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Polycondensed heterocycles. Part 12: An approach to the synthesis of 2-acetyl-1′-methyl-1,2,3,4-tetrahydrospiro-[isoquinoline-1,4′-pyrrolidine]-2′-one

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Abstract—The synthesis of ethyl (2-acetyl-1-cyano-1,2,3,4-tetrahydro-1-isoquinolyl)acetate was accomplished by cyanation/acylation of the dihydroquinoline ring system. The selective cobalt boride catalyzed reduction of the cyano group of the cyanoester intermediate was the key step to obtain the corresponding ethyl (1-aminomethyl-2-acetyl-1,2,3,4-tetrahydro-1-isoquinolyl)acetate which was cyclized by exposure to trimethylaluminum catalysis, leading to the novel spiro-polycondensed heterocyclic system.

1. Introduction

Spiropyrrolidinones derived from the isoquinoline ring system represent an unknown class of heterocyclic compounds that can constitute the basic framework of biologically active compounds, mimicking the core groups of several synthetic and natural products. The interest in the chemistry of this polycondensed heterocyclic system arises from the biological activity shown by related heterocyclic compounds. Several potent aldose reductase inhibitors based on spirosuccinimide, spiropyridazine and spiroazetidine derived from isoquinolinediones have been recently reported for the prevention of secondary complications of diabetes,[1,2] while the spiroisoquinolinepyrrolidinone system could partially mimick the pharmacophoric core system of the diethylamide of lysergic acid (LSD), a natural product that interacts with high affinity with 5-HT_6 receptor subtype (pK_i=8.9), being a natural lead compound for the development of selective ligands.

2. Results and discussion

The aim of the present study was the development of a versatile synthetic strategy for the synthesis of the title compound, and several synthetic approaches have been attempted (Fig. 1).

The main tasks to be accomplished in this synthesis are the double functionalization at position 1 of the isoquinoline ring system, and the discovery of a cyclization method to obtain the novel spiropyrrolidinone system. In order to obtain the key intermediate ethyl (1-cyano-2-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)acetate **3**, as the first synthetic pathway (Fig. 1, Path A; Scheme 1), we applied the method based on the alkylation of a cyanoisoquinoline intermediate **2** in turn prepared by a triphenylcarbenium tetrafluoroborate mediated one-pot synthesis in presence of potassium cyanide, starting from 2-methylisoquinoline (**1**).[3]

Triphenylcarbenium tetrafluoroborate is a bulky hydride abstracting reagent providing an isoquinolinium tetrafluoroborate intermediate that reacts with the cyanide anion.

In similar nitrile derivatives, the cyano group was found to react readily with Grignard reagents, with an apparent nucleophilic displacement of the nitrile function, giving 1-arylisoquinolines; in this case, alkylation of position 1 of 1-cyanoisoquinoline **2** with ethyl bromoacetate to obtain **3**, or with other alkylating agents such as allyl bromide, in various reaction conditions, did not take place. Although it has been previously demonstrated that under normal conditions there was an insignificant proportion of **2**-ionic form **4** at equilibrium,[4] the unsuccessful alkylation reaction could be explained by assuming that, under the reaction

