RAPID SYNTHESIS OF SOME NEW PROPANOL DERIVATIVES ANALOGOUS TO FLUCONAZOLE UNDER MICROWAVE IRRADIATION IN SOLVENTLESS SYSTEM

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Fluconazole and a series of 2-(2,4-difluorophenyl)-1-(1H-1,2,4 triazol-1-yl- methyl)-3-(substituted heterocycl)-propan-2-ol which are analogous to fluconazole,were synthesized via the reaction of 2-(2,4-difluorophenyl)-2-[1-(1,2,4-triazolmethide)]oxiran with various heterocyclic system under microwave irradiation in solventless system.

Introduction

Fluconazole,α(2,4-difluorophenyl)-α-(1H-1,2,4 triazol-1-yl- methyl)-1H-1,2,4 triazol-1-ethanol **5** is a potent inhibitor of the cytochrome P450(CYP)-mediated metabolism of the anti-epileptic agent phenytion ,a well-known human and animal tetragon.[1] Fluconazole was introduced in 1990 as one of the most effective water-soluble oral antifungal agent [2,3].

Because of importance of fluconazole ,we felt that an approach to synthesis of this drug and its analogous in milder ,faster and more eco-friendly conditions than those hitherto described would be a great value.

Due to biological importance of fluconazole ,sevaral routes have been developed for the synthesis of this drug **5** [4].The applicable method in industrial level involves one pot three component reaction of 2,4 difluoro-2-(1H-1,2,4 triazole-1-yl)acetophenone**1**, triazole **2** and trimethylsulfoxonium iodide **3** [5].

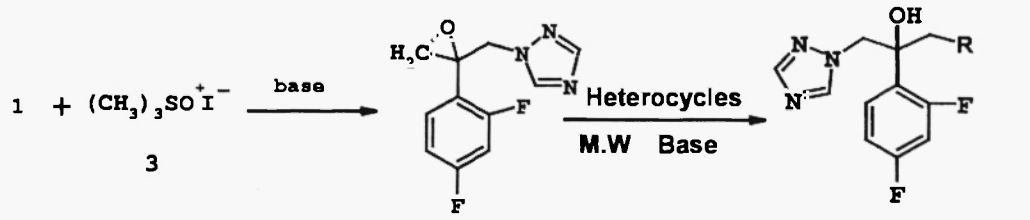
Recently we reported on the synthesis of some new proponal derivatives analogous to fluconazole via ring opening of intermediate epoxide 5 with heterocycles containing thio and amino group (scheme 2)[6].

Recently,microwave-assisted solvent-free synthesis [8] ,in organic reactions has found growing interest as an efficient,economic and clean procedure (green chemistry)[9].

In continuation of our ongoing program to develop the use of microwave irradiation under solvent –free condition[7].Herein we report the synthesis of fluconazole and its analogous under microwave irradiation in solventless system.

The reactions were simply conducted by mixing of starting materials and placed under microwave irradiation.The compounds 6-11 were obtained in %64-78 yields under microwave irradiation (1000W) in 10-15 min. We could obtain fluconazole under microwave irradiation for 10 min in %74 yield which has a better yield than the synthesis of that in the thermal condition (%44).

In conclusion the present procedure for synthesis of fluconazole and its analogous has advantages over our previouse reported method [6] and provides a facile ,useful and important addition to the existing methodologies .The advantages of this procedure are mild reaction conditions ,high yields, minimizination of side products, short reaction times and lack of flamable and hazardous solvent.



Scheme-1

Experimental

Melting points were determined on electrotermal IA-9100 digital melting point apparatus and uncorrected.IR spectra were recorded with Nicolet Magna spectrometer 750-1992-1997.^{1}H NMR Spectra were recorded on a Brucker spectrometer at 500 MHz using TMS as internal standard.Mass spectra were obtained on a GC-Mass HP,GC 689 network GC system, mass 5973 at 70 ev.Thin layer chromatography was developed on Merck silica-gel coated polyester plates containing a 254 mm fluorscent indicator. Triazoles , pyrimidines and 1,2,4 triazoles were prepared according to literature.

