Synthesis of Novel Spiroazetidinones by Selective Lactam-Carbonyl Cleavage in 1-Aryl/Cyclohexyl-3,3-diphenyl-1'-(diphenylacetyl)spiro[azetidin-2,3'-indoline]-2',4-diones

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Titled compounds undergo selective N-C cleavage on treatment with sodium hydroxide in ethanol affording a series of novel isatin-based spiroazetidinones.

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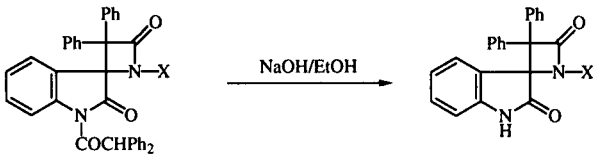
Studies on lactams have drawn considerable attention of chemists due to a wide spectrum of biological activities associated with them [1-6]. Lactams are highly sensitive to acids and bases while the syntheses employing them often require protection and deprotection of N-H using such reagents. The treatment of β-lactam derivatives with sodium hydroxide is known to undergo β-lactam ring-opening leading to the formation of (a) β-amino acids [7] and (b) olefin and primary amines [8]. Some γ- and ω-lactam carbamates are reported to undergo regioselective methanolysis by sodium methoxide to afford cyclic γ- or ω-amino acid methyl esters [9,10].

The present paper reveals a highly selective N-C cleavage in spiroazetidinones **Ia-d** [11] on treatment with sodium hydroxide in ethanol. It results in decarbonylation at nitrogen of γ-lactam ring leading to the formation of the corresponding 1-aryl/cyclohexyl-3,3-diphenyl-2-spiro-[azetidin-2,3'-indoline]-2',4-diones **IIa-d** in almost quantitative yields rather than opening either of the two rings. The products have been characterized on the basis of satisfactory analytical and spectral (ir, ^1H and ^{13}C nmr and ms) data. It is noteworthy to mention here that these products which might be of interest for their biological activities and as synthons due to free N-H are unobtainable by an equimolar reaction of diphenylketene with isatin imines [12].

The ir spectra displayed bands at 3325-50 (N-H), 1750 and 1742 cm^{-1} (C=O). The ^1H nmr spectra exhibited ten aromatic protons less than that in the ^1H nmr spectra of the respective substrates and also the singlet signal of methine proton at δ 6.30 ppm disappeared. A broad singlet signal between δ 8.00 and 9.00, exchangeable on deuteration, is assigned to amido proton. The signals in ^{13}C nmr spectra were also less by one carbonyl, one methine and eight aromatic carbons.

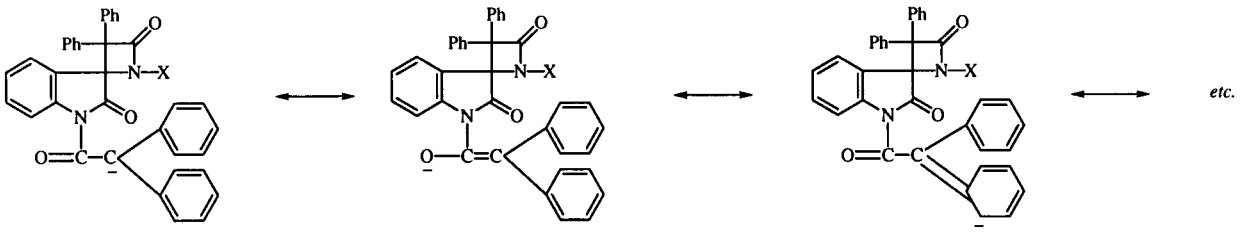
This cleavage seems to be favored due to the possible resonance - stabilized carbanion formed from deprotonation of methine carbon in **I** by hydroxide ion.

Scheme



Ia-d **IIa-d**

X = a: Phenyl; b: 1-Naphthyl; c: 4-Ethoxyphenyl; d: Cyclohexyl.



EXPERIMENTAL

The ir spectra were recorded in potassium bromide on a Perkin-Elmer 720 spectrophotometer, ^1H and ^{13}C nmr spectra in deuteriochloroform on Geol FX spectrometer at 270 MHz and 67.8 MHz, respectively, using tetramethylsilane as an internal standard, and mass spectra on a Hitachi Perkin-Elmer model RMU-6E spectrometer at 70 eV.

A solution of sodium hydroxide (100 mg) and 0.1 mmole of spirozetidinone **I** in 15 ml of ethanol was heated to reflux for 3 hours. After evaporation of ethanol under reduced pressure, the residue was diluted with water (25 ml), neutralized with hydrochloric acid and extracted with dichloromethane (2 x 15 ml). The organic fraction was dried over anhydrous sodium sulphate. The removal of solvent under reduced pressure afforded white solid residue [13] which was recrystallized with *n*-hexane-benzene. The characterization data are given below:

1,3,3-Triphenylspiro[azetidine-2,3'-indoline]-2',4-dione (**IIa**).

