FACILE SYNTHESIS OF 2-(5-ISOPROPYL-5-METHYL-4-OXO-2-IMIDAZOLIN-2-YL)PHENYL PHOSPHONATES

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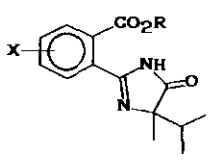
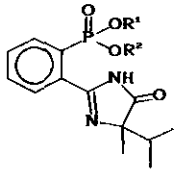
Abstract--The synthesis of 2-(5-isopropyl-5-methyl-4-oxo-2-imidazoline-2-yl)phenyl phosphonates (3-5) from benzoyl chloride is described. The condensation between benzoyl chloride and 2-amino-2,3-dimethylbutanamide (10) afforded 5-isopropyl-5-methyl-4-oxo-2-imidazolin-2-yl-benzene (11). Lithiation of 11 with *sec*-butyllithium, followed by reaction with diethyl chlorophosphate gave diethyl 2-(5-isopropyl-5-methyl-4-oxo-2-imidazolin-2-yl)phenylphosphate (3). Treatment of 3 with bromotrimethylsilane afforded 4 and 2-(5-isopropyl-5-methyl-4-oxo-2-imidazolin-2-yl)phenylphosphonic acid (5).

The discovery of the imidazolinone family of herbicides, exemplified by AC-22614 (1)[1] and Imidazolinone 2,[2] has promoted extensive study of the synthesis of analogous in order to optimize herbicidal activities by a number of research group.[3] The mode of action of imidazolinones 1 and 2 has been studied by Schaner et al.[2] The primary active site of these class of compounds is the inhibition of acetolactate synthase (ALS), an important enzyme in the pathway for branched-chain amino acids biosynthesis. The structural features of 1 and 2 are, (A) imidazolinone ring with isopropyl and methyl groups, and (B) variety of carboxylate group at ortho position on the aromatic ring.

