Synthesis of Some 2-[(5′-Aryl-1′,3′,4′-oxadiazol-2-yl)amino]-1,3-heterazoles as Potential Pesticides

Rahat H. Khan* and Ramesh C. Rastogi

Synthetic Organic Chemistry Division, Regional Research Laboratory, Jorhat-785 006, Assam, India

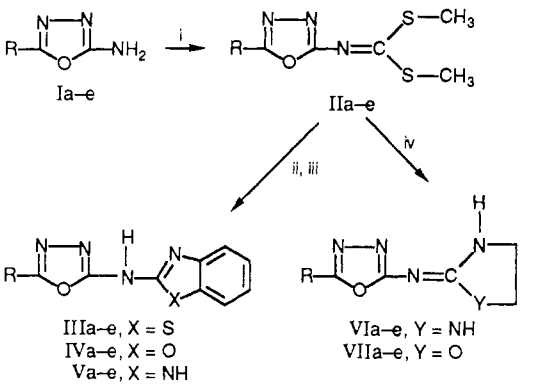
Some new 2-[(5′-aryl-1′,3′,4′-oxadiazol-2-yl)amino]-1,3-heterazoles III–VII were synthesized by reacting synthons, *N*-(5-aryl-1,3,4-oxadiazol-2-yl)carbonimidodithioates II with ortho-disubstituted aromatic and 1,2-disubstituted aliphatic dinucleophiles. The requisite synthons were prepared by reacting 2-amino-5-aryl-1,3,4-oxadiazoles I with carbon disulfide and methyl iodide in the presence of concentrated aqueous sodium hydroxide. Antibacterial and antifungal activities of some of the representative compounds are reported.

Antimicrobial properties of azoles such as oxazolidines, benzoxazoles, benzothiazoles, benzimidazoles, and imidazoles in isolated as well as fused states are well-known (Boyd, 1984; Garimmett, 1984; Hill, 1984; Metzer, 1984). Sometimes the fusion of heterocyclic nucleus enhances the pharmacological activities manyfold over its parent nucleus. The importance of the oxadiazoles nucleus is well established in agricultural and pharmaceutical chemistry as its corresponding derivatives are used as antipyretic, analgesic, antidepressant, and antimicrobial agents. With this objective, the synthesis and evaluation of the antifungal and antibacterial activities of the title compounds were undertaken. Only a limited number of molecules where an –NH– group links to two heterocyclic moieties have been described (Bauer and Safir, 1964; Neidlein and Reuter, 1971; Merchan et al., 1982b; Khan and Rastogi, 1989).

The synthetic route is outlined in Scheme I. Reaction (Merchan et al., 1982a) of 2-amino-5-(substituted phenyl)-1,3,4-oxadiazoles Ia–e with carbon disulfide and methyl iodide in dimethylformamide in the presence of concentrated sodium hydroxide solution gave the corresponding dimethyl *N*-(5-substituted phenyl)-1,3,4-oxadiazol-2-yl)carbonimidodithioates IIa–e. These intermediates (IIa–e) were annulated with 2-aminothiophenol in refluxing dimethylformamide in the presence of 1 equiv of sodium hydroxide to afford IIIa–e in very good yield. The nucleophilicity of the thiolate anion, generated in the reaction, led to the formation of III in good yield in a short period. In a similar way, 2-heteroarylamino derivatives of benzoxazoles (IVa–e) were prepared from *o*-aminophenol and II under nitrogen atmosphere to avoid darkening. In the preparation of V–VII, the reaction condition depended upon the dinucleophiles used. With *o*-phenylenediamine or ethanolamine, a 1:1 mixture of reactants was heated under reflux until no more methyl mercaptan evolved. The nature of substituents on II affected the reaction period (10–16 h generally). In case of ethylenediamine, 3-fold excess of this was used and the reaction that started at room temperature was completed after 10–12 h at 100 °C.

The requisite 2-amino-5-(substituted phenyl)-1,3,4-oxadiazoles were prepared by oxidative cyclization of aldehyde semicarbazones with bromine and sodium acetate in glacial acetic acid (Gibson, 1962). The structures of

Scheme I[a]



[a] R: (a) 4-$MeOC_6H_4$; (b) 3-MeC_6H_4; (c) 4-MeC_6H_4; (d) 3-ClC_6H_4; (e) 4-ClC_6H_4. Key: (i) NaOH (H_2O) DMF, CS_2, MeI; (ii) NaOH/DMF/Δ, *o*-$NH_2C_6H_4XH$, X = O, S; (iii) DMF/Δ, *o*-$H_2NC_6H_4NH_2$; (iv) DMF/Δ, $H_2NCH_2CH_2YH$.

all the compounds were confirmed by elemental analysis and spectral data.