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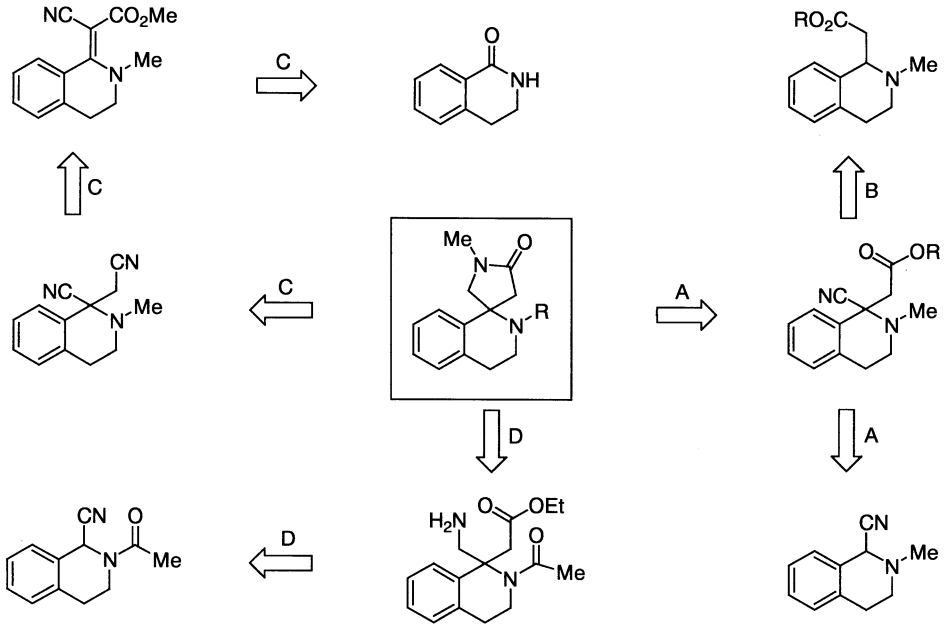
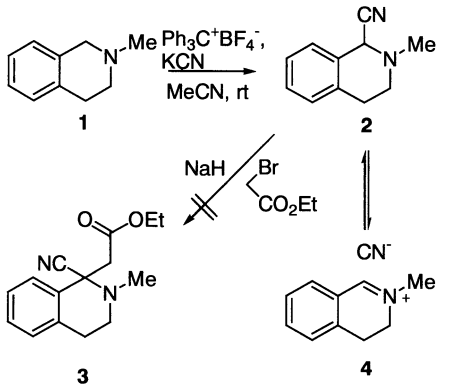


Figure 1. A schematic of the retrosynthetic approach to the title compound.

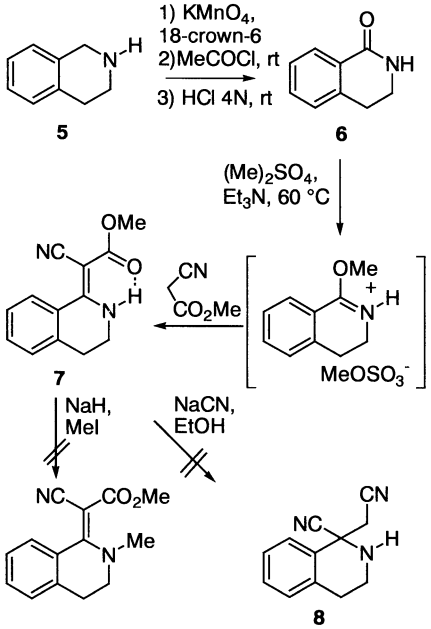
conditions, the intermediate **2** conceivably exist as its ionic form **4** that could not be alkylated. Following a different strategy (Fig. 1, Paths A and B), cyanation of ethyl (2-methyl-1,2,3,4-tetrahydro-1-isoquinolyl)acetate[5] by triphenylcarbenium tetrafluoroborate hydride abstraction and subsequent reaction of the tetrafluoroborate intermediate with cyanide ion, failed, probably because of the hindrance of the reagent.

A similar result was obtained by applying the Pictet–Spengler condensation to *N*-methylphenylethylamine in order to obtain a 1,1-disubstituted tetrahydroisoquinoline intermediate.[6] As shown in Fig. 1 (Path C) and Scheme 2, another strategy could involve the synthesis of a 1-cyano-1-(cyanomethyl)isoquinoline intermediate (**8**).