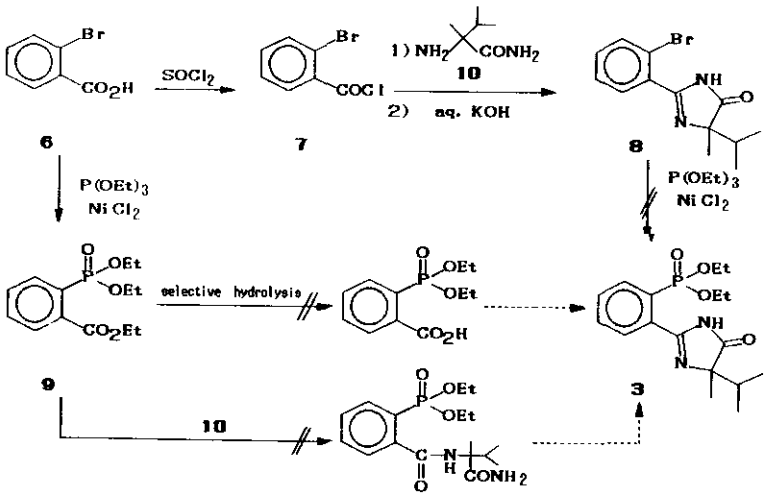


1 X=R=H
2 X=4 or 5-Me
R=Me

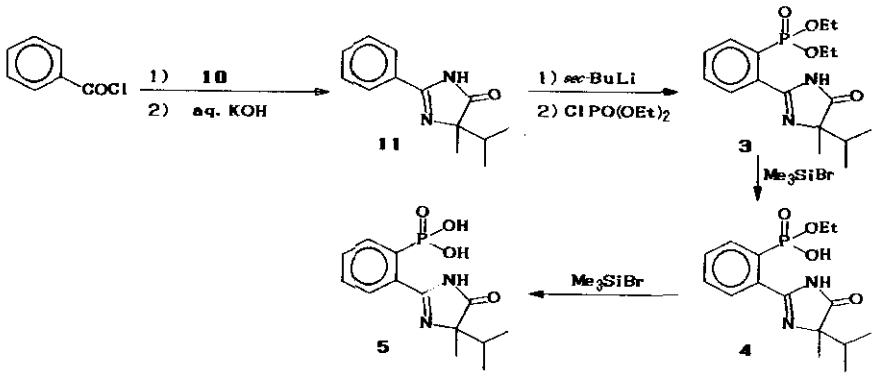


3 $R^1=R^2=Et$
4 $R^1=Et$ $R^2=H$
5 $R^1=R^2=H$

Thus the carboxylate group seems to play an important role for the herbicidal activity. As a part of program to find out a new ALS inhibitor, we have been interested to prepare the analogs 3-5, by replacing the carboxylate into phosphonate group. In the synthesis of 3-5, introduction of the phosphonate functionality is a critical problem. We initially attempted nucleophilic substitution of 2-bromophenylimidazolinone (8), derived from 2-bromobenzoyl chloride (7) with 2-amino-2,3-dimethylbutanamide (10) followed by cyclization with potassium hydroxide, with triethyl phosphite.[4] However, the $NiCl_2$ catalized reaction of 8 with triethyl phosphite was unsuccessful, resulting in recovery of the starting material. Thus we prepared phosphonate-carboxylate 9 by the reaction of bromobenzoic acid (6) with triethyl phosphite in the presence of $NiCl_2$. However the attempted condition of 9 nor selective hydrolysis of ethoxy group from carboxylate was failed. Attempted base catalyzed condensations of **9** and **10** were failed shown in scheme I. As a result, the target molecules 3-5 were prepared smoothly by the procedure shown in scheme Ⅱ. Condensation of benzoyl chloride with 2-amino-2,3-dimethylbutanamide (10) afforded imidazolinone 11 in two steps in 69% yield. Lithiation of 11 with *sec*-butyllithium, followed by reaction with diethyl chlorophosphate afforded desired product 3 in 81% yield.[5] Treatment of 3 with bromotrimethylsilane in dichloromethane at room temperature gave 4 in 75% yield.[6] Further treatment of 4 with excess bromotrimethylsilane for a prolonged reaction period afforded 5 in 83% yield. In this way, the phosphonate analog 3, 4 and 5 was prepared from benzoyl chloride via simple a few steps operation, as shown in scheme Ⅱ, however these analogs were not as active as original carboxylates 1 or 2 against ALS.



Scheme I



Scheme II

EXPERIMENTAL

All melting points were uncorrected. ^{1}H Nmr spectra were determined on a JEOL JNM-PMX 60-Si or GSX-270 spectrometer with tetramethylsilane as an internal standard. Mass spectra were determined on a HITACHI M-68 or M-90 spectrometer. Infrared spectra (ir) were determined on a HITACHI 260-10 spectrophotometer.

2-(4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-2-bromobenzene (8). To a solution of 2-bromobenzoyl chloride (7, 3.00 g, 13.6 mmol) in tetrahydrofuran (20 ml) was added a mixture of 2-amino-2,3-dimethylbutanamide (10, 1.77 g, 13.6 mmol) and triethylamine (1.48 g, 13.6 mmol) in tetrahydrofuran (5 ml) at room temperature, and the mixture was stirred for 4 h at this temperature. The mixture was poured into water, and extracted with ethyl acetate. The combined extracts were dried over magnesium sulfate and then concentrated in vacuo. The residue was dissolved in tetrahydrofuran (20 ml), and to this was added a solution of potassium hydroxide (1.51 g, 27.0 mmol) and water (5 ml). The mixture was refluxed for 12 h. The reaction mixture was poured into water and extracted with ethyl acetate,dried ($MgSO_4$) and evaporated to give an oily product. This oily product was crystallized from CH_2Cl_2-hexane to give 8 (2.90 g, 72 %): mp 125-126° C; ^{1}H-nmr ($CDCl_3$) 0.92 (3H, d, J = 7.0Hz), 1.08 (3H, d, J = 7.0Hz), 1.44 (3H, s), 2.13 (1H, sept, J = 7.0Hz), 7.46-7.58 (3H, m), 7.93 (2H, dd, J = 8.0, 1.5 Hz); ir (KBr) 3100, 2950, 1720, 1610 cm^{-1}; ms (m/z) 216(M^+); HRMS found 216.1260. calcd for $C_{13}H_{16}N_2O$ 216.1261.

