Microwave-assisted Synthesis of Chiral Bibenzimidazoles

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(Received 4th November 2008, accepted in revised form 11th May 2009)

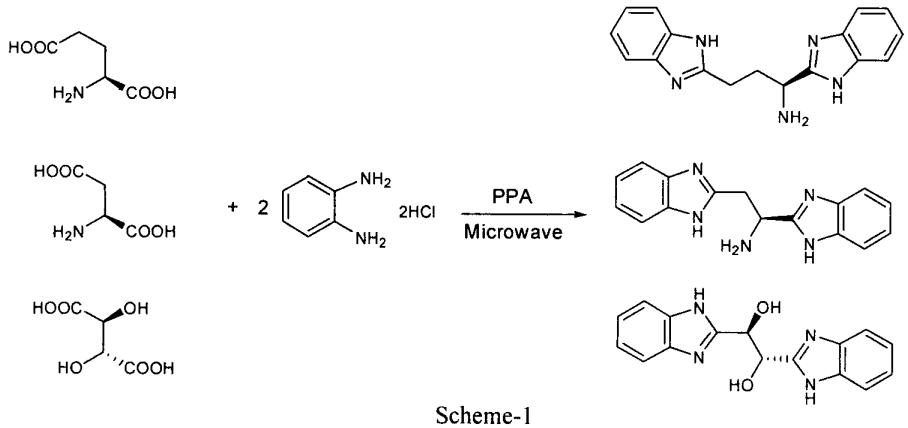
Summary: Three chiral bibenzimidazoles were synthesized by condensation of *o*-phenylenediamine with L-(+)-glutamic acid, L-(+)-aspartic acid and L-(+)-tariaric acid under microwave irradiation, promoted by polyphosphoric acid (PPA). Compared with the conventional heating methods, the synthesis of bibenzimidazole compounds under microwave irradiation is rapid, economic and environmentally friendly method, with much higher yield.

Introduction

Benzimidazoles have received particular attention since they are important intermediates in medicinal chemistry and interesting lingands in coordination chemistry [1-4]. The traditional synthesis of benzimidazoles utilizes the condensation of *o*-phenylenediamine with carboxylic acids in refluxing concentrated hydrochloric acid [5, 6]. However, the serious problem of long time, usually about several hours, and use of concentrated hydrochloric acid can not be ignored. Microwave-assisted synthesis has become increasingly popular for modern chemical synthesis strategies, for its higher efficiency, higher yield and purity [7, 8]. In this work, microwave irradiation was employed in three chiral bibenzimidazole compounds synthesis (as shown in Scheme-1), promoted by polyphosphoric acid (PPA), and the reaction conditions were optimized.

Results and Discussion

The microwave oven reactor was rebuilt from a WP-750B Galanz microwave oven [8]. Firstly, the reaction was carried out at different power levels, and it was found that glycol solution could keep boiling at power 5. Under this condition, the effect of amount of PPA on the yield of (1*S*),3-bis-(1-H-benzimidazol-2-yl)propylamine (BBIMPA) was investigated, with reaction time of 30 minutes, and the result was shown graphically in Fig. 1. It is obvious that the yield depends significantly on the amount of PPA, and the yield gets to highest at the ratio of 0.75 (PPA/Glu). It is remarkable that condensation of *o*-phenylenediamine with L-(+)-glutamic acid produces 4 quantum of water, which is negative to the yield, while this problem can be solved by the hydrolysis reaction of PPA, and the produced phosphoric acid can also catalyze the condensation. But too much PPA leads to low yield.



Scheme-1

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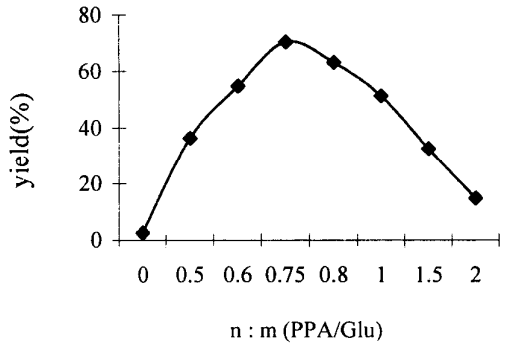

Fig. 1: Effect of amount of PPA on the yield of BBIMPA.

The reason is due to the strong dehydration ability of PPA, which can lead to many side products.

The effect of the microwave irradiation time on the yield of BBIMPA was also investigated, and the result was shown graphically in Fig. 2. It can be easily found that irradiation of 40 minutes gave the maximum yield.

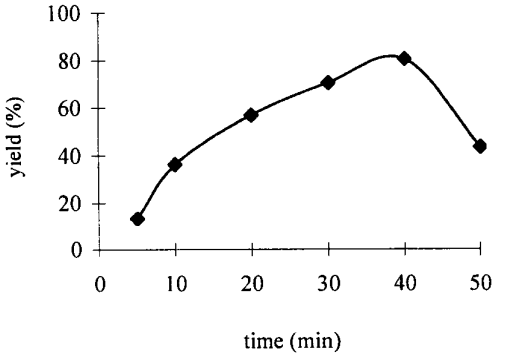

Fig. 2: Effect of microwave irradiation time on the yield of BBIMPA.

