Improved synthesis of fluconazole by using nano-SSA as a green catalyst

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In our on-going interest in the preparation of new antifungal agents, our attention was focused on fluconazole because of its broad antifungal spectrum, low toxicity and excellent pharmacokinetic properties. As a part of our program to develop a new method for synthesis of fluconazole, the conditions of some reactions, especially Grignard reactions, were screened and optimized. The best situation was achieved by using nano-silica sulfuric acid as a green and mild catalyst. The high yield and comfortable isolation in each step were the advantage points in this method.

INTRODUCTION

In recent years, life-threatening systemic fungal infections have become increasingly common, especially in immunocompromised hosts suffering from tuberculosis, cancer or AIDS and in organ transplant cases. [1]. Though there are effective antifungal agents available in the market, they have shortcomings such as toxicity, limited range of activity for the fungal strains, high price and limited penetration through the central nervous system [1]. Several clinical drugs, including azoles, polyenes, echinocandins and allylamines have been developed to reduce the impact of fungal diseases. Among those, azole antifungal drugs, especially triazole agents such as fluconazole, voriconazole and itraconazole, posaconazole and ravuconazole [2] are marketed or in the late stages of clinical trials and proved to be more effective and thus are more widely used for the treatment of invasive fungal infections (Fig. 1). Fluconazole is an important antifungal agent used against various fungal strains which inhibits specific steps in fungal sterol biosynthesis [1, 3]. It is a 1,2,4-triazole based drug which has established an exceptional therapeutic record for *Candida* infections, including oropharyngeal and esophageal candidiasis, vulvovaginal candidiasis, candidemia, and disseminated candidiasis [4]. Usually azoles apply their antifungal activity through inhibition of CYP51 by a mechanism in which the heterocyclic nitrogen (N_3 of imidazole or N_4 of 1,2,4-tiazole) binds to the sixth coordination of heme iron atom of porphyrin in the substrate binding site of the enzyme [4a]. Based on the active site's structure of CYP51 and the extensive investigation of the structure- activity relationships of the azole antifungals, it was found that 1,2,4-triazole ring and 2,4-difluorophenyl group are essential for the high antifungal activity [4a]. Our investigation is based on the development of a new synthetic method for fluconazole by using a heterogeneous catalyst. We tried to set a new procedure in order to increase the rate and yield of the reaction and also reducing hazards to human and environment. Literature reports [5] didn't show any evidence concerning the use of heterogeneous catalysts for synthesis of fluconazole. Here we introduced nano-SSA as a green catalyst in some steps of fluconazole synthesis. In the presence of nano-SSA [6], the yield of the reaction increased and the reaction proceeded in a short time. We also inspected the Grignard reaction in three different states and compared their results with our method. For synthesis of fluconazole, we tried four different methods (*a-d*).

Method a: A Friedel-Crafts acylation was started from diflourobenzene (*1*) and chloroacetyl chloride (*2*) to get 2-chloro-1(2,4-difluorophenyl)1-ethanone (*3*). This step was applied under the same experimental conditions as in [5a]. Then in the second step for N_1-alkylation of 1*H*-1,2,4-triazole by (*3*) we first activated the carbonyl group of (*3*) by nano-SSA in toluene for 0.5 h and then 1,2,4-triazole was added.

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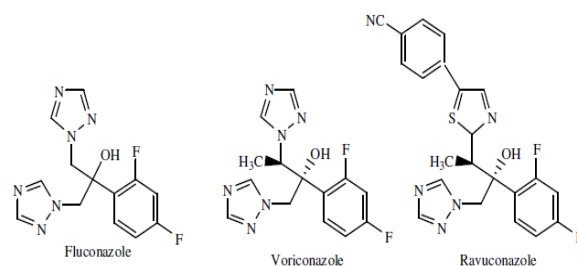
Fig. 1. Several clinical drugs including tri-azole rings

In the presence of nano-SSA, alkylation reaction was easily performed in high yield to get 1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazole-1-yl)1-ethanone *(5)*. In the third step the oxirane intermediate *(6)* was obtained by Corey–Chaykovsky epoxidation in the presence of trimethylsulfoxonium iodide and aqueous solution of NaOH. This step also was done according to the literature. Finally, in the last step again epoxide ring opening of *(6)* was achieved by activating oxirane with nano-SSA and then triazole was added to get fluconazole *(7)* (Scheme 1). In this method steps 2 and 4 were modified by nano-SSA catalyst. Our catalyst could increase dramatically the yield and the rate of reactions in these two steps. We suggested two intermediates (*3'* and *6'*) after using nano-SSA in the above steps.

