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DESIGN AND SYNTHESIS OF NOVEL SPIRO PYRIDINIUM AND QUINOLINIUM SALTS

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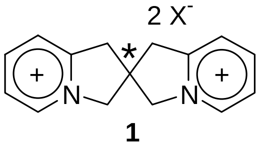
Abstract – Syntheses of novel spiro bis-pyridinium and bis-quinolinium salts have been achieved in three steps *via* intramolecular *N*-alkylation.

Quaternary ammonium salts have attracted great interest due to their ability to promote phase transfer catalyzed reactions[1] and considerable efforts have paved the way for the synthesis of various quaternary ammonium salts.[2] An important class of quaternary ammonium salt is the pyridinium and quinolinium salts, among which molten pyridinium salts are gaining importance as ionic liquids because of their unique physical and chemical properties.[3]

In continuation with our interest in the design and synthesis of new spiro chiral ligands,[4] we envisaged that introduction of spiro chirality into these pyridinium and quinolinium salts would afford novel chiral phase transfer catalysts. Herein we describe a short and simple route for the synthesis of these novel spiro bis-pyridinium and bis-quinolinium salts.



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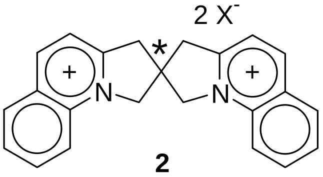

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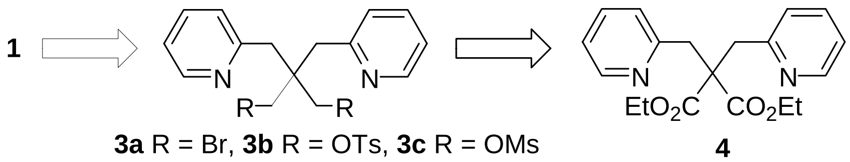
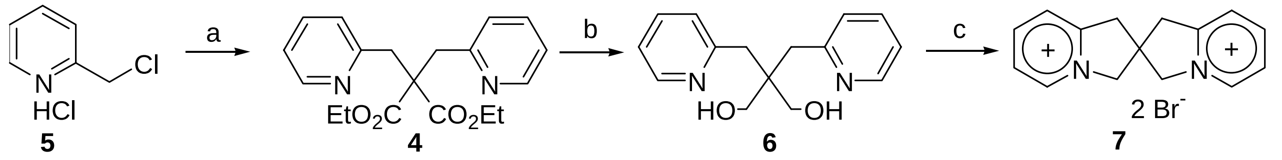
Figure 1 Spiro bis-pyridinium and bis-quinolinium salts