2-Carbethoxyphenyl diethylphosphonate (9). A mixture of 2-bromobenzoic acid (6, 8.97 g, 44.6 mmol), triethyl phosphite (14.8 g, 89.2 mmol) and nickel chloride (1.16 g, 8.9 mmol) was heated at 160° C for 20 h. The mixture was poured into water, extracted with ethyl acetate, dried($MgSO_4$), and the solvents were

removed by evaporation to give an oily product. This product was subjected to a column-chromatography on silica gel (hexane - ethyl acetate 1:1) to give phosphate 9 (5.58 g, 44 %): ^{1}H-nmr ($CDCl_3$) 1.34 (6H, t, J = 7.0Hz), 1.40 (3H, t, J = 7.0Hz), 4.05-4.26 (4H, m), 4.40 (2H, q, J = 7.0Hz), 7.52-7.64 (2H, m), 7.72-7.76 (1H, m), 7.94-8.04 (1H, m); ir (neat) 2950, 1730, 1260, 1020 cm^{-1}; ms (m/z) 287$(M+H)^+$, 241, 213, 185; HRMS found 287.1021, 286.0921, 241.0623. calcd for $C_{13}H_{20}O_5P$ 287.1047, $C_{13}H_{19}O_5P$ 286.0968, $C_{11}H_{14}O_4P$ 241.0628.

4-Isopropyl-4-methyl-5-oxo-2-imidazolin-2-ylbenzene (11). To a solution of benzoyl chloride (2.00 g, 14.2 mmol) in tetrahydrofuran (20 ml) was added a mixture of 2-amino-2,3-dimethylbutanamide (10, 1.84 g, 14.2 mmol) and triethylamine (1.43 g, 14.2 mmol) in tetrahydrofuran (85 ml) at room temperature. The solution was stirred for 12 h at this temperature, and to this was added a solution of potassium hydroxide (1.59 g, 28.4 mmol) and water (5 ml). The mixture was refluxed for 5 h, poured into water, and extracted with ethyl acetate, and dried($MgSO_4$) The solvents were evaporated to give an oily product. This oily product was subjected to column-chromatography on silica gel (ethyl acetate only) to give 11 (2.81 g, 69 %): ^{1}H-nmr ($CDCl_3$) 0.92 (3H, d, J = 7.0Hz), 1.08 (3H, d, J = 7.0Hz), 1.44 (3H, s,) 2.13 (1H, sept, J = 7.0Hz), 7.46-7.58 (3H, m), 7.93 (2H, dd, J = 8.0, 1.5Hz); ir (KBr) 3100, 2950, 1720, 1610 cm^{-1}; ms (m/z) 216(M^+); HRMS found 216.1260. calcd for $C_{13}H_{16}N_2O$ 216.1261.

