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SYNTHESIS of 1-(4-HYDROXYLPHENYL)-4-(4-NITROPHENYL)PIPERAZINE

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Abstract: Triazole medicines are mainstream of the antifungal medicines, especially used in curing deep department fungal infections and its important intermediate is 1-(4-hydroxylphenyl)-4-(4-nitrophenyl)piperazine. As the key intermediate of antifungal medicines of new generation,it has already caused international interest. A general and convenient synthesis of 1-(4-hydroxylphenyl)-4-(4-nitrophenyl) piperazine without the use of catalyst is described.
Key words: 1-(4-hydroxylphenyl)-4-(4-nitrophenyl)piperazine; antifungal intermediate; Triazole

1. INTRODUCTION

1-(4-hydroxylphenyl)-4-(4-nitrophenyl)piperazine **1**(Fig. 1.) (D. J. Sheehan, C. A. Hitchcock & C. M. Sibley, 1999) is a key moiety of a large number of triazole antifungals,These triazoles belong to the class of a widely used orally active broad-spectrum antifungals.Triazole medicines are mainstream of the antifungal medicines, especially in curing deep fungal infection and fungal infection of AIDS at present.

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In the past 20 years, incidence of deep fungal infection has been on the rise apprently. These new medicine is not only safe and durable, but also useful in various kinds of fungal infection, which gives us a new choice to defend and cure the deep fungal infection. Members of this class are,for instance,Sch45009 **2,** Sch45012 **3**, Itraconazole **4**,saperconazole **5**,hydroxyitraconazole **6**,Sch50001 **7,**Sch50002 **8**,Sch51048 **9**, Pasaconzole **10** ◦ All of members above contain the unsymmetrically N,N-diarylated piperazine moiety(Fig. 2.) (F. Bennett et al, 2006; R. G. Lovey, 2002; A. K. Saksena, 2004; J. S. Tkacz & B. DiDomenico, 2001; H. A. Torres, R. Y. Hachem, R. F. Chemaly, D. P. Kontoyiannis & I. I. Raad, 2005; A. K. Saksena, 1996)

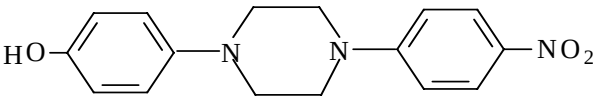

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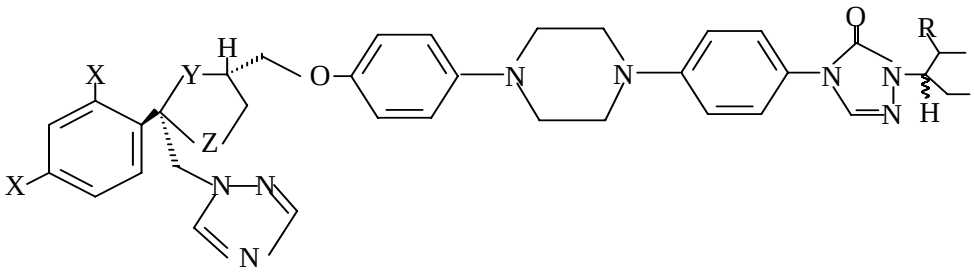
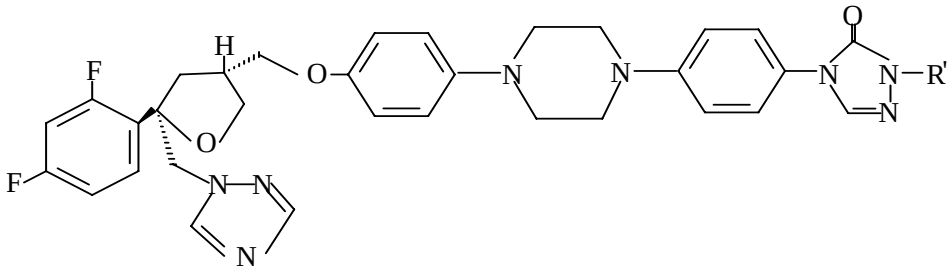
Figure 1. 1-(4-hydroxylphenyl)-4-(4-nitrophenyl)piperazine



2:SCH45009 X=F,Y=O,Z=CH,R=H
3:SCH45012 X=F,Y=CH_2,Z=O,R=H
4:Itraconazole X=Cl,Y=Z=O,R=H
5:Saperconazole X=F,Y=Z=O,R=H
6:Hydroxyitraconzole X=Cl,Y=Z=O,R=OH



7:SCH50001 R'=(R)-[CH(Me)Et]
8:SCH50002 R'=(S)-[CH(Me)Et]
9:SCH51048 R'=$CH(Et)_2$
10:Posaconzole R'=

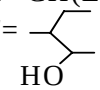


Figure 2. Structures of triazole antifungals

Classical synthetic routes to the unsymmetrically N,N'-diarylated piperazine moiety **1** encompass the reaction of anilines with bis(2-chloroethyl)amine directly (K. G. Liu & A. J. Robichaud, 2005),or prepared via an S_NAr reaction of piperazine with aryl halides containing electron-withdrawing groups to the mono N-aryl piperazine which are then reacted with appropriate arylhalides (T. Cohen, A. G. Dietz Jr, J. R. Miser & J. R. Miser,J., 1977; D. M. T. Chan, K. L. Monaco, R.-P.Wang & M. P. Winters, 1998). Alternatively, **1** can also be .generated in situ from diethanolamine (Z. Budai, T. Galambos & T. Mezei, 1993). Overall the preparation of **1** can be divided into two major steps:the first step is the preparation of N-arylated piperazine which then convert into N,N'-diarylated piperazine with appropriate aryhalides in the second step.

