Asian Journal of Chemistry; Vol. 27, No. 1 (2015), 173-176

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2015.16839

Synthesis and Antifungal Activities of Novel Fluorine-Containing Triazole Compounds

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Received: 7 December 2013; *Accepted*: 4 April 2014; *Published online*: 26 December 2014; AJC-16531

A series of novel triazole compounds containing fluorinated arylphenyl ether group were designed and synthesized. All the new compounds were identified by IR, ^{1}H NMR and elemental analysis. Their *in vitro* antifungal activities against five common pathogens were evaluated by mycelial growth rate method. The preliminary bioassay indicated that all the target compounds possess some fungicidal activities against *Gibberella zeae*, *Alternaria solani*, *Fusarium oxysporum*, *Physalospora pircola* and *Cercospora arachidicola*. In particular, compound **5e** exhibited excellent antifungal activities, its inhibition rates against all selective tested pathogens reached more than 90 % at 50 μg/mL

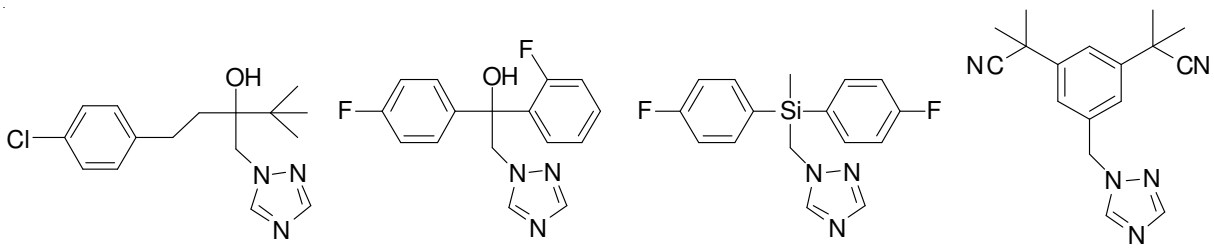
Keywords: Triazole, Fluorine-containing compounds, Antifungal activities, Synthesis.

INTRODUCTION

Heterocyclic compounds, especially triazole compounds, have been attracted considerable attention over the past few decades due to their broad-spectrum biological activities[1-5]. Moreover, many 1,2,4-triazole derivatives have been widely used because of their potent pesticidal, herbicidal, antibacterial, antifungal, antitubercular, anticancer, antiinflammatory and plant growth-regulation activities[6-12]. So far, more than thirty 1,2,4-triazole derivatives have been successfully developed commercial agricultural and medical fungicides, such as tebuconazole, flutriafol, flusilazole, anastrozole (Fig. 1)[13-16]. Among these fungicide molecules, the unit '(1*H*-1,2,4-triazole-1-yl)methyl/methenyl' is key to their antifungal activities. In addition, the aryl phenyl ether group is a highly efficient pharmacophore and is widely used in pesticide and drug molecular design[17,18]. Furthermore, fluorine-containing compounds have been aroused the interest of many researchers due to their unique properties[19-23]. Thus, in search for novel bioactivity compounds, we designed and synthesized a series of novel fluorine-containing triazole compounds by introducing fluorinated aryl phenyl ether group into the unit '(1*H*-1,2,4-triazole-1-yl)methyl/methenyl' and evaluated their antifungal activities against five selected funguses. The target compounds were synthesized through the following described procedure in **Schemes I** and **II**.