In the same way, the reaction conditions of (1*S*),2-bis-(1-H-benzimidazol-2-yl) ethylamine (BBIMEA) and (1*R*,2*R*)-bis-(1-H-benzimidazol-2-yl)-ethane-1,2-diol (HBBIMED) were optimized, and all the result was summarized in Table-1. It is easily found that the microwave-assisted (MA) reactions were much faster than the reference [6], and the yields were much enhanced.

Table-1: Reaction conditions and yields of the three bibenzimidazoles.

Compound	Time (min)		Yield (%)	
	MA[a]	Ref[b]	MA[a]	Ref[b]
BBIMPA	40	1200	91	76
BBIMEA	40	1200	89	78
HBBIMED	60	1200	83	60

a: microwave-assisted synthesis.

b: traditional method described in reference [6].

In conclusion, we provided a microwave-assisted synthesis of bibenzimidazoles by condensation of *o*-phenylenediamine with three different chiral acids with much higher yields than the traditional synthesis, which proceeds simply and rapidly with relatively inexpensive reagents, and which has relatively positive environmental and safety aspects. This method can be applied into the synthesis of more bibenzimidazole derivatives as well as some similar bibenzimidazoles with rapid, economic and environmentally friendly characters. We also are confident that this method will find its use in preparative organic chemistry.

Experimental

All the reagents were AR grade, and were used without further purification. The reactions were performed on a rebuilt WP-750B Galanz microwave oven [8]. The elemental analysis, IR and NMR were operated on Carlo Erba 1106 element analysis instrument, Nicolet 170 SX FT-IR infrared spectrocomparator (KBr) and Varian XL-300 nuclear magnetic resonance appearance.

General Synthetic Procedure

10 mmol o-phenylenediamine was dissolved in concentrated hydrochloric acid, and stirred for 1 hour at room temperature. Then the water was evaporated under vacuum, giving o-phenylenediamine dihydrochloride salt, to this diacid salt, 20 mL glycol and proper amount of PPA were added. The flask was put into the microwave oven, and the oven was started under the pre-adjusted "power" and "time". After the reaction finished, cooled to room temperature, the mixture was poured into a beaker holding 20 mL water. As the pH of the solution was adjusted to 10 with ammonia, gray powder deposited. The deposit was filtrated and washed with hot water and then dried under infrared heaters to afford the target product.

Spectral and analytical data of bibenzimidazole compounds

(1*S*),3-*bis*-(1-H-benzimidazol-2-yl)propyl-amine (bbImpa), white powder. $[\alpha]^{20}_D$ = +5.6° (*c* = 1.1 mol/L HCl). Anal. Found: C, 62.30; H, 6.51; N, 24.35. Calc. for ($C_{17}H_{17}N_5 \cdot 2H_2O$ FW: 327), %: C, 62.38; H, 6.42; N, 24.41. IR (KBr), cm^{-1}: C-H: 3060 (s); N-H: 3170; C-N: 1623(w); C-N: 1274(s); C-N: 1070 (w); C=C: 1580 (w), 1530 (w), 1436 (w); N-H: 3393 (s). ^{1}H-NMR (DMSO, TMS), δ: 7.1~7.4 (8H, m, Ben), 2.48 (2H, $-CH_2$), 2.92 (2H, $-CH_2$), 4.20(1H, -CH (amine)).

(1*S*),2-*bis*-(1-H-benzimidazol-2-yl)ethylamine (bbImea), white powder. $[\alpha]^{20}_D$ = +7.6° (*c* = 1.1 mol/L HCl). Anal. Found: C, 61.30; H, 6.00; N, 22.31. Calc. for ($C_{16}H_{15}N_5 \cdot 2H_2O$ FW: 313), %: C, 61.34; H, 6.07; N, 22.36. IR (KBr), cm^{-1}: C-H: 3051 (s); N-H: 3220; C=N: 1622 (w); C-N: 1275 (s); C-N: 1020 (w); C=C: 1519 (w), 1596 (w), 1450 (w); N-H: 3382 (s). ^{1}H-NMR (DMSO, TMS), δ: 7.5~7.9 (8H, m, the base of benzene), 3.40 (1H, -CH (amine)), 2.52 (2H, $-CH_2-$).

(1*R*,2*R*)-bis-(1-H-benzimidazol-2-yl)ethane-1,2-diol (HbbImed), white powder. $[\alpha]^{20}_D$ = + 220.7° (*c* = 1.1 mol/L HCl). Anal. Found: C, 58.11; H, 5.54; N, 16.90. Calc. for ($C_{16}H_{14}N_4O_2 \cdot 2H_2O$, FW: 330), %: C, 58.18; H, 5.45; N, 16.97. IR (KBr), cm^{-1}: C-H: 3059 (s); N-H: 3178; C=N: 1623 (w); C-N: 1273 (s); C=C 1533 (w), 1488 (w), 1446 (s); O-H: 3400 (s); C-O: 107 (m). ^{1}H-NMR (DMSO, TMS), δ: 7.3~7.6 (8H, m, benzene), 4.11(2H, -OH), 5.20 (2H, -OH (hydroxyl)).

Acknowledgements

This work was financially supported by two grants from Scientific Research Plan Projects of Shaanxi Education Department (08JK414) and Scientific Research Foundation for PhD of Xi'an Shiyou University (Z08009).

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