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A new family of bis-tetrazole (BIZOL) BINOL-type ligands

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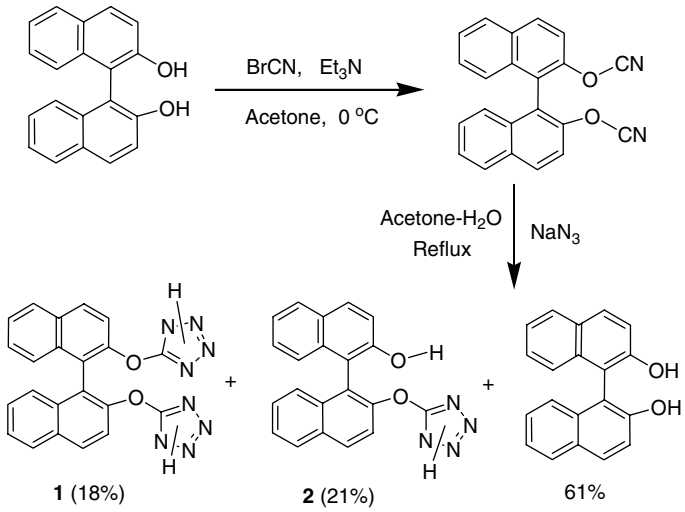
Abstract—The synthesis and characterization of 5-(1-(2-(1*H*-tetrazole-5-yloxy)naphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole (BIZOL) as the first bis-tetrazole BINOL-type ligands is described.

Despite the scarcity of tetrazoles in natural systems, the chemistry of this heterocycle has gained increasing attention since the early 1980s.[1] This interest stems from the ability of tetrazoles to mimic the carboxylic acid group, which has motivated the incorporation of tetrazoles into biologically active molecules.[2] Another research area of major interest is the therapeutic application of tetrazoles, which have been included in pharmacologically active compounds with antihypertensive, antiallergic and antibiotic activities.[3] Tetrazoles have also found wide application in agricultural biology and in explosives.[4]

Asymmetric synthesis[5] deals with the development of stereodifferentiating reactions in which the source of chirality can be present in a stoichiometric (chiral auxiliary) or a catalytic (chiral catalyst) amount, enantioselective catalysis[6] with transition metals in the presence of a chiral ligand probably being one of the most popular research areas in organic chemistry presently. Among chiral ligands, those containing a 1,1′-binaphthyl moiety[3] have played a central role in this field and when constituents are introduced into the 2,2′-positions the atropisomers become configurationally stable and for



Scheme 1.

Keywords: BINOL; Tetrazole; BIZOL; Axial chirality.
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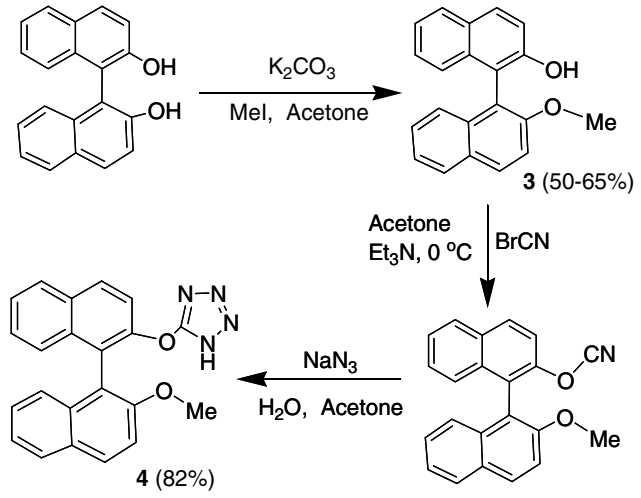
that reason easily resolvable.[7] Apart from the interest in the design of binaphthyls for asymmetric synthesis, they can be used in materials science because of the unique properties derived from their rigidity, chirality and conjugation.[8] As a result of our research on the chemistry of tetrazoles,[9–13] we herein report the synthesis and characterization of tetrazoles possessing a BINOL skeleton. These interesting compounds have both bis-tetrazole and binaphthyl character.

