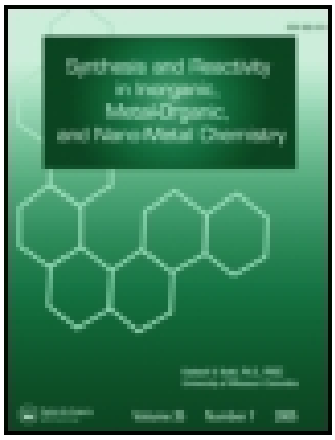

Synthesis and Reactivity in Inorganic, Metal-Organic, and Nano-Metal Chemistry

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Synthesis and Biological Evaluation of Novel Ferrocene-Substituted Triadimefon- and Triadimenol-Analogues

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Synthesis and Biological Evaluation of Novel Ferrocene-Substituted Triadimefon- and Triadimenol-Analogues

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To search potent antifungal agents, a series of new ferrocene-containing analogues of commercial fungicides, namely triadimefon and triadimenol, were synthesized by replacement of the *tert*-butyl group of original agents with ferrocene group. These organometallic derivatives were found to be unactive against various fungi, but show promising plant growth regulatory activity.

Keywords ferrocene, triadimefon, triadimenol, plant growth regulatory activity

INTRODUCTION

Over the past decades, as ameliorants for improving biological activities, several structural variations of established drugs have been developed by modification with metallocenic organometallic compounds, especially ferrocene, for the chemotherapy of drug-resistance in cancer and tropical diseases.[1] Ferrocene and relative derivatives have been characterized by their high stability, non-toxicity, readily membrane-permeation, the accessibility of a large number of derivatives, and their favorable electrochemical properties, both of which made them very suitable for biological applications and for conjugation with biomolecules.[2] To date, several structural modification of established drugs with ferrocenyl moiety have been reported, including ferrocene fluconazole,[3] ferrocene aspirin,[4] the anti-malarial drugs chloroquine (termed ferroquine),[5] quinine, mefloquine, and artemisinin,[6,7] and the anti-cancer drug tamixofen (termed ferrocifen).[8]

1*H*-1,2,4-Triazole derivatives, such as triadimefon **1** and triadimenol **2**, are well known to be highly active as agricultural and horticultural fungicides. However, these fungicides are suspected of having teratogenic potential such as craniofacial and axial skeletal defects on the basis of developmental toxicity studies on rodent mammals with extensive application in agriculture and horticulture.[9–11] It has also been ascertained that triadimefon and triadimenol can produce a neurotoxic syndrome in rats characterized by increased motor activity, stereotyped behavior and altered monoamine metabolism due to inhibition of dopamine uptake.[12] In addition, triadimefon had a significant stimulating side effect on respiration at a concentration of 1–100 mg/kg and on inhibition of nitrification in soil at a concentration of 100 mg/kg.[13] As our ongoing project of searching potent antifungal and plant growth regulatory agents involving 1*H*-1,2,4-triazole compounds with improving biological activities, we herein reported the chemistry and biological evaluation results of a series of novel triadimefon- and triadimenol-analogues modified with ferrocenyl unit.

RESULTS AND DISCUSSION

Synthesis of Ferrocene-Substituted Triadimefon Analogues 6a–i

As outlined in Scheme 1, the starting α-bromoacetylferrocene **3** was synthesized according to the method developed by Tarraga and co-workers.[14] Subsequently, substitution by 1*H*-1,2,4-triazole was accomplished to deliver α-triazolylacetylferrocene **4** as description in our previous work.[15] After further bromination in the α-position of carbonyl group, bromide **5** was produced successfully in satisfied yield. With K_2CO_3 as a base, replacement of bromine atom by substituted phenol smoothly provided the desired triadimefon analogues **6a–h** in moderate yields.

Synthesis of Ferrocene-Substituted Triadimenol Analogues 7a–e

Reduction of triadimefon analogues **6** was finally accomplished to provide ferrocene-substituted triadimenol analogues **7a–e** in the acetonitrile-methanol solvent system (V:V 1:1)