1-[2-(2,4 diflurophenyl)-2,3-epoxypropyl]-1H-1,2,4triazole methansulphonate(4):

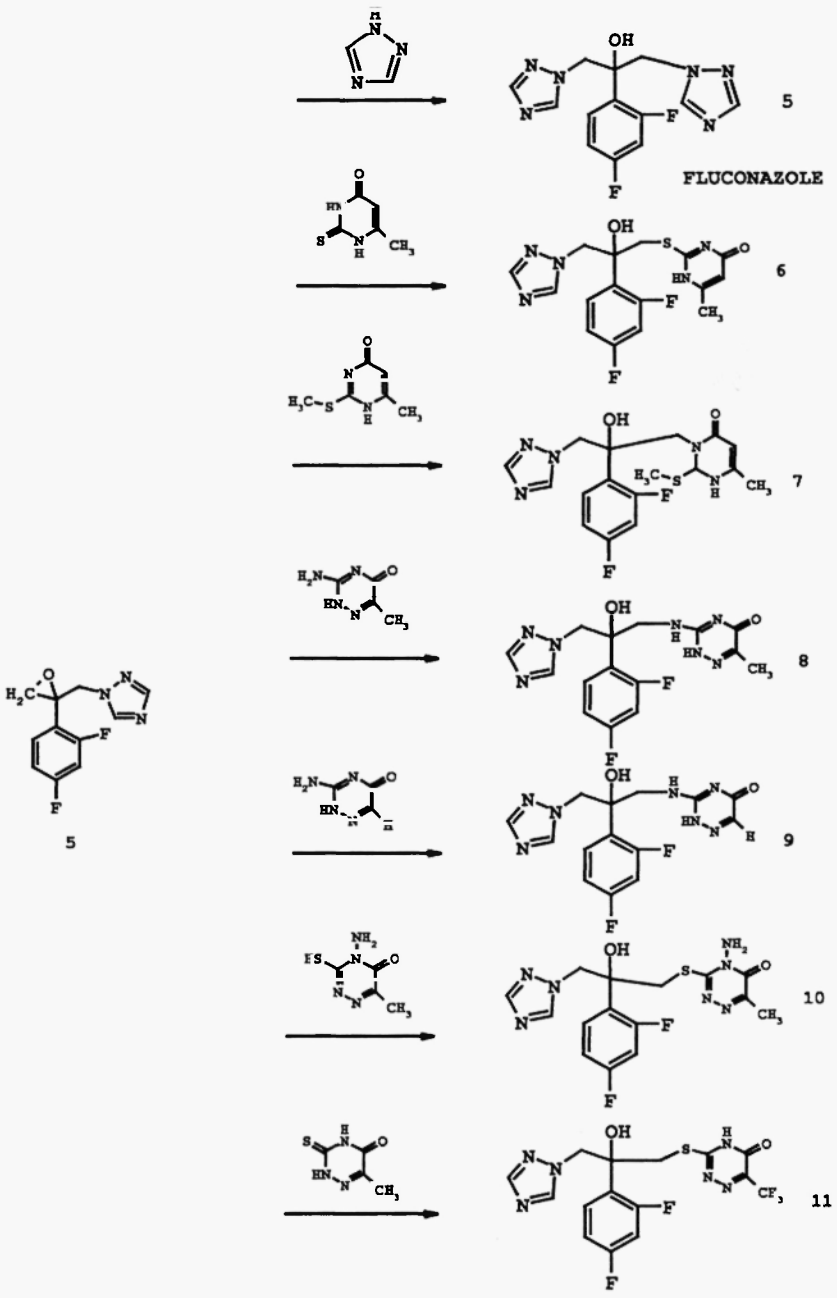
2,4 difluoro-2-(1H-1,2,4 triazol-1-yl)acetophenone hydrochloride(59.6 g,0.23 mol), trimethylsulfoxonium iodide (50.6 g,0.23 mol) and cetrimide (2.1 g) were stirred in a mixture of toluene (370 ml) and 20% w/w aqueous sodium hydroxide at 60°C for 3 hours. The toluene layer was separated and concentrated to 110 ml, then ethyl acetate was added (150 ml). To this mixture a solution of methansulphonic acid (16.6 g,0.172 mol) in ethyl acetate (20ml) was added. More ethyl acetate (100 ml) was added and the mixture was stirred at 0°C for one hour. Filtration of the mixture gave the title compound (43 g. 56%). The crude product was dissolved in hot petroleum ether (60-80°C)(140 ml) and charcoal (2 g) was added. The mixture was filtered and the filtrate was concentrated to 100 ml, then the mixture was stirred at 0°C for one hour. Filration of this mixture gave the title compound (7.8 g, 39%), mp 128-129°C ^{1}H NMR-δ(d_4-MeOH) :2.7(s, 3H), 2.9(d, J=4.57 Hz, 1H), 3.1(d, J=4.57 Hz, 1H), 4.7(d, J=14.83 Hz, 1H), 5.1(d, J=14.83 Hz, 1H), 6.93(m, 1H), 7.0(m, 1H), 7.3(m, 1H), 8.7(s, 1H), 9.8(s, 1H). IR(KBr): 3120 cm-1(CH aromatic), Analysis %: Calculated for $C_{12}H_{13}F_2N_3O_4S$: C, 43.2 ; H, 3.9; N, 12.6, Found: C, 42.83; H, 3.92; N, 12.96.