This method has been used in the synthesis of fluconazole [7] but because it requires expensive material (for example, sulfoxide trimethyl iodide), and the formation yield of an epoxy compound is not very high, a direct result of the production cost of the final product fluconazole is difficult to reduce the impact of its promotion applications.

The present invention used the nano-SSA as a green catalyst; the reaction is easy to control, without complex special equipment. The original equipment can be put into use, each step takes place under mild reaction conditions, the simple and non-destructive environment is suitable for industrial promotion.

In our other approaches we tried to synthesize fluconazole by different methods of Grignard reactions and compared the results of each method in order to optimize the synthetic method for preparing of fluconazole.

Method b: In the second method (Grignard reaction 1) [1,2,4] triazol-1-yl-methanol *(9)* was synthesized by using 1,2,4-triazole *(4)* and 1,3,5-trioxan *(8)*. Then *(9)* was chlorinated by thionyl chloride to achieve 1-chloromethyl-1*H*-[1,2,4] triazole *(10)* in high yield. Compound *10* then reacted with magnesium in dry ether under nitrogen gas to produce the Grignard intermediate *(10')*. Finally, the reaction between *(10')* (eq. 2) and 2,4-

difluoroethylbenzoate *(11)* (eq. 1) *via* Grignard reagent gave the product *7* (Scheme 2). In this procedure we used for the first time 1,3,5-trioxane for preparing fluconazole. This reagent easily substituted a hydroxymethyl group at position 1 of the triazole ring.

In method *b* we used trioxane for the first time as a hydroxymethylene group donor in the synthesis of fluconazole; in the previous work paraformaldehyde was used for the synthesis of hydroxymethyltriazole [7,8]. The present invention avoids the use of the expensive trimethyl iodide sulfoxide or trimethyl iodide sulfoxide, each step uses domestic raw material supply and low prices can effectively reduce production costs.

Method c: In the third procedure (Grignard reaction 2), we obtained 1-(2,4- difluorophenyl)-2-(1*H*-1,2,4-triazole-1-yl)1-ethanone*(5)* by using nano-SSA catalyst, as mentioned in the first method. Then reaction between *10'* (eq. 1) and *5* (eq. 1) gave *7* (Scheme 3).

Method d: In the fourth procedure (Grignard reaction 3), as in the third one, we used both a Grignard reagent and our nano catalyst for synthesis of fluconazole. In this procedure we started from 1,3-dichloroacetone *(12)* and activated its carbonyl group by nano-SSA and then reacted it with triazole to get 1,3-bis-[1,2,4] triazol-1-yl-propan-2- one *(13)*. In this method the Grignard reagent *(15)* was prepared from 2,4-difluorobromobenzene *(14)* with the same procedure as for compound *10'*. This reagent was then reacted with *(12)* to get *7* (Scheme 4). Intermediate *12'* was our suggested structure in this way. However, each method has certain restrictions with regard to scope and reaction conditions; for example, each step of the method gives a low yield, the reaction with 1,3-dichloroacetone lacks selectivity, by-products are more difficult to separate, so there is no industrialization prospect [9]. To avoid these limitations, we investigated the use of nano-SSA for reacting 1,3-dichloro acetone and 1,2,4-1*H*- triazole. It is necessary to mention that using ionic liquids for this step, good results have been achieved [9].
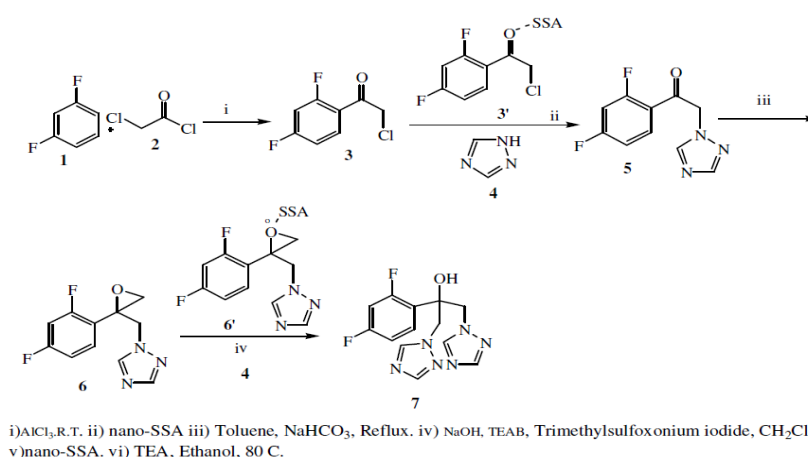
We modified the processes used previously for synthesis of fluconazole by using nano-SSA as a green catalyst in some steps. Our results showed that this catalyst is more efficient as regards yield and time of the reactions (Method *a*). We also used nano-SSA in the synthesis of one of the starting materials for Grignard reactions 3 (Method *d*). The high yield and comfortable isolation in each step were the advantage points in this method.