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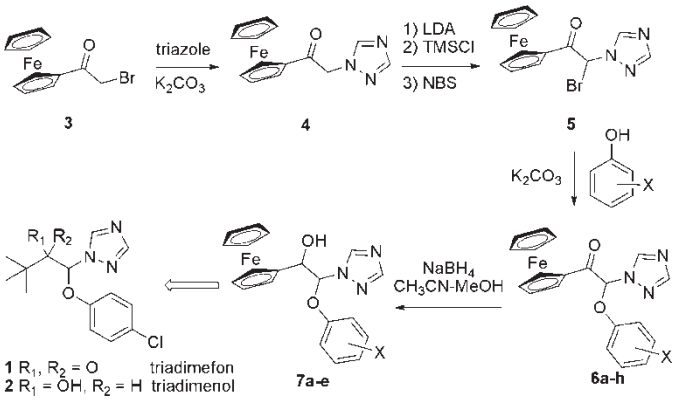

SCH. 1.

using sodium borohydride as reducing agent. After purification by recrystallation or column chromatography, the target compounds **7a**–**e** were ultimately obtained in moderate yields. Synthesis and detail structure characterization, including ^{1}H NMR, MS, and elemental analysis, of compounds **6a**–**h** and **7a**–**e** were reported in the experimental section.

Antifungal Activity

Both compounds **6a**–**h** and **7a**–**e** were evaluated for antifungal activities against mildew and rusts on intravital wheat plants, including five selected fungi *Isariopsis clavispora, Bremia lactucae, Cladosporium fulvum, Erysiphe graminis*, and *Altermaria mali*, according to our procedures described previously.[15] Although compounds **7a**–**e** showed obviously more potential antifungal activities than the corresponding precursor **6a**–**h**, all of them displayed much lower antifungal activity against all selected fungi than parent triadimefon and tridimenol.[15]

Plant Growth Regulatory Activity

Plant growth regulatory activities of new ferrocene-substituted triadimefon and triadimenol derivatives **6a**–**h** and **7a**–**e** were tested using cucumber cotyledon rhizogenesis method.[15] The plant growth refulatory activity data were shown in Table 1.

Like the parent triadimefon **1**, compounds **6a**–**h** almost did not revealed efficient plant growth regulatory activity. In comparison with unactive compounds **6a**–**h**, most ferrocene-analogues **7**, except compound **7e**, showed obvious plant regulatory activity as the same as the corresponding triadimenol **2**. Among them, compound **7b** displayed the comparative activity related to parent triadimenol.

With respect to structure-activity relationship, halogen substituents, such as chloro-, bromo-, etc., may increase their plant growth regulatory activity while electronic-donating group including methyl will cause the decrease of biological activity. However, to verify efficiently the plant growth regulatory activity of these ferrocene-modified analogues, further biological evaluations including wheat gemmale elongation experiments have to be carried out and the results will be reported in the future.

TABLE 1
Plant growth regulatory activity of compounds **6a**–**h** and **7a**–**e**[a]

Compd.	X	Relative ratio[b] (%)	Grade[c]
6	H	+ 50.6	+
6b	4-Br	+ 19.8	−
6c	3-Me-4-Cl	− 11.0	−
6d	3-Me-6-Cl	+ 40.4	−
6e	3,4-Me_2	− 4.1	
6f	4-I	− 4.0	−
6g	2,6-Cl_2	+ 2.7	−
6h	3-Me	− 19.8	−
Triadimefon		+ 57.1	+
7a	H	+ 95.2	+
7b	4-Br	+ 132.8	++
7c	3-Me-4-Cl	+ 84.9	+
7d	3-Me-6-Cl	+ 77.6	+
7e	3,4-Me_2	+ 33.5	−
Triadimenol		+ 144.2	++

[a]At a concentration of 10 mg/L.
[b]+: promotion activity, −: inhibitory activity.
[c]+++: ≥150%, ++: ≥100%, +: ≥50%, −: <50%

Summary

For promotion of their biological activity, the corresponding ferrocene-substituted analogues **6** and **7** of commercial agrochemicals triadimefon **1** and triadimenol **2** were synthesized by replacement of *tert*-butyl group with ferrocene unit. On the basis of bioassay results, both types of the ferrocene-analogues did not reveal antifungal activity of parent compounds. Meanwhile, ferrocene-substituted analogues **7** showed a comparative plant growth regulatory activity related to parent compound. Furthermore, halogen substituents may largely increase their biological activity, while electronic-donating groups will decrease their plant growth regulatory activity.

EXPERIMENTAL

All reactions were carried out under nitrogen atmosphere. Melting points were determined on a Taike apparatus with thermometer uncorrected. ^{1}H NMR spectra were recorded on a Brucker AC-300 spectrometer in DMSO-*d6* or $CDCl_3$ solution with TMS as the internal standard. Elemental analyses were determined on a Yanaco CHN CORDER MT-3 elemental anlyser.

