). ^{13}C NMR (DMSO-d_6), δ: 87.3; 122.5; 122.8; 125.4; 127.7; 128.2; 128.9; 130.6; 132.3; 142.1; 150.8; 168.3. Found: m/z 248.2391 $[M]^+$. Calculated: M = 248.2384.

3-Hydroxy-2,3-dimethylisoindolin-1-one (2c) was obtained by the amidation of methyl ester of ketoacid **1a** (10 g, 0.06 mol)

with methylamine (17.4 g, 0.56 mol) similarly to compound **2a**. White powder. The yield was 6.2 g (62%), m.p. 127—130 °C (*cf.* Ref. 37: m.p. 134—136 °C). Found (%): C, 67.54; H, 6.21; N, 7.82. $C_{10}H_{11}NO_2$. Calculated (%): C, 67.78; H, 6.26; N, 7.90. ^{1}H NMR (DMSO-d_6), δ: 1.58 (s, 3 H, C$\underline{H}_3$—C(OH)); 2.88 (s, 3 H, NCH_3); 6.21 (s, 1 H, OH); 7.42—7.55 (m, 1 H, Ph); 7.65 (s, 3 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 22.8; 23.9; 87.2; 121.8; 122.1; 128.9; 130.7; 131.8; 148.9; 165.3. Found: *m/z* 200.0682 $[M]^+$. Calculated: *M* = 200.1896.

2-Ethyl-3-hydroxy-3-methylisoindolin-1-one (2d) was obtained by the amidation of methyl 2-acetylbenzoate (10 g, 0.06 mol) with anhydrous ethylamine (25.2 g, 0.56 mol) similarly to compound **2a**. White powder. The yield was 8.6 g (80%), m.p. 124—126 °C (*cf.* Ref. 35: m.p. 128—130 °C). Found (%): C, 69.23; H, 6.82; N, 7.27. $C_{11}H_{13}NO_2$. Calculated (%): C, 69.09; H, 6.85; N, 7.32. ^{1}H NMR (DMSO-d_6), δ: 1.28 (t, 3 H, CH_3, *J* = 7.2 Hz); 1.73 (s, 3 H, CH_3); 2.85 (s, 1 H, OH); 3.32—3.44 (m, 1 H, $CH_a\underline{H}_bCH_3$); 3.45—3.60 (m, 1 H, $C\underline{H}_aH_bCH_3$); 7.41—7.50 (m, 1 H, Ph); 7.51—7.60 (m, 2 H, Ph); 7.67 (d, 1 H, Ph, *J* = 7.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 14.54; 24.9; 32.4; 87.8; 121.8; 122.0; 128.9; 130.7; 131.8; 135.3; 149.1. Found: *m/z* 214.0838 $[M]^+$. Calculated: *M* = 214.2162.

2-Ethyl-3-hydroxy-3-phenylisoindolin-1-one (2e). Triethylamine (2.2 g, 0.02 mol) and ethyl chloroformate (2.4 g, 0.02 mol) were sequentially added dropwise to a cooled (0 °C) solution of ketoacid **1b** (5 g, 0.02 mol) in anhydrous THF (150 mL). Anhydrous ethylamine (1 g, 0.02 mol) was added after 20 min. The reaction mixture was stirred for 5 h at ~20 °C. A white precipitate was filtered off and the solvent was evaporated. The combined precipitates were dissolved in CH_2Cl_2, the solution was washed with water, saturated aq. $NaHCO_3$, and brine and dried with $MgSO_4$. The solvent was evaporated, the residue was crystallized from ethanol. White crystals. The yield was 3 g (54%), m.p. 168—170 °C (*cf.* Ref. 38: m.p. 168—170 °C). Found (%): C, 76.51; H, 5.95; N, 5.55. $C_{16}H_{15}NO_2$. Calculated (%): C, 75.87; H, 5.97; N, 5.53. ^{1}H NMR (DMSO-d_6), δ: 1.00 (t, 3 H, CH_3, *J* = 7.2 Hz); 2.96—3.10 (m, 1 H, $CH_a\underline{H}_bCH_3$); 3.32—3.47 (m, 1 H, $C\underline{H}_aH_bCH_3$); 7.04 (s, 1 H, OH); 7.23 (d, 1 H, Ph, *J* = 6.4 Hz); 7.33 (s, 5 H, Ph); 7.56—7.57 (m, 2 H, Ph); 7.71 (d, 1 H, Ph, *J* = 6.3 Hz). ^{13}C NMR (DMSO-d_6), δ: 14.0; 33.5; 90.5; 122.2; 122.6; 125.8; 127.9; 128.4; 129.0; 130.7; 132.3; 140.2; 149.6; 166.3. Found: *m/z* 276.0995 $[M]^+$. Calculated: *M* = 276.2856.

