Synthesis of New C_2 Symmetrical Dibenzospirodiamide and Dibenzospirodiamine as Potential Chiral Auxiliaries and Building Blocks of Ionophores

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2,8-Diazadibenzo[*c*,*i*]spiro[5,5]undecan-1,7-dione **3** are synthesized *via* reaction of malonic ester with 2-nitrobenzyl bromide, followed by reduction-cyclization in 86% overall yield. 2,8-Diazadibenzo[*c*,*i*]-spiro[5,5]undecane **4** was obtained by reduction of **3** with $LiAlH_4$ in 90% yield. *N*-Alkylation of **3** with various alkylating reagents is studied.

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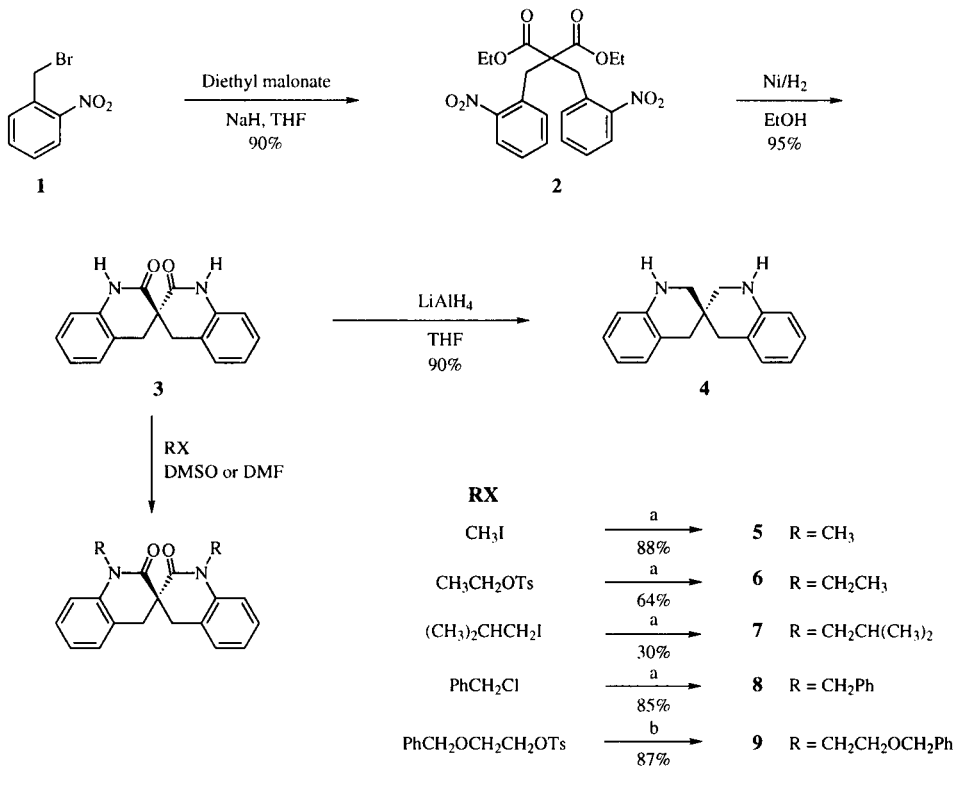
Diamide ligands as ionophores are widely utilized in the alkali and alkaline earth metal ion analysis and ion transportation [1]. The typical diamide, *N,N,N',N'*-tetra-isobutyl-*cis*-cyclohexane-1,2-dicarboxamide is well known for the lithium ionophore and shows high lithium ion selectivity over sodium ion interferent in the biological medium [2]. Many other diamide also exhibit high sensitivity and selectivity on the desired metal ions developed in Simon group [3].

We have reported a new class of diamide ionophores based on 2,8-diazaspiro[5,5]undecane-1,7-dione, which has very low solubility in most organic solvents but it is sparingly soluble in DMF and moderately soluble in DMSO, and has limited reactivity of *N*-alkylation on amide functionality only toward benzylic halides [1b,4].

Thus, to enhance solubility in organic solvents and reactivity of *N*-alkylation on amide with various alkylating agents, we have now developed 2,8-diazadibenzo[*c*,*i*]spiro[5,5]undecan-1,7-dione **3** with anilide moieties and 2,8-diazadibenzo-[*c*,*i*]spiro[5,5]undecane, **4** as a potential chiral diamine catalyst.