EXPERIMENTAL

All chemicals were purchased from Merck and used without any additional purification. The products were characterized by FT-IR (ATR), ^{1}H-NMR, and a comparison of their physical properties with those reported in the literature. FT-IR (ATR) spectra were acquired on a Bruker, Eqinox 55 spectrometer.

i)AlCl$_3$,R.T. ii) nano-SSA iii) Toluene, NaHCO$_3$, Reflux. iv) NaOH, TEAB, Trimethylsulfoxonium iodide, CH$_2$Cl$_2$. v)nano-SSA. vi) TEA, Ethanol, 80 C.

Scheme 1. Synthesis of fluconazole by nano-SSA (**method *a***).

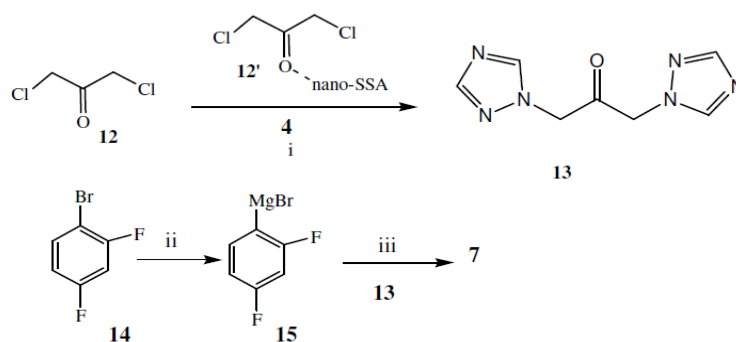i)Et$_3$N, THF. ii) SOCl$_2$ iii) Mg, Dry ether. iv) Dry ether
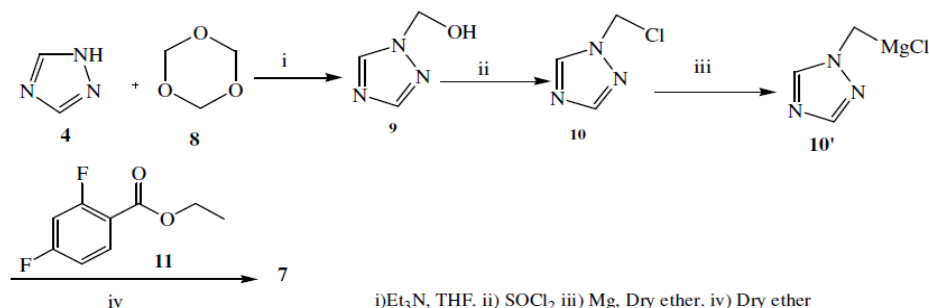
Scheme 2. Synthesis of fluconazole by Grignard reaction 1 (**method *b***).
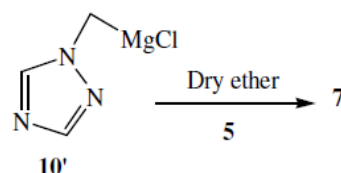
Scheme 3. Synthesis of fluconazole by Grignard reaction 2 (**method *c***).

i) nano-SSA, Toluene. ii) Mg/Dry Ether. iii)Dry Ether

Scheme 4. Synthesis of fluconazole by Grignard reaction 3 (**method d**).

A Bruker (NMR- 300MHz spectrometer) was used to record the ^{1}H NMR spectra. Spectrophotometer (UV/Vis biotek model UVIKONXL). Melting points were determined by using an Electrothermal 9100 digital melting point apparatus (Electrothermal, Essex, UK). The reaction progress and purity of the synthesized compounds were checked on Merck aluminium plates precoated with silica gel 60 F-254. UV radiation and/or iodine were used as the visualizing agents. Silica gel column chromatography was performed with silica gel 60G.

