Two synthetic strategies of (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene

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Abstract. Different effective synthetic strategies of chiral intermediate (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene are described from the original material (S)-3,3′-bis(hydroxymethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphol. The 1HNMR and HRMS spectroscopic analyses have been used to confirm the synthesis of (S)-6.

1. Introduction

Organic azide compounds are compounds that contain an azide group (-N₃) in an organic molecule. The main types of organic azides are aromatic azides, alkyl azides, olefinic azides, 1,2-azido, 1,2- or 1,3-azidoamines, β-azido ketones, and acyl azides and their related compounds. Although the azide compounds are toxic and potentially explosive, they were valuable active intermediates in the field of organic synthesis. They were used in click reactions, cycloaddition reactions, Staudinger reactions, and synthesized heterocycles of azoles, which can be converted to amine groups and introduced into drug molecules as specific functional groups. Currently, organic azide compounds are widely used in organic synthesis [1], chemical biology [2], functional materials [3], and clinical medicine.

Organic azide compounds are mainly obtained through the addition or nucleophilic substitution of substrates containing unsaturated bonds and certain polar bonds with precursors that provide the azide group. Common reagents that used to synthesize azide compounds were include Hydrazoic acid (HN₃), Sodium Azide (NaN₃), Trimethylsilyl Azide (TMSA), Diphenylphosphinyl Azide (DPPA), Tributyltin Azide (TBSnA), Ethyl Azidoacetate (AAE), Tetrabutylammonium Azide (TBAA) and so on.

As a fluorescent chemical sensor, rapid identification of chiral isomers with high selectivity and sensitivity is the remarkable advantage of chiral BINOL derivatives. As the significant advantage of BINOL, it was easy to modify by space effects and electronic effects. The derivatives of chiral BINOL [4-6] have caused enough attention and application in the field of chiral fluorescent sensors [7-10] and synthetic catalysis. Binaphthol has a good rigid structure and C₂ symmetry, and commercially available with both pure enantiomers, (R)- and (S)- BINOL. A variety of chiral BINOL derivatives have the different features: easily modified by functional groups especially tended the 2-, 3-, and 6-positions.

(S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene was an important intermediate which could easily to convert 1,2,3-triazole by click reaction and chiral amide by reduction with NaBH₄. In this paper, two novel synthetic strategies of (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene was provided. To optimize the synthesis way, different azide
resources were applied. DPPA, diphenylphosphoryl azide was used in the nucleophilic reaction with a good leaving group phosphate ester.

2. Results and Discussion

The different procedures for the synthesis of the target chiral intermediate (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene are outlined in Fig. 1. First synthesis strategy of the target compound was synthesized via 4-step reactions with the commercially available reagent (S)-1,1′-bi-2- naphthol (BINOL) [(S)-1] as the starting material. The protection of (S)-BINOL was processed with Chloromethyl methyl ether (MOMCl) to give (S)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene [(S)-2] in high yield (89%). Then n-BuLi was first treated to the solution of (S)-2 and N,N-Dimethylformamide (DMF) was added slowly followed to produce (S)-3 as a yellow solid in 45% yield. The aldehyde groups could be easily converted to hydroxymethyl groups via a reduction reaction with NaBH₄ with high yield (92%).

![Fig. 1](image1.png)