Representative Procedure for Synthesis of Ferrocene-Triadimefon Derivatives (6a–h)

To a suspension solution of 2-bromo-2-(1*H*-1,2,4-triazol-1-yl) acetylferrocene **5** (2 mmol) and anhydrous potassium carbonate (2.2 mmol) in dry acetonitrile (10 mL) was added substituted phenols (2.2 mmol) in 1 portion at room temperature. The mixture was stirred and warmed to reflux for 2 h. the cooled mixture was run into a 10% aqueous NaOH solution (50 mL) and resulting precipitate was collected by filtration. Recrystallization from ethyl acetate-petroleum ether (v/v 1:1) gave the title compounds **6a–h**.

6a: Yield 70%; red solid; m.p. 107–108°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.92(s, 1H, TrH), 8.11(s, 1H, TrH), 7.44(s, 1H, Tr-CH), 7.37∼7.18(m, 5H, aryl), 4.95∼4.75 (d, 4H, C_5H_4), 4.28(s, 5H, C_5H_5); EI-MS (M^+) m/z: 387. Anal. Calc. for $C_{20}H_{17}FeN_3O_2$: C 62.04, H 4.42, N 10.85. Found: C 61.79, H 4.45, N 10.67.

6b: Yield 90%; orange solid; m.p. 165–167°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.98(s, 1H, TrH), 8.16(s, 1H, TrH), 7.49(s, 1H, Tr-CH), 7.58∼7.19(m, 4H, aryl), 4.96∼4.77 (d, 4H, C_5H_4), 4.30(s, 5H, C_5H_5); EI-MS (M^+) m/z: 466. Anal. Calc. for $C_{20}H_{16}BrFeN_3O_2$: C 51.54, H 3.46, N 9.02. Found: C 51.48, H 3.54, N 9.11.

6c: Yield 54.5%; orange solid; m.p. 137–139°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.95(s, 1H, TrH), 8.14(s, 1H, TrH), 7.25(s, 1H, Tr-CH), 7.46∼7.07(m, 3H, aryl), 4.96∼4.77 (d, 4H, C_5H_4), 4.30(s, 5H, C_5H_5), 2.31(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 435. Anal. Calc. for $C_{21}H_{18}ClFeN_3O_2$: C 57.89, H 4.16, N 9.64. Found: C 57.79, H 4.12, N 9.50.

6d: Yield 50.3%; orange solid; m.p. 140–142°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.95(s, 1H, TrH), 8.14(s, 1H, TrH), 7.26(s, 1H, Tr-CH), 7.46∼7.08(m, 3H, aryl), 4.96∼4.77 (d, 4H, C_5H_4), 4.30(s, 5H, C_5H_5), 2.31(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 435. Anal. Calc. for $C_{21}H_{18}ClFeN_3O_2$: C 57.89, H 4.16, N 9.64. Found: C 58.06, H 4.29, N 9.43.

6e: Yield 35%; orange solid; m.p. 130–132°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.90(s, 1H, TrH), 8.11(s, 1H, TrH), 7.37(s, 1H, Tr-CH), 7.11∼6.94(m, 3H, aryl), 4.95∼4.76 (d, 4H, C_5H_4), 4.31(s, 5H, C_5H_5), 2.20(s, 3H, $ArCH_3$), 2.15(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 415. Anal. Calc. for $C_{22}H_{21}FeN_3O_2$: C 63.63, H 5.10, N 10.12. Found: C 63.53, H 5.27, N 10.18.

6f: Yield 60.5%; orange solid; m.p. 162–164°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.95(s, 1H, TrH), 8.14(s, 1H, TrH), 7.47(s, 1H, Tr-CH), 7.72∼7.05(m, 4H, aryl), 4.95∼4.76 (d, 4H, C_5H_4), 4.30(s, 5H, C_5H_5); EI-MS (M^+) m/z: 513. Anal. Calc. for $C_{20}H_{16}FeIN_3O_2$: C 46.82, H 3.14, N 8.19. Found: C 46.92, H 3.33, N 8.12.

6g: Yield 63%; orange solid; m.p. 165–167°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.34(s, 1H, TrH), 8.16(s, 1H, TrH), 7.58(s, 1H, Tr-CH), 7.33∼6.47(m, 3H, aryl), 5.03∼4.51 (d, 4H, C_5H_4), 4.27(s, 5H, C_5H_5); EI-MS (M^+) m/z: 456. Anal. Calc. for $C_{20}H_{15}Cl_2FeN_3O_2$: C 52.67, H 3.31, N 9.21. Found: C 52.60, H 3.20, N 9.08.