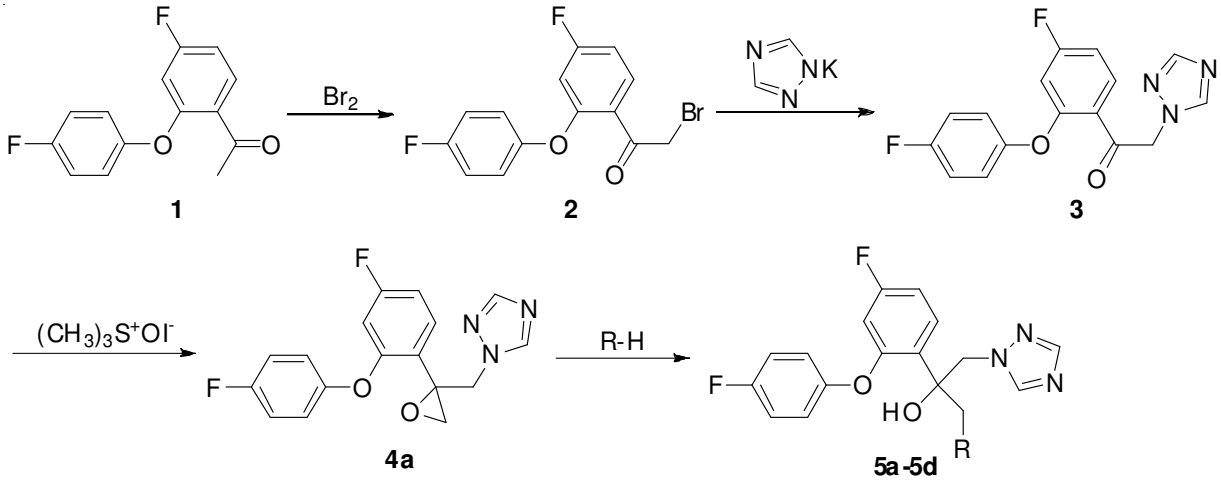
EXPERIMENTAL

All chemicals were obtained from a commercial source and used without further purification. Melting points were determined on a Yanaco MP-500 melting point apparatus and were uncorrected. IR spectra (4000-400 cm^{-1}), as KBr pellets, were recorded on a Nicolet FT-IR 170X spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-500 nuclear magnetic resonance spectrometer at 500 MHz in $CDCl_3$ or DMSO-d_6 solution with TMS as internal standard. Chemical shifts values (δ) are given in parts per million. Elemental

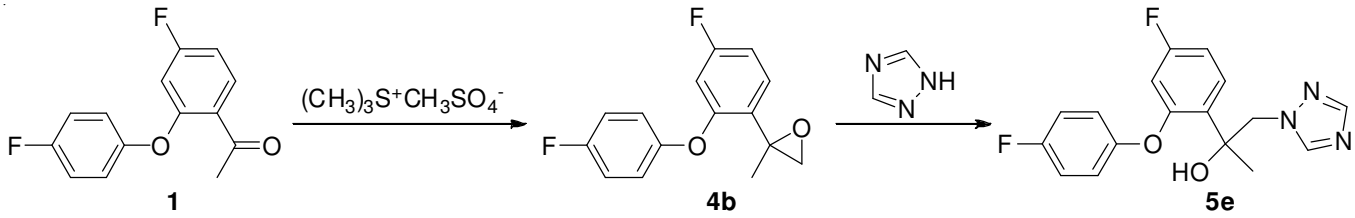


tebuconzole flutriafol flusilazole anastrozole

Fig. 1. Chemical structures of some commercial triazole fungicides



Scheme-I: Synthetic procedure of the target compounds **5a-5d**



Scheme-II: Synthetic procedure of the target compound **5e**

analyses were determined on a Perkin Elmer 240 elemental analyzer. All reactions were monitored by thin layer chromatography (TLC). Visualization was performed by ultraviolet light at 254 nm. All yields refer to isolated products after purification and are not optimized.

Preparation of epoxidizing agent: Trimethylsulfoxonium iodide was prepared by iodomethane reacting with dimethyl sulfoxide according to a literature procedure[24]. Trimethylsulfonium methylsulfate was prepared *via* dimethyl sulfide and dimethyl sulfate according to a literature procedure[25].