The preparation of aryloxy tetrazoles has commonly been achieved by the reaction of phenols with cyanogen bromide in the first stage followed by the addition of sodium azide in acetone–water at reflux.[12,13]

Most phenols give good yields by this method. In the case of 2,2′-dihydroxy-1,1′-binaphthyl, the yields were lower than expected. In fact, cyanate formation using this method was easy, however, a mixture of adducts **1** and **2** was produced in the final stage of the reaction along with recovered starting material, Scheme 1.[14] The low yields of **1** and **2** were attributed to the presence of water. Attempts to eliminate water from the system prevented the formation of adducts **1** and **2**. The same yields were obtained at lower temperature and in a shorter reaction time. However, the ease of recovery of unreacted BINOL and the availability of the starting reagents make the yields of **1** and **2** workable.

In a similar procedure, the preparation of BINOL tetrazole **4** was achieved in high yield when one of the hydroxyl groups was protected using methyl iodide, Scheme 2.[15,16] The results of all the reactions investigated using racemic and optically active BINOL are presented in Table 1. The specific rotations, yields and melting points



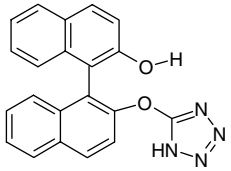
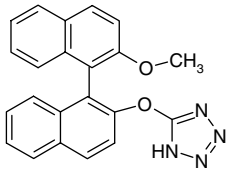
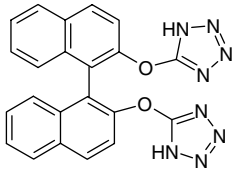
Scheme 2.

of enantiomers and racemic mixtures of BIZOL **1**, tetrazole **2** and 5-(1-(2-methoxynaphthalen-1-yl)naphthalene-2-yloxy)-1*H*-tetrazole **4** are listed in Table 1.

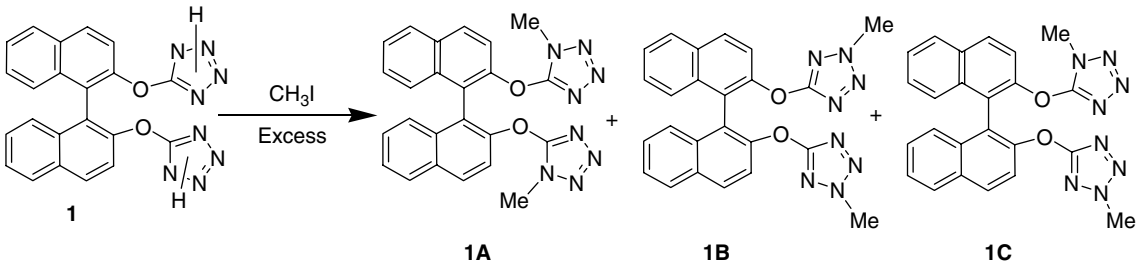
Derivatization is a common tool for confirmation of the structures of tetrazoles. Methylation of BIZOL **1** was achieved using methyl iodide in acetone, Scheme 3.[17] A mixture of 1,1′-dimethyl BIZOL **1A**, 2,2′-dimethyl BIZOL **1B** and 1,2′-dimethyl BIZOL **1C** was produced quantitatively. All attempts to separate the three isomers failed due to their similar polarity.

In conclusion, we have introduced a series of interesting compounds possessing the characteristics of both BINOL and tetrazole. These compounds can be used

Table 1. Specific rotations, melting points and yields of BIZOL derivatives

Compound	Enantiomer	Specific rotation[a]	Melting point °C	Yield[b]
	*S*-(**2**)	−42.7	128–130	21(54)
	R-(**2**)	43.3	122–124	20(57)
	R,*S*-(**2**)	—	172–174	22(52)
	*S*-(**4**)	−24.9	130–132	82
	R-(**4**)	25.1	128–130	75
	R,*S*-(**4**)	—	236–238	90
	*S*-(**1**)	−28.9	186–188	18(46)
	R-(**1**)	29.9	178–180	15(43)
	R,*S*-(**1**)	—	238–240	20(48)

[a] $[\alpha]_D^{25}$ (acetone, *c* 0.5).
[b] Yields in parentheses are isolated yields based on recovered unreacted BINOL.



Scheme 3.

as new BIZOL ligands for the synthesis of novel complexes.