2-Benzyl-3-hydroxy-3-methylisoindolin-1-one (2f) was obtained from ketoacid **1a** (10 g, 0.06 mol) and benzylamine (6.4 g, 0.06 mol) similarly to compound **2e**. Crystallized from benzene. Yellow crystals. The yield was 8.5 g (55%), m.p. 157—159 °C (*cf.* Ref. 35: m.p. 166—168 °C). Found (%): C, 75.96; H, 5.96; N, 5.65. $C_{16}H_{15}NO_2$. Calculated (%): C, 75.87; H, 5.97; N, 5.53. ^{1}H NMR (DMSO-d_6), δ: 1.43 (s, 3 H, CH_3); 4.45 (d, 1 H, $CH_a\underline{H}_b$, *J* = 15.9 Hz); 4.79 (d, 1 H, $C\underline{H}_aH_b$, *J* = 15.9 Hz); 6.42 (s, 1 H, OH); 7.20—7.37 (m, 5 H, Ph); 7.49—7.59 (m, 1 H, Ph); 7.61—7.68 (m, 2 H, Ph); 7.71 (d, 1 H, Ph, *J* = 7.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 25.4; 87.9; 121.9; 122.4; 126.6; 127.3; 128.1; 129.1; 130.3; 132.2; 138.9; 149.1; 166.2. Found: *m/z* 276.0995 $[M]^+$. Calculated: *M* = 276.2856.

2-Benzyl-3-hydroxy-3-phenylisoindolin-1-one (2g) was obtained from ketoacid **1b** (5 g, 0.02 mol) and benzylamine (2.1 g, 0.02 mol) similarly to compound **2e**. The product was crystallized from benzene. Light yellow crystals. The yield was 4.6 g (67%), m.p. 144—146 °C (*cf.* Ref. 39: m.p. 145—147 °C). Found (%): C, 79.57; H, 5.45; N, 4.41. $C_{21}H_{17}NO_2$. Calculated (%): C, 79.98; H, 5.43; N, 4.44. ^{1}H NMR (DMSO-d_6), δ: 4.23 (d, 1 H, $CH_a\underline{H}_b$, *J* = 15.4 Hz); 4.52 (d, 1 H, $C\underline{H}_aH_b$, *J* = 15.5 Hz); 7.09 (s, 1 H, OH); 7.11—7.33 (m, 11 H, Ph); 7.51—7.59 (m, 2 H, Ph); 7.75 (d, 1 H, Ph, *J* = 7.0 Hz). ^{13}C NMR (DMSO-d_6), δ: 122.5; 122.9; 125.9; 126.4; 127.7; 127.8; 127.9; 128.3; 129.2; 130.3; 132.5; 138.1; 139.9; 149.6; 166.9. Found: *m/z* 338.1151 $[M]^+$. Calculated: *M* = 338.3550.