Dibenzospirodiamide **3** and its *N*-alkylated dibenzospirodiamides as well as an analogue dibenzospirodiamine **4** were synthesized from commercially available starting materials as shown in Scheme 1.

Scheme 1



(a) DMSO, 70°, 2 hours; (b) DMF, 60°, 2 hours

Dibenzospirodiamide **3** was synthesized from bis(2-nitrobenzyl)malonate **2**, which was obtained by alkylation of diethyl malonate with 2-nitrobenzyl bromide in THF with sodium hydride as base in 90% yield. 2-Nitrobenzyl bromide is commercially available but easily prepared by bromination of 2-nitrotoluene with NBS in tetrachloromethane [5]. The crystalline **2** from benzene-ether was converted in one step to dibenzospirodiamide **3** by catalytic hydrogenation in ethanol with Raney nickel catalyst, affording 2,8-diazadibenzo[*c*,*i*]spiro[5,5]undecan-1,7-dione **3** in 95% yield. *N*,*N'*-Dialkyl dibenzospirodiamides were synthesized from dibenzospirodiamide **3**, which was converted to the dianion with sodium hydride in anhydrous DMSO or DMF at 60-70°. Alkylation with methyl iodide, ethyl tosylate, isobutyl iodide, benzyl chloride or 2-benzyloxyethyl tosylate yielded **5** (88%), **6** (64%), **7** (30%), **8** (85%) and **9** (87%), respectively. Reduction of dibenzospirodiamide **3** with lithium aluminum hydride in THF gave dibenzospirodiamine **4** in 90% yield.

The diastereotopic benzylic protons of **3** are seen as two doublets (J = 16.4 Hz) in the proton nmr spectrum. The chemical shifts of these geminal benzylic protons are noticeably separated by as much as 0.4 ppm from each other (δ 3.23 and 2.83 ppm) because one of these protons is affected by the deshielding influence of the other aromatic ring, and the other influenced by the much closer and highly anisotropic carbonyl groups. However, the diastereotopic benzylic protons of **4** are seen at δ 2.64 and 2.59 ppm probably due to the more flexible conformation of **4** compared to rigid dibenzospirodiamide **3**.

In addition to the very limited solubility and reactivity on *N*-alkylation of 2,8-diazaspiro[5,5]undecane-1,7-dione [4], its dibenzo analogue, **3** shows some improvement of solubility in organic solvents, but great enhancement in the reactivity observed on *N*-alkylation of the amide functional group. The spirodiamide shows low reactivity of alkylation with the benzylic halide electrophile and no reactivity to other electrophilic reagents [4]. However, the benzospirodiamide **3** could be alkylated not only with benzyl halide but also alkyl iodide and alkyl tosylate. This reactivity enhancement is partially inherent from the anilide functionality in which the amide anion nucleophile is resonance-stabilized by the phenyl moiety.

We could extend this benzospirodiamide **3** to building blocks for polyether macrocycles that can be applicable to many new kinds of potential ionophores.

This racemate diamine **4** with C_2 symmetry could be resolved to enantiomerically pure diamine and utilized as chiral auxiliaries such as chiral catalyst in asymmetric ring opening of epoxides [6], asymmetric 1,2-*cis*-dihydroxylation [7] and asymmetric cyclopropanations [8].

In summary, dibenzospirodiamide **3** and dibenzospirodiamine **4** as potential chiral auxiliaries and building blocks of ionophores were easily synthesized from the 2-nitrobenzyl bromide in 86% overall yield in two steps and in 77% overall yield in three steps, respectively. *N*-Alkylation of **3** with benzyl halides, alkyl iodides and alkyl tosylates afforded *N*,*N'*-dialkyl derivatives in high yield.

EXPERIMENTAL

Diethyl Bis(2-nitrobenzyl)malonate (**2**).