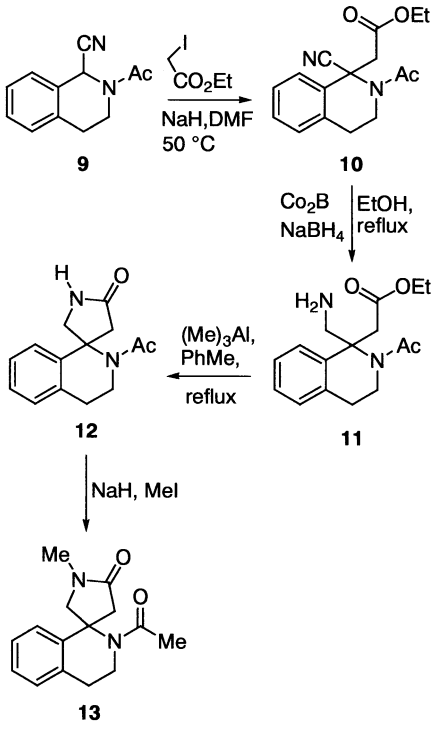
This compound could be prepared starting from 1-(cyanomethoxycarbonylmethylene)-1,2,3,4-tetrahydroisoquinoline (**7**). Thus, the commercially available tetrahydroisoquinoline **5** was transformed, by a standard procedure, into the corresponding lactam **6**. Reaction of the lactam with dimethylsulfate and methyl cyanoacetate led to the olefinic compound **7**.[7] Although described for non-heterocyclic substrates, in this case the reaction with sodium cyanide to obtain the dicyano intermediate **8**, did not provide the desired compound, but a mixture of unidentified byproducts.[8] In this case, the formation of a strong intramolecular hydrogen bond could prevent the reactivity of the intermediate **7**. The same unsuccessful result was obtained alkylating **7** with methyliodide. These results prompted us to develop another synthetic route to **12**. In this case, we replaced the *N*-methyl group by an acyl group, reducing, consequently, the basic character of the nitrogen heteroatom. Transformation of the nitrogen to an amide allowed



Scheme 1.



Scheme 2.



Scheme 3.

us the synthesis of the cyanoester intermediate **10** (Fig. 1, Path D; Scheme 3).

The key ester **10** was obtained by alkylation of 2-acetyl-1-cyano-1,2,3,4-tetrahydroisoquinoline **9**, in turn prepared by a standard procedure from 3,4-dihydroisoquinoline.[9] Subsequently, a one-pot hydrogen catalyzed reduction/cyclization reaction was attempted to obtain **12** by using Ni-Raney as a catalyst, at 60 psi, but the starting material was entirely recovered.[8] On the contrary, the cyano ester could serve as starting material to attempt another cyclization method to **12** based on a cobalt boride selective reduction of the cyano group to amine,[10] followed by cyclization of the aminoester intermediate. Thus the cyano group in **10** was selectively reduced by exposure to cobalt boride in presence of sodium borohydride in a protic solvent at reflux. The aminoester **11** was subjected to various cyclization protocols. In xylene at reflux, in presence or not of 2-hydroxypyridine as a catalyst,[11] as well as in toluene at reflux in presence of a catalytic amount of sodium cyanide,[12] the starting material was recovered. On the contrary, saponification of the aminoester **11** with sodium hydroxide, followed by treatment of the corresponding sodium salt with thionyl chloride and sodium hydrogen carbonate in benzene at 80°C led to a mixture of unidentified byproducts. As a general method, conversion of esters to linear amides could be accomplished with alkylaluminum amides,[13] and this method was successfully applied for the first time to the synthesis of lactam **12**. Thus treatment of **11** with trimethylaluminum in toluene at reflux provided the desired spiroheterocyclic skeleton **12**. The aluminum amide is prepared in situ and it is a mild, non-basic catalyst, compatible with the substrate molecule. After that, the nitrogen of the lactam was alkylated by using iodomethane and sodium hydride in *N*,*N*-dimethylformamide, obtaining the title compound **13**.

3. Conclusions

In conclusion, we have herein described a convenient synthetic strategy which allows the preparation of a new spiroheterocyclic system. Further possibilities for the reported synthetic method can be envisaged in the use, as starting material, of dihydroisoquinolines bearing substituents on the heterocyclic system, thereby obtaining a variety of substituted analogues of **13** for the synthesis of novel aldoso reductase inhibitors and selective 5-HT_6 receptor ligands.

4. Experimental

4.1. General

Melting points were determined using an Electrothermal 8103 apparatus and are uncorrected. IR spectra were taken with Perkin–Elmer 398 and FT 1600 spectrophotometers. ^{1}H NMR spectra were recorded on Bruker 200 MHz spectrometer with TMS as internal standard; the value of chemical shifts (δ) are given in ppm and coupling constants (J) in Hertz (Hz). All reactions were carried out in an argon atmosphere. Mass spectra were recorded using a VG 70-250S spectrometer. Elemental analyses were performed in on a Perkin–Elmer 240C elemental analyser and the results were within ±0.4% of the theoretical values, unless otherwise noted. Yields refer to purified products and are not optimised.

