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Aryloxy Tetrazoles with Axial Chirality: Synthesis and Partial Resolution of 5-(1-(2-Methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole

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ABSTRACT: *5-(1-(2-Methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1H-tetrazole as the first aryloxy tetrazole with axial chirality was synthesized. Partial resolution was achieved using (S)-proline and methylbenzylamine as the resolving agents. Best results were obtained using methylbenzylamine with 75–85% ee.*
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INTRODUCTION

Despite the scarcity of tetrazoles compounds in natural systems, the chemistry of this heterocycles has gained an 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 in biologically active molecules [2]. Another research area of major interest is the therapeutic application of tertrazoles which has been included in pharmacologically active compounds with antihypertensive, antiallergic, and antibiotic activities [3]. Tetrazoles have found wide application in agriculture biology and explosives [4].

Optically active BINOL and its relative compounds with axial chirality have wide application in asymmetric ligands [5,6], Michael addition [7], enantioselective hydrogenation [8], and chiral-reducing agents [9,10] and more [11–14].

Recently Kocovsky et al. reviewed application of nonsymmetrically binaphthyl compounds in enantioselective synthesis [15].

In the course of our research on the chemistry of tetrazoles [16–20], herein we report the first example of synthesis and partial resolution of aryloxy tetrazoles with axial chirality. Chiral tetrazoles, besides their very important role in their own chemistry, are very important precursor to a wide range of functional groups such as amines, aziridines, azapenes, isoureas, and more [1–4,16–20].

EXPERIMENTAL

Potassium carbonate and solvents were purchased from Merck, methyl iodide was purchased from Riedel-Dehaen, and optically active 1,1′-binaphthalen-2,2′-diol was purchased from Fluka. Racemic 1,1′-binaphthalen-2,2′-diol was synthesized by the method described in [21]. IR spectra were recorded on a Jasco FT/IR-680 Plus spectrometer. NMR spectra were recorded on a Bruker 500 ultrasheild NMR and $CDCl_3$, and DMSO-d_6 was used as a solvent. Optical rotation measurements

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were carried out on a JASCO p-1030 polarimeter. Mass spectra were determined on a UK Fisons Trio 1000 spectrometer. The elemental analysis was determined at the Research Institute of Petroleum Industry, Tehran, Iran. The melting points were obtained on a Gallenkamp apparatus and were not corrected. For flash chromatography, Merck silica gel 60 (40–63 μm 230–400 ASTM) was used. All solvents were purified by the standard procedures prior to use.

1-(2-Methoxynaphthalen-1-yl)naphthalen-2-ol **2**

To a solution of 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol **1** (0.57 g, 20 mmol) in acetone was added potassium carbonate (0.35 g, 25 mmol). After 10 min methyl iodide (0.2 mL, 30 mmol) was added dropwise at room temperature. The mixture was stirred for 30 h. The mixture was filtered and washed with acetone three times. Acetone was evaporated under reduced pressure. The racemic mixture was purified by multicrystallization in carbon tetrachloride to give 50% yield. The melting point of the racemic compound (±)-**2** was 152–154°C (lit 152–153°C) [24]. The optically active 2′-methoxy-1,1′-binaphthalen-2-ol was prepared similarly and purified by silica gel column chromatography using cyclohexane-ethyl acetate (90:10) as eluent to give (+) or (−)-2′-methoxy-1,1′-binaphthalen-2-ol as a white solid (55–60% yields). The melting points for (+)-**2** and (−)-**2** was 81–83°C and 83–85°C, respectively (lit. (*S*)-**2**, 82–84°C and 76–77°C for (*R*)-**2**) [23]. ^{1}H NMR ($CDCl_3$-CCl_4): $\delta = 3.85$ (s, 3H), 4.78 (s, 1H), 7.01–8.04 (m, 12H). IR (KBr): 3548, 3480, 3051, 2956, 2931, 1618, 1590, 1507, 1473, 1378, 1359, 1206, 1174, 809, 707 cm^{-1}. MS *m/z* 300, (M^+): 285, 268, 239, 144. $[\alpha]_D^{25} = +38.7$ and −38.2 (acetone, c 0.5) for *R*-**2** and *S*-**2**, respectively.

Typical Preparation of 5-(1-(2-Methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1H-tetrazole **3**

