Chinese Chemical Letters Vol. 14, No. 9, pp 897 – 900, 2003
http://www.imm.ac.cn/journal/ccl.html

Synthesis and Herbicidal Activities of 3-(Substituted phenyl)isoxazole Derivatives

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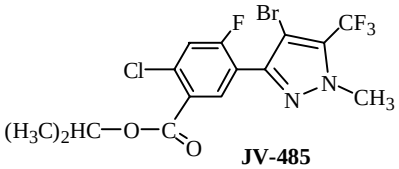
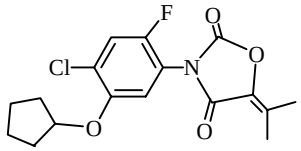
Abstract: Several novel 3-(substituted phenyl)isoxazole derivatives were prepared from phenyl butan-1,3-dione. Their structures were confirmed by ^{1}H NMR, IR, and CIMS. Preliminary bioassay showed that some of them exhibited good activities toward various weeds.

Keywords: Protox-inhibitor, isoxazole derivatives, herbicidal activity.

Herbicides inhibiting protoporphyrinogen oxidase (Protox) are one of the most important class of herbicides. Targeting the porphyrin pathway, these herbicides show high activities and low toxicities, and have been a hot-point of novel pesticides research[1]. In addition to the diphenylether-type herbicides, which have been commercialized for more than 30 years, many other chemical classes belong to this family, such as azafenidin, oxadiazon, carfentrazone, and so on. Substituted phenyl heterocyclic compounds are thought to be potent protox-inhibitors, because they are similar to half of the structure of protoporphyrinogen IX, which is the target of protox. Many researchers have studied on these compounds, and a large number of compounds having high bioactivities were reported, some of them have been commercialized, such as JV-485[2] and KPP-314[3]. Substituted phenyl isoxazoline derivatives have been reported, some of them showed high activities[4]. In this paper, several novel 3-(substituted phenyl)isoxazole derivatives were synthesized, and their herbicidal activities were assayed.



JV-485



KPP-314

At first, isoxazoles was obtained *via* a ring closure reaction of phenyl butan-1,3-dione with hydroxyamine chloride followed by dehydration reaction in hot sulfuric acid (**Scheme 1**). Demethylating reaction would have occurred under the same condition, if R^1 is methoxy.

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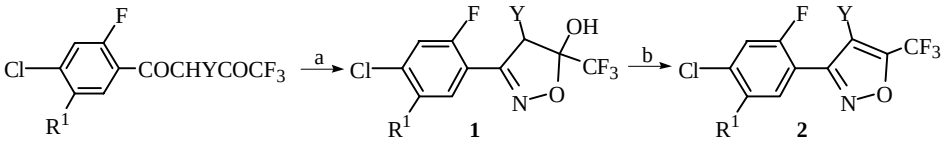
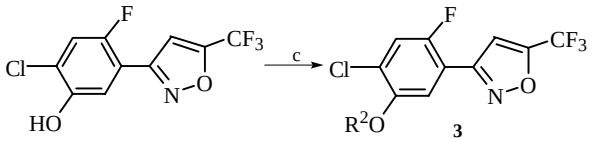
Scheme 1



Reagents and conditions: a. $H_2NOH\cdot HCl$, CH_3COOH, 100℃, 30 min, yield 93%~99%; b: conc. H_2SO_4, 110℃, 2~4 h, yield 89%~98%.

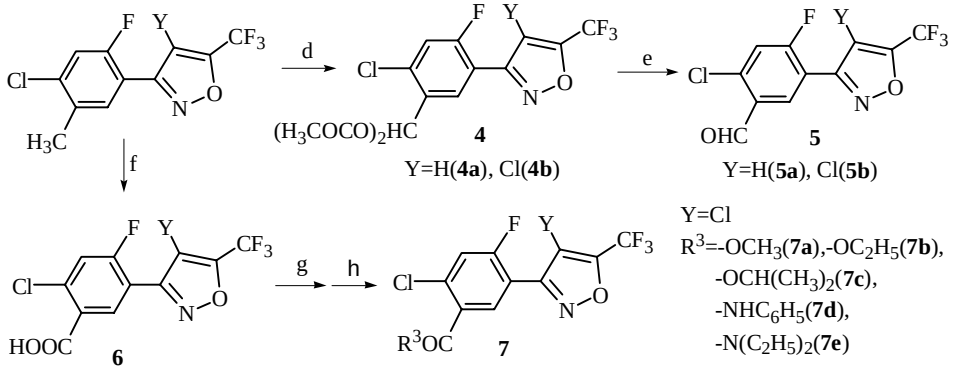
Different aimed compounds can be obtained by changing the substituted group at position 5 of the phenyl ring in compounds **2**. Hydroxy group can be modified by different group *via* alkylation or acylation (**Scheme 2**). Methyl group can be converted to an aldehyde group, an ester group or an acylamino group (**Scheme 3**).