Antifungal and Antibacterial Tests. The antifungal activity of a representative number of the compounds have been evaluated on *Aspergillus niger* at three concentrations, viz., 10, 100, and 1000 ppm, by agar growth technique. The number of replications in each case was 3, and the results were compared with those of a commercial fungicide (carbendazim). The percentage inhibition was calculated by

$$\% \text{ inhibn} = \frac{C - T}{C} \times 100$$

where C = diameter (mm) of the fungus colony in the control and T = diameter (mm) of the fungus colony in the treated plate.

The results thus obtained are recorded in Table II.

The bactericidal activity was determined by the method of Varma (Varma and Nobles, 1975) against *Staphylococcus aureus* and *Bacillus subtilis* at three different concentrations: 1000, 750, and 500 mg/L. Tetracycline was tested under similar conditions for comparison purposes, and the results thus obtained are recorded in Table II.

0021-8561/90/1438-1068$02.50/0

Table I. Characterization Data of Compounds II–VIIa–e

compd	mp, °C	yield, %	molec formula	anal. found (calcd) C	H	N	spectral data[a–c]
IIa	158	78	$C_{12}H_{13}N_3O_2S_2$	48.42 (48.81)	4.13 (4.40)	14.48 (14.23)	^{1}H NMR: 2.72 (6 H, s, 2 SCH_3), 3.80 (3 H, s, OCH_3), 6.70–8.00 (4 H, m, aromatic H) MS: 295 (M^+)
IIb	155	72	$C_{12}H_{13}N_3OS_2$	51.86 (51.61)	4.91 (4.65)	15.76 (15.05)	^{1}H NMR: 2.30 (3 H, s, CH_3), 2.70 (6 H, s, 2 SCH_3), 6.80–8.15 (4 H, m, aromatic H) MS: 279 (M^+)
IIc	145	70	$C_{12}H_{13}N_3OS_2$	51.43 (51.61)	5.04 (4.65)	15.45 (15.05)	^{1}H NMR: 2.35 (3 H, s, CH_3), 2.70 (6 H, s, 2 SCH_3), 7.00–8.10 (4 H, m, aromatic H) MS: 279 (M^+)
IId	180	71	$C_{11}H_{10}N_3OS_2Cl$	44.50 (44.14)	3.67 (3.34)	14.42 (14.04)	^{1}H NMR: 2.80 (6 H, s, 2 SCH_3), 7.20–8.25 (4 H, m, aromatic H) MS: 299 (M^+), 301 (M = 2)
IIe	165	68	$C_{11}H_{10}N_3OS_2Cl$	44.61 (44.14)	2.82 (3.34)	14.24 (14.04)	^{1}H NMR: 2.75 (6 H, s, 2 SCH_3), 7.00–8.30 (4 H, m, aromatic H) MS: 299 (M^+), 301 (M = 2)
IIIa	>250	65	$C_{16}H_{12}N_4O_2S$	58.78 (59.25)	3.84 (3.70)	17.01 (17.28)	^{1}H NMR: 3.75 (3 H, s, OCH_3), 7.10–8.40 (8 H, m, aromatic H) MS: 324 (M^+)
IIIb	>250	55	$C_{16}H_{12}N_4OS$	62.12 (62.33)	3.74 (3.89)	17.04 (18.18)	^{1}H NMR: 2.00 (3 H, s, CH_3), 7.00–7.80 (8 H, m, aromatic H) MS: 308 (M^+)
IIIc	>250	54	$C_{16}H_{12}N_4OS$	62.00 (62.33)	4.27 (3.84)	18.58 (18.18)	^{1}H NMR: 2.20 (3 H, s, CH_3), 7.10–8.20 (8 H, m, aromatic H) MS: 308 (M^+)
IIId	>250	57	$C_{15}H_9N_4OSCl$	55.00 (54.80)	2.90 (2.74)	16.71 (17.07)	^{1}H NMR: 7.10–8.20 (8 H, m, aromatic H) MS: 328 (M^+), 330 (M = 2)
IIIe	>250	50	$C_{15}H_9N_4OSCl$	55.20 (54.80)	2.24 (2.74)	17.52 (17.07)	^{1}H NMR: 7.00–8.25 (8 H, m, aromatic H) MS: 328 (M^+), 330 (M = 2)
IVa	248	45	$C_{16}H_{12}N_4O_3$	61.82 (62.33)	4.17 (3.89)	18.38 (18.18)	^{1}H NMR: 3.60 (3 H, s, CH_3), 7.10–8.30 (8 H, m, aromatic H) MS: 308 (M^+)
IVb	245	48	$C_{16}H_{12}N_4O_2$	65.92 (65.75)	4.30 (4.10)	19.46 (19.17)	^{1}H NMR: 2.18 (3 H, s, CH_3), 7.30–8.40 (8 H, m, aromatic H) MS: 292 (M^+)
IVc	239	47	$C_{16}H_{12}N_4O_2$	65.90 (65.75)	3.88 (4.10)	19.04 (19.17)	^{1}H NMR: 2.20 (3 H, s, CH_3), 7.00–8.20 (8 H, m, aromatic H) MS: 292 (M^+)
