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Research Article

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The green synthesis of liranaftate in ionic liquids

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ABSTRACT

6-methoxy-2-methylaminopyridine was synthesized from 2,6-dichloropyridine;5,6,7,8-tetrahydro-2-naphthyl-sulfuryl chloride was synthesized from 5,6,7,8-tetrahydro-2-naphthol; with the catalysis of K_2CO_3, substitution reaction was happened between 6-methoxy-2-methylaminopyridine and 5,6,7,8-tetrahydro-2- naphthyl-sulfuryl chloride, which generated liranaftate whose structure was confirmed by IR, 1HNMR, MS. In the experiment, the total recovery was 73%, and purity of HPLC is 99.7%. The method presented here has the advantages of mild condition, simple operation, easy isolation, high yield and environmental benignity. Moreover, the ionic liquid, as the reaction medium, can be easily recycled and reused.

Key words: liranaftate, ionic liquid, green synthesis, K_2CO_3, catalysis

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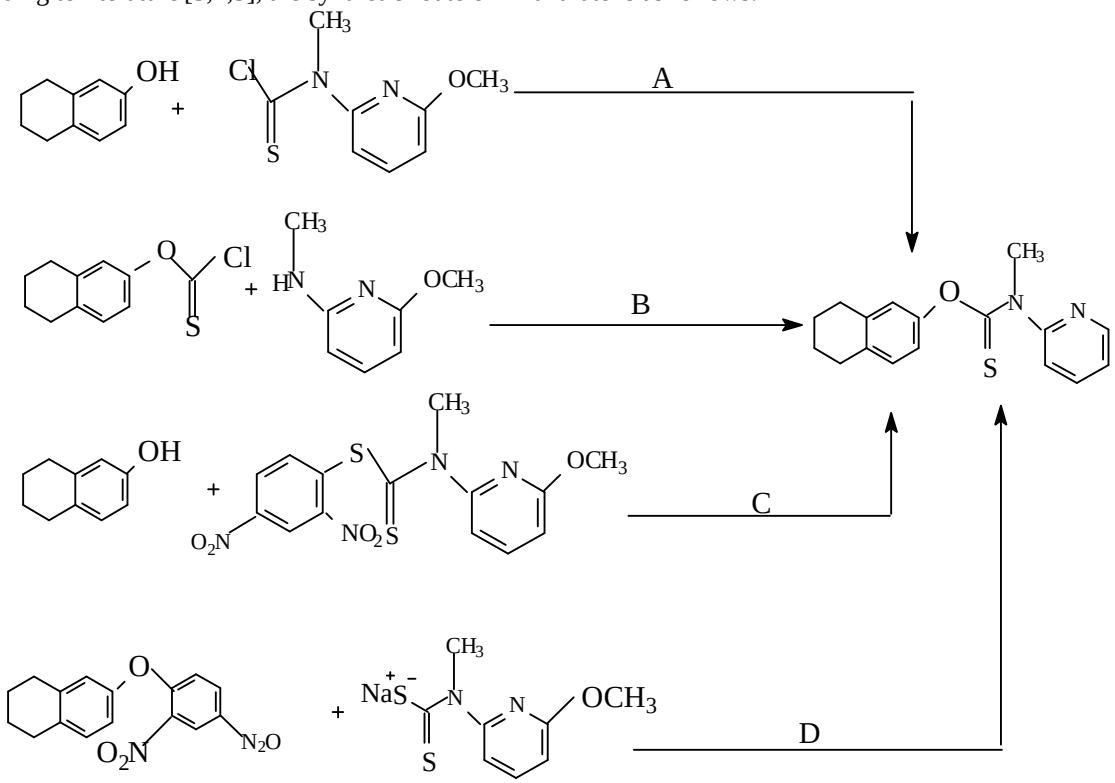
INTRODUCTION

