Original Research Article

Study on the Synthesis of derivative of phenylalanine-azobenzene

ABSTRACT

In this paper, the derivative of phenylalanine-azobenzene was synthesized from p-nitrobenzoic acid and L-ethyl benzoate by condensation, ferric acid reduction and aromatic amine oxidation, and the key compounds were characterized by 1HNMR and MS. At the same time, we optimized the synthetic route. And the optimized route can increase the total yield of target molecule by 10.28%.

Keywords: azobenzene derivative; aromatic amine oxidation; nitro reduction; photoresponsiveness.

1. INTRODUCTION

The first aromatic azo compound was obtained by the diazo coupling reaction in 1816 by the German chemist Mann. But the photochemical reactions of these azo compounds were not really noticed until 1934[1]. Azobenzene and its derivatives are typical photoisomerization and photochromism molecules, which contain azobenzene diazo-bond groups (-N=N-)[2, 3], as shown in Figure 1. Azobenzene and its derivatives are a kind of important fine chemical intermediates, which are widely used in the coloring and dyeing of fabrics and foods[4, 5]. Because of its high modifiability, excellent optical properties and good thermal stability[6], it has been widely used in the fields of non-linear optoelectronic materials[7], optical storage media[8], photochemical sensors[9], liquid crystal materials[10], photochemistry[11] and nanotubes[12, 13]. As a new kind of functional materials, azobenzene and its derivatives have attracted wide attention in recent years.

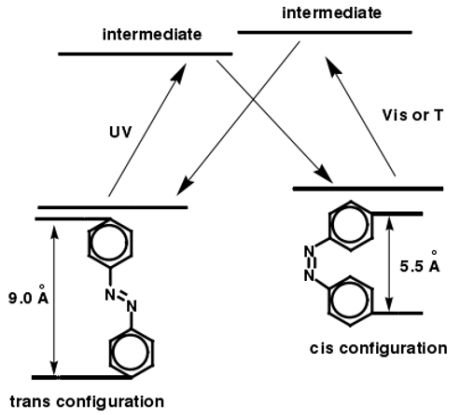
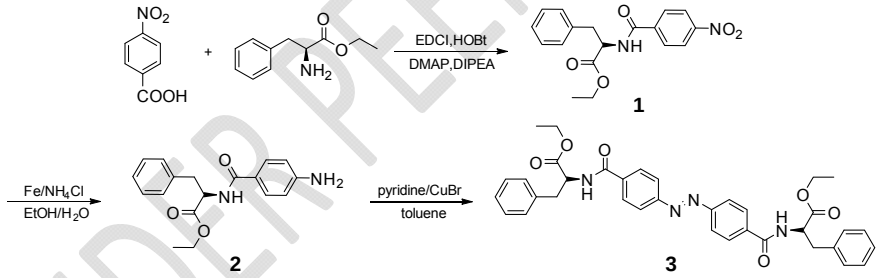


Figure1. Schematic illustration of photoisomerization of azobenzene.

So far, many synthetic methods of azobenzene compounds have been developed, such as azo coupling reaction, hydrazine replacement oxidation, nitro compound reduction, aramid oxidation and solid phase synthesis[14]. In this paper, azo structure was synthesized by aromatic amine oxidation[15, 16] with cuprous bromide as catalyst, as shown in Scheme 1. The target molecule was synthesized from p-nitrobenzoic acid and L-phenylalanine ethyl ester by condensation[17], reduction of ferric acid[18] and aromatic amine oxidation. At the same time, the synthetic route was optimized considering the simplicity of operation, economy and environmental protection.



Scheme 1. Synthesis of compound **3**.

2. MATERIALS AND METHODS

2.1 General Information

All of the starting materials and solvents were odtained from commercial suppliers and used as received without further purification. 4-nitrobenzoic acid, EDCI, HOBt, DMAP, DIPEA and L-phenylalanine ethyl ester were purchased from Energy Chemical,and glucose, zinc powder, sodium hydroxide, Iron powder, ammonium chloride and copper bromide were purchased from Chron Chemicals.