Acknowledgement

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14. *A typical method for the preparation of compounds* **1** *and* **2**: To a solution of a racemic mixture of 1,1′-binaphthalene-2,2′-diol (1.43 g, 5 mmol) in acetone at ice-bath temperature was added cyanogen bromide (1.75 g, 15 mmol). When the temperature reached below 5 °C, triethylamine (2.75 ml, 20 mmol) was added dropwise. After a few minutes tetraethylammonium bromide precipitated as a white solid. The progress of the reaction was followed by thin layer chromatography and when cyanate formation was completed, sodium azide (0.13 g, 20 mmol) dissolved in water–acetone (50:50) was added dropwise with stirring at room temperature for 2 h and then at reflux for 5 h. The reaction mixture was cooled to room temperature and acidified with hydrochloric acid (5%) and then extracted with diethyl ether (2 × 20 ml). Purification of the concentrated reaction mixture by silica gel chromatography (30:70 ethyl acetate–cyclohexane) afforded the products. The first fraction was 1,1′-binaphthalene-2,2′-diol (0.8 g, 61% recovered), mp = 215–216 °C.[18] The next fraction was mono-tetrazolated binaphthol **2**: 1-(2-(1*H*-tetrazole-5-yloxy)naphthalen-1-yl)naphthalen-2-ol (0.40 g, 21% conversion), mp = 172–174 °C [for (+)-**2**, mp = 128–130 °C and for (−)-**2**, mp = 122–124 °C]. IR (KBr): 3435, 3028, 2923, 2854, 2739, 2633, 2478, 1609, 1598, 1577, 1509, 1445, 1416, 1239, 1205, 1108, 777 cm^{-1}; ^1H NMR (DMSO-d_6, 500 MHz): δ 6.98 (1H, d, $J = 8.4$ Hz), 7.07 (1H, d, $J = 8.4$ Hz), 7.20 (1H, t, $J = 7.9$ Hz), 7.28–7.35 (m, 2H), 7.50 (1H, t, $J = 7.4$ Hz), 7.56 (1H, d, $J = 9.1$ Hz), 7.68 (1H, d, $J = 9.0$ Hz), 7.92 (1H, d, $J = 8.0$ Hz), 8.08 (2H, t, $J = 8.3$ Hz), 8.15 (1H, d, $J = 9.0$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 114.2, 116.2, 120.3, 123.7, 123.9, 124.6, 125.9, 126.0, 126.2, 127.5, 128.5, 128.7, 129.0, 130.2, 130.8, 131.7, 133.4, 133.6, 149.9, 155.2, 161.6; MS (EI), m/z = 354 (M^+), 339, 326, 311, 296, 287, 267, 252, 246, 239, 212, 155, 127, 115; Anal. Calcd for $C_{21}H_{14}N_4O_2$: C, 71.2, H, 4.0, N, 15.8. Found: 71.3, 3.8, 14.0. $[\alpha]_D^{25}$ +43.3 and −42.7 (acetone, *c* 0.5) for (*R*)-**2** and (*S*)-**2**, respectively. The final fraction was 5-(1-(2-(1*H*-tetrazole-5-yloxy)-naphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole **1** (0.7 g, 18% conversion), mp = 238–240 °C [for (+)-**1**, mp = 178–180 °C and for (−)-**1**, mp = 186–188 °C]; IR (KBr): 3062, 2910, 2730, 2642, 1578, 1505, 1206, 1075 cm^{-1}; ^1H NMR(DMSO-d_6, 500 MHz): δ 7.85 (2H, d, $J = 8.4$ Hz), 7.35 (2H, t, $J = 7.7$ Hz), 7.50 (2H, t, $J = 7.3$ Hz), 7.62 (2H, d, $J = 9.0$ Hz), 8.00 (2H, d, $J = 8.0$ Hz), 8.20 (2H, d, $J = 9.0$ Hz); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 115.0, 119.1, 125.8, 126.9, 127.5, 127.7, 130.1, 130.7, 133.7, 151.8, 166.5; MS (EI), $m/z = 422$ (M^+), 394, 382, 365, 354, 337, 309, 297, 286, 268, 239, 226, 125, 119; Anal. Calcd for $C_{22}H_{14}N_8O_2$: C, 62.6, H, 3.4, N, 26.5. Found: C. 62.8, H, 3.8, N, 24.5. $[\alpha]_D^{25}$ +29.9 and −28.9 (acetone, *c* 0.5) for (*R*)-**1** and (*S*)-**1**, respectively.
15. *1-(2-Methoxynaphthalen-1-yl)naphthalene-2-ol* (**3**):[19] To a solution of 1-(2-hydroxynaphthalene-1-yl)naphthalene-2-ol (0.57 g, 20 mmol) in acetone was added potassium carbonate (0.35 g, 25 mmol). After stirring for 10 min, methyl iodide (0.2 ml, 30 mmol) in acetone was added dropwise at room temperature and the mixture stirred for 30 h. The mixture was filtered and washed with acetone three times. Acetone was evaporated under reduced pressure and the racemic mixture was purified by recrystallization from carbon tetrachloride to give a 50% yield of **3**. The melting