Liranafate (6-methoxy-2-N-methyl-aminopyridine-thiocarboxylic acid-(5,6,7,8 tetrahydro)-β-Naphthyl ester), a new antifungal drug, is synthesis inhibitor of squalene epoxidase inhibitor and cytoderm inhibitor, which was manufactured by Tosoh Corporation and Zenyaku Kogyo Corporation. It firstly came to the market in August 2000 in Japan. By inhibiting the squalene epoxide reactions of fungal cells and detering the synthesis of ergosterol, which is a constituent of cell membrane. The antifungal activity of Liranafate is 8 times as high as that of Tolnaftate. Liranafate is especially effective against trichophyton rubrum [1] .As pollution has increasingly received much attention all over the world, it has been the focus for the Institute of Drug Synthesis to find new methods to synthesize green effective drugs. In recent, Room-temperature ionic liquids, as a new-type environmentally benign reaction media, has found its wide application in organic synthetic reactions [2].Compared with the traditional organic solvents, ionic liquid is characterized with low vapor pressure, nonflammability, good thermal stability and recycling, etc.

EXPERIMENTAL SECTION

According to literature [3,4,5], the synthetic route of Liranafate is as follows.



Scheme-1

Preparation of intermediates, pyridine derivatives, requires multistep reaction in the Method C and D. Method C and D also have many disadvantages, such as long process, tedious steps, the troubled operation and high costs, which are not suitable for industrialized production. Method A is simple, but the yield of preparation of pyridine derivatives is low. The intermediate structure is relatively simple and easy to prepare in Method B.

We mainly investigated Method B and accordingly made certain improvement as follows. (1) We find a new way to synthesize the raw material of Liranafate. (2) When compound I was synthesized, we adopted isopropyl alcohol-water system on the basis of literature; however results showed that when the reaction proceeded, the reaction solution was becoming thicker and thicker, so it was difficult to fully react. In the research, the author adopted Acetone system. The results showed that response time is shorter than the former, and it was fully reacted. At the same time, the aftertreatment is easier than before, and the yield had increased to 93. 2%. The synthetic route of is as Fig 1.

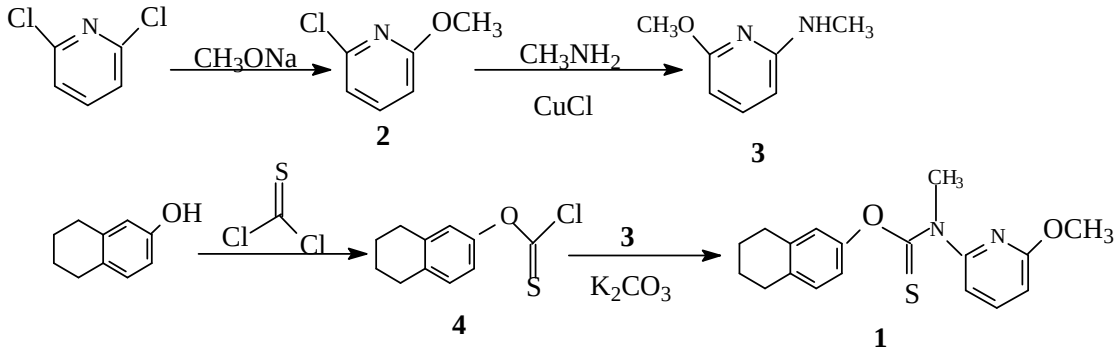


Fig 1 The synthetic route of liranafate

Synthesis experiment

Kofler micro melting point apparatus (thermometer not calibrated); electronic balance (Beijing Dolly, balance co., LTD）; FTS-40 Fourier transform infrared spectrophotometer (BIO-RAD, American); DPX-400M nuclear magnetic

resonance (Bruker, Germany); HP1100 Combined automatic high performance liquid chromatograph(including Agilent G 1311A Quaternary Pump, Agilent G1315B diode array detector and Agilent G 1313A ALS autosampler, Agilent, American); ZAB-3F mass spectrometer(VG, Britain). All reagents are analytically pure.