2.2 Synthesis Section

2.2.1 The specific operation of synthetic route 1:

Compound 1: P-nitrobenzoic acid (0.629 g, 3.77 mmol, 1eq.) and dry dichloromethane (DCM, 50 mL) were added in flask, the mixture was stirred at -15°C. EDCI (1.445 g, 7.54 mmol, 2eq.), HOBt (1.018 g, 7.54 mmol, 2eq.) and DMAP (0.460 g, 3.77 mmol, 1eq.) were joined in the flask in order under nitrogen atmosphere. Stir at above condition for 1 h. N, N-Diisopropylethylamine (DIPEA, 1.945 g, 15.08 mmol, 4eq.) and L-phenylalanine ethyl ester (0.794 g, 4 mmol, 1.4eq.) was dissolved in dry dichloromethane (DCM, 10 mL). The solution was added in the reaction mixture and stirred at room temperature for 2 days. After that the reaction mixture was diluted by moderate amount dichloromethane then washed by distilled water and HCl (1M). The organic layer was dried by anhydrous Na2SO4 and evaporated under vacuum to obtain the crude product. The crude product was purified by column chromatography on silica gel (EA: PE=1: 6; EA: PE=1: 3) for next step. The yield was 81.06 %. ^{1}H NMR (600 MHz, CDCl3) δ 8.25 (d, J = 8.7 Hz, 2H), 7.86 (d, J = 8.7 Hz, 2H), 7.29 (dd, J = 13.0, 5.7 Hz, 2H), 7.28 – 7.24 (m, 1H), 7.14 (d, J = 6.6 Hz, 2H), 6.75 (d, J = 6.5 Hz, 1H), 5.12 – 4.99 (m, 1H), 4.24 (q, J = 7.1 Hz, 2H), 3.27 (ddd, J = 41.9, 13.9, 5.7 Hz, 2H), 1.30 (t, J = 7.1 Hz, 3H).

Compound 2: The product from step 1 (0.454 g, 1.33 mmol) was added in the flask and absolute ethanol (40 mL) was joined in the flask. The mixture was warmed up to 50°C and the solid was dissolved gradually. Ammonium chloride (NH_4Cl, 0.285 g, 5.33 mmol) was dissolved in distilled water and added in the flask. Reducing iron powder (0.446 g, 7.96 mmol) was added in the solution (the solution turned into brown from transparent immediately) and refluxed under 70°C for 1 h. After that the reaction mixture was filtered by diatomite and the diatomite was washed by ethanol. The filtrate was evaporated under vacuum to remove some solvent. Moderate amount ethyl acetate and water were added in the solution then separate the liquid. The water layer was extracted by ethyl acetate and merged into the organic layer. The organic phase was washed by brine and dried by anhydrous Na_2SO_4. The solution was evaporated under vacuum and purified by column chromatography on silica gel (PE: EA=1: 2). The yield was 99.03 %.

Compound 3: The product from step 2 (0.860 g, 2.76 mmol) and distilled toluene (80 mL) were added in the flask, stirred and dissolved, then warmed up to 50°C. CuBr (0.258 g, 1.804 mmol) and pyridine (540 μL, 6.72 mmol) were added in the solution, the reaction mixture was stirred at 70°C for 20 h, the reaction was controlled by TLC. After that the reaction mixture was evaporated under vacuum and purified by column chromatography on silica gel (DCM: EA=20: 1), the yield was 58.18%. ^{1}H NMR (600 MHz, CDCl3) δ 7.99 – 7.94 (m, 4H), 7.91 – 7.86 (m, 4H), 7.33 – 7.28 (m, 4H), 7.28 – 7.26 (m, 2H), 7.19 – 7.14 (m, 4H), 6.68 (d, J = 7.5 Hz, 2H), 5.09 (dt, J = 7.5, 5.7 Hz, 2H), 4.26 – 4.21 (m, 4H), 3.36 – 3.20 (m, 5H), 1.30 (t, J = 7.1 Hz, 6H); calculated for $C_{36}H_{36}N_4O_6[M+H]^+$:620.26; found 621.2.

2.2.2 The specific operation of synthetic route 2:

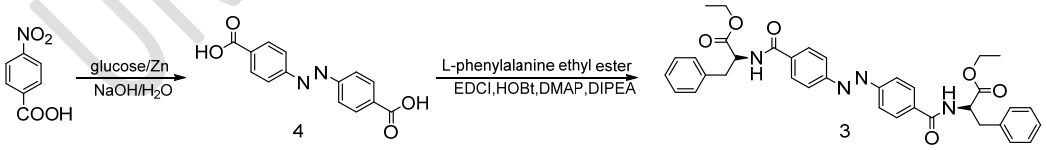
Compound 4:6.68 g(0.167 mol) NaOH was dissolved in distilled water(30 mL) and P-nitrobenzoic acid(2 g, 0.012 mol, 1 eq.) was added in flask. Glucose(13.36 g, 0.074 mol, 6

eq.) was dissolved in water and added dropwise into the flask.The solution was stirred at 60°C for 5h and then was stirred at room temperature overnight. After that the suspension was filtered, the solid was dissolved in 150 mL water under heating. The aqueous solution was acidified by HCl(1 M) to pH 4. The precipitated solid was filtered and washed by distilled water. The wet solid was evaporated to obtain the dry product. The yield was 66.73 %.

