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A novel synthesis of spiro[(2,2-dimethyl-[1,3]-dioxane)-5,2′-(2′,3′-dihydroindole)] using $S_{RN}1$ reaction conditions

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Abstract—A concise synthesis of the spiro[(2,2-dimethyl-[1,3]-dioxane)-5,2′-(2′,3′-dihydroindole)] nucleus from substituted benzyl chlorides and 5-(hydroxymethyl)-2,2-dimethyl-5-nitro-1,3-dioxane **5** as starting materials is reported. The nitro intermediates **6** and **7** were prepared under $S_{RN}1$ reaction conditions.

The indoline (2,3-dihydroindole) framework is included in a wide range of natural alkaloids and synthetic compounds. Each of these structural groups has provided molecules possessing interesting, and clinically useful, pharmaceutical profiles (Fig. 1).[1]

Due to their biological activity, significant effort has gone into the development of efficient methods for their preparation.[2] The preparation of 3-spiroindolines **B** has been described, but several methods reported for the synthesis of 3-spiroindolines[3] and other substituted indolines failed with 2-spiroindolines **A**. This report describes our preliminary studies on the preparation of 2-spiroindolines using a novel strategy. The sequence of reactions used to obtain the objective of our study is illustrated in Schemes 1 and 2.

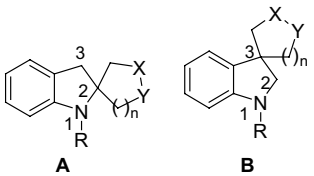

Figure 1. 2- or 3-Spiroindoline structures. R = CH_3, benzyl, acetyl; X = NH, *N*-alkyl, *N*-aryl, CH_2; Y = NH, *N*-alkyl, *N*-aryl, CH_2; *n* = 0, 1, 2, 3.

Initially we attempted the reaction of 2-nitrobenzyl chloride **1** with the nitronate anion derived from 5-(hydroxymethyl)-2,2-dimethyl-5-nitro-1,3-dioxane **5** under $S_{RN}1$ reaction conditions.[4] This reaction has been studied and extended to the preparation of several heterocyclic compounds such as 5-nitroimidazole derivatives,[5] imidazo[1,2-*a*]pyridines[6] and 5-nitrothiophenes,[7] as well as to the synthesis of chlorambucil analogues.[8]

Several bases can be used for the formation of the nitronate anion in situ, e.g. NaOH,[4b] tetrabutylammonium hydroxide,[9] LDA, $LiOCH_3$,[5c,8,10] and $NaOCH_3$. A number of these bases were tried for the reaction of **1** with **5**, and the results are shown in Table 1. When an aqueous solution of 2 M NaOH was used only the benzyl alcohol **12** was obtained as the major product (Table 1, entry 2). The utilization of lithium derivatives gave the expected compound in lower yields (entries 4 and 5).

Treatment of 5-(hydroxymethyl)-2,2-dimethyl-5-nitro-1,3-dioxane **5** with tetrabutylammonium hydroxide gave the desired dinitro compound **6** in moderate yield, and the olefin **10** was also obtained in 8% yield (entry 3). As shown in Table 1, when freshly prepared sodium methoxide was used the dinitro compound **6** was obtained in better yield, and $NaOCH_3$ proved to be the best out of a large number of bases tested for the formation of the nitronate (entry 1). It appears from these

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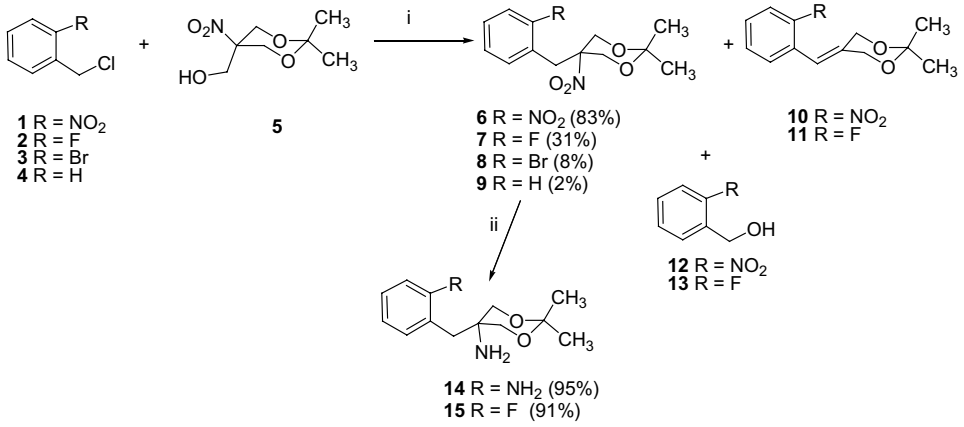
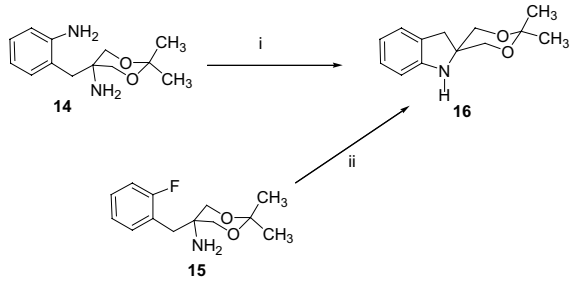