point of the racemic compound (±)-**3** was 152–154 °C [lit 152–153 °C].[20] Optically active 2′-methoxy-1,1′-binaphthalen-2-ols were prepared similarly and purified by silica gel column chromatography using cyclohexane–ethyl acetate (90:10) as eluent to give (+)- or (−)-1-(2-methoxynaphthalen-1-yl)naphthalene-2-ol as white solids (55–60% yields). The melting points for (+)-**3** and (−)-**3** were 81–83 °C and 83–85 °C, respectively [lit. (*S*)-**3**, 82–84 °C and 76–77 °C for (*R*)-**3**].[20,21] ^{1}H NMR ($CDCl_3$–CCl_4, 500 MHz): δ 3.85 (s, 3H), 4.78 (s, 1H), 7.01–8.04 (m, 12H). IR (KBr) cm^{-1}: 3548, 3480, 3051, 2956, 2931, 1618, 1590, 1507, 1473, 1378, 1359, 1206, 1174, 809, 707. MS (EI), $m/z = 300$ (M^+): 285, 268, 239, 144. $[\alpha]_D^{25}$ +38.7 and −38.2 (acetone, *c* 0.5) for (*R*)-**3** and (*S*)-**3**, respectively.

16. *5-(1-(2-Methoxynaphthalen-1-yl)naphthalene-2-yloxy)-1H-tetrazole* (**4**):[19] To a solution of 1-(2-methoxynaphthalen-1-yl)naphthalene-2-ol **3** (0.6 g, 20 mmol) in acetone was added cyanogen bromide (0.25 g, 25 mmol) at 0 °C. Next, triethylamine (0.25 ml, 0.25 mmol) was added dropwise over a period of 0.5 h. The mixture was stirred for 0.5 h and precipitated triethylammonium bromide was removed by filtration. To the residue was added a solution of sodium azide (0.16 g, 0.25 mmol) in acetone and water mixture (50:50). The resulting mixture was stirred for 0.5 h and then refluxed for 2 h. The temperature was reduced to room temperature and the solution acidified with 6 N hydrochloric acid. Compound (±)-**4** precipitated as a white solid, which was recrystallized from methanol–water (50:50) to give an 82% yield (0.61 g of product, mp = 238–240 °C) [for (+)-**4**, mp = 128–130 °C and (−)-**4**, mp = 130–132 °C]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 3.61 (s, 3H), 7.01–8.16 (m, 12H) 16.50 (br, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 55.9, 113.7, 115.8, 119.9, 123.3, 123.5, 124.1, 125.4, 125.7, 126.6, 127.0, 128.0, 128.2, 128.5, 129.8, 130.3, 131.3, 133.0, 133.1, 149.4, 154.7 (2C). IR (KBr) cm^{-1}: 3053, 2731, 2626, 1619, 1590, 1506, 1458, 1261, 1053, 817. MS (EI), $m/z = 368$ (M^+): 354, 311, 297, 286, 268, 239, 226, 134, 120, 43. Anal. Calcd for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.70; H, 4.40; N, 14.80. $[\alpha]_D^{25}$ +25.1 and −24.9 (acetone, *c* 0.5) for (*R*)-**4** and (*S*)-**4**, respectively.

17. *Methylation of BIZOL* **1**: To a solution of a racemic mixture of **1** (0.422 g, 1 mmol) in acetone at ice-bath temperature was added triethylamine (0.25 ml, 25 mmol). After 10 min, excess methyl iodide (0.2 ml, 30 mmol) in acetone was added dropwise at room temperature. The reaction progress was monitored by TLC. The mixture was stirred overnight and then filtered and washed with acetone. The solvent was evaporated under reduced pressure. All efforts to separate the mixture by column chromatography failed. IR (KBr): 2996, 2940, 2839, 1576, 1588, 1260, 1080 cm^{-1}; MS (EI), $m/z = 450$ (M^+), 379, 368, 351, 323, 308, 295, 281, 268, 239, 236, 212, 175, 161, 124; ^{1}H NMR (DMSO-d_6, 500 MHz): δ (ppm): 6.97–8.32 (m, 12H), 4.1 (br, 6H).
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