Synthetic procedure of key intermediate 1-[(2-(4-fluoro-2-(4-fluorophenoxy)phenyl)oxiran-2-yl)methyl]-1*H*-1,2,4-triazole (4a): Intermediate 2-bromo-1-(4-fluoro-2-(4-fluorophenoxy)phenyl)ethanone (**2**) was prepared using arylethanone **1** and bromine according to a literature reported procedure[26]. yield 90.1 %; white solid; m.p. 38-39 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.00 (m, 1H, Ar-H), 7.20-7.13 (m, 4H, Ar-H), 6.90-6.86 (m, 1H, Ar-H), 6.47-6.45 (m, 1H, Ar-H), 4.61 (s, 2H, Br-CH_2).

2-Bromo-1-(4-fluoro-2-(4-fluorophenoxy)phenyl)ethanone (**2**) (0.1 mol), 1*H*-1,2,4-triazole (0.12 mol) and potassium carbonate (0.12 mol), in turn, were added to ethyl acetate (70 mL) and refluxed for 6 h. Then the resulting mixture was filtered, the filtrate was condensed, the residual was recrystallized with ethyl acetate to afford intermediate 1-(4-fluoro-2-(4-fluorophenoxy)phenyl)-2-(1*H*-1,2,4-triazol-1-yl)ethanone (3). yield 71.3 %; yellowish solid; m.p. 146-148 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.35 (s, 1H, Tr-H), 8.04 (m, 1H, Ar-H), 8.00 (s, 1H, Tr-H), 7.18-7.10 (m, 4H, Ar-H), 6.89-6.85 (m, 1H, Ar-H), 6.47-6.44 (m, 1H, Ar-H), 5.67 (s, 2H, Tr-CH_2).

Intermediate 1-[(2-(4-fluoro-2-(4-fluorophenoxy)phenyl)-oxiran-2-yl)methyl]-1*H*-1,2,4-triazole (**4a**) was synthesized according to literatures procedure[27,28]. Trimethylsulfoxonium iodide (0.12 mol), tetrabutyl ammonium bromide (0.3 g) and intermediate **3** (0.1 mol) were dissolved in 100 mL toluene, subsequently heated to 60 °C. The aqueous solution of sodium hydroxide (20 %, 80 mL) was added dropwise to above the blend over 2 h. The resultant mixture been stirred at 60 °C for 3 h, the organic phase was separated and condensed. The residual was recrystallized with ethyl acetate to afford intermediate **4a**. yield 82.3 %; yellowish solid; m.p. 72-74 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.13 (s, 1H, Tr-H), 7.85 (s, 1H, Tr-H), 7.20-7.07 (m, 5H, Ar-H), 6.71-6.67 (m, 1H, Ar-H), 6.44-6.42 (m, 1H, Ar-H), 4.96 (d, $^2J_{HH}$ = 15 Hz, 1H, Tr-CH_2), 4.52 (d, $^2J_{HH}$ = 15 Hz, 1H, Tr-CH_2), 2.95 (d, $^2J_{HH}$ = 5 Hz, 1H, O-CH_2), 2.90 (d, $^2J_{HH}$ = 5 Hz, 1H, O-CH_2).

Synthetic procedure of key intermediate 2-[4-fluoro-2-(4-fluorophenoxy)phenyl]-2-methyloxirane (4b): Intermediate 2-[4-fluoro-2-(4-fluorophenoxy)phenyl]-2-methyloxirane (**4b**) was synthesized according to literature reported procedure[29]. To the solution of 1-[4-fluoro-2-(4-fluorophenoxy)-phenyl]ethanone (**1**) (10 mmol), trimethylsulfonium methylsulfate (12 mmol) in 20 mL ethyl ether was added potassium hydroxide (40 mmol) powder in the ice-water bath. Afterwards, the suspension was heated to boiling and lasted for 6 h. After complete reaction, the resulting mixture was cooled, poured into water, acidified with 30 % H_2SO_4 to pH 7-8 and extracted with ethyl ether. The organic extract was washed with water twice and dried with sodium sulfate. After filtering, the solvent was removed under reduce pressure to give intermediate **4b**. yield 85.4 %; yellowish liquid; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.85 (m, 1H, Ar-H), 7.17-6.94 (m, 4H, Ar-H), 6.87-6.71 (m, 1H, Ar-H), 6.58-6.37 (m, 1H, Ar-H), 2.93 (d, $^2J_{HH}$ = 5 Hz, 1H, O-CH_2), 2.87 (d, $^2J_{HH}$ = 5 Hz, 1H, O-CH_2), 1.55 (s, 3H, CH_3).