Scheme 1. Reagents and conditions: (i) $NaOCH_3$, MeOH, hν, 16 h; (ii) H_2/Raney-Ni, MeOH, rt.



Scheme 2. Reagents and conditions: (i) $(CF_3CO)_2O/CF_3COOH$ 1:1, reflux, 12 h, 65% yield; (ii) DMF/K_2CO_3, 120–130 °C, 12 h, 62% yield.

Table 1. Results of the $S_{RN}1$ reaction between 2-nitrobenzyl chloride **1** and 1,3-dioxane **5** using different bases

Entry	Base	Reaction time (h)	**6** yield (%)
1	NaOMe	12	83
2	NaOH	24	—[a]
3	Bu_4NOH	12	60[b]
4	LDA	24	21[c]
5	LiOMe	12	5[c]

[a] Compound **12** isolated in 82% yield.
[b] Compound **10** isolated in 8% yield.
[c] Other by-products formed.

results that the choice of base is crucial to achieve the expected compounds with good yields.

These conditions[11] have been extended to other benzyl chlorides. 2-Fluorobenzyl chloride afforded the desired nitro compound **7** in 31% yield, and 2-bromobenzyl chloride gave **8** in 8% yield, unreacted starting material being recovered in both cases. Benzyl chloride gave the expected compound in only 2% yield. It is noteworthy that the best results were obtained with 2-nitrobenzyl chloride, from which it may be concluded that an electron-withdrawing group at the *ortho* or *para* position of the benzyl chloride favored the $S_{RN}1$ reaction.[10a] Moreover, it is noteworthy that irradiation of the reaction is required; reaction under the same conditions but without irradiation led to recovery of the starting material after 24 h. Radical trapping experiments concerning the reaction between **2** and **5** have been carried out using nitroxides, and in this study only products resulting from radical scavenging or degradation were detected.[12]

Both the aliphatic and aromatic nitro groups of **6** were reduced to amines in good yield by catalytic hydrogenation using Raney-Ni.[13] The reduction of **7** under the aforementioned conditions afforded the corresponding amine **15**. Cyclization of the diamine **14** was accomplished using a mixture of trifluoroacetic anhydride/trifluoroacetic acid 1:1 at reflux in 65% yield. Our prior experience of intramolecular aromatic fluoride displacement[14] suggested a facile method to construct the indoline system by using the same concept applied to the fluoroamine **15**, and in this way the spiroindoline **16** was obtained in 62% yield.[15]

In summary, we have described an operationally simple and efficient method for the preparation of 2-spiroindolines[16] based on the cyclization of amino compounds obtained as intermediates from 2-nitro or 2-fluorobenzyl chloride in two steps. Further work is under way to examine the introduction of other substituents at the 2-position of the indoline system.

