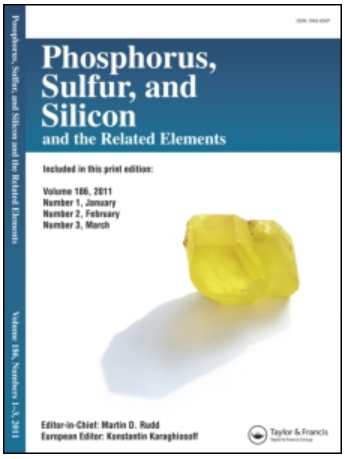

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Is the Herbicidal Activity of 3-Cyanopyridin-2-yl Phosphates Related to Phosphatase?

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The herbicidal activity of 3-cyanopyridin-2-yl phosphates, which were designed according to the idea of a mechanism-based inactivator, is probably related to a phosphatase.

Keywords Atherton–Todd reaction; 3-cyanopyridin-2-yl phosphates; herbicidal activities; mechanism-based inactivator

INTRODUCTION

Enzyme inhibitors are widely used in the treatment of human diseases. Some important structural subunits for irreversible inactivators have been discovered. Widlanski and colleagues[1–4] designed and synthesized 4-(fluoromethyl)phenyl phosphate as a mechanism-based inactivator, which is likely to function as a phosphotyrosine phosphatase. 4-(Fluoromethyl)phenyl phosphate undergoes a phosphatase-catalyzed hydrolytic reaction to give a reactive intermediate quinone methide, which can irreversibly inactivate the phosphatase by forming a covalent bond to an active site residue.

We recently reported the synthesis and activity of *o*- or *p*-trifluoromethylphenyl phosphate,[5] which would also be a mechanism-based inactivator as an analog of 4-(fluoromethyl)phenyl phosphate. It is very interesting that trifluoromethylphenyl phosphates exhibit herbicidal activities related to a phosphoryl group. To further confirm the result, we investigated the herbicidal activity of 3-cyanopyridin-

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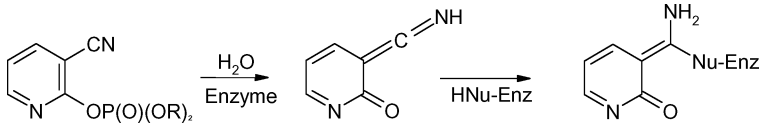
2-yl phosphates. 3-Cyanopyridin-2-yl phosphates could also undergo a phosphatase-catalyzed hydrolytic reaction to give a ketene imine as electrophlic intermediate, which could inactivate the phosphatase by forming a covalent bond to a nucleophilic site residue (Scheme 1). In this article, we report the study on the herbicidal activities of 3-cyanopyridin-2-yl phosphates.

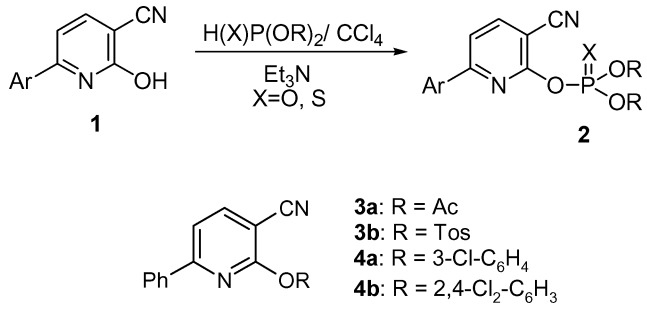


SCHEME 1

RESULTS AND DISCUSSION

The 3-cyano-2-hydroxypyridines (**1**) were readily prepared by literature known procedures[6] using piperidine as a catalyst via the cyclization of cyanoacetamide with sodium formylacetone, which was obtained by the reaction of acetone with ethyl formate in the presence of sodium methoxide.

3-Cyanopyridin-2-yl phosphates (**2**) were prepared by phosphorylation of the corresponding 3-cyano-2-hydroxypyridine. By use of phosphoryl chloride as phosphorylating reagent,[7] only moderate yields were achieved. The yields of 3-cyanopyridin-2-yl phosphates were improved by the Atherton–Todd procedure.[8] When 1.2 equiv. of diethyl phosphite were used, the isolated yields of the products increased to more than 90%. All the compounds are stable; soluble in DMSO, DMF, and trichloromethane; but are insoluble in water (Scheme 2).