Synthesis of fluconazole 5

The epoxide 5 (0.3 gr,0.001 mol) and triazole (0.1 gr,0.001 mol) and NaCO3 (0.4 gr) was mixed thoroughly using spatula.The beaker is placed in a microwave (1000 W) for 10 min .Then the solid was crystallized from ethylacetate (0.19 gr,%74),m.p.138°C (lit[4] 138°C -140°C), ^{1}H NMR-δ(d_3-MeOD): 4.4 (d, J=14.31 Hz, 2H), 4.7 (d, J=14.31 Hz, 2H), 5.9 (s,1H), 6.82-6.89 (m,2H),7.5 (m,1H),7.7 (s,1H),8.3 (s,1H),8.6 (s,1H). IR(KBr): 3117.97cm-1(OH), Ms, m/z:307(M^+), 224(100%), 170(21%), 142(62%), 127(70%), 82 (62%), 55(19%).

Synthesis of triazolylpropanol derivatives 6-11

The appropriate heterocylic compound (0.001 mol), NaOMe(0.002 mol) and epoxide **4** (0.3 g,0.001 mol) was mixed in a beaker thoroughly using spatula.The beaker is placed in a microwave oven (1000 W) for specified time (10-15 min).To the crude, CHCl3 (50 ml) was added,filtered and was concentrated under reduced pressure.The crude was subjected to column chromatography using $CHCl_3$:MeOH(1:60- 1: 20) as the eluent to affored the pure product .



Scheme-2

Selected data for 6

Yield: 78%, m.p: 165 °C (lit[6]: 165°C), 'H NMR-δ (d_6-DMSO): 2.03(s, 3H), 2.5(d, J=12 Hz, 1H), 2.7(d, J=12 Hz, 1H), 4.71(d, J=14.1 Hz, 1H), 4.78(d, J=14.1 Hz, 1H), 5.6(s, 1H), 6.2(s, 1H), 6.8(m, 1H), 6.9(m, 1H), 7.4 (m, 1H), 7.78(s, 1H), 8.3(s, 1H), 10.2(br s,1H). IR(KBr): 3436.70 cm-1(OH), Ms, m/z, 379(M^+), 239(14%), 224(100%), 173(70%), 155(28%), 141(39%), 83(66%), Time of irradiation:10 min.