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11. *Preparation of nitro compounds. General procedure*. To a stirred solution of the nitroacetal (200 mg, 1.05 mmol) in methanol (10 mL) was added sodium methoxide (97.2 mg, 1.8 mmol). The reaction mixture was stirred for 30 min at room temperature under an inert atmosphere. After 30 min, the corresponding benzyl chloride (1.05 mmol) was added and the mixture was heated to reflux, and irradiated with a 100 W lamp for 24 h. The solvent was removed, water (15 mL) was added, and the residue was extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with H_2O (15 mL), dried over Na_2SO_4, the solvent removed on a rotary evaporator and silica gel column chromatography of the residue (SiO_2, 70–230 mesh, hexane/ethyl acetate) gave the products. Solids were purified by column chromatography, followed by crystallization (hexane/ethyl acetate). The yields of the pure compounds are indicated in Scheme 1.
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13. *Reduction*. To a solution of the nitro compound (2 mmol) in methanol (20 mL) was added Raney-Ni (50% slurry in water) (3 mmol). The mixture was stirred at room temperature under H_2 until the starting material had been consumed or no further reaction was evident (according to TLC analysis). The catalyst was separated by filtration, the solvent was removed under reduced pressure and the residue was subjected to column chromatography (silica gel, hexane/ethyl acetate) to afford the corresponding amine.
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15. *Cyclization*. (a) A stirred solution of **14** (2 mmol) in a mixture of trifluoroacetic anhydride/trifluoroacetic acid 1:1 (5 mL) was heated with stirring for 12 h. 2 M NaOH (20 mL) was added and the residue was extracted with dichloromethane (3×30 mL). The organic layer was washed with 2 M NaOH solution, dried over Na_2SO_4, filtered, and the solvent removed under vacuum. Purification of the residue by column chromatography (silica gel, hexane/ethyl acetate) gave the indoline **16** in 65% yield. (b) To a stirred solution of **15** (0.3 mmol) in freshly distilled DMF (2 mL), K_2CO_3 (0.6 mmol) was added at rt under argon. The mixture was stirred for 12 h at 130 °C. Then, water (10 mL) and ether (10 mL) were added, and the organic extracts were washed with water (3×20 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give a residue which was purified by silica gel chromatography (hexane/ethyl acetate as eluent). The indoline **16** was obtained in 62% yield as a yellow oil.[14]
16. *Analytical data of some representative compounds synthesized:* 2,2-Dimethyl-5-nitro-5-(nitrobenzyl)-[1,3]-dioxane (**6**). Mp 122–124 °C (hexane/ethyl acetate). IR (KBr): ν (cm^{-1}) 1607 (N=O); 1544 (C=C); 1360 (N–O); 1199 (C–O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.37 (s, 3H, CH_3); 1.48 (s, 3H, CH_3); 3.63 (s, 2H, CH_2); 4.05 (d, $J=13$ Hz, 2H, CH_2–O); 4.34 (d, $J=13$ Hz, 2H, CH_2–O); 7.18 (dd, $J_1=8$ Hz, $J_2=2$ Hz, 1H, H-6); 7.53 (m, 2H, H-4, H-5); 7.98 (dd, $J_1=8$ Hz, $J_2=2$ Hz, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) 21.2 (CH_3, A); 23.8 (CH_3, B); 25.3 (CH_3, C); 34.9 (CH_2); 60.0 (CH_2–O, A); 63.4 (CH_2–O, B); 64.1 (CH_2–O, C); 88.8 (C, C-2); 99.0 (C, C-5, A); 99.3 (C, C-5, B); 118.8 (CH, C-5′); 124.7 (CH, C-3′); 127.5 (C, C-1′); 128.1 (CH, C-6′); 132.5 (CH, C-4′); 137.8 (C, C-2′). Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.70; H, 5.44; N, 9.46. Found: C, 52.93; H, 5.69; N, 9.17.

2,2-Dimethyl-5-(2-fluorobenzyl)-5-nitro-[1,3]-dioxane (**7**). Yellow oil. IR (KBr): ν (cm^{-1}) 1623 (N=O); 1589 (C=C); 1378 (N–O); 1098 (C–O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.40 (s, 6H, CH_3); 4.25 (s, 2H, CH_2–O); 4.55 (s, 2H, CH_2–O); 5.12 (s, 2H, CH_2–Ar); 7.18 (m, 3H, Ar); 7.28 (m, 1H, Ar). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) 24.0 (CH_3); 58.1 (CH_2, CH_2–O); 59.6 (CH_2, CH_2–O); 69.6 (CH_2); 100.3 (C, C-2); 115.1 (CH, $J=21$ Hz, C-3′); 123.8 (CH, $J=3.6$ Hz, C-5′); 129.7 (CH, $J=8.2$ Hz, C-4′); 130.4 (CH, $J=4$ Hz, C-6′); 156.1 (C, C-1′); 161.4 (C, $J=254$ Hz, C-2′). Anal. Calcd for $C_{13}H_{16}FNO_4$: C, 57.98; H, 5.98; N, 5.20. Found: C, 58.23; H, 6.21; N, 5.72.

5-(2-bromobenzyl)-2,2-dimethyl-5-nitro-[1,3]-dioxane (**8**). Red oil. IR (KBr): ν (cm^{-1}) 1643 (N=O); 1578 (C=C); 1356 (N–O); 1102 (C–O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.40 (s, 6H, CH_3); 3.46 (s, 2H, CH_2–Ar); 4.26 (s, 2H, CH_2–O); 4.58 (s, 2H, CH_2–O); 7.44 (m, 4H, Ar).

5-Benzyl-2,2-dimethyl-5-nitro-[1,3]-dioxane (**9**). Yellow oil. IR (KBr): ν (cm^{-1}) 1605 (N=O); 1551 (C=C); 1090 (C–O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.39 (s, 6H, CH_3); 3.39 (s, 2H, CH_2); 4.23 (s, 2H, CH_2–O); 4.46 (s, 2H, CH_2–O); 4.55 (s, 2H, CH_2–O); 5.06 (s, 2H, CH_2–O); 7.34 (m, 5H, Ar); Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.15; H, 6.82; N, 5.57. Found: C, 61.95; H, 6.53; N, 5.89.