**Fig. 1** the synthesis of (S)-4

Synthesis of bis(azidomethyl)-1,1′-binaphthalene from bis(methoxymethyl)-1,1′-binaphthalene was introduced in this paper. In the synthesis strategy I, (S)-3,3′-bis(hydroxymethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene [(S)-4] was first treated with Methanesulfonyl chloride and Et₃N and then LiBr was added to generate the intermediate (S)-3,3′-bis(bromomethyl) -2,2′-dimethoxy-1,1′-binaphthalene [(S)-5]. The desired chiral (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene was generated in high yield by nucleophilic reaction between NaN₃ and (S)-5. To improve the reaction efficiency, another effective synthetic strategy II was studied. In the method, diphenylphosphoryl azide DPPA was used as the source of the azide group. Compared with traditional nucleophilic reaction by NaN₃, the second synthetic method has advantages of simplified reaction procedure, elevated reaction rate, simple (workup) procedure and high overall yield. The mechanism of the reaction between (S)-4 and DPPA under alkaline conditions of DBU was that hydroxymethyl of (S)-4 was inverted to phosphate ester first. The new phosphate ester group was found to be a good leaving group and inverted quickly by the nucleophilic reaction with the new intermediate DBU compound with Hydronitric acid. The by-products of the reaction, diphenyl phosphate and DBU salts, can be washed off with water. The target compound could be easily purified by column chromatography.

![Fig. 2](image2.png)

**Fig. 2** two procedures for the synthesis of (S)-6

The ¹H NMR experiments were carried out in CDCl₃ to confirm the synthesis of (S)-6. As shown in Fig. 3, the nuclear magnetic peaks of the methylene hydrogen atoms in -CH₂OH linking binaphthalene group of (S)-4 are split into two sets of signals which combined to one set signal at 5.00 ppm of (S)-5.
Compared to (S)-4, the methylene hydrogen atoms in -CH2N3 linking binaphthalene group of (S)-6 are also split into two sets of signals. One group with the displacement peaks migrate \( \Delta \delta \) 0.21 ppm to upfield from 5.00 ppm to 4.79 ppm, while another group of displacement peaks shift to upfield for 0.22 ppm (from 5.90 ppm to 4.68 ppm). The changes demonstrated the formation of azidomethyl group. Especially, the H atom of hydroxyl group in -CH2OH at 3.65 ppm were disappeared, which explained the response of the end of the reaction. Another evidence for the synthesis of (S)-6 was achieved according to the TOF mass data. The peak at \( m/z = 507.1638 \) (calcd 507.1757) was found to correspond to the \([S(\cdot)6 + Na]\).

Fig. 3 the \(^1\)HNMR and HRMS spectroscopic analyses

3. Experimental section

All starting reagents were purchased from Energy Chemical and Bide Pharm and used without further purification. All solvents were purchased from Innochem. All the analytical grade solvents were distilled before used. The optical purity was characterized by a Rudolph AUTOPOL IV automatic polarimeter. \(^1\)HNMR and \(^{13}\)CNMR were recorded on a Bruker AM-400WB spectrometer with CD3OD, DMSO, CDCl3 and D2O as solvents. Mass spectral data were based on a Bruker amazon SL Ion Trap Mass spectrometer.

3.1 Synthesis of (S)-3,3'′-bis(bromomethyl)-2,2′-dimethoxy-1,1′-binaphthalene.

To the stirred solution of (S)-3,3′-bis(hydroxymethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene (0.5 g, 1.2 mmol) in 20 mL of anhydrous toluene in a 100 mL triple flask under argon atmosphere at 0°C, then stir in an ice bath for 10 min, methanesulfonyl chloride (0.5 mL, 6 mmol) was added dropwise. After the solution was stirred for 10 min, triethylamine was added slowly (1.2 mL, 8.4 mmol), and continue the reaction for 1h. Add 15 mL of DMF-solubilized lithium bromide mixture (0.52 g, 6.0 mmol) in an ice bath for 2 h. After 1 h of reaction and TLC to monitor the disappearance of the material, slowly add 20 mL of ice water to quench the reaction and extract with 90 mL of EA in three times, wash the organic phase with water and saturated salt water several times, dry anhydrous sodium sulfate and remove by decompression distillation. Solvent, column chromatography (PE:EA=10:1) separation and purification yielded 0.51 g of white solid with Y=79% yield. \(^1\)H NMR (400 MHz, CDCl3) \( \delta \) 8.12 (s, 2H), 7.91 (d, \( J = 8.2 \) Hz, 2H), 7.44 (dd, \( J = 8.0, 6.8 \) Hz, 2H), 7.29 (dd, \( J = 8.0, 6.8, 2H \)), 7.18 (d, \( J = 8.5 \) Hz, 2H), 5.06 – 4.89 (m, 4H), 4.63 (d, \( J = 5.6 \) Hz, 2H), 4.52 (d, \( J = 5.7 \) Hz, 2H), 2.98 (d, \( J = 2.8 \) Hz, 6H).