Scheme 2



Reagents and conditions: c. CH_3COCH_3, K_2CO_3, alkylating reagent or acylating reagent, room temperature or reflux, 1~8 h, yield 87%~99%.

Scheme 3



Reagents and conditions: d. CrO_3, H_2SO_4, $(CH_3CO)_2O/CH_3COOH$, room temperature, 6 h, yield 63%~73%; e. C_2H_5OH/H_2O, $NaHCO_3$, reflux, 2 h, yield 81%~89%; f. CrO_3, H_2SO_4, CH_3COOH, room temperature, 15 h, yield 76%; g. SO_2Cl_2, toluene, reflux, 2 h; h. R^3H (alcohol or amine), reflux 1 h, yield 87%~98%.

Their structures were confirmed by CIMS, ^1H NMR, and IR. Their melting points, CIMS and elemental analysis data were shown in **Table 1**.

Table 1 Data of 3-(substituted phenyl)isoxazole derivatives*

Comp.	m.p. / ℃	CIMS, *m/z*	Elemental analysis (%, Calcd.)		
			C	H	N
3a	80~80.5	329.6([M+Cl]$^-$)	44.61(44.69)	2.00(2.05)	4.54(4.74)
3b	97~98	375.8([M+Na]$^+$)	44.43(44.15)	2.31(2.28)	3.87(3.96)
3c	92~94	375.8([M+Na]$^+$)	44.39(44.15)	2.38(2.28)	4.07(3.96)
3d	72.5~73	368.0([M+H]$^+$)	45.50(45.73)	2.66(2.74)	3.86(3.81)
3e	78.5~80	416.9([M+Na]$^+$)	49.24(48.93)	3.29(3.34)	7.01(7.13)
3f	82~82.5	333.9([M-H]$^-$)	49.89(50.09)	2.90(3.00)	3.98(4.17)
4a	87~88.5	417.7([M+Na]$^+$)	45.86(45.53)	2.67(2.55)	3.39(3.54)
4b	97~98.5	451.7([M+Na]$^+$)	42.03(41.89)	2.17(2.11)	3.31(3.26)
5a	78.5~80	359.6([M+CH_3OH+Cl]$^-$)	44.86(45.00)	1.31(1.37)	4.95(4.77)
5b	77.5~78.5	393.6([M+CH_3OH+Cl]$^-$)	40.55(40.28)	0.97(0.92)	4.49(4.27)
7a	60.5~61.5	379.8([M+Na]$^+$)	40.01(40.25)	1.50(1.41)	4.13(3.91)
7b	25.5~26	393.7([M+Na]$^+$)	42.09(41.96)	1.98(1.90)	3.84(3.76)
7c	40~40.5	407.7([M+Na]$^+$)	43.28(43.55)	2.27(2.35)	3.42(3.63)
7d	173~175	440.8([M+Na]$^+$)	48.53(48.71)	2.01(1.92)	6.86(6.68)
7e	87.5~88.5	398.9([M+H]$^+$)	45.13(45.14)	2.96(3.03)	6.91(7.02)

* MS were performed on a HP1100 High Performance Liquid Chromatography/Mass Selective Detector. Melting points were determined using a YanacoMP-500 apparatus. Elemental analysis was carried on a MOD.1106 elemental analysis apparatus.

Table 2 Herbicidal activities of 3-(substituted phenyl)isoxazole derivatives

Comp.	*Echinochloa crusgalli*/%	*Setaria viridis*/%	*Abutilon theophrasti*/%	*Acalypha australis*/%
3a	80.95	64.51	79.79	42.49
3b	80.08	68.04	91.22	26.37
3c	78.01	70.56	89.51	36.99
3d	81.51	77.04	83.97	52.01
3e	74.15	60.81	90.81	15.75
3f	80.78	49.62	82.38	17.95
4a	76.22	86.21	87.09	35.90
4b	80.95	93.52	91.34	36.63
5a	74.82	49.62	87.39	19.80
5b	79.85	97.31	93.22	46.15
7a	68.21	91.91	54.15	96.98
7b	87.84	98.25	82.89	100.00
7c	68.25	95.43	45.69	90.21
7d	63.68	9.68	38.22	65.50
7e	76.70	73.25	64.69	97.54
fomesafen	56.96	48.29	69.89	64.55

Preliminary bioassay showed that the aimed compounds exhibited good activities toward various weeds. Their herbicidal activities to different weeds by stem and leaf treatment at a dose of 150 g/hm^2, contrasting with fomesafen, which was high-effect herbicide widely used, were shown in **Table 2**. Most of them have higher activities than fomesafen.