4.1.1. 1-(Cyano-methoxycarbonylmethylene)-1,2,3,4-tetrahydroisoquinoline (7). A mixture of 3,4-dihydro-1(2H)-isoquinolinone (**6**) (2.8 g, 19.0 mmol) and dimethylsulfate (2.2 mL, 23.4 mmol) was heated at 60°C and stirred for 12 h. After cooling at 0°C, triethylamine (3.3 mL, 23.8 mmol) and methyl cyanoacetate (1.7 mL, 19.0 mmol) were added. After stirring at 80°C for 2 h the mixture was poured into water and the aqueous phase was extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash chromatography (30:1, chloroform/methanol) to give the title compound as pale yellow solid (2.5 g, 60%), mp=128–129°C. ^{1}H NMR ($CDCl_3$) δ 7.68 (d, J=7.7 Hz, 1H), 7.40–7.25 (m, 3H), 3.85 (s, 3H), 3.62 (t, J=6.9 Hz, 2H), 2.75 (t, J=7.3 Hz, 2H). IR (nujol) ν 2198, 1716, 1638 cm^{-1}. m/z 228 (M^+, 100%), 197, 170, 130. Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.58; H, 5.23; N, 12.11.

4.1.2. (±) Ethyl (2-Acetyl-1-cyano-1,2,3,4-tetrahydro-1-isoquinolyl)acetate (10). A solution of 2-acetyl-1-cyano-1,2,3,4-tetrahydroisoquinoline (**9**) (0.4 g, 2.0 mmol) in anhydrous *N*,*N*-dimethylformamide (2.0 mL) was added to a suspension of sodium hydride (53.0 mg, 2.2 mmol) in *N*,*N*-dimethylformamide (2.0 mL). After 30 min, ethyl iodoacetate (370 μL, 3.1 mmol) was added and the resulting mixture was heated at 50°C for 12 h. After cooling at room temperature, water (3.0 mL) was added and the aqueous phase was extracted with chloroform. The organic extract was dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash chromatography (1:2, ethyl acetate/hexane) to obtain the title compound

(260 mg, 45%) as colourless oil. ^{1}H NMR ($CDCl_3$) δ 7.63–7.58 (m, 1H), 7.36–7.27 (m, 2H), 7.24–7.20 (m, 1H), 4.02 (d, J=15.7 Hz, 1H), 3.94–3.82 (m, 3H), 3.68–3.56 (m, 1H), 3.27 (d, J=15.7 Hz, 1H), 3.10–2.80 (m, 2H), 2.27 (s, 3H), 1.04 (t, J=7.0 Hz, 3H). IR ($CHCl_3$) ν 2399, 1732, 1660 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 163.74, 160.90, 127.56, 125.49, 121.67, 121.53, 120.67, 119.99, 111.92, 53.70, 46.88, 36.81, 36.24, 22.37, 16.71, 6.84. m/z 286 (M^+), 260, 172 (100%), 144. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.39; H, 6.13; N, 9.40.

4.1.3. (±) Ethyl (1-Aminomethyl-2-acetyl-1,2,3,4-tetrahydro-1-isoquinolyl)acetate (11). Freshly prepared cobalt boride (89.2 mg, 0.70 mmol) was added to a solution of cyanoester **10** (200 mg, 0.70 mmol) in anhydrous ethanol (8.0 mL). The suspension was stirred at room temperature and after 15 min sodium borohydride (131 mg, 3.5 mmol) was added in small portions. After 12 h the suspension was concentrated in vacuo and the residue was diluted with water. The aqueous phase was extracted with ethyl acetate, the organic extract dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash chromatography (10:1:1, ethyl acetate/methanol/triethylamine) to obtain the title compound as colourless oil (120 mg, 59%). ^{1}H NMR ($CDCl_3$) δ 7.24–7.00 (m, 4H), 4.40 (d, J=13.7 Hz, 1H), 4.13–3.92 (m, 3H), 3.69–3.46 (m, 2H), 2.95–2.61 (m, 4H), 2.08 (s, 2H), 1.96 (s, 3H), 1.22 (t, J=7.0 Hz, 3H). IR ($CHCl_3$) ν 3308, 2930, 1730, 1659 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 162.89, 155.37, 134.87, 126.00, 122.03, 120.06, 119.75, 118.7, 59.5, 58.06, 53.5, 38.49, 31.53, 21.01, 7.38, 7.13. m/z 290 (M^+), 273 (100%), 245, 185. Anal. Calcd for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.17; H, 7.32; N, 9.53.