Preparation of nano-SSA

A 500 mL suction flask containing nano-silica gel (60.0 g) was equipped with a constant pressure dropping funnel containing chlorosulfonic acid (23.3 g, 0.2 mol) and gas inlet tube for conducting HCl gas over the adsorbing solution (water). Chlorosulfonic acid was added dropwise at room temperature over a period of 30 min. HCl gas was evolved from the reaction vessel immediately. After the addition was complete, the mixture was shaken for 30 min and a white solid of nano-SSA (76.0 g) was collected [6a].

2-Chloro-1-(2,4-difluoro-phenyl)-ethanone (3)

1,3-Difluorobenzene (5 mmol) and anhydrous aluminium chloride (6 mmol, 0.798 g) were stirred in 6 ml of dichloroethane at 30ºC for 30 min. The mixture was then cooled to 0ºC in ice bath and was charged dropwise with chloroacetyl chloride solution (5.1 mmol, 0.586 g) while stirring during 30 min. Stirring was continued for further 30 min keeping the reaction mixture at 0-10ºC. Then the mixture was warmed to room temperature and stirred for 24 h. After TLC showed complete conversion, the reaction was quenched by addition of hydrochloric acid (1M) and the mixture was extracted with dichloroethane at 0-5ºC. The combined organic layers were washed with 2×20 ml of saturated $NaHCO_3$ and then with cold water and brine, dried over anhydrous sodium sulfate (Na_2SO_4), and concentrated in vacuum. The white product was purified by recrystallization from *n*-hexane to get **3**, yield= 98%, mp= 44-48ºC.

1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazole-1-yl)1-ethanone (5)

A flask equipped with a reflux condenser was charged with a mixture of 2-chloro-1-(2,4-difluoro-phenyl)-ethanone (4 mmol) and nano-SSA (0.1 g) in toluene solvent, the carbonyl group was activated after 0.5 h, then a mixture of 1,2,4 triazole (4 mmol, .0331g) and sodium bicarbonate (4.8 mmol, 0.404 g) in 4 ml of toluene was added to it and refluxed for 24 h. Then the reaction mixture was poured in crashed ice and extracted with ethyl acetate (2×5 ml). The combined organic layers were washed with water and brine, dried over anhydrous sodium sulfate and concentrated in vacuum. The yellow product **5** was obtained by recrystallization from diethyl ether; yield = 80%; mp=103-107˚C.

1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1H-1,2,4-triazole (6)

A mixture of 1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazole-1-yl)1-ethanone in 15 ml of dichloromethane, trimethylsulfoxonium iodide (TMSI), (1.8 mmol, 0.397 g) and 3 ml toluene was charged by sodium hydroxide solution (20%, 1.3 ml) and tetraethylammonium bromide (TEAB) (0.3 mmol, 0.063 g). The reaction mixture was heated at 60ºC for 7 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the product was diluted with water and extracted with ethyl acetate (2×4 ml). The organic layer was washed and dried over anhydrous sodium sulfate and concentrated. White crystals were obtained by recrystallization from absolute ethanol; yield= 68%; mp=123-125˚C.

Fluconazole (7) via method a

A mixture of 1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1*H*-1,2,4-triazole (0.3 mmol) and nano-SSA (0.1 g) was stirred in 2 ml of absolute ethanol for 0.5 h. Then a mixture of triethylamine (0.18-0.29 ml) and 1,2,4 triazole (0.4 mmol, 0.0316 g) was added and refluxed in absolute ethanol for 15-24 h. TLC monitoring was used to control reaction progress. The mixture was filtered, concentrated and diluted with 3 ml of water. Then the filtrate was extracted with ethyl acetate (3×8 ml). The combined organic layers were washed with water and then with brine, dried over anhydrous sodium sulfate and concentrated in vacuum. The white product was purified by thin layer chromatography in a solvent system containing chloroform and methanol (88:12); yield = 55%; mp = 138-140°C [7].

Hydroxymethyltriazole (9)

In a round-bottomed flask equipped with stirring system and cooler, dissolve triazole (1 mmol, 0.069 g), 1,3,5-trioxane (0.33 mmol, 0.03 g) and 0.5 mL of Et$_3$N in 5 mL of THF. Keep the reaction stirred under inert atmosphere and refluxing for 18 h. To purify the product, concentrate the solution in a rotavapor and wash the white solid formed with diethyl ether. The product was crystallized from hot acetone; yield = 88%; mp =70- 73°C [7].

