CHEM. RES. CHINESE U. 2006, 22(6), 717—720

Synthesis and Characterization of Novel 4-Methyl-3-isoxazolidinone Derivatives

GAO Fei-fei[1], ZHANG Guang-liang[1], ZHENG Liang-yu[2], LI Yao-xian[1] and ZHANG Suo-qin[1]*
1. *College of Chemistry*, 2. *Key Lab for Molecular Enzymology and Engineering*,
Ministry of Education, *Jilin University*, *Changchun* 130021, *P. R. China*

Received Dec. 26, 2005

A novel type of acetohydroxyacid synthase inhibitors, 4-methyl-3-isoxazolidinone derivatives of sulfonylurea, was designed and synthesized. The structures of these compounds were confirmed by using MS, NMR, and elemental analysis. The results of preliminary active tests indicate that the compounds show a herbicidal activity.

Keywords 4-Methyl-3-isoxazolidinone; Sulfonylureas; Acetohydroxyacid synthase; Herbicidal activity
Article ID 1005-9040(2006)-06-717-04

Introduction

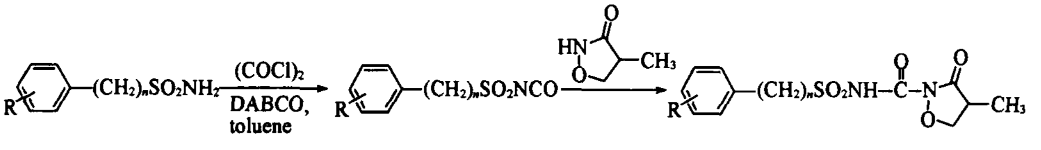
Sulfonylureas, as inhibitors of acetohydroxyacid synthase (AHAS), are a class of herbicides that are used for crop protection. They are used for low concentration ranges (10—100 g of active ingredient/ha) and are advanced herbicides used in agriculture. They exhibit a high efficiency, extremely low mammalian toxicity, and excellent crop selectivity, as a result of which they are effective at very low application rates and their detrimental effect on the environment is less[1].

Acetohydroxyacid synthase (AHAS) serves as the first common enzyme in the biosynthesis pathway of the branched-chain amino acids isoleucine, valine, and leucine. This pathway has been found in bacteria, fungi, algae, and higher plants but not in animals[2]. It is believed that a novel herbicide with a high activity can be obtained by investigating the interaction between the sulfonylurea molecules and AHAS. Recently, complexes of crystal structures of yeast AHAS with some commercially important sulfonylureas have been obtained. The conformations of all the bound sulfonylureas are nearly similar, and it is most important that the guanidinium group of Arg 380 is hydrogen bonded to the carbonyl oxygen within the sulfonylurea bridge[3,4].

The novel sulfonylurea derivatives were synthesized by introducing the 4-methyl-3-isoxazolidinone moiety into the sulfonylurea molecule. The sulfonylamide part was left unchanged for the formation of the hydrogen bond. The compounds containing the 3-isoxazolidinone structure are also highly active herbicides[5]. The heterocyclic part of CE is close to the active center and plays an important role in the inhibitory action.

The title compounds **3a**—**3i** were prepared by condensation of 4-methyl-3-isoxazolidinone with substituted aryl sulfonylisocyanates **2a**—**2i**, as shown in Scheme 1[6].

4-Methyl-3-isoxazolidinone was prepared as shown in Scheme 2[7].



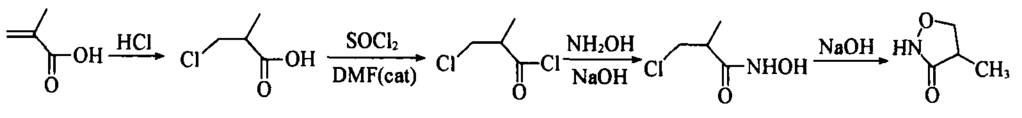
1a—**1i** **2a**—**2i** **3a**—**3i**

a: $n=0$, R = 2-$COOCH_3$; b: $n=0$, R = 2-$COOCH_2CH_3$; c: $n=0$, R = 3-$COOCH_3$, 4-CH_3; d: $n=0$, R = 2-CH_3, 4-$COOCH_3$; e: $n=0$, R = 3-$COOCH_3$, 4-OCH_3; f: $n=0$, R = 2-OCH_3, 5-$COOCH_3$; g: $n=1$, R = 2-$COOCH_3$; h: $n=1$, R = H; i: $n=1$, R = 2-Cl.

Scheme 1 Synthetic route of the title compounds 3a—3i.

---

* To whom correspondence should be addressed. E-mail: zhangsq@jlu.edu.cn



Scheme 2 **Synthetic route of 4-Methyl-3-isoxazolidinone.**

Experimental

Melting points were obtained without correction *via* a Pekin-X4 apparatus. Elementary analysis was carried out with a Perkin-Elmer 240-C instrument. Mass spectrometry was carried out with a AM1MA-CFR laser ionization TOFMS(SHIMADZU). ^1H NMR and ^{13}C NMR spectra were obtained on a 300 MHz NMR Mercury-300B(Varian) spectrometer, with tetramethylsilane as an internal standard.

