Synthesis and cyclization of 1’-\([N\text{-propylcarbamoyl}]\) methyl|spiro|1-benzopyran-2,2’-indo|es\]

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INTRODUCTION

The formation of heterocyclic rings on cyclization reactions of in situ generated azomethine ylides has emerged as a widely used synthetic method [1]. The attraction of this synthetic construction is the ease of generation of 1,3-dipoles and a high degree of molecular complexity provided in a single cyclization reaction step. Recent examples of this approach included the synthesis of a wide variety of fused [2], spiro [3] and bridged [4] heterocyclic ring systems.

We have recently developed a new method for the construction of the pyrrolo[2,1-\(a\)]isoquinoline ring system based on condensation of 2-carbamoylmethyl-1-methyl-3,4-isoquinolinium salts or their cyclic form 10b-methylimidazo[2,1-\(a\)]isoquinolines with aromatic and heteroaromatic aldehydes followed by intramolecular addition of the methylene carbon atom to the double bond of the ethenyl moiety [5]. The proposed mechanism of such transformation includes generation of an intermediate azomethine ylide. It was found also that condensation of 1-carbamoylmethyl-2,3,3-trimethyl-3\(H\)-indolium salts with salicyl aldehydes produced 1-(N-substituted carbamoylmethyl)indole spiro[1-benzopyran-2,2’-indole] derivatives which easily underwent rearrangement to the bridged oxazepino[3,2-\(a\)]indole derivatives under treatment with strong bases [7]. The latter found application in preparation of imprinted polymer stationary phases. It has been shown that the structure of a substituent at the nitrogen atom of the carbamoylmethyl group has a significant influence on enantioselection of chiral molecules [8].

We now report further synthetically useful examples where indoline spiro[1-benzopyran-2,2’-indole] derivatives are transformed to bridged oxazepino[3,2-\(a\)]indole derivatives. In the present work, synthesis and base catalysed cyclization of 1’-(N-propylcarbamoylmethyl)-1’,3’-dihydros|p|yro[1-benzopyran-2,2’-indole] have been explored.

RESULTS AND DISCUSSION

The starting 9,9,9a-trimethyl-1,2,3,9a-tetrahydro-9H-imidazo[1,2-\(a\)]indol-2-one 1 was prepared by the reaction of 2,3,3-trimethyl-3\(H\)-indole with \(\alpha\)-chloroacetamide [9]. Alkylation of 1 with propyl iodide afforded 1-propylimidazo[1,2-\(a\)]indol-2-one 2a [10], while the use 3-bromopropylbenzene gave new derivative 2b.

Reaction of 1-substituted imidazo[1,2-\(a\)]indol-2-ones 2, a, b with 5-nitosalicylaldehyde was carried out in acetic acid. Work-up of the reaction mixture with base gave 6-nitrospirobenzopyrans 3a, b. The

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Condensation of 1-propyl- and 1-(3-phenylpropyl)imidazo[1,2-\(a\)]indo|es| with \(o\)-|h|ydroxy-substituted aromatic aldehydes afforded 1’-\([N\text{-propyl- and } N-(3-phenylpropyl)carbamoyl]methyl|spiro|1-benzopyran-2,2’-indo|es|]. Treatment of the latter with potassium hydroxide gave bridged oxazepino[3,2-\(a\)]indole derivatives.
1H NMR spectra of 3a, b contained a characteristic doublet of the methine proton in the area of 5.80-5.89 ppm with vicinal 3JH-H of the optimized structures for the dihedral angle H-C(12)-C(13)-H of the optimized structure of cis-4b and trans-5b. The 12-H and 13-H (J12,13) is 4.8 Hz for cis-4b and 0 Hz for trans-5b. Monte Carlo conformational searches using the MM3* force field of the optimized structures followed by energy minimizations gave the dihedral angle H-C(12)-C(13)-H of the optimized structures of cis-4c and trans-5c 40.68° and 88.46°. In such case, J12,13 calculated by the Karplus equation [12] is 6.99 Hz for cis-4b and 1.98 Hz for trans-5b, and agrees satisfactorily with the experimental values.