To sodium hydride (60% dispersion in oil, 1.92 g, 48 mmoles) washed with hexane was added a solution of diethyl malonate (3.20 g, 20 mmoles) in dry THF (20 mmoles) and stirred for 20 minutes at room temperature under nitrogen. The solution of 2-nitrobenzyl bromide (8.46 g, 40 mmoles) in dry THF (20 ml) was slowly added to the stirred suspension, and then the mixture was stirred for 3 hours under nitrogen, then quenched with brine. The organic phase was separated, and the aqueous phase was extracted with methylene chloride (2 x 20 ml). The combined organic phase was dried (magnesium sulfate) and evaporated, and the solid residue was recrystallized from benzene-ether to give pale yellow crystals **2** (7.74 g, 90%): mp 96-98°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 7.89 (d, J = 8.4 Hz, 2H, Ar-*H*), 7.44 (m, 6H, Ar-*H*), 4.00 (q, J = 7.2 Hz, 4H, -OC*H*$_2$CH$_3$), 3.68 (s, 4H, -C*H*$_2$-), 1.03 (t, J = 7.2 Hz, 6H, -OCH$_2$C*H*$_3$); ^{13}C nmr (100 MHz, deuteriochloroform): δ 170.0, 150.4, 133.3, 132.4, 131.5, 128.0, 124.8, 61.9, 59.4, 36.2, 13.6; ir (potassium bromide): 2988, 1729, 1529, 1258 cm^{-1}; ms: m/z 384 (100), 282 (34), 134 (80), 92 (45), 77 (68).

Anal. Calcd. for $C_{21}H_{22}N_2O_8$: C, 58.60; H, 5.15; N, 6.51. Found: C, 58.59; H, 5.35; N, 6.46.

2,8-Diazadibenzo[*c*,*i*]spiro[5,5]undecan-1,7-dione (**3**).

Raney nickel (1.0 g) was added to a solution of diethyl bis(2-nitrobenzyl)malonate (4.32 g, 10 mmoles) in absolute ethanol (70 ml) in an autoclave. After the autoclave was flushed and then pressurized with hydrogen (10 atmospheres), the mixture was stirred at 80° for 12 hours. The mixture was evaporated under reduced pressure, and the solid residue was dissolved in DMF (150 ml) and then filtered through Celite. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from DMF-methylene chloride to give a white solid (2.64 g, 95%): mp 360° (dec); ^{1}H nmr (400 MHz, DMSO-d$_6$): δ 10.35 (s, -N*H*), 7.15 (m, 4H, Ar-*H*), 6.89 (m, 4H, Ar-*H*), 3.23 (d, J = 16.4 Hz, 2H, ArC*H*$_a$H$_b$-), 2.83 (d, J = 16.4 Hz, 2H, ArCH$_a$*H*$_b$-); ^{13}C nmr (100 MHz, DMSO-d$_6$): δ 173.7, 142.6, 133.3, 132.5, 127.3, 126.4, 119.8, 51.8, 38.8; ir (potassium bromide): 3205, 3080, 2988, 1676, 1598 cm^{-1}; ms: m/z 279 (11), 278 (50), 250 (100), 172 (74).

Anal. Calcd. for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 72.34; H, 5.01; N, 9.83.

2,8-Diazadibenzo[*c*,*i*]spiro[5,5]undecane (**4**).

To a mixture of 2,8-diazadibenzo[*c*,*i*]spiro[5,5]undecan-1,7-dione (2.78 g, 10 mmoles) in dry THF (100 ml) was added slowly lithium aluminum hydride (2.4 g, 60 mmoles). This suspension was gently heated at reflux for 12 hours, then quenched

with ethyl acetate and saturated ammonium chloride (2 drops). The mixture was filtered through Celite and the filtrate was evaporated *in vacuo* to yield white solid (2.5 g, 90%): mp 203-204°; ^{1}H nmr (400 MHz, deuteriochloroform): δ 6.99 (t, J = 7.6 Hz, 2H, Ar-*H*), 6.94 (d, J = 7.6 Hz, 2H, Ar-*H*), 6.62 (d, J = 7.6 Hz, 2H, Ar-*H*), 6.50 (d, J = 7.6 Hz, 2H, Ar-*H*), 3.88 (s, 2H, -N*H*), 3.11 (d, J = 11.4 Hz, 2H, -NCH_aH$_b$-), 3.03 (d, J = 11.4 Hz, 2H, -NCH$_a$$H_b$-), 2.64 (d, J = 16.2 Hz, 2H, ArCH_aH$_b$-), 2.59 (d, J = 16.2 Hz, 2H, -ArCH$_a$$H_b$-); ^{13}C nmr (100 MHz, deuteriochloroform): δ 143.7, 130.1, 126.9, 119.3, 117.2, 113.7, 48.3, 37.1, 29.5.