Scheme 1 Retrosynthetic analysis for the synthesis of spiro bis-pyridinium salt

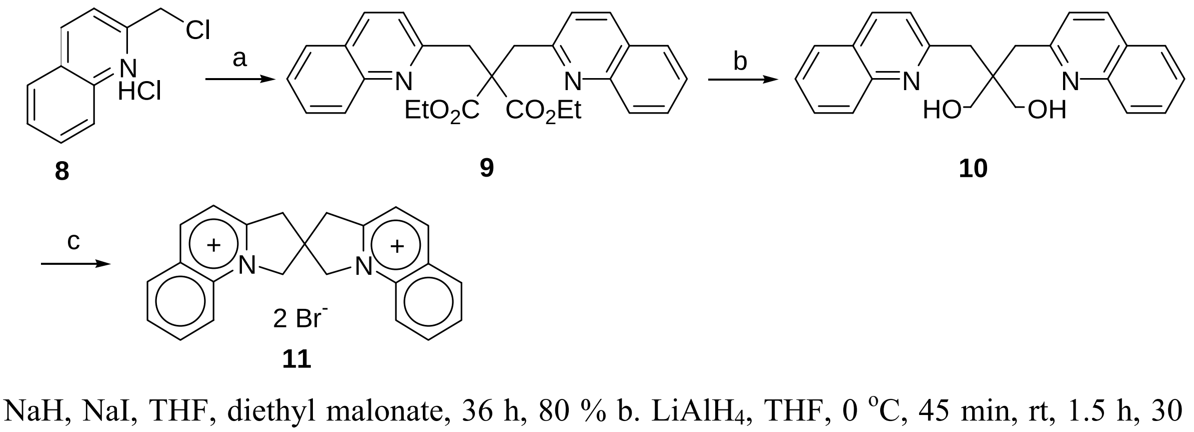
Our synthetic strategy was based on the utilization of intramolecular *N*-alkylation approach. Accordingly diethyl malonate was alkylated using commercially available 2-chloromethylpyridine hydrochloride (**5**), followed by LAH reduction to afford diol (**6)**. Our immediate aim was to convert the diol (**6**) into the corresponding bromide (**3a**), which would set the stage for intramolecular *N*-alkylation. But under almost all attempted conditions this conversion afforded complex reaction mixture. Further conversion of the diol (**6**) to **3b** or **3c** also gave similar results. Conversion of diol (**6**) into the corresponding compounds (**3a**), (**3b**) or (**3c**) are neopentyl displacement reactions, which are very slow and often results in rearranged products. Nevertheless, preparations of neopentyl halides from the alcohol by a variety of phosphorous reagents have been achieved. [5] We anticipated that conversion of diol (**6**) to bromide (**3a**) and further its *N*-alkylation in one step would provide the desired spiro pyridinium salts. After screening several reaction conditions we were pleased to find out one pot procedure for the synthesis of desired pyridinium salts.[6] Thus spiro bis-pyridinium salt (**7**) was obtained by the treatment of diol (**6**) with PBr_3 in refluxing toluene for 48 h in 75 % yield (Scheme 2).



a. 60 % NaH, NaI, THF, diethyl malonate, 15 h, 84 % b. $LiAlH_4$, THF, 0 °C, 45 min, rt, 1.5 h, 45 % c. PBr_3, toluene (1:2.5), reflux, 75 %

Scheme 2. Synthesis of spiro bis-pyridinium salts

After the development of this simple, short and efficient methodology for the synthesis of bis-pyridinium salts we explored its utility for the construction of spiro bis-quinolinium salts.



a. 60 % NaH, NaI, THF, diethyl malonate, 36 h, 80 % b. $LiAlH_4$, THF, 0 °C, 45 min, rt, 1.5 h, 30 % c. $PBr_{3,}$ toluene, reflux, 72 %

Scheme 3. Synthesis of spiro bis-quinolinium salts

Thus alkylation of diethyl malonate using commercially available 2-chloromethylquinoline hydrochloride (**8**) and subsequent reduction by LAH afforded diol (**10**) which upon treatment with PBr_3 in refluxing toluene resulted in the formation of desired spiro bis-quinolinium salt (**11**) in 72 % yield (Scheme 3).

These spiro bis-pyridinium and bis-quinolinium salts showed great stability under acidic conditions but were found to be unstable under basic conditions. These novel spiro bis-pyridinium and bis-quinolinium salts exhibited satisfactory spectroscopic data and further the formation of spiro skeleton was confirmed by the X-Ray crystallographic analysis of spiro bis-pyridinium salt (**7**)[7] (Figure 2).

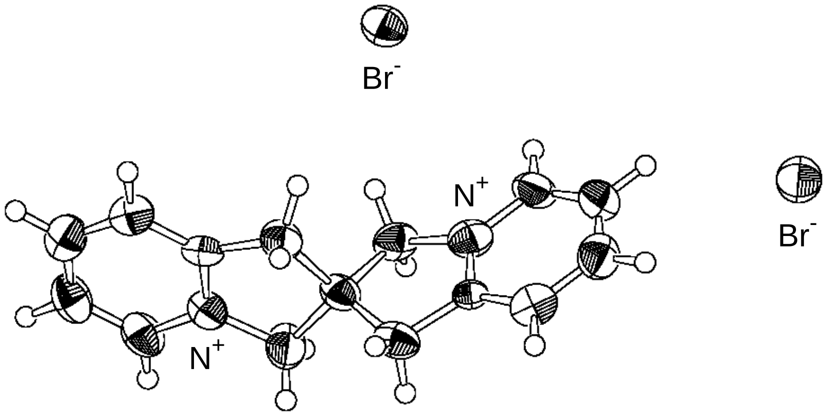


Figure 2. X-Ray crystal structure of spiro bis-pyridinium salt (**7**)

