

· Research Notes ·

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

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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 banyard 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 () : 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

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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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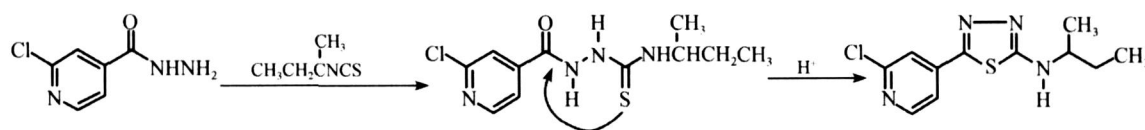
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It is of great interest to find whether the combination of these two heterocyclic moieties in a same molecule can provide novel classes agrochemicals. Although Zhang et al.^[4] have reported the synthetic method and plant growth regulation evaluation 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-thiadiazoles^[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-thiadiazole (BCPT). When treated at a dose of 375 g a.i./hm² 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 thiadiazole of BCPT and herbicidal activity. Here the synthesis and preliminary biological evaluation of R-, S-enantiomers and their racemate were reported. 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 Yanaginoto micro melting point apparatus and were uncorrected. ¹H NMR was determined with a Bruker Avance DPX300 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-chloropyrid-4-yl)-1,3,4-thiadiazole

2.3.1 Preparation of N-(2-chloropyrid-4-yl) formamido-N'-sec-butylthiourea

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-thiadiazole

The thiourea obtained above was dissolved in 40 g of concentrated H₂SO₄ 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 crushed 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 were in Table 1, ¹H NMR was in Table 2, ¹³C 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-thiadiazole prepared above was formulated as emulsifiable 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 ¹H NMR data of synthesized compounds (solvent: CDCl₃)

Compounds	¹ H NMR,
S-(+)-BCPT	1.01 (t, 3H, CH ₂ CH ₃), 1.35 (d, 3H, CHCH ₃), 1.63 ~ 1.78 (m, 2H, CH ₂ CH ₃), 3.48 ~ 3.54 (m, 1H, CHCH ₃), 6.53 (s, 1H, N-H), 7.62 (dd, 1H, Py-H), 7.70 (dd, 1H, Py-H), & 4.4 (dd, 1H, Py-H)
R-(-)-BCPT	1.02 (t, 3H, CH ₂ CH ₃), 1.35 (d, 3H, CHCH ₃), 1.63 ~ 1.78 (m, 2H, CH ₂ CH ₃), 3.48 ~ 3.54 (m, 1H, CHCH ₃), 6.53 (s, 1H, N-H), 7.62 (dd, 1H, Py-H), 7.70 (dd, 1H, Py-H), & 4.4 (dd, 1H, Py-H)

Table 3 ¹³C NMR data of synthesized compounds (solvent: CDCl₃)

Compounds	¹³ C NMR,
S-(+)-BCPT	10.35 (CH ₂ CH ₃), 20.01 (CH ₂ CH ₃), 29.48 (CHCH ₃), 56.24 (CHCH ₃), 119.09 (Py-C), 120.66 (Py-C), 141.15 (Py-C), 150.17 (thiodiazole-5-C), 150.18 (Py-C), 152.28 (Py-C), 171.28 (thiodiazole-2-C)
R-(-)-BCPT	10.35 (CH ₂ CH ₃), 20.01 (CH ₂ CH ₃), 29.48 (CHCH ₃), 56.24 (CHCH ₃), 119.09 (Py-C), 120.66 (Py-C), 141.15 (Py-C), 150.17 (thiodiazole-5-C), 150.18 (Py-C), 152.28 (Py-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. LC₅₀, LC₉₀ 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
	100	1.0	98
S-(+)-BCPT	50	1.0	98
	25	1.0	98
	12.5	2.03	95.0
	100	1.0	98
R-(-)-BCPT	50	1.0	98
	25	2.97	93.2
	12.5	4.8	89.0
	100	1.0	98
	50	1.0	98

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公告

据中国科学技术信息研究所 07年核心版“中国科技期刊引证报告”对核心库 1723种核心刊源的统计分析,《农药学报》的影响因子为 0.581,比 06年(0.458)提高了 27%,在全部 1723种核心期刊中列第 388位,比 06年提升了 105位,在所属的化学工程类 77种期刊中列第 8位,比 06年提升 5位。

另据清华同方“中国科学文献计量评价研究中心”2006年对该数据库 6500余种统计刊源统计分析后颁布的“中国学术期刊综合引证年度报告(2007)”数据,《农药学报》总被引频次为 440次,影响因子为 0.794,比 06年(0.585)提高 36%,5年影响因子为 0.959,比 06年(0.717)提高 34%,网络即年下载率为 42.0,比 06年(23.2)提高 81%。