General Procedure of *N*-Alkylation on 2,8-Diazabibenzo[*c,i*]-spiro[5,5]undecan-1,7-dione to **5**, **6**, **7** and **8**.

To sodium hydride (60% dispersion in oil, 160 mg, 4 mmoles) washed with hexane was added dry DMSO (15 ml) and stirred at 70° for 20 minutes under nitrogen. To the mixture, a solution of dibenzospirodiamide **3** (278 mg, 1 mmole) in dry DMSO (20 ml) was added and the mixture was stirred at 70° for 30 minutes. A solution of alkyl halide or alkyl tosylate (10 mmoles) in dry DMSO (10 ml) was slowly added and stirred at 70° for 2 hours under nitrogen. The solvent was removed *in vacuo* and brine (10 ml) was added to the residue. The mixture was extracted with methylene chloride (2 x 20 ml). The organic layer was dried (magnesium sulfate) and evaporated under reduced pressure. The solid residue was recrystallized to give solid product.

N,N'-Dimethyl-2,8-diazadibenzo[*c,i*]spiro[5,5]undecan-1,7-dione (**5**).

Compound **3** (278 mg, 1 mmole) with methyl iodide (1.42 g, 10 mmoles): white solid from hexane-ethyl acetate (270 mg, 88%): mp 204-205°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.30 (t, J = 7.6 Hz, 2H, Ar-*H*), 7.09 (d, J = 7.6 Hz, 2H, Ar-*H*), 7.03 (d, J = 7.6 Hz, 2H, Ar-*H*), 7.02 (t, J = 7.6 Hz, 2H, Ar-*H*), 3.43 (d, J = 16.2 Hz, 2H, ArCH_aH$_b$-), 3.38 (s, 6H, -NCH_3), 2.76 (d, J = 16.2 Hz, 2H, ArCH$_a$$H_b$-); ^{13}C nmr (75 MHz, deuteriochloroform): δ 168.5, 139.8, 128,2, 127.9, 123.1, 123.1, 114.4, 48.3, 34.1, 30.3.

Anal. Calcd. for $C_{19}H_{18}N_2O_2$: C, 74.48; H, 5.92; N, 9.14. Found: C, 74.21; H, 6.23; N, 9.14.

N,N'-Diethyl-2,8-diazadibenzo[*c,i*]spiro[5,5]undecan-1,7-dione (**6**).

Compound **3** (278 mg, 1 mmole) with ethyl tosylate (1 g, 5 mmoles): white solid from hexane-methylene chloride (214 mg, 64%); mp 148-150°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.29 (t, J = 7.8 Hz, 2H, Ar-*H*), 7.10-6.97 (m, 6H, Ar-*H*), 3.99 (m, 2H, -NCH_aH$_b$-), 3.94 (m, 2H, -NCH$_a$$H_b$-), 3.39 (d, J = 16.0 Hz, 2H, ArCH_aH$_b$-), 2.74 (d, J = 16.0 Hz, 2H, ArCH$_a$$H_b$-), 1.23 (d, J = 7.1 Hz, 6H, -CH$_2$CH_3); ^{13}C nmr (75 MHz, deuteriochloroform): δ 167.8, 138.8, 128,6, 127.9, 123.3, 122.8, 114.1, 47.4, 38.0, 33.9, 12.5; ms: m/z 335 (17), 334 (79), 186 (29), 187 (25), 158 (28), 159 (25), 134 (100), 135 (91); ir (potassium bromide): 3173, 2973, 1668 cm^{-1}.

Anal. Calcd. for $C_{21}H_{22}N_2O_2$: C, 75.42; H, 6.63; N, 8.38. Found: C, 75.38; H, 6.93; N, 8.33.

N,N'-Diisobutyl-2,8-diazadibenzo[*c,i*]spiro[5,5]undecan-1,7-dione (**7**).