3-Hydroxy-2-(*p*-methoxybenzyl)-3-methylisoindolin-1-one (2h) was obtained from ketoacid **1a** (10 g, 0.06 mol) and *p*-methoxybenzylamine (8.4 g, 0.06 mol) similarly to compound **2e**. White powder. The yield was 12.6 g (73%), m.p. 164—166 °C. Found (%): C, 72.38; H, 6.09; N, 4.91. $C_{17}H_{17}NO_3$. Calculated (%): C, 72.07; H, 6.05; N, 4.94. ^{1}H NMR (DMSO-d_6), δ: 1.41 (s, 3 H, CH_3); 3.71 (s, 3 H, OCH_3); 4.35 (d, 1 H, $CH_a\underline{H}_b$, *J* = 15.6 Hz); 4.71 (d, 1 H, $C\underline{H}_aH_b$, *J* = 15.5 Hz); 6.37 (s, 1 H, OH); 6.85 (d, 2 H, Ph, *J* = 8.5 Hz); 7.28 (d, 2 H, Ph, *J* = 8.5 Hz); 7.48—7.53 (m, 1 H, Ph); 7.61 (m, 2 H, Ph); 7.67 (d, 1 H, Ph, *J* = 7.4 Hz). ^{13}C NMR (DMSO-d_6), δ: 25.5; 40.4; 54.9; 87.9; 113.6; 121.9; 122.3; 128.7; 129.0; 130.3; 130.9; 132.1; 149.1; 158.1; 166.1. Found: *m/z* 306.1101 $[M]^+$. Calculated: *M* = 306.3116.

3-Hydroxy-3-methyl-2-[(1*S*)-1-phenylethyl]isoindolin-1-one (2i) was obtained from ketoacid **1a** (10 g, 0.06 mol) and (*S*)-(−)-1-ethyl-1-phenylamine (7.4 g, 0.06 mol) according to the procedure.[22]

3-Hydroxy-2-(*p*-methoxyphenyl)-3-methylisoindolin-1-one (2l) was obtained from ketoacid **1a** (10 g, 0.06 mol) and anisidine (7.4 g, 0.06 mol) similarly to compound **2e**. White powder. The yield was 9.5 g (56%), m.p. 135—137 °C. Found (%): C, 71.58; H, 5.65; N, 5.23. $C_{16}H_{15}NO_3$. Calculated (%): C, 71.36; H, 5.61; N, 5.20. ^{1}H NMR (DMSO-d_6), δ: 1.58 (s, 3 H, CH_3); 3.83 (s, 3 H, OCH_3); 3.88 (s, 1 H, OH); 6.88 (d, 2 H, Ph, *J* = 8.9 Hz); 7.32 (d, 2 H, Ph, *J* = 8.8 Hz); 7.29—7.48 (m, 2 H, Ph); 7.58 (d, 2 H, Ph, *J* = 3.9 Hz). ^{13}C NMR (DMSO-d_6), δ: 24.8; 55.2; 89.2; 113.9; 122.1; 122.7; 128.3; 129.1; 129.4; 130.3; 132.5; 148.9; 158.1; 165.4. Found: *m/z* 292.0944 $[M]^+$. Calculated: *M* = 292.2850.

3-Hydroxy-2-(*p*-methoxyphenyl)-3-phenylisoindolin-1-one (2m) was obtained from ketoacid **1b** (5 g, 0.02 mol) and anisidine (2.5 g, 0.02 mol) similarly to compound **2e**. White powder. The yield was 4.8 g (66%), m.p. 200—202 °C (*cf.* Ref. 40: m.p. 200—201 °C). Found (%): C, 76.76; H, 5.19; N, 4.26. $C_{21}H_{17}NO_3$. Calculated (%): C, 76.12; H, 5.17; N, 4.23. ^{1}H NMR (DMSO-d_6), δ: 3.69 (s, 3 H, OCH_3); 6.83 (d, 2 H, Ph, *J* = 8.9 Hz); 7.18—7.35 (m, 8 H, Ph, OH); 7.53—7.63 (m, 3 H, Ph); 7.82 (d, 1 H, Ph, *J* = 7.2 Hz). ^{13}C NMR (DMSO-d_6), δ: 55.1; 92.0; 113.5; 122.8; 122.9; 126.0; 127.7; 127.8; 128.2, 128.9; 129.3; 130.0; 132.9; 140.0; 149.5; 157.3; 166.2. Found: *m/z* 354.1101 $[M]^+$. Calculated: *M* = 354.3544.