Selected data for 7

Yield: 72%, m.p: 142°C (lit[6]: 140-142°C), 'H NMR-δ(d_3-MeOD): 2.03(s, 3H), 2.5(s, 3H), 3.9(d, J=13.5 Hz, 1H), 4.0(d, J=13.5 Hz, 1H), 4.7(d, J=14.4 Hz, 1H), 4.8(d, J=14.4 Hz, 1H), 5.9(s, 1H), 6.81-6.91(m, 2H), 7.0(s, 1H), 7.4 (m, 1H), 8.3(s, 1H), 8.5(s,

1H).IR(KBr): 3480 cm-1(OH), Ms, m/z, 393 (M^+), 281(21%), 238 (27%), 224(100%), 169(16%), 155(28%), 82(8.2%), 63(16%),Time of irradiation: 10 min .

Selected data for 8
Yield:68%, m.p: 183°C (lit[6]: 181-183°C), ^{1}H NMR-δ (d_6-DMSO): 2.2(s,3H), 3.4-3.6(m, 2H), 4.5 (br s, 1H). 4.6(d, J=14.2 Hz, 1H), 4.7(d, J=14.2 Hz, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.1(m, 1H), 7.3 (m, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 11.5 (br s,1H). IR(KBr): 3450.22 cm-1(OH), Ms, m/z:363 (M^+), 298(%6.4), 282(18%), 238(%19%), 224(100%), 173(72%), 127(73%), 125(27%), 68(20%), Time of irradiation: 10 min.

Selected data for 9
Yield:70%, m.p: 175°C (lit[6]: 173-175°C), ^{1}H NMR-δ (d_6-DMSO): 3.48-3.54(m, 2H), 4.39(d, J=14.4 Hz, 1H), 4.43(d, J=14.4 Hz. 1H). 4.8(br s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 6.9 (m, 1H), 7.1 (m, 1H), 7.3 (m, 1H), 7.7 (s, 1H), 8.3 (s, 1H), 12.0 (br s, 1H). IR(KBr): 3541.38 cm-1(OH), Ms, m/z:349(M^+), 332(9.3%), 267(30%), 238(22%), 224(100%), 125(32%), 111(15%), 82(40%), Time of irradiation:15 min.

Selected data for 10
Yield:66%,m.p: 153-155°C (lit[6]: 155°C), ^{1}H NMR-δ (d_6-DMSO): 2.2(s, 3H), 2.8(d, J=12.8 Hz, 1H), 2.9(d, J=12.8 Hz, 1H), 4.6(d, J=14.1 Hz, 1H), 4.7(d, J=14.1 Hz, 1H). 5.8 (br s, 1H), 6.4 (s, 2H), 7.0 (m, 1H), 7.2 (m, 1H), 7.4 (m. 1H), 7.7 (s, 1H), 8.3 (s, 1H). IR(KBr): 3550.84 cm-1(OH). Ms, m/z:395(M^+), 327(27.6%), 282(23%), 238(39.5%), 224(100%), 171(71%), 157(26%), 127(17%), 82(8%), Time of irradiation:15 min.

Selected data for 11
Yield:64%, m.p: 177-179°C (lit[6]: 179°C). ^{1}H NMR-δ(d_3-MeOD) : 2.0(s, 3H), 2.6(d, J=11.5 Hz, 1H), 2.7(d, J=11.5 Hz, 1H), 4.6(d, J=14.2 Hz, 1H), 4.7(d, J=14.2 Hz, 1H), 5.9 (s, 1H), 6.8 (m, 1H), 6.9 (m, 1H). 7.8 (m, 1H), 8.2 (s, 1H), 8.5 (s, 1H), 11.0 (br s, 1H). IR(KBr): 3467.76 cm-1(OH), Ms, m/z:381(M+1), 312(12%), 238(38%), 224(100%), 155(11%), 142(78%), 86(39%), 68(15%), 42(38%), Time of irradiation:15 min.

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