SCHEME 2

To find out a relationship between the herbicidal activities and the phosphate substructure, we also synthesized 3-cyanopyridin-2-yl acetate (**3a**), *p*-toluenesulfonate (**3b**), 2-(3-chlorophenoxy)-3-cyano-6-phenylpyridine (**4a**), and 2-(2,4-dichlorophenoxy)-3-cyano -6-phenylpyridine (**4b**). 3-Cyanopyridin-2-yl acetate and its *p*-toluenesulfonate analog were prepared from 3-cyano-2-hydroxypyridine and acetyl chloride or *p*-toluenesulfonyl chloride in the presence of a base. The phenoxyderivatives **4a** and **4b** were obtained by the reaction of sodium phenolate with 2-bromo-3-cyanopyridine.[9,10]

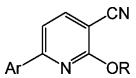
We have determined the herbicidal activity of the compounds with respect to the growth inhibition of rape roots under the condition of darkness. The results of the tests proved that some of the compounds exhibited herbicidal activities. The rape roots growth inhibition rates (%) of these compounds at concentrations of 10 μg/mL and 1 μg/mL are listed in Table I. They have no or only low activity against *Echinochloa crusgalli*.

The comparison of **2a** with **2c**, **2b** with **2d**, and **2h** with **2i** indicated that the activities of the isopropyl phosphates were obviously much lower as compared with the corresponding methyl and ethyl phosphates. The results are similar to the *o*- and *p*-trifluoromethylphenyl phosphates.[5] The possible reason is that the hydrolysis of phosphate influences the herbicidal activity. Isopropyl phosphates are more difficult to be hydrolyzed to form the postulated electrophilic ketene imine intermediates. Isopropyl thiophosphates are as inactive as isopropyl phosphates. The 3-cyano-2-pyridin-2-yl ethers (**4**) exhibit rarely herbicidal activities. Although 3-cyanopyridin-2-yl acetate (**3a**) or tosylate (**3b**) could also be hydrolyzed to give reactive ketene imines, they do not show any herbicidal potential. Therefore, a phosphoryl group is necessary for the herbicidal activity. We presume that the herbicidal activity of 3-cyanopyridin-2-yl phosphates is related to a phosphatase. The result puts an interesting question to us as to whether some phosphatases can be a target for herbicides.

EXPERIMENTAL

All reagents and solvents were dried before use. The reactions were performed under a nitrogen atmosphere. ^{1}H NMR spectra were recorded on a Varian EM-360A (300 Hz) spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Elemental analyses were performed by a Rapid CHN-O-S elemental analysis instrument. Mass and HRMS spectra were taken on a Finnigan 4021 spectrometer. The IR spectra (KBr pellets, ν in cm^{-1}) were obtained with a Y-Zoom CUROR

TABLE I Syntheses and Herbicidal Activities of the *O*-Substituted 6-Aryl-3-cyano-2-hydroxypyridines 2–4



	R	Ar	Yield %	Mp °C	Rape roots growth inhibition rates (%)	
					10 μg/mL	1 μg/mL
2a	$P(O)(OEt)_2$	Ph	94	74–76	68.6	26.7
2b	$P(O)(OEt)_2$	4-MeO-Ph	96	108–109	64.1	45.0
2c	$P(O)(OPr\text{-}i)_2$	Ph	89	82–83	5.4	0
2d	$P(O)(OPr\text{-}i)_2$	4-MeO-Ph	75	120–121	4.9	0
2e	$P(S)(OPr\text{-}i)_2$	4-Cl-Ph	56	109–111	0	0
2f	$P(O)(OPr\text{-}i)_2$	Pyrid-4-yl	80	109–110	21.4	12.0
2g	$P(S)(OPr\text{-}i)_2$	Pyrid-4-yl	89	98–99	0	0
2h	$P(O)(OPr\text{-}i)_2$	Thien-2-yl	85	95–96	0	0
2i	$P(O)(OMe)_2$	Thien-2-yl	81	118–119	78.2	50.4
3a	Ac	Ph	91	oil	0	0
3b	Ts	Ph	85	136–138	5.6	0
4a	3-Cl-Ph	Ph	68	162–164	0	0
4b	$2,4\text{-}Cl_2\text{-}Ph$	Ph	62	198–199	0	0
Commercial herbicide	Methsulfuron-methyl				77.5	28
	DPX-T6376					
	Miekuotin DUS-06				19.5	

instrument. Melting points were determined in Thiele melting point tubes and are uncorrected.