IVd	>250	49	$C_{15}H_9N_4O_2Cl$	57.82 (57.69)	3.11 (2.88)	17.60 (17.94)	^{1}H NMR: 7.25–8.30 (8 H, m, aromatic H) MS: 312 (M^+), 314 (M = 2)
IVe	>250	50	$C_{15}H_9N_4O_2Cl$	57.60 (57.69)	2.74 (2.88)	17.63 (17.94)	^{1}H NMR: 7.30–8.30 (8 H, m, aromatic H) MS: 312 (M^+), 314 (M = 2)
Va	>250	52	$C_{16}H_{13}N_5O_2$	62.80 (62.54)	3.90 (4.23)	21.52 (22.80)	^{1}H NMR: 3.75 (3 H, s, OCH_3), 6.90–8.48 (8 H, m, aromatic H) MS: 307 (M^+)
Vb	>250	50	$C_{16}H_{13}N_5O$	66.40 (65.97)	4.08 (4.46)	23.78 (24.05)	^{1}H NMR: 2.25 (3 H, s, CH_3), 7.00–8.30 (8 H, m, aromatic H) MS: 291 (M^+)
Vc	>250	54	$C_{16}H_{13}N_5O$	65.62 (65.97)	4.50 (4.46)	24.52 (24.05)	^{1}H NMR: 2.28 (3 H, s, CH_3), 7.20–8.31 (8 H, aromatic H) MS: 291 (M^+)
Vd	>250	48	$C_{15}H_{10}N_5OCl$	57.40 (57.87)	3.52 (3.21)	22.83 (22.50)	^{1}H NMR: 6.90–8.40 (8 H, m, aromatic H) MS: 311 (M^+), 313 (M^+)
Ve	>250	47	$C_{15}H_{10}N_5OCl$	56.45 (57.87)	2.93 (3.21)	22.24 (22.50)	^{1}H NMR: 7.00–8.30 (8 H, m, aromatic H) MS: 311 (M^+), 313 (M = 2)
VIa	>250	65	$C_{12}H_{13}N_5O_2$	55.38 (55.59)	4.80 (5.01)	27.33 (27.02)	IR: 1610 (C=N) ^{1}H NMR: 3.80 (8 H, s, OCH_3), 3.85–4.15 (4 H, m, CH_2CH_2), 6.80–7.45 (4 H, m, aromatic H) MS: 259 (M^+)
VIb	>250	58	$C_{12}H_{13}N_5O$	59.04 (59.25)	5.41 (5.34)	29.12 (28.80)	IR: 1610 (C=N) ^{1}H NMR: 2.30 (3 H, s, CH_3), 3.80–4.20 (4 H, m, CH_2CH_2), 6.80–7.70 (4 H, m, aromatic H) MS: 243 (M^+)
VIc	>250	60	$C_{12}H_{13}N_5O$	59.42 (59.25)	5.50 (5.34)	28.44 (28.80)	IR: 1615 (C=N) ^{1}H NMR: 2.35 (3 H, s, CH_3), 3.81–4.20 (4 H, m, CH_2CH_2), 6.80–7.72 (4 H, m, aromatic H) MS: 243 (M^+)
VId	>250	62	$C_{11}H_{10}N_5OCl$	50.53 (50.19)	4.02 (3.80)	26.82 (26.61)	IR: 1610 (C=N) ^{1}H NMR: 3.90–4.16 (4 H, m, CH_2CH_2), 6.97–7.70 (4 H, m, aromatic H) MS: 263 (M^+), 265 (M = 2)
VIe	>250	65	$C_{11}H_{10}N_5OCl$	50.00 (50.19)	4.15 (3.80)	26.80 (26.61)	IR: 1615 (C=N) ^{1}H NMR: 3.90–4.17 (4 H, m, CH_2CH_2), 7.08–7.55 (4 H, m, aromatic H) MS: 263 (M^+), 265 (M = 2)
VIIa	>250	50	$C_{12}H_{12}N_4O_3$	55.64 (55.38)	4.52 (4.61)	21.81 (21.53)	IR: 1615 (C=N) ^{1}H NMR: 3.80 (3 H, s, OCH_3), 3.90–4.16 (2 H, m, CH_2N), 4.20–4.50 (2 H, m, CH_2O), 7.08–7.55 (4 H, m, aromatic H) MS: 260 (M^+)
VIIb	>250	55	$C_{12}H_{12}N_4O_2$	58.70 (59.01)	6.32 (4.91)	23.25 (22.95)	IR: 1620 (C=N) ^{1}H NMR: 2.30 (3 H, s, CH_3), 3.80–4.20 (2 H, m, CH_2N), 4.30–4.70 (2 H, m, CH_2O), 6.98–7.75 (4 H, m, aromatic H) MS: 244 (M^+)
VIIc	>250	60	$C_{12}H_{12}N_4O_2$	59.42 (59.01)	5.12 (4.91)	23.34 (22.95)	IR: 1620 (C=N) ^{1}H NMR: 2.32 (3 H, s, CH_3), 3.80–4.22 (2 H, m, CH_2N), 4.35–4.60 (2 H, m, CH_2O), 7.00–7.80 (4 H, m, aromatic H) MS: 244 (M^+)
VIId	>250	55	$C_{11}H_9N_4O_2Cl$	49.72 (50.00)	3.63 (3.40)	21.50 (21.21)	IR: 1615 (C=N) ^{1}H NMR: 3.90–4.10 (2 H, m, CH_2N), 4.30–4.68 (2 H, m, CH_2O), 6.97–7.80 (4 H, m, aromatic H) MS: 264 (M^+), 266 (M = 2)
VIIe	>250	60	$C_{11}H_9N_4O_2Cl$	50.40 (50.00)	3.68 (3.40)	21.30 (21.21)	IR: 1620 (C=N) ^{1}H NMR: 4.04–4.20 (2 H, m, CH_2N), 4.25–4.70 (2 H, m, CH_2O), 7.20–8.10 (4 H, m, aromatic H) MS: 264 (M^+), 266 (M = 2)

