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• Research Notes•

Studies on Pyridine Derivatives (XI): Synthesis and Herbicidal Activities of Both Enantiomers of 2-*sec*-Butylamino-5-(2-chloropyrid-4-yl)-1, 3, 4-thiodiazoles

RAN Zhao-jin, CHE Chao, LIN an, XIAO Yu-mei, QIN Zhao-hai*
(College of Sciences, China Agricultural University, Beijing 100094, China)

Abstract: Both enantiomers of 2-sec-butylamino-5-(2-chloropyrid-4-yl)-1, 3, 4-thiodiazoles (BCPT), a powerful racemic herbicidal compound which was found in previous research, were synthesized from R- and S-butylamine respectively. The preliminary bioassay results showed that three of the thiodiazoles (racemate and enantiomers) were excellent growth inhibitors to both roots and stems of barnyard grass. The S-(+) enantiomer was the strongest for stem growth inhibition, and R-(-) enantiomer was the weakest. But they had little inhibiting difference on root growth.

Key words: pyridine derivatives; sec-butylamine; 1, 3, 4-thiodiazole; herbicidal activity

吡啶衍生物研究(XI): 2-仲丁胺基-5-(2-氯吡啶-4-基)-1, 3, 4-噻二唑对映异构体的合成及除草活性

冉兆晋, 车 超, 李 楠, 肖玉梅, 覃兆海*
(中国农业大学 理学院, 北京 100094)

摘 要: 2-仲丁胺基-5-(2-氯吡啶-4-基)-1, 3, 4-噻二唑(BCPT)是早期发现的一个具有良好除草活性的外消旋先导化合物, 报道了使用R/S-仲丁胺为原料分别合成BCPT的两个对映异构体的方法。初步生测结果显示, 3种噻二唑化合物(外消旋体和两个对映异构体)对稗草的根和茎均表现出较强的抑制作用, 其中S-(+)对映异构体对茎的抑制作用强于R-(-)对映异构体和外消旋体, 但对根的生长抑制作用三者间没有显著差异。

关键词: 吡啶衍生物; 仲丁胺; 1, 3, 4-噻二唑, 除草活性
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1 Introduction

It is well known that heterocyclic compounds having a 1, 3, 4-thiodiazolyl or pyridyl group exhibit various biological, such as antidepressant, insecticidal, herbicidal and plant growth regulating activities[1~3]. A lot of compounds containing one of the two heterocyclic moieties have been marketed as plant protecting agents.

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Biography: RAN Zhao-jin (1982-), mail, Ph.D.; * **Corresponding author**: QIN Zhao-hai (1964-), mail, ph.D., professor. **Tel**: 010-62892958; **Fax**: 010-62891719; **E-mail**: qinzhaoha@263.net
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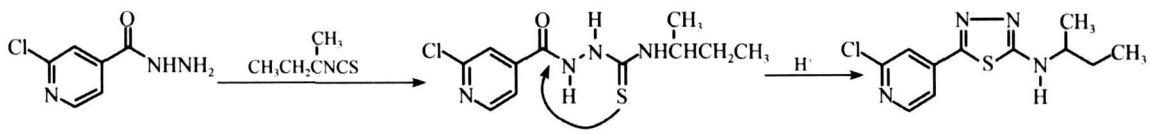
It is of great interest to find whether the combination of these two heterocyclic moieties in a same molecule can provide novel classes agrochemicals. Although Zhang et al.[4] have reported the synthetic method and plant growth regulation evaluation of non-chloro substituted title molecules, but the results were still uncertain.