Condensation of 2c with 2-hydroxynaphthaldehyde afforded 1-[(3-phenylcarbamoyl)methyl]indolin-2-one by fractional crystallization.

**EXPERIMENTAL**

Melting points were determined on a Klenf held melting point apparatus. IR spectra were recorded on a Perkin Elmer Spectrum BXII spectrophotometer using KBr pellets. 1H NMR spectra were recorded at 300 MHz and 13C NMR spectra were recorded at 75 MHz on a Varian Gemini 2000 instrument. Tetramethylsilane was used as the internal standard. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (silica gel 60 F254) were used. Separations by flash chromatography were performed on silica gel Merck, 9385, 230-400 mesh.

1,2,3,9a-Tetrahydro-9,9a-trimethyl-1-(3-phenylpropyl)-9H-imidazol[1,2-a]indol-2-one (2b). A mixture of 1.29 g (7.0 mmol) of 3a, b and 5.5 mmol) was dissolved in DMF (8 ml), and finely powdered potassium hydroxide (1.98 g, 17.5 mmol) was added dropwise, and the solution was stirred for 2 h at room temperature. Then the mixture poured into water (100 ml) and extracted with ether (3 x 50 ml). The organic layer was separated, washed with water (20 ml) and dried with CaCl2. Most the solvent was distilled off in vacuo and the residue kept at 4 °C overnight. The precipitated crystals were filtered off and recrystallized from ethanol. Yield of 2b 1.06 g (45%), m.p. 84-85 °C. IR spectrum: 1710 cm–1 (C=O). 1H NMR spectrum (CDCl3): 0.87-1.02 (3H, t, J = 7.2 Hz, CH2), 6.72–7.33 ppm (2H, AB-q, J = 15.4 Hz, CH2CO), 2.15–2.32 (1H, m, ½ NCH2), 2.56–2.80 (2H, m, CH2C6H5), 2.88-3.00 (1H, m, ½ NCH2), 3.51–3.63 (1H, m, ½ NCH2), 3.86 (2H, AB-q, J = 15.4 Hz, CH2CO), 6.72–7.33 ppm (9H, m, Ar-H). 13C NMR spectrum (CDCl3): 22.74 (9-CH3), 23.68 (9-CH3), 28.78 (9a-CH3), 39.21, 33.38 (CH2C6H5), 42.04 (1-CH3), 49.52 (C-9), 54.78 (C-3), 91.93 (C-9a), 114.02 (CH), 122.00 (CH), 122.16 (CH), 125.97 (CH), 3 × 128.24 (3 × CH), 2 × 128.35 (2 × CH), 2 × 140.91 (2 × C), 148.40 (C), 171.15 ppm (C=O). Found: C, 79.20; H, 7.91; N, 8.22. 2H2sN2O requires: C, 79.00; H, 7.84; N, 8.38%.
1.36 (3H, s, 3'-CH₃), 1.48 (2H, sext., J = 7.2 Hz, NCH₂CH₃), 0.82 (2H, AB-q, J = 7.7 Hz, CH₂CO), 6.54-8.08 ppm (9H, m, ArH, CH=CH), 6.20-8.17 ppm (8H, m, ArH, NH). 13C NMR spectrum (CDCl₃): 11.14 (CH₃), 16.87 ppm (C=O). Found: C, 68.70; H, 6.42; N, 10.31%.