Synthetic procedure of target compounds: Intermediate 2-[4-fluoro-2-(4-fluorophenoxy)phenyl]-2-methyloxirane (**4a**) (5 mmol) and sodium methanolate (6 mmol) were refluxed for 4 h in 10 mL methanol. When intermediate **4a** were completely consumed (monitored by TLC), the solvent was evaporated in vacuum. The residual was extracted with dichloromethane, washed with water twice, dried with sodium sulfate, condensed and recrystallized with absolute methanol to obtain 2-[4-fluoro-2-(4-fluorophenoxy)phenyl]-1-methoxy-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (**5a**). yield 53.5 %; white solid; m.p. 97-99 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.13 (s, 1H, Tr-H), 7.82 (s, 1H, Tr-H), 7.60-7.57 (m, 1H, Ar-H), 7.15-7.14 (m, 4H, Ar-H), 6.73-6.72 (m, 1H, Ar-H), 6.41-6.39 (m, 1H, Ar-H), 4.93 (d, $^2J_{HH}$ = 14 Hz, 1H, Tr-CH_2), 4.71 (d, $^2J_{HH}$ = 14 Hz, 1H, Tr-CH_2), 4.10 (s, 1H, OH), 3.83 (s, 2H, O-CH_2), 3.41 (s, 3H, O-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3420, 1601, 1503, 1197, 1145. Elemental Anal. Calc. (%) for $C_{12}H_{13}N_3O_2$ (Mr = 231.25): C 59.83, H 4.74, N 11.63; found (%): C 59.85, H 4.71, N 11.65

To the solution of intermediate (**4a**) (5 mmol) in 10 mL methanol was added dropwise aqueous methylamine (6 mmol) at 0 °C and stirred for 4 h at room temperature subsequently. Upon completion of the reaction, the reaction solution was poured into water, extracted with dichloromethane, washed with water twice, dried with sodium sulfate, condensed and recrystallized with absolute methanol to obtain 2-[4-fluoro-2-(4-fluorophenoxy)phenyl]-1-(methylamino)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (**5b**). yield 69.4 %; yellowish solid; m.p. 135-137 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.16 (s, 1H, Tr-H), 7.71 (s, 1H, Tr-H), 7.35-7.33 (m, 1H, Ar-H), 7.17-7.08 (m, 4H, Ar-H), 6.62-6.60 (m, 1H, Ar-H), 6.39-6.36 (m, 1H, Ar-H), 4.75 (d, $^2J_{HH}$ = 13.5 Hz, 1H, Tr-CH_2), 4.62 (d, $^2J_{HH}$ = 13.5 Hz, 1H, Tr-CH_2), 3.63 (s, 1H, OH), 3.45 (d, $^2J_{HH}$ = 14 Hz, 2H, N-CH_2), 3.16 (m, 1H, NH), 2.25 (d, $^2J_{HH}$ = 14 Hz, 3H, N-CH_3). IR (KBr, ν_{max}, cm^{-1}): 3425, 1601, 1504, 1195, 1142. Elemental anal. calc. (%) for $C_{12}H_{13}N_3O_2$ (Mr = 231.25): C 59.99, H 5.03, N 15.55; found (%): C 60.02, H 5.00, N 15.57.