2-Benzoyl-*tert*-bulylbenzamide (4) was obtained from ketoacid **1b** (5 g, 0.02 mol) and *tert*-bulylamine (1.5 g, 0.02 mol) similarly to compound **2e**. White powder. The yield was 3.6 g (58%), m.p. 98—100 °C. Found (%): C, 77.34; H, 6.79; N, 5.01. $C_{18}H_{19}NO_2$. Calculated (%): C, 76.84; H, 6.81; N, 4.98. ^{1}H NMR (DMSO-d_6), δ: 1.07 (s, 9 H, 3 CH_3); 7.41—7.49 (m, 3 H, Ph); 7.57—7.67 (m, 5 H, Ph); 7.98 (s, 1 H, Ph). ^{13}C NMR (DMSO-d_6), δ: 27.9; 50.6; 128.0; 128.2; 128.4; 128.5; 128.9; 129.6; 129.9; 132.6; 137.3; 137.4; 139.0; 166.7; 196.5. Found: *m/z* 304.1308 $[M]^+$. Calculated: *M* = 304.3388.

Pd-Catalyzed hydrogenolysis of hydroxylactams 2 (general procedure). A mixture of Pd(1%)/sibunit (39 mg, 0.0037 mg-at.

of Pd) and hydroxylactam **2** (0.3700 mmol) were placed in a glass tube preliminary evacuated and filled with argon, then anhydrous methanol (3 mL) was added. The tube was placed in a steel autoclave (50 mL), which then was purged and filled with purified hydrogen (20 atm). The reaction mixture was stirred with a magnetic stirrer (700 rpm) at ~20 °C for a required time (see Table 1). Once the reaction was completed, the solution was passed through a layer of silica gel to remove the catalyst, the solvent was evaporated. The conversion level was determined by ^{1}H NMR spectroscopy.

3-Methylisoindolin-1-one (3a). Yellow crystals, m.p. 98—100 °C (*cf.* Ref. 41: m.p. 117—118 °C). Found (%): C, 73.67; H, 6.26; N, 9.49. C_9H_9NO. Calculated (%): C, 73.45; H, 6.16; N, 9.52. ^{1}H NMR ($CDCl_3$), δ: 1.51 (d, 3 H, $CHC\underline{H}_3$, J = 6.7 Hz); 4.71 (q, 1 H, $C\underline{H}CH_3$, J = 6.5 Hz); 7.40—7.50 (m, 2 H, Ph); 7.51—7.59 (m, 1 H, Ph); 7.85 (d, 1 H, Ph, J = 7.0 Hz); 8.02 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 20.3; 52.8; 122.2; 123.8; 128.1; 131.7; 131.9; 134.2; 149.0; 171.3. Found: m/z 170.1598 $[M]^+$. Calculated: M = 170.1637.

3-Phenylisoindolin-1-one (3b). Colorless oil.[42] Found (%): C, 80.74; H, 5.26; N, 6.72. $C_{14}H_{11}NO$. Calculated (%): C, 80.36; H, 5.30; N, 6.69. ^{1}H NMR (DMSO-d_6), δ: 5.73 (s, 1 H, $C\underline{H}Ph$); 7.27—7.39 (m, 6 H, Ph); 7.42—7.59 (m, 2 H, Ph); 7.72 (d, 1 H, Ph, J = 7.1 Hz); 9.06 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 59.5; 122.8; 123.4; 126.5; 127.8; 128.1; 128.7; 131.3; 131.8; 139.6; 148.1; 169.6. Found: m/z 232.1989 $[M]^+$. Calculated: M = 1232.233.

2,3-Dimethylisoindolin-1-one (3c). Colorless oil.[43] Found (%): C, 74.96; H, 6.79; N, 8.75. $C_{10}H_{11}NO$. Calculated (%): C, 74.51; H, 6.88; N, 8.69. ^{1}H NMR ($CDCl_3$), δ: 1.48 (d, 3 H, $CHC\underline{H}_3$, J = 6.8 Hz); 3.11 (s, 3 H, NCH_3); 4.41 (q, 1 H, $C\underline{H}CH_3$, J = 6.7 Hz); 7.37—7.44 (m, 2 H, Ph); 7.46—7.52 (m, 1 H, Ph); 7.80 (d, 1 H, Ph, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 17.9; 26.9; 57.5; 121.8; 123.3; 128.0; 131.2; 131.3; 132.0; 146.7; 168.0. Found: m/z 184.2231 $[M]^+$. Calculated: M = 184.1902.