References and Notes

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5. IR($\nu_{(C=O)}$/cm^{-1}, KBr): **3b**: 1772; **3c**: 1735; **3d**: 1729; **3e**: 1647; **4a**: 1768; **4b**: 1773,1759; **5a**: 1621; **5b**: 1694; **7a**: 1711; **7b**: 1739; **7c**: 1735; **7d**: 1651; **7f**: 1640; ^{1}H NMR(400 MHz, $CDCl_3$, δ ppm): **3a**: 7.54(d, 1H, *J*=6.4 Hz, Ph), 7.28(d, 1H, *J*=10.0 Hz, Ph), 7.15(d, 1H, *J*=3.2 Hz, isoxazole), 3.96(s, 3H, OCH_3); **3b**: 7.94(d, 1H, *J*=7.2 Hz, Ph), 7.37(d, 1H, *J*=10.0 Hz, Ph), 7.15(d, 1H, *J*=2.4 Hz, isoxazole), 4.37(q, 2H, *J*=7.2 Hz, CH_2), 1.42(t, 1H, *J*=7.2 Hz, CH_3); **3c**: 7.50(d, 1H, *J*=6.0 Hz, Ph), 7.32(d, 1H, *J*=10.0 Hz, Ph), 7.15(d, 1H, *J*=2.4 Hz, isoxazole), 4.78(s, 2H, OCH_2COO), 3.83(s, 3H, CH_3); **3d**: 7.51(d, 1H, *J*=6.0 Hz, Ph), 7.32(d, 1H, *J*=10.0 Hz, Ph), 7.15(d, 1H, *J*=2.4 Hz, isoxazole), 4.76(s, 2H, OCH_2COO), 4.29(q, 2H, *J*=7.2 Hz, Et-CH_2), 1.32(t, 3H, *J*=7.2 Hz, Et-CH_3); **3e**: 7.54(d, 1H, *J*=6.0 Hz, Ph), 7.28(d, 1H, *J*=9.6 Hz, Ph), 7.12(d, 1H, *J*=2.8 Hz, isoxazole), 4.82(s, 2H OCH_2CO), 3.3~3.5(m, 4H, 2Et-CH_2), 1.26(t, 3H, *J*=7.2 Hz, Et-CH_3), 1.13(t, 3H, *J*=7.2 Hz, Et-CH_3); **3f**: 7.54(d, 1H, *J*=6.4 Hz, Ph), 7.28(d, 1H, *J*=10.0 Hz, Ph), 7.15(d, 1H, *J*=3.6 Hz, isoxazole), 5.18(s, 1H, =CH), 5.05(s, 1H, =CH), 4.55(s, 2H, OCH_2), 1.87(s, 3H, CH_3); **4a**: 8.27(d, 1H, *J*=8.0 Hz, Ph), 7.97(s, 1H, CH), 7.34(d, 1H, *J*=10.0 Hz, Ph), 7.15(d, 1H, *J*=2.4 Hz, isoxazole), 2.16(s, 6H, CH_3); **4b**: 7.97(s, 1H, CH),7.81(d, 1H, *J*=6.8 Hz, Ph), 7.37(d, 1H, *J*=9.2 Hz, Ph), 2.14(s, 6H, CH_3); **5a**: 10.42(s, 1H, CHO), 8.56(d, 1H, *J*=7.2 Hz, Ph), 7.40(d, 1H, *J*=10.0 Hz, Ph), 7.14(s, 1H, isoxazole); **5b**: 10.44(s, 1H, CHO), 8.21(d, 1H, *J*=7.2 Hz, Ph), 7.43(d, 1H, *J*=8.8 Hz, Ph); **7a**: 8.17(d, 1H, *J*=7.2 Hz, Ph), 7.42(d, 1H, *J*=9.2 Hz, Ph), 3.95(s, 3H, CH_3); **7b**: 8.15(d, 1H, *J*=7.2 Hz, Ph), 7.41(d, 1H, *J*=9.6 Hz, Ph), 4.42(q, 2H, *J*=7.2 Hz, CH_2), 1.41(t, 3H, *J*=7.2 Hz, CH_3); **7c**: 8.12(d, 1H, *J*=7.6 Hz, Ph), 7.41(d, 1H, *J*=9.6 Hz, Ph), 5.29(sept, 1H, *J*=6.4 Hz, CH), 1.40(d, 6H, *J*=6.4 Hz, CH_3); **7d**: 7.0~8.1(m, 8H, Ph+NH); **7e**: 7.50(d, 1H, *J*=7.2 Hz, Ph), 7.36(d, 1H, *J*=9.6 Hz, Ph), 3.3~3.9(bd, 2H, Et-CH_2), 3.20(br, 2H, Et-CH_2), 1.28(t, 3H, *J*=7.2 Hz, Et-CH_3), 1.12(t, 3H, *J*=7.2 Hz, Et-CH_3).

Received 20 September, 2002