According to the above synthetic procedure of **5a-5b**, target compounds **5c-5e** were synthesized. A mixture of intermediate **4a** (or **4b**) (5 mmol), potassium carbonate (5 mmol), ring-opening reagent (6 mmol) in 20 mL of DMF was refluxed for 5-6 h, the reaction had been taken completely. Then the reaction solution was poured into water, simultaneously crude product was precipitated out. Crude product was purified by recrystallization or vacuum column chromatography on silica gel to afford the desired compounds **5c-5e**. Data for compounds **5c-5e** as follow.

2-[4-Fluoro-2-(4-fluorophenoxy)phenyl]-1-(1*H*-imidazol-1-yl)-3-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (5c): Yield 73.8 %; white solid; m.p. 147-149 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.95 (s, 1H, Tr-H), 7.80 (s, 1H, Tr-H), 7.42 (s, 1H, Im-H), 7.41-7.40 (m, 1H, Ar-H), 7.19-7.16 (m, 2H, Ar-H), 7.10-6.90 (m, 4H, Ar-H + Im-H), 6.64-6.60 (m, 1H, Ar-H), 638-6.36 (m, 1H, Ar-H), 5.07 (d, $^2J_{HH}$ = 13.5 Hz, 1H, Tr-CH_2), 4.58 (d, $^2J_{HH}$ = 14.5 Hz, 1H, Im-CH_2), 4.43 (d, $^2J_{HH}$ = 14.5 Hz, 1H, Im-CH_2), 4.35 (d, $^2J_{HH}$ = 13.5 Hz, 1H, Tr-CH_2), 2.03 (s, 1H, OH). IR (KBr, ν_{max}, cm^{-1}): 3428, 1601, 1504, 1207, 1146. Elemental anal. calc. (%) for $C_{12}H_{13}N_3O_2$ (Mr = 231.25): C 60.45, H 4.31, N 17.62; found (%): C 60.50, H 4.35, N 17.57.

2-[4-Fluoro-2-(4-fluorophenoxy)phenyl]-1,3-di(1*H*-1,2,4-triazol-1-yl)propan-2-ol (5d): Yield 51.3 %; white solid; m.p. 203-204 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.10 (s, 2H, Tr-H), 7.82 (s, 2H, Tr-H), 7.42-7.39 (m, 1H, Ar-H), 7.18-7.12 (m, 4H, Ar-H), 6.61-6.58 (m, 1H, Ar-H), 6.34-6.31 (m, 1H, Ar-H), 4.95 (d, $^2J_{HH}$ = 14 Hz, 2H, Tr-CH_2), 4.53 (d, $^2J_{HH}$ = 14 Hz, 2H, Tr-CH_2), 1.83 (s, 1H, OH). IR (KBr, ν_{max}, cm^{-1}): 3428, 1602, 1504, 1197, 1145. Elemental anal. calc. (%) for $C_{12}H_{13}N_3O_2$ (Mr = 231.25): C 57.28, H 4.05, N 21.10; found (%): C 57.25, H 4.08, N 21.12.

2-[4-Fluoro-2-(4-fluorophenoxy)phenyl]-1-(1*H*-1,2,4-triazol-1-yl)propan-2-ol (5e): Yield 87.6 %; white solid; m.p. 115-117 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.05 (s, 1H, Tr-H), 7.82 (s, 1H, Tr-H), 7.65-7.62 (m, 1H, Ar-H), 7.15-7.13 (m, 4H, Ar-H), 6.85 (m, 1H, Ar-H), 6.52 (m, 1H, Ar-H), 5.25 (d, $^2J_{HH}$ = 14 Hz, 1H, Tr-CH_2), 4.73 (d, $^2J_{HH}$ = 14 Hz, 1H, Tr-CH_2), 4.07 (s, 1H, OH), 1.75 (s, 3H, CH_3). IR (KBr, ν_{max}, cm^{-1}): 3305, 1601, 1503, 1195, 1143. Elemental anal. calc. (%) for $C_{12}H_{13}N_3O_2$ (Mr = 231.25): C 61.63, H 4.56, N 12.68; found (%): C 61.60, H 4.61, N 12.67.