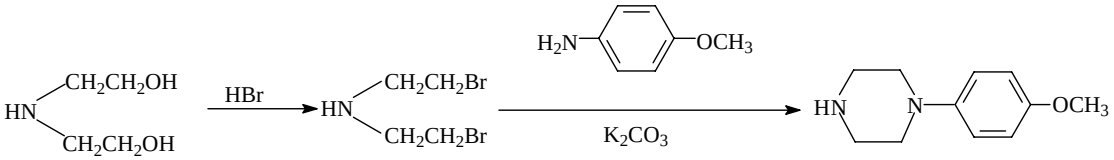
We developed a route to obtain the desire product **1** in three steps.First 1-(4-methoxyphenyl) piperazine were generated in situ from diethanolamine using one-pot synthesis method.1-(4-methoxyphenyl)piperazine react with p-chloronitrobenzene to synthesize 1-(4-methoxyphenyl)-4-(nitrophenyl) piperazine by N-arylation. Then demethoxy to synthesize the key antifungal intermediate.

2. EXPERIMENT

General procedure:With the presence of 0.26mol diethanolamine,360ml HBr(0.5mol)is slowly added into the flask over an hour.After complete addition, the reaction mixture is stirred and refluxed for 12 h. The reaction mixture is distilling off the excessed HBr which could be recycled.The crude product followed by its reaction with p-anisidine, without isolation treatment,can be carried out in one pot to obtain 1-(4-methoxyphenyl) piperazine in order to avoid purification carcinogenic bis(2-chloroethyl)amine.

In an atmosphere of dry N_2, a mixture of p-anisidine (0.24 mol), sodium carbonate(0.16mol)and 80ml 1-butanol is added into the same flask and heated at 120ºC for 5 h.Another sodium carbonate(0.13mol) is added and continue to heat for 24h..After being cooled to room temperature, the suspension washes twice with 100ml water.The pH is adjusted to12 by the addition of sodium hydroxide,the suspension washes by saturated salt water.After the pH of the combined organic layers are adjusted to 5 by the addition of about 30ml concentrated HCl. Water and 1-butanol is distilled to provide HCl salt. The HCl salt is dissolved in ethanol to recrystallize.The product is dried under vacuum at 100ºC to constant weight.(Scheme 1.)

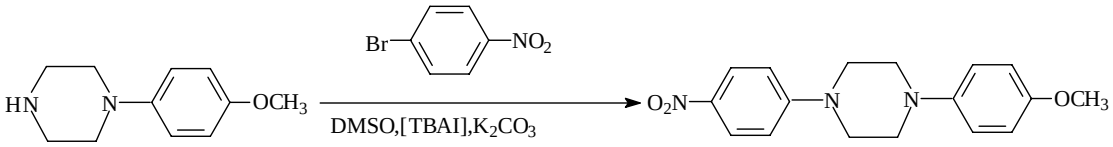
Yield:23.5g(37%)



Scheme 1

A mixture of 0.07mol 1-(4-methoxyphenyl) piperazine dihydrochloride,0.073mol 1-chloro-4-nitrobenzene,0.12mol potassium carbonate ,50ml N,N-Dimethylformamide is stirred and refluxed for 24h at 110ºC.After complete conversion, the reaction mixture is diluted with water and the product is extracted twice with trichloromethane.The combined extracts are dried,filtered and evaporated.The residue is triturated in 4-methyl-2-pentanone. The product is filtered off and crystallized from 1,4-dioxane.The product is dried under vacuum at 100ºC to constant weight (H. Jan & L. J. J. Backx, 1980). (Scheme 2.)

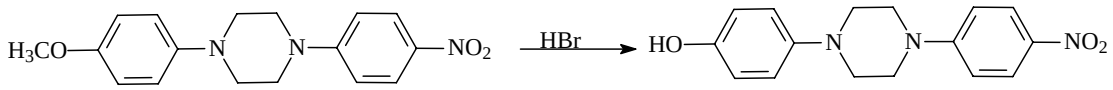
Yield:16.3g(74.4%)



Scheme 2

1-(4-methoxyphenyl)-4-(nitrophenyl) piperazine is then converted to the desired antifungal intermediate via demethylation.However demethylation requires an excess of refluxing aqueous HBr for prolonged period of time.In an atmosphere of dry N_2, With the presence of 0.014mol1-(4-methoxyphenyl)-4-(nitrophenyl) piperazine a mixture of 40mlHBr and acetic anhydride with the same volume is slowly added.After complete addition, the reaction mixture is stirred and refluxed for 12 h.at 140ºC.After the excessed HBr is distilled,The residue is washed by cold water then filtered off.The yellow crystals are dried under vacuum at 100ºC to constant weight.(Scheme 3.)

Yield:1.9g(44.2%)



Scheme 3

3. CONCLUSIONS

In summary, we have developed a general and convenient procedure for the synthesis of 1-(4-hydroxylphenyl)-4-(4-nitrophenyl)piperazine from anilines using diethanolamine in the absence of catalyst and high reaction temperature.

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