In conclusion we have designed and developed a short and simple methodology for the synthesis of spiro bis-pyridinium and bis-quinolinium salts. Further optical resolution and applications of these novel spiro compounds are under investigation.

EXPERIMENTAL

General procedures

^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-EX270 (^{1}H NMR-270 MHz, ^{13}C NMR-67.7 MHz). All signals were expressed as ppm down field from tetramethylsilane used as an internal standard. IR spectra were obtained with SHIMADZU FTIR-8300 instrument. Elemental analysis was performed on PERKIN-ELMER 2400. MS spectra were obtained on JMS-T100LC. X-Ray crystallographic analysis was carried out with RIGAKU AFC-7R, and all calculations were performed using the teXsan crystallographic software package of Molecular Structure Corporation. Melting points were measured with Yanaco MICRO MELTING POINT APPARATUS MODEL MP-S9. Column chromatography was performed using Kanto Silica Gel 60 (40-100 μm). Anhydrous THF and toluene were purchased from Kanto Chemicals, Tokyo.

Diethyl 2,2-bis(pyridin-2-ylmethyl)malonate (4): To a stirred solution of diethyl malonate (5 mL, 30 mmol) in anhydrous THF (50 mL) was added 60 % NaH (5.7 g, 150 mmol) at 0 °C under argon atmosphere. This mixture was allowed to stir at rt for 30 min. The reaction mixture was then cooled to 0 °C and 2-chloromethylpyridine hydrochloride (12 g, 73 mmol) was added in portions (10 min) followed by addition of NaI (10 g, 67 mmol). The resulting mixture was allowed to stir at rt for 15 h. The reaction mixture was then poured into ice-cold water (100 mL) and acidified using 1 N HCl (10 mL). After stirring 10 min, pH was adjusted to 7 by using 15 % NaOH followed by extraction with dichloromethane (50 mL x 3). The combined organic layer was washed with water, brine and dried over sodium sulfate. The residue obtained on evaporation of solvent was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$ = 3/97 as eluent) to afford compound (**4**) (9 g, 85 %) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, *J* = 7.2 Hz, 6H), 3.45 (s, 4H), 4.19 (q, *J* = 7.2 Hz, 4H), 7.00-7.16 (m, 4H), 7.50-7.57 (m, 2H), 8.48-8.50 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 14.0, 39.7, 58.1, 61.3, 121.3, 124.5, 135.7, 148.8, 157.4, 170.7. IR (neat): 2970, 1728, 1591, 1473, 1434, 1234, 1174, 1097, 1039, 866, 775, 748 cm^{-1}. *Anal.* Calcd for $C_{19}H_{22}N_2O_4$: C, 66.65; H, 6.48; N, 8.18. Found: C, 66.51; H, 6.47; N, 8.03.

2,2-Bis(pyridin-2-ylmethyl)propane-1,3-diol (6) : Lithium aluminum hydride (633 mg, 17.6 mmol) was added portion wise to a stirred solution of ester (**4**) (1.37 g, 4 mmol) in anhydrous THF (20 mL) at 0 °C under argon atmosphere. The resulting reaction mixture was stirred at 0 °C for 45 min and then at rt for 1.5 h. Excess lithium aluminum hydride was quenched by slow addition of reaction mixture to ice-cold water (50 mL) followed by adjustment of pH to 7 using 1 N HCl. After extraction with dichloromethane (50 mL x 3), the combined dichloromethane layer was washed successively with water (50 mL), brine and dried over sodium sulfate. Evaporation of the solvent and purification by silica gel column chromatography ($MeOH/CH_2Cl_2$ = 5/95 as eluent) afforded diol (**6**) (465 mg, 45 %) as a white foamy solid: mp 79-82 °C (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 2.89 (s, 4H), 3.14 (s, 4H), 7.15-7.21 (m, 2H), 7.25-7.28 (m, 2H), 7.63-7.69 (m, 2H), 8.48-8.51 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 41.0, 47.1, 63.7, 121.5, 125.2, 136.8, 148.3, 158.4. IR (neat): 3400, 2868, 1589, 1566, 1473, 1438, 1313, 1172, 1035, 831, 773, 750 cm^{-1}. *Anal.* Calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84. Found: C, 69.90; H, 7.07; N, 10.68.