Preparation of ionic liquids

The mixture of N-methylimidazole（14.8g ，0.18mol）and trichloroethane (80mL) was stirred in a dried three-necked bottle, and distilled *n*-butyl bromide（26.03g，0.19mol）was added into the bottle, and the reflux reaction had lasted for 4~5h. The color of the mixture becomes darker and darker, and at last it turned into brown-red. After the reaction is completed, the mixture was separated by tap funnel. Ionic liquid had been washed by trichloroethane twice. The liquid of [bmim]Br became clear after it had been sucked by pump, and then the liquid was dried in vaccum. [bmim]Br was acquired. [bmim]Br (6.58g) and water (5~10mL) were stirred in the bottle, after the ice-water bath, $NaBF_4$ (0.03mol) was added into the bottle. The mixture had been extracted with dichloromethane twice, and the combined dichloromethane had been washed by water twice, and then it was dried by $MgSO_4$. After it was filtered, it had a water bath, and then dichloromethane was evaporated. Deep yellow viscous liquid was acquired, it is [bmim]BF_4. [bmim]BF_4 had been dried at 90℃ in vaccum for 10-12h.

Preparation of 6-methoxy-2-(methylamino)pyridine 2

2,6-dichloropyridine (10g,0.068mol) and 30% of sodium methoxide (24.5g, 0.136mol） were stirred in bottle, and after 4-5-hour heating reflux. the reaction was completed under the monitor of TLC (ethyl acetate: Petroleum Ether=1:15) .The mixture was concentrated and methanol was elminated. Then water (100mL) was added into the bottle. The mixture was extracted with ethyl acetate, and then the organic phase was combined. They were brined, dried and filtered. At last we got colorless oily crude compound (9g). The yield is 92.5%. The product was used in next reaction without further purification.

Preparation of 6-methoxy-2-(methylamino)pyridine 3

Compound **2**, (9g, 0.127mol), cuprous chloride（1.72g, 0.0017mol）and methylamine water solution（29mL, 25%-30%）were added in autoclave at 120℃ for 7h. After the reaction, the mixture was extracted with ethyl acetate, and then the combined organic phase was brined and dried. After the filtrate was concentrated, brown oily compound (6.18g, 71.2％) was acquired. The purity of HPLC was 98%.

Preparation of o-5,6,7,8-tetrahydro-2-naphthyl-thiochloroformate 4

5,6,7,8-tetrahydro-2-naphthol (6.3g, 0.0425mol), thiophosgene (4.25mL, 0.056mol), and ethyl acetate (50mL) were stirred in the bottle. After the icy bath, the tempeture was under 0℃. And then aqueous solution (10mL) with potassium carbonate (3g, 0.022mol) was added into the bottle. Stir the mixture until the reaction was completed, which was under the motior of TLC (ethyl acetate: Petroleum ether). And then water (100mL) was added into the bottle. After that, the mixtru was extracted with ethyl acetate. And the combined organic phase was brined, dried and filtered. At last yellow oily compound (8.7g) was acquired.the yield is 90.4%. The product was used in next reaction without further purification.

Preparation of ((6-methoxy-2-pyridinyl)-methylcarbamothioic acid o-(5,6,7,8-tetrahydro-2-naphthalenyl) ester)1

Compound 4 (8.7g, 0.0385mol) was slowly added to the mixture of ionic liquids ([bmim]BF_4) (100mL)， compound 3 (5.7g, 0.0413mol), and potassium carbonate (5.7g, 0.0413mol) under ice-water bath, and stirred for 4h. Water (150mL) was added to the reaction mixture and stirred for 20min, filtrated and washed with water, afforded crude target compound (12.2g, 96.8%) .The crude target compound was purified by crystallization from acetone to give white solid (11g) with 90% yield. The purity was 99.7% by HPLC. mp:98.8～99.5℃，IR(2973cm^{-1}，2930cm^{-1}，2852cm^{-1}，1416cm^{-1}，1264cm^{-1}，1037cm^{-1}), ^{1}HNMR：1.8(m,4H); 6.68(d,1H); 6.86(dd,1H); 3.78(s,3H); 3.98(s,3H), 6.68(d,1H); 6.86(dd,1H); 7.05(d,1H); 7.10(d.1H); 7.65(dd,1H), MS(m/z: 328,181,165,108)。