The herbicidal activity of the synthesized compounds was tested by the Research Institute of Elemento-organic Chemistry, NanKai University, with rape disc bioassay experiments under the condition of darkness for 48 h at 28°C.[11]

The 6-aryl-3-cyano-2-hydroxypyridines (**1**)[6] and 2-bromo-3-cyano-6-phenylpyridine were prepared according to the literature.[9]

General Procedure for the Preparation of 6-Aryl-3-cyanopyridin-2-yl Phosphates (2)

To an ice-cooled solution of the 6-aryl-3-cyano-2-hydroxypyridine **(1)** (1.0 mmol) and triethylamine (3.0 mmol) in acetonitrile (15 mL), a mixture of CCl_4 (4.0 mmol) and dialkyl phosphite (1.2 mmol) was slowly added. Then the reaction was kept for 6–24 h at r.t. The reaction mixture was neutralized with AcOH, extracted with ether, washed with water, dried over Na_2SO_4, filtrated, and evaporated in vacuo. The resulting residue was purified by flash column chromatograghy using hexane/ethyl acetate as eluent. Physical and spectroscopic data are as follows:

3-Cyano-6-phenylpyridin-2-yl Diethyl Phosphate (2a)

Mp 86–87 °C (lit.[12] 88 °C).

3-Cyano-6-(4-methoxyphenyl)pyridin-2-yl Diethyl Phosphate (2b)

^{1}H NMR: δ 1.43 (t, 6 H, $J = 7.0$ Hz, 2 CH_3), 3.87 (s, 3 H, CH_3), 4.43 (m, 4 H, 2 CH_2), 6.93∼8.07 (m, 6 H, C_6H_4, C_5H_2N). IR: 3070, 2837, 2225, 1594, 1459, 1252, 1172, 1030, 950. m/z (%) 362 (100) [M^+], 226 (67), 363 (52), 236 (40), 237 (17), 253 (11), 183 (10), 238 (8). Anal. Calcd. for $C_{17}H_{19}N_2O_5P$: C, 56.36; H, 5.29; N, 7.73; Found: C, 56.41; H, 5.32; N, 7.69.

3-Cyano-6-phenylpyridin-2-yl Diisopropyl Phosphate (2c)

^{1}H NMR: δ 7.92–8.02 (m, 1 H), 7.58–7.67 (m, 2 H), 7.50–7.58 (m, 2 H), 7.26–7.32 (m, 2 H), 4.53–4.67 (m, 2 H), 1.37 (dd, 12 H, $J_1 = 15.7$ Hz, $J_2 = 5.7$ Hz). IR: 3450, 2333, 1595, 1391, 1285, 1034, 950, 841, 784. MS (EI): m/z (%): 360 (8) [M^+], 277 (73), 220 (23), 197 (24), 196 (100), 168

(14); Anal. Calcd. for $C_{18}H_{21}N_2PO_4$: C, 60.00; H, 5.83; N, 7.78. Found: C, 60.01; H, 5.84; N, 7.87.

3-Cyano-6-(4-methoxyphenyl)pyridin-2-yl Diisopropyl Phosphate (2d)

Light yellow solid, ^{1}H NMR: δ 7.92–8.01 (m, 1 H), 7.72 (d, 1 H, J = 3.7 Hz), 7.50–7.56 (m, 2 H), 7.13–7.17 (m, 2 H), 5.03–5.08 (m, 2 H), 4.20 (s, 3 H), 1.37 (dd, 12 H, $J_1 = 11.0$ Hz, $J_2 = 6.0$ Hz). IR: 2983, 2225, 1592, 1460, 1257, 1174, 1010, 948, 824, 608. MS (EI): m/z (%): 390 (23) [M^+], 289 (17), 227 (18), 226 (100). Anal. Calcd. for $C_{19}H_{23}N_2PO_5$: C, 58.46; H, 5.90; N, 7.18. Found: C, 58.30; H, 6.00; N, 6.96.