6h: Yield 47%; orange solid; m.p. 129–131°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.93(s, 1H, TrH), 8.13(s, 1H, TrH), 7.44(s, 1H, Tr-CH), 6.91∼6.28(m, 4H, aryl), 4.95∼4.76 (d, 4H, C_5H_4), 4.31(s, 5H, C_5H_5), 2.30(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 401. Anal. Calc. for $C_{21}H_{19}FeN_3O_2$: C 62.86, H 4.77, N 10.47. Found: C 62.86, H 4.92, N 10.58.

Representative Procedure for Synthesis of Ferrocene-Triadimenol Derivatives (7a–e)

To a stirred solution of 2-aryloxy-1-ferrocenyl-2-(1*H*-1,2,4-triazol-1-yl)ethanone **6** (3 mmol) in acetonitrile (5 mL) and methanol (5 mL) below 0°C was added sodium boronhydride (6 mmol) in small portions. After stirring at room temperature for 30 minutes, the reaction mixture was poured into cooled water (50 mL) and neutralized to pH 7 with 5% diluted hydrochloric acid. The product was precipitated and collected by filtration. Recrystallization from ethyl acetate gave the title compounds **7a–e** as analytically pure samples.

7a: Yield 65.2%; yellow solid; m.p. 180°C ; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.83(s, 1H, TrH), 8.01(s, 1H, TrH), 6.10(d, 1H, Tr-CH), 7.27∼6.94(m, 5H, aryl), 4.34∼4.11 (d, 4H, C_5H_4), 4.21(s, 5H, C_5H_5); EI-MS (M^+) m/z: 389. Anal. Calc. for $C_{20}H_{19}FeN_3O_2$: C 61.72, H 4.92, N 10.80. Found: C 61.59, H 5.10, N 10.96.

7b: Yield 61.5%; yellow solid; m.p. 181–183°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.81(s, 1H, TrH), 8.01(s, 1H, TrH), 6.10(d, 1H, Tr-CH), 7.43∼6.92(m, 4H, aryl), 4.32∼4.11 (d, 4H, C_5H_4), 4.21(s, 5H, C_5H_5); EI-MS (M^+) m/z: 468. Anal. Calc. for $C_{20}H_{18}BrFeN_3O_2$: C 51.31, H 3.88, N 8.98. Found: C 51.40, H 4.01, N 9.03.

7c: Yield 62.5%; yellow solid; m.p. 152–155°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.81(s, 1H, TrH), 8.01(s, 1H, TrH), 6.12(d, 1H, Tr-CH), 7.29∼6.80(m, 3H, aryl), 4.32∼4.11 (m, 4H, C_5H_4), 4.21(s, 5H, C_5H_5), 2.22(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 437. Anal. Calc. for $C_{21}H_{20}ClFeN_3O_2$: C 57.62, H 4.61, N 9.60. Found: C 57.65, H 4.73, N 9.75.

7d: Yield 58.7%; yellow solid; m.p. 152–154°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.81(s, 1H, TrH), 8.01(s, 1H, TrH), 6.12(d, 1H, Tr-CH), 7.29∼6.80(m, 3H, aryl), 4.32∼4.11 (m, 4H, C_5H_4), 4.18(s, 5H, C_5H_5), 2.22(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 437. Anal. Calc. for $C_{21}H_{20}ClFeN_3O_2$: C 57.62, H 4.61, N 9.60. Found: C 57.70, H 4.63, N 9.71.

7e: Yield 53.1%; yellow solid; m.p. 163–165°C; ^{1}H NMR δ (300 MHz, DMSO-*d6*): 8.79(s, 1H, TrH), 8.00(s, 1H, TrH), 6.01(d, 1H, Tr-CH), 6.97∼6.63(m, 3H, aryl), 4.31∼4.11 (d, 4H, C_5H_4), 4.21(s, 5H, C_5H_5), 2.11(s, 3H, $ArCH_3$), 2.07(s, 3H, $ArCH_3$); EI-MS (M^+) m/z: 417. Anal. Calc. for

$C_{22}H_{23}FeN_3O_2$: C 63.32, H 5.56, N 10.07. Found: C 63.25, H 5.42, N 10.08.

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