[a] IR (KBr), cm^{-1}. [b] ^{1}H NMR, $CDCl_3$–DMSO-d_6. [c] MS, M^+, m/z.

Table II. Fungicidal and Bactericidal Activities

	% inhibn after 24 h at concn (mg/L)								
	St. aureus			*B. subtilis*			% inhibn after 96 h at concn (mg/L) of *A. niger*		
compd	1000	750	500	1000	750	500	1000	100	10
IId	15.3	9.4	3.6	13.4	7.5	1.9	52.4	32.2	20.5
IIId	14.5	8.8	2.1	13.2	7.2	1.5	42.9	22.7	15.4
IVd	25.4	18.6	6.7	22.2	14.4	5.3	80.3	75.2	69.7
Va	16.1	9.7	3.7	14.1	7.9	2.1	40.3	24.9	13.8
VIb	12.5	8.3	1.9	11.0	6.7	0.0	25.5	11.6	6.5
VId	20.4	12.6	5.8	20.2	11.6	5.1	83.4	78.9	70.2
VIIb	12.4	8.4	1.9	11.4	7.2	1.6	38.8	20.2	10.6
tetraacycline	94.4	88.6	79.8	95.8	89.0	81.2			
carbendazim							98.8	88.8	80.2

RESULTS AND DISCUSSION

A perusal of fungicidal data indicates that all the compounds under investigation are moderately toxic to the test fungus at 10 ppm, their toxicity increasing considerably at 100 and 1000 ppm. On the other hand, compounds IVd and VId have an activity quite comparable to that of a commercial fungicide, carbendazim, tested under similar conditions. This activity is probably due to the presence of a strong polar substituent –Cl at position 3 of the phenyl ring on the oxadiazole moiety. Further investigation of these compounds on a wider range of fungi as well as higher dilution is desirable.