Bioassays of target compounds: *in vitro* Antifungal activities of all the target compounds were evaluated by mycelial growth rate method according to the literature[30]. Five common pathogens, *Gibberella zeae*, *Alternaria solani*, *Fusarium oxysporum*, *Physalospora pircola* and *Cercospora arachidicola* were used to test. The inhibition rate was expressed as the mean of values obtained in three independent experiments. The antifungal activities data are summarized in Table-1.

RESULTS AND DISCUSSION

Synthesis: The target compounds **5a-5e** were synthesized from 1-[4-fluoro-2-(4-fluorophenoxy)phenyl]ethanone (**1**) as shown in **Scheme-I** and **II**. Arylethanone **1** was reacted with bromine in anhydrous diethyl ether and subsequently reacted with 1*H*-1,2,4-triazole to afford triazolylarylethanone **3**. Triazolylarylethanone **3** or arylethanone **1** was epoxidized further by trimethylsulfoxonium iodide or trimethylsulfonium methylsulfate to provide the epoxide **4**, the key intermediate for this study, employing the described procedure[27-29]. The epoxide **4a** (or **4b**) was attacked by the ring-opening reagent

TABLE-1
ANTIFUNGAL ACTIVITIES OF THE TARGET COMPOUNDS **5a-5e**

	Antifungal activities (50 µg/mL, inhibition (%))				
Compound	*G. zeae*	*A. solani*	*C. archidicola*	*F. oxysporum*	*P. pircola*
5a	41.2	66.7	55.6	61.5	47.1
5b	20	20	30	80	30
5c	11.8	6.7	29.2	46.2	11.8
5d	44.1	20.0	50.0	38.5	41.2
5e	95	95	98	100	90

at the less sustituted carbon atom to provide target compounds **5a-5e**.

The structures of all the target compounds were characterized by IR, ^{1}H NMR and elemental analyses. The result data are good agreement with their structure. In the IR spectrum, strong absorption bands at about 3428-3305 cm^{-1} and strong absorption at about 1146-1142 cm^{-1} are attributed to O-H and C-O stretching vibration absorption in the tertiary alcohol group. In the ^{1}H NMR spectrum, the chemical shifts for the two protons of the triazole ring appears at about 8.16-7.95 and 7.82-7.71, respectively. The chemical shifts for the two protons of the CH_2 group connecting with a triazole ring appears as two doublets at about 5.25-4.75 and about 4.73-4.35. The chemical shifts for the proton of the OH at about 4.10-1.83.

In the ^{1}HNMR spectra of epoxides **4** and target compounds **5**, the signal of the two protons of the CH_2 group all splits into two doublets, whether connecting the heterocycle or lying in epoxide group. It is ascribed to the fact they are attached to an asymmetrical carbon atom, which makes the magnetic environments of the two CH_2 group protons different.

Bioassays: The results of preliminary biological tests showed that all the target compounds possess some fungicidal activities against all selective tested pathogens. It is noteworthy that compound **5e** exhibited excellent antifungal activities. Its inhibition rates against *Gibberella zeae*, *Alternaria solani*, *Fusarium oxysporum*, *Physalospora pircola* and *Cercospora arachidicola* reached 95, 95, 98, 100 and 90 % at 50 µg/mL, respectively.

Conclusion

By use of epoxidation and nucleophilic addition reaction, introducing fluorinated aryl phenyl ether group into triazole moiety, a series of novel fluorine-containing triazole compounds was synthesized and explored. The preliminary bioassay indicated that all the target compounds possess some fungicidal activities. Especially compound **5e**, its inhibition rates against *Physalospora pircola* reached 100 % at 50 µg/mL. We'll study its fungicidal activities for other diseases and explore their efficiency value further.

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