1,1’,2,2’,3,3’-Hexahydro-2,2’-spirobi[indolizinium] dibromide (7): A solution of diol (**6**) (250 mg, 0.96 mmol) and PBr_3 (2 mL) in toluene (5 mL) was stirred at reflux for 48 h under argon atmosphere. The reaction mixture was then allowed to cool and the toluene layer was decanted. The residue was washed three times with toluene and then dissolved in methanol (20 mL) followed by filtration and silica gel column chromatography ($MeOH/CH_2Cl_2$ = 30/70 as eluent) to afford spiro bis-pyridinium salt (**7**) (278 mg, 75 %) as a white solid: mp > 300 °C (acetone/methanol). ^{1}H NMR (CD_3OD): δ 3.79-3.96 (m, 4H), 5.05-5.19 (m, 4H), 7.93 (t, *J* = 7.0 Hz, 2H), 8.03 (d, *J* = 8.0 Hz, 2H), 8.47 (t, *J* = 8.0 Hz, 2H), 8.87 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (CD_3OD): δ 43.6, 47.3, 67.3, 126.3, 127.3, 142.8, 147.1, 157.8. IR (neat): 3030, 1627, 1496, 1425, 1174, 773, 694 cm^{-1}. ESI-HRMS. Calcd for $C_{15}H_{16}N_2Br$ $[M - Br]^+$: 303.0497. Found: 303.0468.

Diethyl 2,2-Bis(quinolin-2-ylmethyl)malonate (9): To a stirred solution of diethyl malonate (2.5 mL, 15 mmol) in anhydrous THF (50 mL) was added 60 % NaH (2.8 g, 75 mmol) at 0 °C under argon atmosphere. This mixture was allowed to stir at rt for 30 min. The reaction mixture was then cooled to 0 °C and 2-chloromethylquinoline hydrochloride (**8**) (9.6 g, 45 mmol) was added in portions (10 min) followed by addition of NaI (6.5 g, 44 mmol). The resulting mixture was allowed to stir at rt for 36 h. The reaction mixture was then poured into ice-cold water (100 mL) and acidified using 1 N HCl (10 mL). After stirring 10 min, pH was adjusted to 7 by using 15 % NaOH followed by extraction with dichloromethane (50 mL x 3). The combined organic layer was washed with water, brine and dried over sodium sulfate. The residue obtained on evaporation of solvent was purified by silica gel column chromatography ($MeOH/CH_2Cl_2$ = 3/97 as eluent) to afford compound (**9**) (5.51 g, 80 %) as a pale yellow oil. ^1H NMR ($CDCl_3$): δ 1.23 (t, J = 7.0 Hz, 6H), 3.74 (s, 4H), 4.27 (q, J = 7.0 Hz, 4H), 7.24 (d, J = 8.5 Hz, 2H), 7.44-7.49 (m, 2 H), 7.62-7.69 (m, 2H), 7.74 (d, J = 8.0 Hz, 2H), 7.96-8.01 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 14.1, 40.1, 58.0, 61.4, 122.7, 125.7, 126.6, 127.3, 129.0 (2C), 135.6, 147.5, 158.0, 170.7. IR (neat): 2979, 1730, 1596, 1560, 1504, 1425, 1176, 1045, 831, 746 cm^{-1}. ESI-HRMS. Calcd for $C_{27}H_{26}N_2O_4Na$ $[M + Na]^+$: 465.1790. Found: 465.1776.