O-[6-(4-Chlorophenyl)-3-cyanopyridin-2-yl] O,O-Diisopropyl Phosphorothioate (2e)

Light yellow solid, ^{1}H NMR: δ 8.03–8.11 (m, 1 H), 7.71–7.78 (m, 1 H), 7.55–7.67 (m, 2 H), 7.13–7.20 (m, 1 H), 4.77–4.86 (m, 2 H), 1.37 (dd, 12 H, $J_1 = 14.7$ Hz, $J_2 = 5.3$ Hz); IR: 2924, 2231, 1592, 1454, 1261, 1093, 992, 830. MS (EI): m/z (%): 293 (11), 292 (20), 243 (10), 221 (21), 197 (38), 196 (100), 168 (12). Anal. Calcd. for $C_{18}H_{20}ClN_2PO_3S$: C, 52.55; H, 4.87; N, 6.81. Found: C, 52.60; H, 4.97; N, 6.67.

5-Cyano-2,4′-bipyridin-6-yl Diisopropyl Phosphate (2f)

Light yellow solid, ^{1}H NMR: δ 8.03–8.10 (m, 1 H), 7.80–7.88 (m, 1 H), 7.50–7.56 (m, 2 H), 7.16–7.23 (m, 2 H), 4.36–4.45 (m, 2 H), 1.37 (dd, 12 H, $J_1 = 13.0$ Hz, $J_2 = 6.7$ Hz). IR: 2983, 2937, 2233, 1596, 1458, 1398, 1289, 1007, 948, 828. MS (EI): m/z (%): 361 (6) [M^+], 319 (16), 278 (53), 260 (45), 221 (19), 198 (33), 197 (100), 169 (17), 43 (24). Anal. Calcd. for $C_{17}H_{20}N_3PO_4$: C, 56.51; H, 5.54; N, 11.63. Found: C, 55.81; H, 5.45; N, 11.44.

O-(5-Cyano-2,4′-bipyridinyl-6-yl) O,O-Diisopropyl Phosphorothioate (2g)

Light yellow solid, ^{1}H NMR: δ 8.04–8.13 (m, 1 H), 7.76–7.85 (m, 1 H), 7.50–7.58 (m, 2 H), 7.16–7.20 (m, 2 H), 4.37–4.50 (m, 2 H), 1.29 (dd, 12 H, $J_1 = 12.5$ Hz, $J_2 = 7.0$ Hz). IR: 2978, 2230, 1596, 1265, 1022, 986, 948, 843, 824, 792. MS (EI): m/z (%): 377 (2) [M^+], 197 (100), 293 (43), 276 (12), 222 (16), 198 (54), 169 (16). Anal. Calcd for $C_{17}H_{20}N_3PO_3S$: C, 54.11; H, 5.31; N, 11.10. Found: C, 54.72; H, 5.53; N, 10.73.

3-Cyano-6-(thien-2-yl)pyridin-2-yl Diisopropyl Phosphate (2h)

Light yellow solid, ^{1}H NMR: δ 7.92–7.96 (m, 1 H), 7.72 (d, 1 H, J = 3.7 Hz), 7.50–7.56 (m, 2 H), 7.13–7.17 (m, 1 H), 5.03–5.13 (m, 2 H), 1.37

(dd, 12 H, $J_1 = 11.0$ Hz, $J_2 = 6.0$ Hz); IR: 3100, 2230, 1595, 1459, 1287, 1021, 923, 821. MS (EI): *m/z* (%): 366 (11) [M^+,], 265 (18), 203 (18), 202 (100), 174 (10), 41 (8). Anal. Calcd. for $C_{16}H_{19}N_2O_4PS$: C, 52.46; H, 5.19; N, 7.65; Found: C, 52.50; H, 5.23; N, 7.37.

3-Cyano-6-(thien-2-yl)pyridin-2-yl Dimethyl Phosphate (2i)

Light yellow acicular crystal, ^{1}H NMR: δ 7.85–7.90 (m, 1 H), 7.65–7.70 (m, 1 H), 7.50–7.57 (m, 2 H), 7.10–7.16 (m, 1 H), 4.11 (d, 6 H, $J = 15.0$ Hz). IR: 3430, 2231, 1600, 1459, 1283, 1038, 933, 835,732; MS (EI): *m/z* (%) 310 (100) [M^+], 311 (15), 216 (24), 215 (85), 202 (40), 187 (13), 109 (35), 79 (13). Anal. Calcd. for $C_{12}H_{11}N_2O_4PS$: C, 46.45; H, 3.55; N, 9.03. Found: C, 46.42; H, 3.67; N, 9.08.