Although an attempt was made to combine various toxophoric groups on these molecules with the hope of achieving compounds of better potency, the results are not very encouraging in all cases. This indicates that activity of any compound may not be necessarily related to the numerical sum of all toxophores present in the molecule.

The antibacterial activity indicated that all the compounds were almost inactive. Compounds IVd and VId, which were quite active on the test fungi, were much weaker as bactericides.

EXPERIMENTAL SECTION

Melting points (mp) are uncorrected. IR spectra in potassium bromide were recorded on a Perkin-Elmer Model 337 spectrophotometer (γ_{max}, cm^{-1}), ^1H NMR spectra in $CDCl_3$ or DMSO-d_6 on a Varian T-60 instrument with TMS as internal standard (chemical shifts in δ), and mass spectra on an AEI-MS-30 mass spectrometer. Purity of compounds was checked by TLC with silica gel layer (0.25 mm) using benzene–ethyl acetate as irrigant.

Dimethyl *N*-(5-Aryl-1,3,4-oxadiazol-2-yl)carbonimidodithioates IIa–e. *General Procedure.* To a well-stirred solution of the corresponding 2-amino-5-aryl-1,3,4-oxadiazole (0.05 mol) in dimethylformamide (50 mL) in an ice–water bath were added dropwise successively (a) aqueous 20 M sodium hydroxide (3 mL), (b) carbon disulfide (6 mL), (c) aqueous 20 M sodium hydroxide (3 mL), and (d) methyl iodide (15 g). Portionwise addition of the base at a regular interval of 30 min was necessary in order to improve yields. Stirring was continued for 2–4 h, and the mixture was poured into water (500 mL). The solid thus obtained was filtered, washed, and recrystallized from methanol (Table I).

2-[(5′-Aryl-1′,3′,4′-oxadiazol-2-yl)amino]benzothiazoles/benzoxazoles IIIa–e/IVa–e. A solution of 2-aminothiophenol or 2-aminophenol (2.0 mmol) in dimethylformamide (10 mL) was heated with aqueous 5 M sodium hydroxide (0.4 mL, 2.0 mmol), and the mixture was stirred at room temperature for 30 min. A solution of the appropriate dimethyl *N*-(5-aryl-1,3,4-oxadiazol-2-yl)carbonimidodithioate (2.0 mmol) in dimethylformamide was then added dropwise, and the reaction mixture was heated under reflux (5–6 h) (in the case of 2-aminophenol, a nitrogen atmosphere was maintained to avoid oxidation). After cooling, the mixture was poured into water (300 mL) and neutralized to litmus with concentrated HCl. The precipitate thus obtained was filtered, washed with water, dried in vacuo, and recrystallized from methanol/acetone (Table I).

2-[(5′-Aryl-1′,3′,4′-oxadiazol-2-yl)amino]benzimidazoles/oxazolidines Va–e/VIIa–e. To a solution of the *o*-phenylenediamine or ethanolamine (2.0 mmol) in dimethylformamide (15 mL) was added a solution of dimethyl *N*-(5-aryl-1,3,4-oxadiazol-2-yl)carbonimidodithioate (2.0 mmol) in dimethylformamide (20 mL) with vigorous stirring at room temperature. After the addition was over, the reaction mixture was heated under reflux for 10–16 h and cooled in an ice–water bath. The precipitated solid was filtered by suction and dried. The filtrate was poured into water (400 mL), yielding a second crop of solid that was filtered and dried. Both portions were put together, washed with ether, and recrystallized from methanol (Table I).

2-[(5′-Aryl-1′,3′,4′-oxadiazol-2-yl)amino]imidazolidines VIa–e. To a solution of ethylenediamine (9.0 mmol) in dimethylformamide (15 mL) was added a solution of the corresponding dimethyl *N*-(5-aryl-1,3,4-oxadiazol-2-yl)carbonimidodithioate (3.0 mmol) in dimethylformamide (15 mL) with stirring at room temperature. The reaction mixture was heated at 100 °C for 10–12 h and then cooled in an ice–water bath. Precipitated solid was filtered by suction and dried. The filtrate was poured into water (400 mL). The second crop of solid thus obtained was filtered and dried. Both portions were put together, washed with ether, and recrystallized from acetone (Table I).