Diethyl 2-(5-isopropyl-5-methyl-4-oxo-2-imidazolin-2-yl)phenylphosphonate (3). To a stirred solution of 11 (1.00 g, 4.63 mmol) in tetrahydrofuran (20 ml) was 1.02 M of *sec*-butyllithium (10 ml, 10.2 mmol) was added under argon atmosphere at -50° C. After stirring for 2 h, a solution of diethyl chlorophosphate (0.96 g, 5.56 mmol) in tetrahydrofuran (3 ml) was added, and the mixture was stirred for an additional 20 h at room temperature. To this was added an aq. ammonium chloride, and the mixture was neutrized with aq. HCl, and extracted with ethyl acetate, and dried($MgSO_4$). The solvents were evaporated to give crude product. Column-chromatography on silica gel (ethyl acetate only) afforded 3 (1.32 g, 81 %): ^{1}H-nmr ($CDCl_3$) 0.93 (3H, d, J = 6.7Hz), 1.10 (3H, d, J = 6.7Hz), 1.37 (6H, t, J = 7.0Hz), 1.41 (3H, s), 2.11 (1H, sept, J = 6.7Hz), 4.18 (4H, quint, J = 7.0Hz), 7.56-7.72 (2H, m), 7.95 (1H, dd, J = 7.0, 1.4Hz), 8.12 (1H, m); ir (neat) 3450, 3150, 2950, 1740, 1640, 1240, 1050 cm^{-1}; ms (m/z) 353$(M+H)^+$, 352(M^+), 337, 309, 240, 212, 184, 166; HRMS found 353.1609, 352.1546, 337.1309. calcd for $C_{17}H_{26}N_2O_4P$ 353.1627, $C_{17}H_{25}N_2O_4P$ 352.1549, $C_{16}H_{22}N_2O_4P$ 337.1315.

Ethyl-2-(5-isopropyl- 5-methyl-4-oxo-2-imidazolin-2-yl)phenylphosphonic acid (4). To a solution of 3 (1.20 g, 3,55 mmol) in dichloromethane (20ml) was added bromotrimethylsilane (2.17 g, 14.2 mmol) at 0° C. After stirring for 2 h, excess bromotrimethylsilane was evaporated to give silyl ester. Water (20 ml) was

added to the residue and stirred for 2 h at this temperature. The reaction mixture was concentrated in vacuo, and the resulting residue was crystallized from ethanol to give 4 (862 mg, 75 %): mp 123-125° C; ^{1}H-nmr ($CDCl_3$) 1.04 (3H, d, J = 7.0Hz), 1.34 (3H, t, J = 7.0Hz), 1.64 (3H, s), 2.32 (1H, sept, J = 7.0Hz), 7.67-7.80 (2H, m), 7.86-7.97 (1H, m), 8.10-8.16 (1H, m); ir (KBr) 3350, 2950, 2750, 1780, 1630, 1240, 1030, 1000 cm^{-1}; ms (*m/z*) 324(M^+), 307(M-OH)$^+$, 278(M-EtOH)$^+$, 236; HRMS found 278.0789, 236.0327. calcd for $C_{13}H_{15}N_2O_3P$, 278.0818, $C_{10}H_9N_2O_3P$, 236.0349.

2-(5-Isopropyl-5-methyl-4-oxo-2-imidazolin-2-yl)phenylphosphonic acid (5). To a suspension of 4 (450 mg, 0.720 mmol) in dichloromethane (10 ml) was added bromotrimethylsilane (440 mg, 1.35 mmol) at 0° C. After stirring for 4 h, excess bromotrimethylsilane was evaporated. Water (10 ml) was added to the residue and stirred 2 h at room temperature, and the mixture was concentrated in vacuo, and the resulting residue was recrystallized from ethanol to give 3 (334 mg, 83%): ^{1}H-nmr (*d*6-DMSO) 0.83 (3H, d, J = 7.0Hz), 1.05 (3H, d, J = 7.0Hz), 1.34 (3H, s), 2.00 (1H, sept, J = 7.0Hz), 7.71-7.79 (2H, m), 7.85- 7.9[illegible] (1H, m), 8.03-8.13 (1H, m); ir (KBr) 3400, 2950, 1760, 1625, 1240, cm^{-1}; ms (*m/z*) 296(M^+), 278(M-H_2O)$^+$, 263, 236, 167, 166; HRMS found 278.0798, 263.0620, 236.0314. calcd for $C_{13}H_{15}N_2O_3P$ 278.0819, $C_{12}H_{12}N_2O_3P$ 263.0585, $C_{10}H_9N_2O_3P$ 236.0349.

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