Compound **3** (278 mg, 1 mmole) with isobutyl iodide (1.84 g, 10 mmoles): white solid from hexane-ethyl acetate (117 mg, 30%); mp 172-173°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.26 (t, J = 7.5 Hz, 2H, Ar-*H*), 7.10-6.96 (m, 6H, Ar-*H*), 3.91 (dd, J = 14.1 Hz, 2H, 7.8 Hz, -NCH_aH$_b$-), 3.72 (dd, J = 14.1, 7.8 Hz, 2H, -NCH$_a$$H_b$-), 3.43 (d, 2H, ArC$H_aH_b$-), 2.75 (d, J = 16.5 Hz, 2H, ArCH$_a$$H_b$-), 2.04 (sep, J = 6.9 Hz, 2H, -C*H*(CH$_3$)$_2$), 0.92 (d, J = 6.9 Hz, 6H, -CH(CH_3)$_2$), 0.84 (d, J = 6.9 Hz, 6H, -CH(CH_3)$_2$); ^{13}C nmr (75 MHz, deuteriochloroform): δ 168.5, 139.1, 128,5, 127.7, 123.7, 122.8, 115.1, 49.1, 48.1, 34.3, 26.5, 20.1, 19.9; ms: m/z 392 (11), 391 (41), 320 (100), 130 (15), 131 (20), 118 (43), 119 (57), 91 (32), 92 (46); ir (potassium bromide): 2957, 1668 cm^{-1}.

Anal. Calcd. for $C_{25}H_{30}N_2O_2$: C, 76.89; H, 7.74; N, 7.17. Found: C, 76.55; H, 7.77; N, 6.91.

N,N'-Dibenzyl-2,8-diazadibenzo[*c,i*]spiro[5,5]undecan-1,7-dione (**8**).

Compound **3** (278 mg, 1 mmole) with benzyl chloride (1.26 g, 10 mmoles): white solid from hexane-methylene chloride (390 mg, 85%); mp 225-226°; ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.33-7.14 (m, 14H, Ar-*H*), 7.04 (t, J = 7.2 Hz, 2H, Ar-*H*), 6.91 (d, J = 7.8 Hz, 2H, Ar-*H*), 5.25 (d, J = 16.2 Hz, 2H, NCH_aH$_b$Ar), 5.11 (d, J = 16.2 Hz, 2H, NCH$_a$$H_b$Ar), 3.62 (d, J = 16.2 Hz, 2H, ArCH_aH$_b$-), 2.93 (d, J = 16.2 Hz, 2H, ArCH$_a$$H_b$-); ^{13}C nmr (75 MHz, deuteriochloroform): δ 168.4, 139.6, 136.7, 128.7, 128.3, 128.0, 127.0, 126.2, 123.3, 123.2, 115.4, 48.2, 47.5, 34.3, 31.0.

Anal. Calcd. for $C_{31}H_{26}N_2O_2$: C, 81.20; H, 5.72; N, 6.11. Found: C, 81.18; H, 5.78; N, 5.99.

N,N'-Bis(2-benzyloxyethyl)-2,8-diazadibenzo[*c,i*]spiro[5,5]-undecan-1,7-dione (**9**).

To sodium hydride (60% dispersion in oil, 384 mg, 9.6 mmoles) washed with hexane was added a solution of **3** (1.1 g, 4 mmoles) in dry DMF (60 ml) and stirred for 20 minutes at room temperature under nitrogen. A solution of 2-benzyloxyethyl tosylate (4.9 g, 16 mmoles) in dry DMF (20 ml) was slowly added to the stirred suspension, and then the mixture was stirred at 60° for 2 hours under nitrogen. The solvent was removed *in vacuo* and brine was added to the residue. The mixture was extracted with methylene chloride, dried (magnesium sulfate) and concentrated. The oily residue was purified by column chromatography on silica gel in methylene chloride to give the pale yellow oil (1.9 g, 87%); ^{1}H nmr (300 MHz, deuteriochloroform): δ 7.27 (m, 14H, Ar-*H*), 6.98 (m, 4H, Ar-*H*), 4.48 (s, 4H, -OCH_2Ar-), 4.14 (m, 4H, -CH_2CH$_2$O-), 3.67 (m, 4H, -CH$_2$CH_2O-), 3.39 (d, J = 15.9 Hz, 2H, ArCH_aH$_b$-), 2.72 (d, J = 15.9 Hz, 2H, ArCH$_a$$H_b$-); ^{13}C nmr (75 MHz, deuteriochloroform): δ 168.3, 139.4, 138,1, 128.3, 128.1, 127.8, 127.5, 127.4, 123.2, 123.0, 115.3, 73.1, 67.1, 47.8, 42.4, 33.8.

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