4.1.4. (±) 2-Acetyl-1,2,3,4-tetrahydrospiro[isoquinoline-1,4′-pyrrolidine]-2′-one (12). Trimethylaluminum (170 μL, 0.34 mmol, 2 M solution in toluene) was added to a solution of amine **11** (100 mg, 0.34 mmol) in anhydrous toluene (1.5 mL) and the mixture was refluxed for 24 h. After cooling at room temperature, water was added and the mixture was concentrated in vacuo. The aqueous phase was extracted with ethyl acetate and the organic extract was dried (Na_2SO_4). After solvent removing, the residue was purified by flash-chromatography (5:1, ethyl acetate/methanol) to obtain the title compound (84.0 mg, 50%) as white crystalline solid, mp 135–136°C. ^{1}H NMR ($CDCl_3$) δ 7.33–7.08 (m, 4H), 6.42 (s, 1H), 4.08 (d, J=9.7 Hz, 1H), 3.64 (t, J=5.0 Hz, 2H), 3.56 (d, J=7.6 Hz, 1H), 3.29 (d, J=17.2 Hz, 1H), 2.88 (t, J=5.6 Hz, 2H), 2.50 (d, J=17.6 Hz, 1H), 2.22 (s, 3H). IR ($CHCl_3$) ν 3430, 3011, 1697, 1644 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 169.33, 163.85, 136.12, 125.85, 121.07, 120.92, 119.85, 117.46, 54.50, 49.63, 38.99, 37.52, 23.34, 17.50. m/z 245 (M^{+1}, 100%), 235, 203, 186, 158. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 69.02; H, 6.53; N, 11.56.

4.1.5. (±) 2-Acetyl-1′-methyl-1,2,3,4-tetrahydro spiro-[isoqui-noline-1,4′-pyrrolidine]-2′-one (13). A solution of **12** (100 mg, 0.41 mmol) in anhydrous *N*,*N*-dimethylformamide (1.5 mL) was added to a suspension of sodium hydride (3.8 mg, 0.41 mmol) in *N*,*N*-dimethylformamide (1.0 mL). After 30 min, methyl iodide (39 μL, 0.61 mmol) was added and the resulting mixture was stirred at room temperature for 12 h. The solution was diluted with water and the aqueous phase was extracted with chloroform. The organic extracts were dried (Na_2SO_4) and the solvent was removed in vacuo. The residue was purified by flash chromatography (5:1, ethyl acetate/methanol) to obtain the title compound (73.8 mg, 70%) as white crystalline solid, mp 142–143°C. ^{1}H NMR ($CDCl_3$) δ 7.40–7.18 (m, 4H), 4.08 (d, J=8.7 Hz, 1H), 3.90–3.69 (m, 2H), 3.48 (d, J=8.5 Hz, 1H), 3.31 (d, J=16.2 Hz, 1H), 2.93–2.84 (m, 5H), 2.51 (d, J=16.6 Hz, 1H), 2.22 (s, 3H). IR ($CHCl_3$) ν 3417, 2998, 1685, 1632 cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 172.83, 170.76, 143.27, 132.97, 128.11, 127.99, 126.85, 124.37, 63.57, 58.63, 47.06, 44.52, 30.37, 29.33, 24.47. m/z 258 (M^+), 228, 215, 198 (100%), 187, 172, 159, 145, 129, 115, 103. Anal. Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.42; H, 7.25; N, 11.18.

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