2,2-Dimethyl-5-(2-nitrobenzylidene)[1,3]-dioxane (**10**). Colorless oil. IR (KBr): ν (cm^{-1}) 1589 (N=O); 1372 (N–O); 1098 (C–O). ^1H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.44 (s, 6H, CH_3); 4.49 (m, 2H, CH_2); 5.11 (m, 2H, CH_2); 7.17 (t, $J_1=1.5$ Hz, 1H, olefin); 7.54 (m, 3H, Ar); 7.93 (m, 1H, H-3). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) 28.9 (CH_3); 32.2 (CH_3); 60.2 (CH_2–O); 67.8 (CH_2–O); 98.7 (C, C-2); 120.2 (CH, C-3′); 123.4 (C, C-5); 126.2 (CH, C-4′); 127.5 (C, C-1′); 128.5 (CH, C-6′); 135.5 (CH, C-5′); 140.3 (C, C-2′). Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.31; H, 6.34; N, 5.89.

5-Amino-5-(2-aminobenzyl)-2,2-dimethyl-[1,3]-dioxane (**14**). Yellow oil. IR (KBr): ν (cm^{-1}) 3357 (N–H); 1197

(C–O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.45 (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 2.81 (s, 2H, CH_2); 3.47 (m, 4H, NH_2); 3.60 (d, $J = 12$ Hz, 2H, CH_2–O); 3.73 (d, $J = 12$ Hz, 2H, CH_2–O); 6.72 (m, 2H, H-3′, H-5′); 7.04 (m, 2H, H-4′, H-6′). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) 23.1 (CH_3); 23.7 (CH_3); 36.0 (CH_2); 50.4 (C-5); 68.1 (CH_2, $2 \times CH_2$–O); 98.4 (C, C-2); 116.5 (CH, C-3′); 118.4 (CH, C-5′); 120.2 (C, C-1′); 128.0 (CH, C-6′); 132.0 (CH, C-4′); 145.8 (C, C-2′). Anal. Calcd for $C_{13}H_{20}N_2O_2$: C, 66.07; H, 8.53; N, 11.85. Found: C, 66.34; H, 8.86; N, 11.59.

5-Amino-5-(2-fluorobenzyl)-2,2-dimethyl-[1,3]-dioxane (**15**). Colorless oil. IR (KBr): ν (cm^{-1}) 3386 (N–H); 1122 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.40 (s, 3H, CH_3); 1.42 (s, 3H, CH_3); 2.78 (s, 2H, CH_2); 3.20 (bs, 2H, NH_2); 3.86 (d, $J = 10$ Hz, 2H, CH_2–O); 3.96 (d, $J = 10$ Hz, 2H, CH_2–O); 6.88–7.12 (m, 4H, Ar). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) 24.9 (CH_3); 34.5 (CH_2, CH_2–Ar); 56.8 (C, C-5); 68.9 (CH_2, $2 \times CH_2$–O); 69.2 (CH_2, CH_2–O); 101.3 (C, C-2); 115.8 (CH, $J = 21$ Hz, C-3′); 122.9 (CH, $J = 4$ Hz, C-5′); 129.9 (CH, $J = 8$, C-4′); 131.4 (CH, $J = 4$ Hz, C-6′); 155.0 (C, C-1′); 160.9 (C, $J = 249$ Hz, C-2′). Anal. Calcd for $C_{13}H_{18}FNO_2$: C, 65.25; H, 7.58; N, 5.85. Found: C, 65.55; H, 7.42; N, 5.76.

Spiro[(2,2-Dimethyl-[1,3]-dioxane)-5,2′-(2′,3′-dihydroindole)] (**16**). Yellow oil. IR (KBr): ν (cm^{-1}) 3290 (N–H); 1158 (C–O). ^{1}H NMR ($CDCl_3$, 200 MHz): δ (ppm) 1.24 (s, 3H, CH_3); 1.25 (s, 3H, CH_3); 3.02 (m, 2H, CH_2); 3.45 (m, 4H, CH_2–O); 5.80 (bs, 1H, NH); 7.24 (m, 3H, H-4′, H-5′, H-6′); 7.83 (d, $J = 8$ Hz, 1H, H-7). ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ (ppm) 29.7 (CH_3); 31.7 (CH_3); 61.7 (CH_2, CH_2–O); 63.9 (CH_2, CH_2–O); 69.2 (C); 69.9 (C); 125.1 (CH, C-7); 126.5 (CH, C-6); 128.3 (CH, C-4); 131.2 (C, C-3a); 136.2 (C, C-7a); 132.3 (CH, C-5). Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.08; H, 7.52; N, 6.45.