In the course of our continuous studies on pyridine derivatives, we have synthesized a series of 2-alkyl (aryl) amino-5-(2-chloropyrid-4-yl)-1, 3, 4-thiodiazoles[5]. Preliminary bioassay showed that they have good herbicidal activity and the most active one is 2-sec-butylamino-5-(2-chloropyrid-4-yl)-1, 3, 4-thiodiazole (BCPT). When treated at a dose of 375 g a.i./hm^2 in foliar mode on weeds, the leaves became deep green and withered at the edges several hours later and exhibited an 84% mean inhibiting rate to Barnyard grass, Amaranth, Rape and Lucerne after 72 hours of administration. In consideration of that a lot of pesticides with a secondary amine moiety exhibited interesting bioactivity difference between their enantiomers, for instance, S-metolachlor demonstrated equivalent efficacy on major grass weeds and tolerance to different maize cultivars at 65% the use rate of racemized metolachlor[6], the experiment was designed to test the correlation of chiral factor of side chain on 2-position of thiodiazole of BCPT and herbicidal activity. Here the synthesis and preliminary biological evaluation of R-, S-enantiomers and their racemate were report

The compound was prepared as the procedure of Scheme 1.



Scheme 1 Synthetic procedure of target compound

2 Materials and Methods

2.1 Synthetic procedures

Melting points were measured with an Yanagimoto micromelting point apparatus and were uncorrected. ^{1}H NMR was determined with a Bruker Avance DPX 300 spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane as standard. sec-Butylamine and D/L-tartaric acid were purchased from ACROS company (purity 99%); R-Binaphthol was prepared by ourselves and optical purity was over 99%; 001 × 7 × 7 strong acidic ion exchange resin (exchange capacity: 4.2 mmol/g dry resin) was purchased from Nankai University, Tianjing, P. R. China.

2.2 Preparative resolution and enantiomeric Purity assessment of *sec*-butylamine

Preparative resolution of R-and S-sec- butylamine were carried out according to Ref.[7] by using D/L-tartaric acid as resolution agents.

2.3 Preparation of 2-*sec*-butylamino-5-(2-chlropyrid-4-yl)-1, 3, 4-thiodiazole

2.3.1 Preparation of N-(2-chloropyrid-4-yl) formamido-N′-sec-butyl thiourea

In a 50 mL flask were placed 3.12 g of 2-chloroisonicotinyl hydrazide (18.2 mmol), 2.20 g of sec-butyl isothiocyanate (19.1 mmol)[8] and 35 mL of absolute ethanol. The mixture was refluxed for 4 h. After cooling, mass crystals precipitated and were collected, washed with ethanol. 4.30 g of pale yellow product was obtained with a yield of 83%, m. p. 168-170℃.

2.3.2 Preparation of 2-sec-butylamino-5-(2-chloropyrid-4-yl)-1, 3, 4-thiodiazole

The thiourea obtained above was dissolved in 40 g of concentrated H_2SO_4 with stirring in an ice bath. The mixture was stirred for 2 h at this temperature and for another 3 h at room temperature. The mixture was poured into 100 g of crashed ice and the pH was adjusted to 8 with concentrated ammonia. The precipitates were filtered off and washed with water to give 3.9 g of crude product. It was recrystallized from acetone to give 2.8 g of pure product. Physicochemical constants was in Table 1, ^{1}H NMR was in Table 2, ^{13}C NMR was in Table 3.

3 Herbicidal activities

3.1 Materials

Racemate, R-(-) and S-(+)-2-sec-butylamino-5-(2-chloropyrid-4-yl)-1, 3, 4-thiodiazole prepared above was formulated as emulsfiable concentrate respectively which was then diluted to different concentrations with water.

Table 1 Physico-chemical constants of synthesized compounds

Compounds	M. p /℃	$[\alpha]_D^{20}$ (c = 2, EtOH) /(°)	Elemental analysis(Calcd., %)		
			C	H	N
(±)-BCPT[5]	140~142	-			
S-(+)-BCPT	135~136	+ 42.5	49.23(49.15)	4.86(4.89)	20.88(20.85)
R-(-)-BCPT	135~136	- 41.7	49.19(49.15)	4.87(4.89)	20.88(20.85)

Table 2 ^{1}H NMR data of synthesized compounds (solvent $CDCl_3$)