3.2 Synthesis of (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene

The mixture of (S)-5 (0.5 g, 0.9 mmol), sodium azide (0.15 g, 2.3 mmol) and 20 mL of high purity anhydrous DMF were added to a 100 mL vial. The solution was stirred overnight at room temperature and monitored by TLC. After the reaction finished, 10 mL of water was added to extinguish the reaction and 60 mL of EA was extracted in three times. The organic layer washed with 10 mL of saturated brine and dried by anhydrous magnesium sulfate. The solvent was reduced by pressure distillation. 2.4 g of yellow viscous solids was obtained by 98% yield. \(^1\)H NMR (400 MHz, CDCl3) \( \delta \)
8.13 (d, $J = 4.8$ Hz, 2H), 7.91 (d, $J = 8.3$ Hz, 2H), 7.45 (m, 2H), 7.30 (m, 2H), 7.19 (d, $J = 8.6$ Hz, 2H), 5.06 (m, 4H), 4.64 (d, $J = 5.7$ Hz, 2H), 4.53 (d, $J = 5.8$ Hz, 2H), 2.98 (d, $J = 1.3$ Hz, 6H).

3.3 Synthesis from (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene under DPPA

Under 0 ℃, DBU (0.3 mL, 2.0 mmol) was added to the solution of (S)-4 (0.45 g, 1.0 mmol) in a 100 mL triple flask and stirred until completely dissolved. Then DPPA (0.44 mL, 2.0 mmol) in 3 mL THF was added dropwise. The mixture was increased to room temperature and stirred for 6 h until (S)-4 was disappeared by TLC monitoring. The reaction was quenched by 10 mL of ice-cold water. The mixture was extracted with 60 mL of ethyl acetate and washed repeatedly with water and saturated brine. The organic layer was then dried with MgSO$_4$ and washed repeatedly with water and saturated brine. The resulting crude product was purified by column chromatography by using silica gel column with gradient elution consisting of ethyl acetate and petroleum ether to obtain pale yellow solid (0.39 g, 83% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (s, 2H), 7.93 (d, $J = 8.2$ Hz, 2H), 7.45 (dd, $J = 8.1$, 6.8 Hz, 2H), 7.30 (dd, $J = 8.4$, 6.8 Hz, 2H), 7.18 (d, $J = 8.5$ Hz, 2H), 4.79 (d, $J = 14.2$ Hz, 2H), 4.68 (d, $J = 14.2$ Hz, 2H), 4.53 (d, $J = 5.9$ Hz, 2H), 4.48 (d, $J = 5.9$ Hz, 2H), 3.01 (s, 6H).

4. Conclusion

Two different effective synthetic strategies of chiral intermediate (S)-3,3′-bis(azidomethyl)-2,2′-bis(methoxymethyl)-1,1′-binaphthalene are outlined in this paper. In synthetic strategy II, diphenylphosphoryl azide DPPA was used as the source of the azide group while NaN$_3$ need two step nucleophilic reaction to obtain (S)-6 from (S)-4. The second method has several advantages of simplified reaction procedure, elevated reaction rate, simple (workup) procedure and high overall yield.

5. Acknowledgements

The authors are grateful for the financial support of the National Natural Science Foundation of China (No.21462018), the Science Fund of the Technology Office of Jiangxi, China (20192BAB203003) and Jiangxi Science and Technology Normal University Program for Graduate Innovation Fund (YC2020-X21).

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