RESULTS AND DISCUSSION

The effect of response time on yield

Other conditions stay the same, and we only change the r response time. Then we examined the relation between response time of the final step reaction in the synthesis of compound **1** and the yield of product, which was descripted in figure 2.

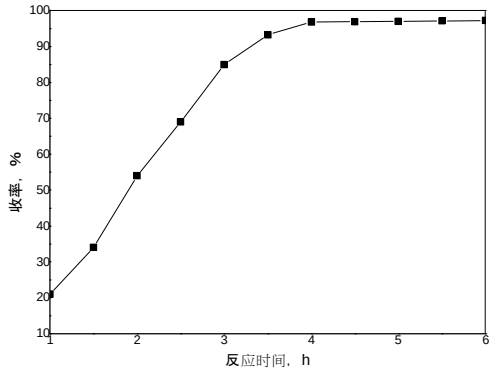


Fig 2 the effect of response time on yield

From Fig 2, it is clear that when response time is relatively shorter, the yield is lower. While response time is longer, the yield doesn't increase sharply, and byproduct increase and purity of product reduce. The best time of reaction time is 4h, and the yield and purity of product are higher and more economical.

The impact of the frequency of reuse of Ionic Liquid on yield

"Green chemistry" focuses on the reuse of the reaction medium. We investigate the reuse of the ionic liquid in the reaction. The result was described in Fig 3.

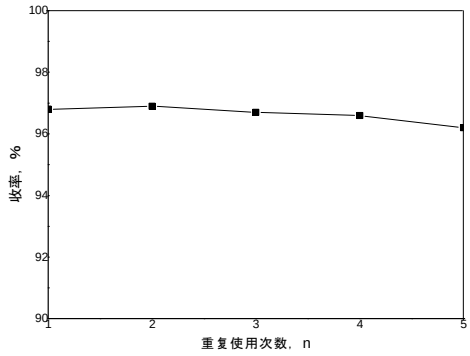


Fig 3 the impact of the frequency of reuse of Ionic Liquid on yield

It is clear that after the ionic liquid had been used for 5 times, yield began to decrease, which implies that ionic liquid is reusable and its reusability is good. The ionic liquid is green and recyclable.

CONCLUSION

The experiment tells us that we got liranafate with ionic liquid as reaction medium. compared with literaure[3-5], the method has many advantages, for example, mild reaction, easy operation, easy purification, high yield and high purity, less residual, which can meet the medical srandards. Ionic liquid acts as both solvent and catalyst, and it is environment-friendly. After the reaction, ionic liquid can be recovered and reused. The method provides an effective and green way for the synthesis of drug. The property of recycle and reuse will decrease environmental pollution caused by emissions, and it can avoid the waste of resources. Ionic liquid has good application prospect.

REFERENCES

[1] Zhong Qian. Liranafat, *World Notes on synthetic drugs and biochemistry drugs*，**2001**, 22(3):190.
[2] Dupont J,De Souza R F,Suarez P A Z. *Chem Rev*, **2002**, 102(10): 3667-3691.
[3] Li Wei, Chang Xuanniu, Hao Erjun. *Chinese Journal of Medicinal Chemistr*，**2006**, 16(2): 106-107.
[4] Deng Jiyong, Xia Zancheng, Su Jiaolian. *Speciality Petrochemicals*，**2002**, (5): 28-30.
[5] Kagawa T, Tenma H, Awano Y, et al. Production of thiocarbamates[P]. JP: 06192226, 1994-07-12. (CA **1994**, 121:255424