The starting materials **1a**—**1i** were prepared according to the previously published reports[8]. The reagents and solvents were commercially available and were purified by using conventional methods.

1 General Procedure for the Synthesis of 4-Methyl-3-isoxazolidinone

Dry hydrogen chloride was introduced to a mixture containing 2-methylpropenoic acid(86 g, 1.0 mol), 1,4-benzenediol(10 mg), and ether(250 mL) at 0 ℃ for 10 h and then left undisturbed for 2 days. Ether was evaporated, and the residue was distilled under reduced pressure. The fraction of 106—107 ℃/1.99 kPa was collected to yield 115 g of 3-chloro-2-methylpropionic acid. The yield was 93%.

A mixture of 3-chloro-2-methylpropionic acid(100 g, 0.82 mol), $SOCl_2$(180 mL, 2.5 mol), and DMF (1 mL) was heated at reflux temperature for 6 h. $SOCl_2$ was then evaporated, and the residue was distilled under reduced pressure. The fraction of 67—69 ℃/6.67 kPa was collected to yield 84 g of 3-chloro-2-me-thylpivaloyl chloride. The yield was 73.1%.

To a solution of hydroxylamine hydrochloride (43.8 g, 0.63 mol) in water(100 mL), 30% (mass fraction) aqueous sodium hydroxide solution was added at 0—5 ℃ drop by drop for approximately 0.5 h. After the solution was cooled to −5 ℃, 3-chloro-2-methylpivaloyl chloride(44.4 g, 0.315 mol) was added drop by drop under vigorous stirring for 2 h. The reaction mixture was stirred at room temperature for 3 h, cooled to 0 ℃, filtered, and washed with a small amount of water. The solid was dried to yield 13.1 g of 3-chloro-*N*-hydroxy-2-methylpropanamide. The yield was 30%.

To a slurry of 3-chloro-*N*-hydroxy-2-methylpropanamide(16.5 g, 0.12 mol) in water(70 mL), 50% aqueous sodium hydroxide solution was added, with pH being 8.8 and temperature at 38 ℃. When the pH did not decrease, the addition of aqueous sodium hydroxide was stopped and Na_2CO_3(0.63 g, 5.9 mmol) was added. The mixture was maintained at 38 ℃ for 18 h. 4-Methyl-3-isoxazolidinone was extracted with $CHCl_3$(50 mL) and dried over anhydrous magnesium sulfate. The solvent was removed on a rotary evaporator under reduced pressure. Recrystallization from acetic ether/petroleum ether(volume ratio = 1∶6) yielded 5.8 g of 4-methyl-3-isoxazolidinone. The yield was 47.9%; m.p. 30—32 ℃; ^1H NMR($CDCl_3$, 300 MHz), δ: 1.26(d, J = 7.2 Hz, 3H, CH_3), 2.94 (m, J = 10.4 Hz, 1H, CH), 3.98(t, J = 8.2 Hz, 1H, OCH_2), 4.55(q, J = 8.2 Hz, 1H, OCH_2), 9.550(s, 1H, NH). Elemental analysis, calculated for $C_4H_7NO_2$(%): C 47.52, H 6.98, N 13.85; found(%): C 47.48, H 6.95, N 13.90.

2 General Procedure for the Synthesis of the Title Compounds 3a—3i

A mixture of 10 mmol of each of compounds **1a**—**1i**, 50 mL of dry toluene, 25 mg of 1,4-diazabicyclo[2.2.2]octane(DABCO), and 8.6 mL of oxalyl chloride was refluxed for 5 h and then concentrated on a rotary evaporator under reduced pressure. The residue was diluted with 2 mL of dry methylene chloride and then 1.0 g of 4-methyl-3-isoxazolidinone was added. The reaction mixture was stirred at room temperature for 1 h. To the mixture, 5 mL of methanol was added and filtered to yield the title compounds **3a**—**3i**, respectively.

2.1 2-(2-Methoxycarbonylphenylsulfonylamide-carbonyl)-4-methyl-3-isoxazolidinone(**3a**)

Yield: 67.5%; m.p. 118—120 ℃; MS, *m/z* (M + Na$^+$ − 1): 364.1; ^1H NMR($CDCl_3$, 300 MHz), δ: 1.333(d, J = 6.9 Hz, 3H, CH_3), 3.201 (m, 1H, CH), 3.998(s, 3H, $COOCH_3$), 4.019 (q, 1H, OCH_2), 4.621(t, 1H, OCH_2), 7.666—7.764(m, 3H, ArH), 8.351(d, J = 9.3 Hz, 1H, ArH), 10.378(s, 1H, NH); ^{13}C NMR($CDCl_3$, 300 MHz), δ: 12.168, 39.686, 53.666, 74.133, 130.406, 131.505, 132.146, 132.314, 134.237, 136.542, 142.845, 167.356, 172.851; Elemental analysis(%), calculated for $C_{13}H_{14}N_2O_7S$: C 45.61, H 4.12, N 8.18; found: C 45.58, H 4.13, N 8.26.