3-Cyano-6-phenylpyridin-2-yl Acetate (3a)

^{1}H NMR: δ: 7.93–8.04 (m, 1 H), 7.48–7.67 (m, 2 H), 7.25–7.38 (m, 2 H), 6.96–7.12 (m, 2 H), 2.38 (s, 3 H). IR (film): 2923, 2227, 1664, 1605, 1563, 1500, 1333, 1233, 901, 756. MS (EI): m/z (%): 238 (1) [M^+], 196 (100), 168 (30), 152 (1), 140 (9), 114 (4), 77 (4), 64 (5), 43 (24). Anal. Calcd. for $C_{14}H_{10}N_2O_2$: C, 70.58; H, 4.23; N, 11.76. Found: C, 70.31; H, 4.49; N, 1152.

3-Cyano-6-phenylpyridin-2-yl Tosylate (3b)

To a solution of 3-cyano-2-hydroxy-6-phenylpyridine (196 mg, 1.0 mmol) in dichloromethane (10 mL), triethylamine (0.14 mL) and *p*-toluenesulfonyl chloride (191 mg, 1.0 mmol) were added on an ice bath. The mixture was stirred at room temperature for 1 h and washed three times with brine. The organic layer was dried over Na_2SO_4, filtrated, and concentrated. 297 mg of light yellow crystals were obtained after recrystallization.

^{1}H NMR: δ 7.81–8.19 (m, 5 H), 6.97–7.35 (m, 6 H), 2.35 (s, 3 H). IR: 3064, 2911, 2240, 1596, 1548, 1461, 1377, 1198, 1178, 1167, 1085, 780. MS (EI): *m/z* (%): 286 (70) [M^+—SO_2], 258 (3), 194 (3), 166 (4), 155 (24), 140(9), 91 (100), 65 (20). Anal. Calcd for $C_{19}H_{14}N_2O_3S$: C, 65.13; H, 4.03; N, 7.99. Found: C, 65.38; H, 3.89; N, 7.72.

General Procedure for the Preparation of 2-Aryloxy-3-cyano-6-phenylpyridines (4)

To a mixture of 2-bromo-3-cyano-6-phenylpyridine, sodium hydride, and anhydrous DMF a solution of 3-chloro- or 2,4-dichlorophenol in DMF was slowly added under a dry nitrogen atmosphere at 100°C for 3 h. The reaction solution was diluted with water, extracted with ether,

and dried over Na_2SO_4. The pure products were obtained by flash column chromatograghy.

2-(3-Chlorophenoxy)-3-cyano-6-phenylpyridine (4a)

^{1}H NMR: δ 8.04–8.07 (m, 1 H), 7.82–7.87 (m, 1 H), 7.57–7.61 (m, 1 H), 7.33–7.47 (m, 3 H), 7.26–7.31 (m, 4 H), 7.17–7.22 (m, 1 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 162.30, 158.89, 148.80, 143.94, 136.45, 130.65, 130.40, 129.36, 128.83 (2 C), 127.75 (2 C), 127.18, 126.81, 124.13, 121.66, 115.00, 114.16. IR: 2925, 2225, 1595, 1556, 1441, 1393, 1258, 1213, 934, 750. MS (ESI): m/z (%): 307.1 (100) [M^+], 309.1 (30) [M^+]. HRMS (ESI): Calcd. for $C_{18}H_{11}ClN_2O$ (M^+): 306.75073. Found: 306.75127.

3-Cyano-2-(2,4-dichlorophenoxy)-6-phenylpyridine (4b)

^{1}H NMR: δ 8.07 (d, 1 H, J = 8.0 Hz), 7.75–7.78 (m, 1 H), 7.58 (d, 2 H, J = 8.1 Hz), 7.53 (d, 1 H, J = 2.6 Hz), 7.34–7.43 (m, 6 H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 162.04, 159.05, 147.58, 144.06, 136.35, 131.65, 130.85, 130.24, 128.97 (2 C), 127.98, 127.22 (2 C), 125.02, 124.54, 124.02, 114.81, 114.50. IR: 2924, 2233, 1596, 1480, 1381, 1264, 1124, 1104, 934, 838. MS (ESI): m/z (%): 341 (100) [M^+], 342 [M^+] (20), 343 [M^+] (60), 345 [M^+] (10). HRMS (ESI): Calcd. for $C_{18}H_{10}Cl_2N_2O$ (M^+): 341.19583. Found: 341.19497.

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