2-Ethyl-3-methylisoindolin-1-one (3d). Colorless oil.[43] Found (%): C, 74.87; H, 7.61; N, 8.03. $C_{11}H_{13}NO$. Calculated (%): C, 75.40; H, 7.48; N, 7.99. ^{1}H NMR ($CDCl_3$), δ: 1.22 (t, 3 H, $CH_aH_bC\underline{H}_3$, J = 7.2 Hz); 1.44 (d, 3 H, $CHC\underline{H}_3$, J = 6.7 Hz); 3.22—3.36 (m, 1 H, $CH_a\underline{H}_bCH_3$); 3.89—4.10 (m, 1 H, $C\underline{H}_aH_bCH_3$); 4.54 (q, 1 H, $C\underline{H}CH_3$, J = 6.7 Hz); 7.36—7.45 (m, 2 H, Ph); 7.48—7.55 (m, 1 H, Ph); 7.80 (d, 1 H, Ph, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 13.7; 18.1; 34.6; 55.1; 121.8; 123.4; 128.0; 131.2; 132.1; 146.8; 167.7. Found: m/z 198.2631 $[M]^+$. Calculated: M = 198.2168.

2-Ethyl-3-phenylisoindolin-1-one (3e). White powder, m.p. 80—82 °C (*cf.* Ref. 44: m.p. 97—98 °C). Found (%): C, 81.14; H, 6.59; N, 5.87. $C_{16}H_{15}NO$. Calculated (%): C, 80.98; H, 6.37; N, 5.90. ^{1}H NMR ($CDCl_3$), δ: 1.12 (t, 3 H, CH_3, J = 7.2 Hz); 2.90—3.02 (m, 1 H, $CH_a\underline{H}_bCH_3$); 3.89—4.02 (m, 1 H, $C\underline{H}_aH_bCH_3$); 5.46 (s, 1 H, $C\underline{H}Ph$); 7.10—7.18 (m, 3 H, Ph); 7.31—7.39 (m, 3 H, Ph); 7.40—7.48 (m, 2 H, Ph); 7.83—7.90 (m, 1 H, Ph). ^{13}C ($CDCl_3$), δ: 13.5; 35.0; 64.1; 123.0; 123.4; 127.5; 128.3; 128.4; 128.6; 129.1; 131.6; 131.8; 137.1; 146.3; 168.4. Found: m/z 260.3127 $[M]^+$. Calculated: M = 260.2862.

2-Benzyl-3-methylisoindolin-1-one (3f). Colorless oil.[43] Found (%): C, 81.17 H, 6.18; N, 5.79. $C_{16}H_{15}NO$. Calculated (%): C, 80.98; H, 6.37; N, 5.90. ^{1}H NMR ($CDCl_3$), δ: 1.43 (d, 3 H, $CHC\underline{H}_3$, J = 6.7 Hz); 4.26 (d, 1 H, $PhCH_a\underline{H}_b$, J = 5.1 Hz); 4.37 (q, 1 H, $C\underline{H}CH_3$, J = 6.7 Hz); 5.33 (d, 1 H, $PhC\underline{H}_aH_b$, J = 5.1 Hz); 7.29 (s, 5 H, Ph); 7.35 (d, 1 H, Ph, J = 7.5 Hz); 7.43—7.55 (m, 2 H, Ph); 7.89 (d, 1 H, Ph, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.0; 43.5; 43.7; 53.4; 54.9; 121.9; 123.8; 127.5; 128.0; 128.1; 128.7; 131.5; 131.7; 137.3; 147.0; 168.1. Found: m/z 260.3518 $[M]^+$. Calculated: M = 260.2862.