ACKNOWLEDGMENT

We are thankful to Dr. J. N. Baruah, Director, Regional Research Laboratory, Jorhat, for providing necessary research facilities. We thank the Analytical Department for running IR, NMR, and mass spectra.

LITERATURE CITED

Bauer, V. J.; Safir, S. R. Bis(ethylene-biguanide). *J. Heterocycl. Chem.* **1964**, *1*, 288–289.

Boyd, G. V. Oxadiazoles and their Benzoderivatives. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 6, pp 177–233.

Garimmett, M. R. Imidazoles and their Benzoderivatives. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 6, pp 457–498.

Gibson, M. S. Hydrazones III. Intramolecular 1,3-Dipolar Addition Involving Nitro and Carbonyl groups. *Tetrahedron* **1962**, *18*, 1377–1380.

Hill, J. 1,3,4-Oxadiazoles. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 6, pp 427–446.

Khan, R. H.; Rastogi, R. C. Synthesis and biological activity of 2-(4-aryl-2-thiazolylamino)benzothiazoles/benzoxazoles/benzimidazoles/imidazolidines. *Indian J. Chem., Sect. B* **1989**, *28B*, 529–531.

Merchan, F.; Garin, J.; Melendez, F. A facile synthesis of Dimethyl N-(2-Benzothiazolyl)-dithiocarbonimidates and Methyl N-(Benzothiazolyl)-dithiocarbamates. *Synthesis* **1982a**, 590–592.

Merchan, F.; Garin, J.; Melendez, E.; Tejero, T. 2-(2-Benzimidazolylamino)benzothiazoles and 2-(2-Imidazolidinylidinylidenamino)benzothiazoles. *Synthesis* **1982b**, 1066–1067.

Metzer, J. V. Thiazoles and their Benzoderivatives. *Comprehensive Heterocyclic Chemistry*; Potts, K. T., Ed.; Pergamon: Oxford, 1984; Vol. 6, pp 235–331.

Neidlein, R.; Reuter, H. 2-2′-Iminobis(benzothiazoles) from Cyanoimidodithiocarboxylic and esters. *Synthesis* **1971**, 540–541.

Varma, R. S.; Nobles, W. L. Antiviral Antibacterial and Antifungal activities of N-Mannich bases. *J. Pharm. Sci.* **1975**, *64*, 881–882.

Received for review April 13, 1989. Accepted September 8, 1989.

Registry No. Ia, 5711-61-5; Ib, 109060-64-2; Ic, 33621-60-2; Id, 1673-45-6; Ie, 33621-61-3; IIa, 124266-62-2; IIb, 124266-63-3; IIc, 124266-64-4; IId, 124266-65-5; IIe, 124266-66-6; IIIa, 124266-67-7; IIIb, 124266-68-8; IIIc, 124266-69-9; IIId, 124266-70-2; IIIe, 124266-71-3; IVa, 124266-72-4; IVb, 124266-73-5; IVc, 124266-74-6; IVd, 124266-75-7; IVe, 124266-76-8; Va, 124266-77-9; Vb, 124266-78-0; Vc, 124266-79-1; Vd, 124266-80-4; Ve, 124266-81-5; VIa, 124266-82-6; VIb, 124266-83-7; VIc, 124266-84-8; VId, 124266-85-9; VIe, 124266-86-0; VIIa, 124266-87-1; VIIb, 124266-88-2; VIIc, 124266-89-3; VIId, 124266-90-6; VIIe, 124266-91-7; 2-aminothiophenol, 137-07-5; 2-aminophenol, 95-55-6; *o*-phenylenediamine, 95-54-5; ethanolamine, 141-43-5; ethylenediamine, 107-15-3.

Ethyl 2(*R*)-[4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]-propanoate. A New Selective Postemergent Herbicide†

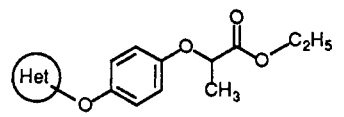
Klaus Bauer,‡ Hermann Bieringer,‡ Erwin Hacker,‡ Volker Koch,§ and Lothar Willms*,§

Pflanzenschutz-Biologie, H 872, and Pflanzenschutz-Chemie, G 836, Hoechst AG, Postfach 800320, D 6230 Frankfurt 80, FRG

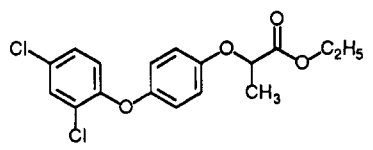
The two-step synthesis of ethyl 2(*R*)-[4-[[3-chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]propanoate starting from 2,3-chloro-5-(difluoromethoxy)pyridine, hydroquinone, and ethyl (2*S*)-*O*-tosyllactate is described, and its herbicidal properties are compared to those of known herbicides.