Compound 3: The product from step 1 (0.331 g, 4.8 mmol) and distilled dichloromethane (DCM, 30 mL) were added in the flask and stirred at -30°C. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDCI, 0.921 g, 4.8 mmol), 1-Hydroxybenzotriazole (HOBt, 0.294 g, 2.4 mmol) and 4-dimethylaminopyridine (DMAP, 0.649 g, 4.8 mmol) were joined in the flask in order. After stirred at -30°C for 30 min, L-phenylalanine ethyl ester (0.579 g, 3 mmol) was added in the solution. N,N-Diisopropylethylamine (DIPEA, 0.930 g, 7.2 mmol) was added in the reaction mixture dropwise. Then the reaction mixture was stirred at room temperature overnight. The reaction was controlled by TLC. After that the reaction mixture was acidfied by HCl (1M). The organic layer was washed by $NaHCO_3$ solution and water. Finally the organic phase was evaporated under vacuum and purified by column chromatography (EA: PE=1: 4). The yield was 85.39 %.

3. RESULTS AND DISCUSSION

Because the reduction process of ferric acid requires the use of reduced iron powder, if amplified to industrial production will have a certain risk and produce more industrial waste residue, or even cause damage to the instrument.The nitro reduction method has the advantages of low cost and low pollution.Although azobenzene compounds synthesized by nitro reduction are limited in type, many simple compounds can be synthesized. Therefore, we optimized the synthetic route, using p-nitrophenyl acid as raw material, azobenzene-4,4'-dicarboxylic acid was obtained by nitro reduction method, and then condensation with L-phenylalanine ethyl ester to obtain the target compound, as shown in Scheme 2. The optimized synthesis route is characterized by simple operation, low cost and high total yield. Under the optimized synthesis route, the total yield of the target molecule can reach 56.98%, while the original route is only 46.70%. Also, this route can be used for the synthesis of other amino acid derivatives.



Scheme 2. The optimized synthetic route.

Also, we investigated the photoresponsiveness of compound 3, as shown in Figure 2. Upon irradiation of UV by the typical spectral changes, the decrease in the π-π* absorption band of the trans-azobenzene moieties at 333 nm with the concomitant increase of the π-π* and n-π* bands of the cis isomer at around 260 nm and 443 nm, respectively (Figure 2a). Furthermore, irradiation of natural light to the cis-rich solution recovered the photostationary

state within 160 min. From what has been discussed above, we can see clearly that compound 3 has typical photoisomerism.

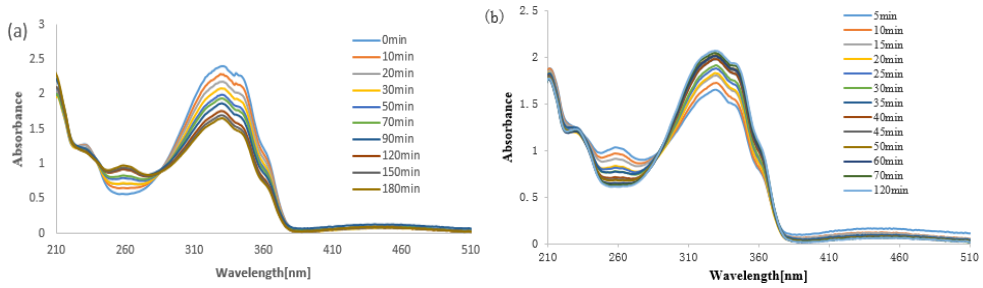


Figure 2. (a) UV-vis spectra of **compound 3** in $CNCH_3$ under irradiation at 365 nm for diferent time period at room temperature; (b) UV-vis spectra of **compound 3** in $CNCH_3$ under irradiation at natural light for diferent time period at room temperature.

4. CONCLUSION

In conclusion, the target molecule is obtained according to the designed synthesis route. And the optimized route can increase the total yield of target molecule by 10.28%, and this route also can be used for the synthesis of other amino acid derivatives. Further more, the compound 3 has typical photoisomerism.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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