2-Benzyl-3-phenylisoindolin-1-one (3g). White powder, m.p. 102—106 °C (*cf.* Ref. 45: m.p. 136 °C). Found (%): C, 84.57; H, 5.74; N, 4.71. $C_{21}H_{17}NO$. Calculated (%): C, 84.25; H, 5.72; N, 4.68. ^{1}H NMR ($CDCl_3$), δ: 3.73 (d, 1 H, $CH_a\underline{H}_bPh$, J = 4.8 Hz); 5.24 (s, 1 H, $C\underline{H}Ph$); 5.38 (d, 1 H, $C\underline{H}_aH_bPh$, J = 4.8 Hz); 7.01—7.10 (m, 3 H, Ph); 7.13—7.19 (m, 2 H, Ph); 7.22—7.26 (m, 3 H, Ph); 7.30—7.36 (m, 3 H, Ph); 7.41—7.50 (m, 2 H, Ph); 7.91—7.98 (m, 1 H, Ph). ^{13}C NMR ($CDCl_3$), δ: 44.0; 63.8; 123.3; 123.9; 127.7; 127.9; 128.5; 128.6; 128.8; 129.3; 132.0; 136.8; 137.1; 146.5; 168.7. Found: m/z 322.3671 $[M]^+$. Calculated: M = 322.3556.

2-(*p*-Methoxybenzyl)-3-methylisoindolin-1-one (3h). Colorless oil. Found: C, 76.43; H, 6.54; N, 5.36. $C_{17}H_{17}NO_2$. Calculated (%): C, 76.38; H, 6.41; N, 5.24. ^{1}H NMR ($CDCl_3$), δ: 1.14 (d, 3 H, $CHC\underline{H}_3$, J = 6.7 Hz); 3.95 (d, 1 H, $NCH_aC\underline{H}_b$, J = 15.0 Hz); 4.09 (q, 1 H, $C\underline{H}CH_3$, J = 6.7 Hz); 4.91 (d, 1 H, $NC\underline{H}_aCH_b$, J = 15.0 Hz); 6.55 (d, 2 H, Ph, J = 8.6 Hz); 6.93 (d, 2 H, Ph, J = 8.6 Hz); 7.09—7.27 (m, 3 H, Ph); 7.53 (d, 1 H, Ph, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$), δ: 17.4, 42.4, 54.2, 54.6, 113.5, 121.5, 122.8, 127.4, 128.6, 128.7, 130.9, 146.4, 158.3, 167.2. Found: m/z 290.3731 $[M]^+$. Calculated: M = 290.3122.

3-Methyl-2-[(1*S*)-1-phenylethyl]isoindolin-1-one (3i). Colorless oil[22] was obtained as a mixture of two diastereoisomers (1 : 1).

2-*tert*-Bulyl-3-phenylisoindolin-1-one (3k). ^{1}H NMR ($CDCl_3$), δ: 1.20 (s, 9 H, 3 CH_3); 5.83 (s, 1 H, $C\underline{H}Ph$); 7.12—7.40 (m, 9 H, Ph).

2-(*p*-Methoxyphenyl)-3-methylisoindolin-1-one (3l). Cream powder, m.p. 85—86 °C (*cf.* Ref. 46: m.p. 88—90 °C). Found (%): C, 75.92; H, 6.14; N, 5.49. $C_{16}H_{15}NO_2$. Calculated (%): C, 76.34; H, 5.97; N, 5.53. ^{1}H NMR ($CDCl_3$), δ: 1.42 (d, 3 H, $CHC\underline{H}_3$, J = 6.7 Hz); 3.82 (s, 3 H, OCH_3); 5.09 (q, 1 H, $C\underline{H}CH_3$, J = 6.7 Hz); 6.97 (d, 2 H, Ph, J = 8.9 Hz); 7.41—7.51 (m, 4 H, Ph); 7.55—7.61 (m, 1 H, Ph); 7.90 (d, 1 H, Ph, J = 7.5 Hz). ^{13}C NMR ($CDCl_3$), δ: 18.7; 55.5; 57.4; 114.4; 122.0; 124.0; 125.4; 128.3; 130.0; 131.9; 132.7; 146.4; 157.5; 166.9. Found: m/z 276.3124 $[M]^+$. Calculated: M = 276.2856.

2-(*p*-Methoxyphenyl)-3-phenylisoindolin-1-one (3m). ^{1}H NMR ($CDCl_3$), δ: 3.68 (s, 3 H, OCH_3); 6.05 (s, 1 H, $C\underline{H}Ph$); 6.71—6.84 (m, 2 H, Ph); 7.14—7.52 (m, 10 H, Ph); 7.81—7.91 (m, 1 H, Ph).

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