[4-[(Heteroaryl)oxy]phenoxy]propanoic acid derivatives 1 are highly active and selective herbicides for the control of gramineous weeds in broadleaf crops and tolerant cereals.

All these compounds can be regarded as heterocyclic analogues of the wild oat herbicide diclofop-methyl (2) (Nestler et al., 1978) in which the halogen-substituted



1



2

phenyl ring is replaced by a heterocycle, e.g., pyridine (Nishiyama et al., 1977; Plowman et al., 1980; Johnston et al., 1977), quinoline (Ura et al., 1979), quinoxaline (Ura et al., 1979; Sakata et al., 1983), benzothiazole (Handte et al., 1982a), or benzoxazole (Handte et al., 1982b). Compounds 1 exhibit a marked difference in crop selectivity with respect to the heterocyclic moiety and its substitution pattern.

† Dedicated to Prof. Hilger on the occasion of his 60th birthday.

‡ Pflanzenschutz-Biologie.

§ Pflanzenschutz-Chemie.

SYNTHESIS

During our investigations in this field we found a new selective herbicide, **1a** (Koch et al., 1985), which was synthesized in a two-step sequence as outlined in Scheme I. Reaction of 2,3-dichloro-5-(difluoromethoxy)pyridine (**3**) (Koch et al., 1985; Koch and Fuss, 1990) with hydroquinone (**4**) in the presence of 2 equiv of sodium hydroxide yielded (pyridyloxy)phenol **5**. Compound **5** was further O-alkylated with ethyl 2(*S*)-*O*-tosyllactate (Kenyon et al., 1924) to give by inversion of configuration the target compound ethyl 2(*R*)-[4-[[3-chloro-5-(difluoromethoxy)-2-pyridyl]-oxy]phenoxy]propionate (**1a**).

4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenol (5). Hydroquinone (**4**; 66.10 g, 0.6 mol) is dissolved in DMSO (100 mL), dibenzo-18-crown-6 (1.8 g, 5 mmol) and 50% KOH (90 mL) are added, and the mixture is warmed to 80 °C. 2,3-Dichloro-5-(difluoromethoxy)pyridine (**3**; 42.8 g, 0.2 mol) (Koch et al., 1985; Koch and Fuss, 1990) in DMSO (110 mL) is added dropwise, and the solution is stirred for 3 h. To the cooled mixture is added water (70 mL), and pH is adjusted to 5 with acetic acid. The mixture is extracted with toluene (3 × 400 mL), the organic layer washed with water (2 × 400 mL) and dried with $MgSO_4$, the solvent evaporated, and the residue dried under vacuum: yield 53.0 g (92%) of crude product; mp 73–76 °C. Recrystallization from cyclohexane/toluene (20:1, v/v) gave **5** as a white solid: yield 41.0 g (71%); purity 95% (HPLC); mp 82–84 °C; ^{1}H NMR (DMSO-d_6, TMS) δ 6.78 (d, 2 H, J = 9.5 Hz), 6.97 (d, 2 H, J = 9.5 Hz), 7.22 (t, 1 H, J = 72.5 Hz, $OCHF_2$), 8.01 (d, 1 H, J = 2.5 Hz), 8.08 (d, 1 H, J = 2.5 Hz), 9.43 (s, 1 H, OH). Anal. Calcd for $C_{12}H_8ClF_2NO_3$ (287.65): C, 50.11; H, 2.80; Cl, 12.32; F, 13.21; N, 4.87. Found: C, 49.9; H, 2.9; Cl, 12.4; F, 13.0; N, 4.6.

Ethyl 2(*R*)-[4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenoxy]propanoate (1a). 4-[[3-Chloro-5-(difluoromethoxy)-2-pyridyl]oxy]phenol (**5**; 14.4 g, 0.05 mol), ethyl (2*S*)-

0021-8561/90/1438-1071$02.50/0