Compounds	^{1}H NMR, δ
S-(+)-BCPT	1.01(t, 3H, CH_2CH_3), 1.35(d, 3H, $CHCH_3$), 1.63~1.78(m, 2H, CH_2CH_3), 3.48~3.54(m, 1H, $CHCH_3$), 6.53(s, 1H, N-H), 7.62(dd, 1H, Py-β-H), 7.70(dd, 1H, Py-β′-H), 8.44(dd, 1H, Py-α-H)
R-(-)-BCPT	1.02(t, 3H, CH_2CH_3), 1.35(d, 3H, $CHCH_3$), 1.63~1.78(m, 2H, CH_2CH_3), 3.48~3.54(m, 1H, $CHCH_3$), 6.53(s, 1H, N-H), 7.62(dd, 1H, Py-β-H), 7.70(dd, 1H, Py-β′-H), 8.44(dd, 1H, Py-α-H)

Table 3 ^{13}C NMR data of synthesized compounds (solvent $CDCl_3$)

Compounds	^{13}C NMR, δ
S-(+)-BCPT	10.35(CH_2CH_3), 20.01(CH_2CH_3), 29.48($CHCH_3$), 56.24($CHCH_3$), 119.09(Py-β-C), 120.66(Py-β′-C), 141.15(Py-γ-C), 150.17(thiodiazole-5-C), 150.18(Py-α-C), 152.28(Py-α′-C), 171.28(thiodiazole-2-C)
R-(-)-BCPT	10.35(CH_2CH_3), 20.01(CH_2CH_3), 29.48($CHCH_3$), 56.24($CHCH_3$), 119.09(Py-β-C), 120.66(Py-β′-C), 141.15(Py-γ-C), 150.17(thiodiazole-5-C), 150.18(Py-α-C), 152.28(Py-α′-C), 171.28(thiodiazole-2-C)

3.2 Testing method

At the bottom of a 50 mL of cup was placed a layer of glass pearls which diameters were about 6 millimeters and a piece of filtering paper was covered on them. 5 mL of herbicide solution was added and 10 pieces of buds of barnyard grass were planted in. After 24 h of administration, reasonable amount of distilled water was added to recuperate the loss of water. 72 h later, the length of both underground part (root) and above ground part (stem) was measured. LC_{50}, LC_{90} and inhibition ratios were calculated and the results were listed in Table 4 and Table 5.

4 Conclusion

From the preliminary bioassay results we can conclude that three of the thiodiazoles were excellent growth inhibitors to both roots and stems of barnyard grass. The S-(+)-BCPT was the strongest inhibiting on stem growth, and R-(-)-BCPT was the weakest. But they had little inhibiting difference on root growth. The results suggest that the chiral factor of side chain on 2-position of thiodiazole ring correlates to the herbicidal activity weakly.

Table 4 Inhibition to stem growth (determined after 72 h of administration)

Compounds	Concentration/(mg/L)	Y = a + bX	LC_{50}/(mg/L)	LC_{90}/(mg/L)
(±)-BCPT	100	Y = 2.16 + 2.29X	17.44	63.20
	50	r = 0.991		
	25	[> 0.01(0.99)]		
	12.5			
S-(+)-BCPT	100	Y = 2.83 + 2.07X	11.19	46.57
	50	r = 0.988		
	25	[> 0.05(0.95)]		
	12.5			
R-(-)-BCPT	100	Y = 2.14 + 2.21X	19.63	74.44
	50	r = 0.984		
	25	[> 0.05(0.95)]		
	12.5			

Table 5 Inhibition to root growth (determined after 72 h of administration)

Compounds	Concentration /(mg/L)	Inhibition activity	
		Length of root/mm	Inhibition ratio (%)
CK	0	43.5	0
(±)-BCPT	100	≈ 1.0	⩾98
	50	≈ 1.0	⩾98
	25	2.1	95.2
	12.5	3.7	91.5
S-(+)-BCPT	100	≈ 1.0	⩾98
	50	≈ 1.0	⩾98
	25	≈ 1.0	⩾98
	12.5	2.03	95.0
R-(-)-BCPT	100	≈ 1.0	⩾98
	50	≈ 1.0	⩾98
	25	2.97	93.2
	12.5	4.8	89.0

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