1',3'-Dihydro-3',3'-dimethyl-6-nitro-1'-[N-(3-phenylpropyl)carbamoyl]methylspiro[1-benzopyran-2,2'-indole] (3b) was synthesized from 2b (1.67 g, 5.0 mmol) and 5-nitrosalicylaldehyde (0.92 g, 5.5 mmol) by a similar method as compound 3a. Yield 1.01 g (42%), m.p. 140-141 °C (from ethanol). IR spectrum: 3240 (N-H), 1660 (C=O), 1515 (amid II), 1490, 1470, 1450, 1430 cm⁻¹ (NO₂). 1 H NMR spectrum (DMSO-d₆): 0.89 (3H, t, J = 7.2 Hz, CH₃), 1.69 (3H, s, CH₃), 2.34–2.47 (4H, m, 2CH₂), 3.80–3.84 (1H, m, 13-H), 3.96 (1H, d, J = 4.9 Hz, 2-H), 6.48-8.10 ppm (8H, m, Ar-H, NH). 13C NMR spectrum (DMSO-d₆): 17.90 (CH₂), 24.50 (NCH₂), 41.76 (C₁₂), 71.83 (C₁₂), 107.37 (CH), 110.63 (C-5a), 120.14, 121.36, 121.92, 123.55, 126.14, 126.17, 128.26, 140.82, 148.45, 148.76, 149.70 ppm (C=O). Found: C, 67.71; H, 6.59; N, 9.89. C₁₂H₁₉N₂O₄ requires: C, 67.60; H, 6.22; N, 10.13%. The yield 1H NMR spectrum (CDCl₃): 1.480–1.54 (2H, m, CH₃CH=CH₂), 1.66 (3H, s, CH₃), 1.69 (3H, s, CH₃), 2.34–2.47 (4H, m, CH₂).
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CONCLUSIONS

1. Indole spiropyrans possessing N-propyl- and N-(3-phenylpropyl)carbamoylmethyl moieties at the indole ring nitrogen atom can be easily prepared by condensation of 1-propyl- and 1-(3-propylphenyl)imidazo[1,2-a]indol-2-one derivatives with ortho-hydroxy-substituted aromatic aldehydes.


References


14-H2, C6H4CH2), 2.98–3.09 (1H, m, ½ NHCH2), 3.30–3.42 (1H, m, ½ NHCH2), 3.99–4.01 (1H, m, 13-H), 4.14 (1H, d, J = 4.8 Hz, 12-H), 6.66–8.17 ppm (13H, m, ArH, NH). 13C NMR spectrum (CDCl3): 23.80 (CH3), 27.09 (CH3), 31.49 (CH2CH2NH), 33.29 (C=CH2), 33.49 (C=CH=), 38.90 (NHCH2), 42.76 (C-7), 45.80 (C-6), 78.26 (C-12), 111.10 (C-1), 116.65 (C-5a), 116.89 (CH2), 123.20 (CH), 123.32 (CH), 125.33 (CH), 125.80 (CH), 126.44 (C), 126.65 (CH), 128.76 (2C, CH2), 129.11 (2C, CH2), 129.21 (CH), 139.02 (C), 141.62 (C), 142.03 (C), 149.18 (C), 158.88 (C), 169.98 ppm (C=O). Found: C, 71.94; H, 6.17; N, 8.41. C29H29N3O4 requires: C, 72.03; H, 6.04; N, 8.69%.

The yield of compound trans 5b is 0.32 g (36%), m.p. 153–155 °C (from acetone). IR spectrum: 3425 (NH), 1650 (C=O), 1520 cm–1 (amide 5c). Ether (2 ml) was poured into water (30 ml) and extracted with the solution. The mixture was refluxed for 4 h and the residue crystallized from ethanol to afford yield of 0.37 g (38%), m.p. 129–131 °C. IR spectrum of 1-propyl- and 1-(3-propylphenyl)imidazo[1,2-a]indol-2-one derivatives with ortho-hydroxy-substituted aromatic aldehydes.

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1-[(V-PROPIILKARBAMOIL)METIL]SPIRO[1-BENZPIRAN-2,2'-INDOLŲ] SINTEZĖ IR CIKLIZACIJA