X = Phenyl; mp 117-118 °C; δ H, 8.98 (bs, 1H, NH, D_2O ex), 7.65 (m, 2H, arom), 7.36-7.16 (m, 13H, arom), 7.05 (m, 1H, arom), 6.75 (d, J = 7.58 Hz, 1H, arom), 6.65 (m, 1H, arom), 6.15 (d, J = 7.58 Hz, 1H, arom); δ C, 175.96, 166.13, 140.67, 138.03, 137.53, 136.79, 130.60, 129.18, 128.62, 128.33, 128.11, 127.78, 127.46, 127.01, 126.74, 124.75, 122.80, 122.45, 117.36, 111.15, 76.47, 71.60; ms, m/z (relative intensity), 416 (M^+, 12), 387, 296, 222 (24), 194 (100), 165 (38), 139, 78, 51.

Anal. Calcd. for $C_{28}H_{20}N_2O_2$: C, 80.76; H, 4.80; N, 6.73. Found: C, 80.91; H, 4.92; N, 6.52.

1-(1-Naphthyl)-3,3-diphenylspiro[azetidine-2,3'-indoline]-2',4-dione (**IIb**).

X = Naphthyl; mp 197-198 °C; δ H, 8.46 (bs, 1H, NH, D_2O ex), 8.28 (d, J = 8.57 Hz, 1H), 7.78-7.12 (m, 17H), 6.66 (m, 2H), 6.31 (d, J = 7.58 Hz, 1H); δ C, 176.18, 167.79, 141.41, 138.73, 138.38, 134.29, 131.30, 130.53, 129.82, 129.10, 128.49, 128.35, 128.22, 128.05, 127.76, 127.65, 127.36, 126.79, 126.66, 126.46, 125.05, 124.04, 123.61, 123.09, 122.12, 110.71, 77.19, 74.96; ms, m/z (relative intensity), 446 (M^+, 4), 296 (5), 272 (100), 243 (40), 220, 194 (17), 165 (30), 139, 127, 82.

Anal. Calcd. for $C_{32}H_{22}N_2O_2$: C, 82.40; H, 4.72; N, 6.00. Found: C, 82.64; H, 4.85; N, 5.92.

1-(4-Ethoxyphenyl)-3,3-diphenylspiro[azetidine-2,3'-indoline]-2',4-dione (**IIc**).

X = 4-Ethoxyphenyl; mp 130 °C; δ H, 8.05 (bs, 1H, NH, D_2O ex), 7.65 (m, 2H), 7.42-7.20 (m, 12H), 6.90 (d, J = 7.92 Hz, 1H), 6.65 (m, 2H), 6.18 (d, J = 7.59 Hz, 1H), 3.87 (q, 2H, methylene), 1.32 (t, 3H, methyl); δ C, 176.36, 165.86, 156.07, 140.87, 138.26, 137.73, 130.50, 129.94, 128.31, 128.27, 128.09, 127.71, 127.34, 126.85, 126.73, 122.81, 122.29, 119.24, 114.90, 111.32, 76.40, 71.89, 63.50, 14.67; ms, m/z (relative intensity), 460 (M^+, 5), 296, 266 (100), 238 (25), 210, 194 (15), 165 (25), 82, 65.

Anal. Calcd. for $C_{30}H_{24}N_2O_3$: C, 78.26; H, 5.27; N, 6.08. Found: C, 78.35; H, 5.44; N, 5.85.

1-Cyclohexyl-3,3-diphenylspiro[azetidin-2,3'-indoline]-2',4-diones (**IId**).

X = Cyclohexyl; mp 154-155 °C; δ H, 8.25 (bs, 1H, NH, D_2O ex), 7.60 (m, 2H), 7.39-7.10 (m, 9H), 6.80 (d, J = 7.92 Hz, 1H), 6.64 (m, 1H), 6.15 (m, 1H), 3.40 (m, 1H, N-CH), 2.20-2.18 (m, 2H), 1.70-0.90 (m, 8H); δ C, 177.84, 168.29, 140.79, 138.80, 138.69, 134.31, 130.11, 128.31, 128.23, 128.14, 127.44, 127.15, 127.05, 126.76, 124.31, 110.84, 75.85, 71.66, 54.26, 31.91, 30.55, 25.14 (two carbons), 25.03; ms, m/z (relative intensity), 422 (M^+, 15), 297 (5), 194 (100), 166 (30), 147, 118, 55.

Anal. Calcd. for $C_{28}H_{26}N_2O_2$: C, 79.62; H, 6.16; N, 6.63. Found: C, 79.38; H, 6.28; N, 6.50.

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[13] In some cases the organic fraction contained diphenylacetic acid in trace amount which was removed during recrystallization.