Chloromethyl-1H-[1,2,4]triazole (10)

Dissolve the product (**9**) (0.45 g) in 5 mL of THF and stir vigorously at 40°C for some time. Add slowly 0.6 mL of SOCl$_2$ using a dropping funnel and stir the reaction mixture, keeping the temperature at about 45°C. A white precipitate should form. Recover the precipitate by filtration and wash it with AcOEt; yield = 75%; mp =82-84°C [7].

Preparation of Grignard reagent from 1-chloromethyl-1H-[1,2,4]triazole (10′)

0.05 g of Mg powder was placed in a dry reaction tube and 0.5 mL of anhydrous diethyl ether was added. In a separate dry vial, 0.117 g of 1-chloromethyl-1*H*-[1,2,4]triazole and 0.70 mL of anhydrous diethyl ether were mixed and immediately added to the reaction tube.

Fluconazole 7 via method b

2,4-difluoroethylbenzoate (1mmol, 0.186 g) was dissolved in 1 mL of anhydrous diethyl ether and added to the Grignard reagent (10′) under gentle reflux. After finishing the reaction, 0.5 mL of HCl (3 M) was added dropwise while stirring, forming a white precipitate. Ether was added to dissolve the precipitate, then the aqueous layer was removed and an equal volume of aqueous NaCl solution was added. The aqueous layer was again removed and the ether was evaporated. The final product was obtained; yield= 42%; mp = 138-141°C [7].

Fluconazole 7 via method c

1-(2,4-difluorophenyl)-2-(1*H*-1,2,4-triazole-1-yl)1-ethanone (1 mmol, 0.22 g) was dissolved in 1 mL of anhydrous diethyl ether and added to the Grignard reagent (10′) under gentle reflux. After finishing the reaction, 2 mL of HCl (3 M) was added dropwise while stirring, forming a white precipitate. Ether was added to dissolve the precipitate, then the aqueous layer was removed and an equal volume of aqueous NaCl solution was added. The aqueous layer was again removed and the ether was evaporated. The final product was identified by TLC and spectroscopy data; yield = 38%; mp = 137-140°C [7].

1,3-Bis-[1,2,4]triazol-1-yl-propan-2-one (13)

To 1,3-dichloroacetone (1 mmol, 0.127 g) in toluene, 0.1 g of nano-SSA was added, and stirred for 0.5 h. After activation of the carbonyl group, 1,2,4-triazole (2 mmol) was added and refluxed for 24 h. After completion the reaction, the mixture was cooled to room temperature and filtered. The catalyst was separated from the reaction mixture by boiling ethanol. The crude solid product was purified by recrystallization in ethanol: water, 80:20; yield = 80%; mp =136-138°C [9].

Preparation of Grignard reagent from 1-bromo-2,4-difluoro-benzene (15)

0.07 g of Mg powder was placed in a dry reaction tube and 0.6 mL of anhydrous diethyl ether was added. In a separate dry vial, 0.19 g of 1-bromo-2,4-difluoro-benzene and 0.82 mL of anhydrous diethyl ether were mixed and immediately added to the reaction tube.

Fluconazole 7 via method d

0.36 g of 1,3-bis-[1,2,4]triazol-1-yl-propan-2-one was dissolved in 1 mL of anhydrous diethyl ether and added to the Grignard reagent (15) under gentle reflux. After finishing the reaction, 2 mL of HCl (3 M) was added dropwise while stirring, forming a white precipitate. Ether was added to dissolve the precipitate, then the aqueous layer was removed and an equal volume of aqueous NaCl solution was added. The aqueous layer was again removed and the ether was evaporated. The final product was identified by TLC and spectroscopy data; yield = 35%; mp = 139-140°C [7].

1-Chloro-1-(2,4-difluoro-phenyl)-ethanone (3): White solid; yield= 98%, mp= 44-48℃; FT-IR: ΰ (KBr) = 2900, 2800, 1703, 1614, 1486, 1433, 1392, 1316, 1269, 1193, 1142, 969, 822, 739, 606, 550 cm^{-1}.