2,2-Bis(quinolin-2-ylmethyl)propane-1,3-diol (10) : Lithium aluminum hydride (759 mg, 20 mmol) was added in portions to a stirred solution of ester (**9**) (2.1 g, 4.7 mmol) in anhydrous THF (20 mL) at 0 °C under argon atmosphere. The resulting reaction mixture was stirred at 0 °C for 45 min and then at rt for 1.5 h. Excess lithium aluminum hydride was quenched by slow addition of reaction mixture to ice cold water (50 mL) and pH was adjusted to 7 using 1 N HCl. The product was extracted with dichloromethane (50 mL x 3) and the combined dichloromethane layer was washed successively with water (50 mL) and brine and then dried over sodium sulfate. Evaporation of the solvent and purification by silica gel column chromatography ($MeOH/CH_2Cl_2$ = 5/95 as eluent) afforded diol (**10**) (510 mg, 30 %) as a pale yellow foamy solid: mp 129-132 °C (hexane/ethyl acetate). ^1H NMR ($CDCl_3$): δ 3.15 (s, 4H), 3.27 (s, 4H), 7.41 (d, J = 8.3 Hz, 2H), 7.50-7.56 (m, 2H), 7.68-7.75 (m, 2H), 7.80-7.84 (m, 2H), 8.02 (d, J = 8.2 Hz), 8.14 (d, J = 8.2 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 41.8, 47.9, 64.5, 123.4, 126.2, 126.6, 127.4, 128.2, 129.7, 136.7, 146.9, 159.4. IR (neat): 3350, 2910, 1595, 1560, 1504, 1425, 1305, 1087, 1035, 831 cm^{-1}. ESI-HRMS. Calcd for $C_{23}H_{22}N_2O_2Na$ $[M + Na]^+$: 381.1579. Found: 381.1581.

1,1’,2,2’3,3’-Hexahydro-2,2’-spirobi[benz[5,6-*a*]indolizinium] dibromide (11): A solution of diol (**10**) (300 mg, 0.83 mmol) and PBr_3 (1.6 mL) in toluene (5 mL) was stirred at reflux for 48 h under argon atmosphere. The reaction mixture was then allowed to cool and toluene layer was decanted. The residue was washed three times with toluene and then dissolved in methanol (20 mL) followed by filtration and silica gel column chromatography ($MeOH/CH_2Cl_2$ = 30/70 as eluent) afforded spiro bis-quinolinium salt (**11**) (290 mg, 72 %) as a pale yellow solid: mp > 300 °C (acetone/methanol). ^1H NMR (CD_3OD): δ

4.27-4.45 (m, 4H), 5.54-5.72 (m, 4H), 8.01-8.07 (m, 2H), 8.17 (d, *J* = 8.5 Hz, 2H), 8.23-8.31 (m, 4H), 8.45 (d, *J* = 8.5 Hz, 2H), 9.19 (d, *J* = 8.5 Hz, 2H). ^{13}C NMR (CD_3OD): δ 45.6, 46.5, 66.3, 119.8, 120.8, 130.1, 130.9, 131.3, 136.7, 138.1, 148.4, 161.9. IR (neat): 2999, 2883, 1598, 1525, 1444, 1413, 1224, 1149, 1058, 827, 775 cm^{-1}. ESI-HRMS. Calcd for $C_{23}H_{20}N_2Br$ [M - Br] $^+$: 403.0810. Found: 403.0785.

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7. The single-crystal of **7** was obtained by recrystallization from acetone/methanol solvents. Crystal structure data for **7**: $C_{15}H_{16}N_2Br_2$, Mw = 384.11, monoclinic, space group $P2_1/c$ (# 14), a = 10.934 (2) Å, b = 13.575 (3) Å, c = 11.177 (2) Å, β = 114.34 (1)°, V = 1511.7 (5) Å^3, Z = 4, D calcd = 1.688 g/cm^3, R_1 = 0.067.