To a solution of 1-(2-methoxynaphthalen-1-yl)-naphthalen-2-ol **2** (0.6 g, 20 mmol) in acetone was added cyanogen bromide (2.65 g, 25 mmol) at 0°C. Triethylamine (4.3 mL, 30 mmol) was added dropwise over a period of 0.5 h. The mixture was stirred for additional 0.5 h. Triethylammonium chloride salt was filtered. To the residue was added a solution of sodium azide (1.6 g, 25 mmol) in acetone and water mixture (50:50). This mixture was stirred for 0.5 h, and then was refluxed for 2 h. The temperature was reduced, and solution was acidified using 6 N hydrochloric acid. The (±)-**3** was precipitated as a white solid. The solid was recrystallized in methanol–water (50:50) to give 82% yield (0.61 g), mp 238–240°C (for (+)-**3**, mp 128–130°C and for (−)-**3** mp 130–132°C). ^{1}H NMR (DMSO-d_6): $\delta = 3.61$ (s, 3H), 7.01–8.16 (m, 12H) 16.50 (br, 1H).^{13}C NMR (DMSO-d_6): $\delta = 55.9$, 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. IR (KBr): 3053, 2731, 2626, 1619, 1590, 1506, 1458, 1261, 1053, 817 cm^{-1}. MS: *m/z* 368.0 (M^+): 354, 311, 297, 286, 268, 239, 226, 134, 120, 43. $C_{22}H_{16}N_4O_2$ (368.354): Calcd C, 71.73, H 4.38, N 15.21; Found C 71.70, H 4.40, N 14.80.

The above procedure was repeated with the chiral substrates in a smaller scale for optical rotation measurements (Table 2). $[\alpha]_D^{25} = +25.1$ and $[\alpha]_D^{25} = -24.9$ (acetone, c 0.1) for R-**3** and S-**3**, respectively.

The above procedure was repeated with different equivalents of acetone, THF, or acetonitrile using triethylamine or pyridine as a base to obtain optimum condition (Table 1).

Partial Resolution of Racemic 5-(1-(2-Methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1H-tetrazole **3** *Using (S)-Proline*

5-(1-(2-Methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole **3** (0.39 g 1 mmol) and (*S*)-Proline (0.12 g 1 mmol) were dissolved in methanol (15 mL). The mixture was refluxed for 24 h. The temperature was brought to room temperature. Methanol was evaporated to obtain a solid residue. The precipitate and residue were treated with diethyl ether (20 mL) and diluted HCl (3 N, 10 mL) in separate runs. The organic layer was separated, washed successively with water (2 × 10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain compound **3**.

A Typical Procedure for Partial Resolution of Racemic 5-(1-(2-Methoxynaphthalen-1-yl) naphthalen-2-yloxy)-1H-tetrazole **3** *Using Methylbenzylamine*

5-(1-(2-Methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole **3** (0.39 g 1 mmol) and methylbenzylamine (0.24 g, 2 mmol) were dissolved in toluene (15 mL) and refluxed for 1 h. The temperature brought down to room temperature, and then the system was allowed to stand in refrigerator overnight. The mixture was filtered to obtain the precipitate and filtrate. After evaporation of solvent, the residue and precipitate were treated with diethyl ether (20 mL) and diluted HCl (3 N, 10 mL) in separate runs. The organic layer was separated,

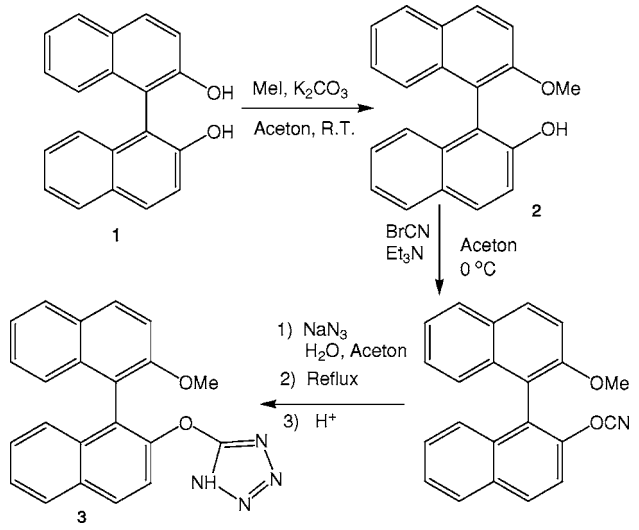
washed successively with water (2×10 mL) and brine (10 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated to obtain the compound **3**.

RESULTS AND DISCUSSION

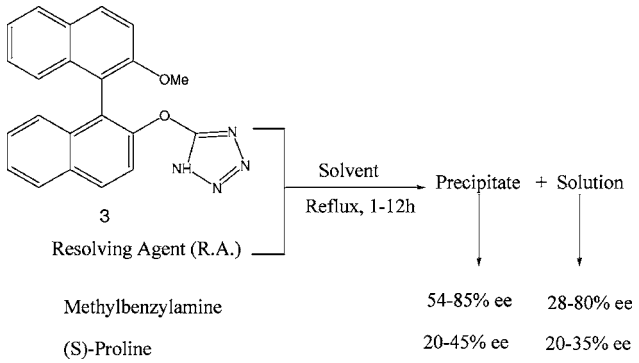
The synthesis of (±)-aryloxy tetrazole **3** was achieved in high yields. In the first attempt, 1-(2-methoxynaphthalen-1-yl)naphthalen-2-ol **2** was prepared by methylation of 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol **1** in acetone. 1-(2-Methoxynaphthalen-1-yl)naphthalen-2-ol was purified by recrystallization in carbon tetrachloride. The 1-(2-methoxynaphthalen-1-yl)naphthalen-2-ol was reacted with BrCN to produce 1-(2-cyanatonaphthalen-1-yl)-2-methoxynaphthalene. Finally, to the latter compound in acetone was added a solution of sodium azide in acetone–water mixture (1:1). The final step was repeated in THF, acetonitrile, or acetone–water (1:1) using different equivalents of triethylamine or pyridine as a base (Table 1). The optimum condition for higher yield was a mixture of acetone–water (1:1) as a solvent and 1.5 equivalent of triethylamine as a base (Table 1; Scheme 1).