1-(2,4-difluorophenyl)-2-(1H-1,2,4-triazole-1-yl)1-ethanone (5): Pale yellow solid; yield = 80%; mp =103-107 ˚ C; FT-IR: ΰ (KBr) = 3100, 2900, 2800, 1692, 1612, 1545, 1488, 1416, 1354, 1298, 1267, 1243, 1144, 1101, 994, 833, 608 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d6*): 8.80 (s, 1H), 8.26 (s, 1H), 8.01-8.08 (m,1H), 7.50-7.58 (m, 1H), 7.28-7.35 (dt, *J*=11.6, *J*=2.4, 1H), 5.86 (d, *J*=3, 2H) ppm; ^{13}C- NMR (300 MHz, DMSO-*d6*) δ = 189, 167, 150, 145, 133, 113, 106, 105, 58 ppm, MS: (m/z, %), 141 (100), 70.1 (10).

1-[2-(2,4-difluorophenyl)-2,3-epoxypropyl]-1H-1,2,4-triazole (6): White solid; yield=55%; mp =123-125 ℃ FT-IR: ΰ (KBr)= 3139, 1621, 1558, 1508, 1458, 1424, 1383, 1242, 1160, 1033, 965, 882, 820, 797, 774, 654 cm^{-1}; ^{1}H NMR (300) MHz, DMSO): 8.70 (s, 1H), 8.16 (s, 1H), 7.19-7.31 (m, 2H), 6.98-7.05 (m, 1H), 4.83 (d, *J*= 20, 1H), 4.63 (d, *J*= 15, 1H), 3.12 (d, *J*= 4.8, 1H), 2.97 (d, *J*= 4.8, 1H) ppm; ^{13}C-NMR (300 MHz, DMSO) δ = 164, 162, 159, 150, 144, 130, 120, 112, 104, 56, 54, 52 ppm; MS: (m/z, %), 237 (4), 168 (60), 139 (100).

Fluconazole (7): White solid; isolated yield = 45%; mp = 138-140 ˚ C;FT-IR: ΰ (KBr) = 3119, 3012, 1773, 1620, 1504, 1451, 1414, 1272, 1210, 1137, 1075, 964, 910, 846, 767, 732, 710, 673, 613, 576 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-*d6*): 8.32 (s, 2H), 7.80 (s, 2H), 7.11-7.25 (m, 2H), 6.84-6.91 (dt, *J*=18, *J*=2.4, 1H), 6.36 (s, 1H), 4.73 (d, *J*=14.2, 2H), 4.55 (d, *J*=14.2, 2H) ppm.

Hydroxymethyltriazole(9): White solid; yield = 88%; mp =70-73 ℃; FT-IR: ΰ (KBr) = 3104, 3038, 2957, 2738, 2637, 2544, 2402, 1555, 1419, 1360, 1104, 988, 856, 766, 654 cm^{-1}, ^{1}H NMR (300 MHz, DMSO): 6.45 (s, 2H), 8.30 (s, 1H), 9.17 (s, 1H) ppm.

1-Chloromethyl-1H-[1,2,4]triazole (10): White solid; isolated yield = 75%; mp = 82-84 C; ^{1}H NMR (300 MHz, DMSO): 6.27 (s, 2H), 8.30 (s, 1H), 9.17(s, 1H) ppm, ^{13}C-NMR (300 MHz, DMSO) δ = 55.4, 145.9, 151.7 ppm; MS: (m/z, %), 117 (35), 82 (100).

1,3-Bis-[1,2,4]triazol-1-yl-propan-2-one (13): White crystal; yield = 80%; mp =136-138˚ C; ^{1}H NMR (400 MHz, DMSO): 4.48 (s, 4H), 8.05 (s, 1H), 8.14 (s, 1H) ppm.

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Подобрен синтез на флуконазол с използване на наносилика-сярна киселина като „зелен" катализатор

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(Резюме)

В съответствие с нашия интерес към получаването на нови противогъбични агенти, насочихме вниманието си към флуконазола поради широкия му противогъбичен спектър, ниската токсичност и отличните фармакокинетични свойства. Като част от нашата програма за разработване на нов метод за синтез на флуконазол са изследвани и оптимизирани условията на някои реакции, включително Гринярдови реакции. Най-добри резултати са получени с използване на наносилика-сярна киселина като мек „зелен" катализатор. Предимства на метода са високият добив и лесната изолация на продуктите във всеки етап.