The reaction was repeated with chiral 1-(2-hydroxynaphthalen-1-yl)naphthalen-2-ol (see Scheme 2). The methylation reaction was performed at room temperature. Under this condition no racemization was observed. 1-(2-Methoxynaphthalen-1-yl)naphthalen-2-ol was purified using column chromatography to give 55% yield. Specific rotation values of all compounds are listed in Table 2. Despite the reported melting points (107–110°C) and specific rotation value (−49.1) for **2** [22], our results are in agreement with the work of Jaques and Liu [23,24].

To resolve racemic aryloxy, tetrazole **3** (+) and (−) methylbenzylamine and (*S*)-proline were used. The resolving agent was added to the solution of tetrazole **3**, and the mixture was refluxed to obtain a homogeneous system. The reaction mixture allowed to stand inside a refrigerator overnight. The precipitate and filtrate treatment with diluted HCl gave partially resolved tetrazoles **3** (see Table 3). The best resolutions were obtained using methylbenzylamine. This could be attributed to the acidic nature of tetrazoles. Tetrazole's hydrogen has a pk_a of about 5, and therefore aryloxy tetrazole **3** can form a better diastreomeric salt with methylbenzylamine; but amino acids such as proline are in



SCHEME 1 Preparation of 5-(1-(2-methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole **3**.



SCHEME 2 Partial resolution of 5-(1-(2-methoxynaphthalen-1-yl)naphthalen-2-yloxy)-1*H*-tetrazole **3**.

TABLE 1 Effect of Solvent and Equivalent of Base on Tetrazole **3** Yields

Entry	*Solvent*	*Base (Equivalent)*	*Tetrazole* **3** *Yields (%)*
1	THF	Et_3N (1.0)	65
2		Et_3N (1.5)	65
3		Pyridine (1.5)	55
4	Acetonitrile	Et_3N (1.0)	70
5		Et_3N (1.5)	80
6		Pyridine (1.5)	40
7	Acetone: water(1:1)	Et_3N (1.0)	70
8		Et_3N (1.5)	80—98
9		Pyridine (1.5)	50

TABLE 2 Speci c Rotations for Binaphthyl Derivatives

Compound	*(+) Enantiomer*	*(−) Enantiomer*
1	34.1	−33.9
2	38.7	−38.2
3	25.1	−24.9

TABLE 3 Partial Resolution of Aryloxy Tetrazole **3**, Effect of Solvent and Resolving Agent

			Precipitate		*Filtrate*	
Solvent	*Resolving Agent*	*3:R.A.*[a]	*% ee*	*yield (%)*[b]	*% ee*	*yield*[b]*(%)*
Methanol	(+)Methylbenzylamine	1:1	58 (R)[c]	37	28 (S)	33
	(+)Methylbenzylamine	1:2	54 (R)	36	40 (S)	45
Toluene	(+)Methylbenzylamine	1:1	49 (R)	41	35 (S)	30
	(+)Methylbenzylamine	1:2	54 (R)	36	38 (S)	30
	(−)Methylbenzylamine	1:2	85 (S)	40	80 (R)	43
	(−)Methylbenzylamine	10:1	65 (S)	70	75 (R)	18
Methanol	(*S*)-Proline	1:2	45 (S)	40	35 (R)	58
	(*S*)-Proline	1:1	35 (S)	30	23 (R)	62
	(*S*)-Proline	10:1	30 (S)	65	30 (R)	30
Toluene	(*S*)-Proline	2:1	20 (S)	42	30 (R)	50
	(*S*)-Proline	1:1	30 (S)	35	20 (R)	50
Benzene	(*S*)-Proline	1:1	None[d]		None[d]	
	(*S*)-Proline	2:1	None[d]		None[d]	

[a]Resolving agent.
[b]Isolated yields.
[c]Absolute con gur ation.
[d]A homogenous solution was not obtained.

the form of zwitterions with nitrogen as ammonium salt. Toluene consistently gave the best ee and yields. We examined different ratios of tetrazole: resolving agent in different solvents and found a ratio of 2:1 in toluene to give the highest ee. In the case of benzene, after 12 h refluxing, we did not obtain a homogeneous mixture or partial resolution (Table 3).

CONCLUSIONS

In conclusion, 5-(1-(2-methoxynaphthalen-1-yl)-naphthalen-2-yloxy)-1*H*-tetrazole was prepared as a class of aryloxy tetrazole with axial chirality. Furthermore, this compound can be used as an auxiliary optically active nitrene and as a ligand in asymmetric organic synthesis. The highest resolution was achieved using methylbenzylamine as a resolving agent.

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