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1 - 芳基取代咪唑的合成及其生物活性研究①

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摘要:合成了一系列 1 - 芳基取代咪唑,测试了部分 1 - 芳基咪唑化合物对月季灰霉病菌、西瓜炭疽病菌的生物活性.

关键词:咪唑;1 - 芳基取代咪唑;合成;生物活性
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咪唑作为五元杂环体系中的重要一员,存在于众多的具有生理活性的天然产物中,其用途非常广泛. 在高性能复合材料、电子化学品、金属防腐蚀、感光材料、生物、医药等诸多领域显示出独特的性能. 咪唑衍生物已经成为很多重要的药物,用于抗真菌、抗癌,以及治疗低血糖和生理紊乱等疾病[1];另外,咪唑结构的化合物还可以用于模拟天然超氧化物歧化酶(SOD)的活性部位研究生物活性[2]、作为环氧树脂新型固化剂及催化剂[3]、作为某些金属的表面处理剂[4]等;在农业上用做杀虫剂和植物生长调节剂[5]. 近年来,由咪唑为原料合成的离子液体以及氮杂环咪唑类卡宾配体在金属有机催化领域取得了巨大的成功[6].

1 结果和讨论

按照最近改进 1 - 芳基取代咪唑的制备方法[7],合成了一系列咪唑衍生物,并对它们进行了结构鉴定. 所采用的分 2 步合成 1 - 取代咪唑的方法较 Gridnev[8]和 Herrmann[9]提供的合成方法有了较大的改进,尤其是可以得到较高收率的 1 - 芳基取代咪唑. 经过对部分 1 - 芳基取代咪唑对灰霉病和西瓜炭疽病抑制作用的测试,结果表明 4 个咪唑化合物均在对灰霉病和西瓜炭疽病有不同程度的抑制作用. 其中,7 的 5 mg/L 溶液对月季灰霉病菌、8 的 100 mg/L 溶液对西瓜炭疽病菌的抑制作用较好,测试结果见表 2,3.

2 实验部分

2.1 试剂与仪器 上海精密科学仪器有限公司 WRS - 1 数字熔点测定仪;Bruker Avance 300 型核磁共振仪,TMS 做内标,^{1}H NMR(300 MHz),^{13}C NMR(75 MHz);Agilent G3250AA 型液相/飞行时间质谱仪;Finnigan Trace 2000 型气 - 质联用仪;Perkin - Elmer 1800 型 FT - IR 红外光谱仪,KBr 压片;所有反应试剂来自 Acros, Aldrich, Fluka 公司提供的商用试剂,未做任何纯化;96 %咪鲜胺原药由南通江山农业化工股份有限公司生产;青岛海洋化工厂生产的 GF254 薄层层析硅胶板及柱层析硅胶(0.054～0.077 mm).

2.2 1 - 芳基取代咪唑的合成(图 1) 在 500 mL 的圆底烧瓶里加入取代的芳香胺(0.1 mmol)和 50 mL 甲醇,搅拌下滴加 30 %的乙二醛水溶液(16.2 mL,0.1 mmol),加料完毕继续在室温下搅拌 16 h. 随着反应的进行,可见有黄色固体生成. 之后依次加入氯化铵(10.7 g,0.2 mmol),35 %甲醛水溶液(16 mL,0.2 mmol),40 mL 甲醇,加热回流反应 1 h. 缓慢滴入 85 %的磷酸(14 mL),继续回流 4～8 h,反应程度由 TLC 监测. 反应完全后减压蒸馏除

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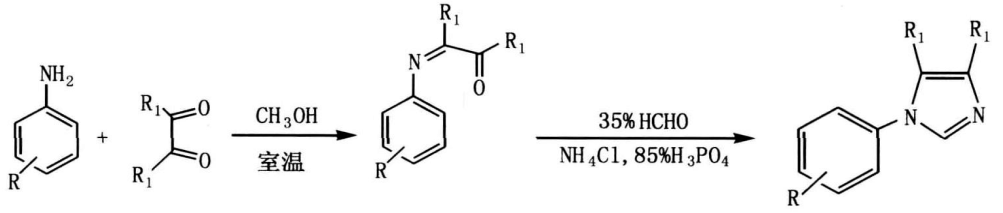


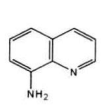
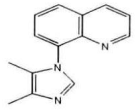
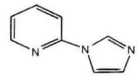
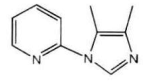
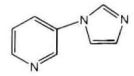
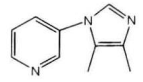
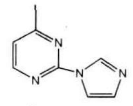
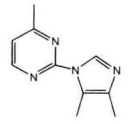
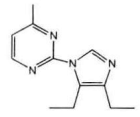
图 1 合成路线

Fig. 1 Synthesis route

去甲醇,把剩余的黑色液体倒在碎冰(300 g)上,用 40 %氢氧化钾水溶液中和到 pH = 9. 乙酸乙酯萃取,萃取液用饱和食盐水洗,再用无水硫酸镁干燥,过滤,浓缩,柱层析纯化即可得到目标产物(表 1).

表 1 1 – 芳基咪唑化合物的合成

Tab. 1 synthesis of 1 – Alrylimidazoles

序号	芳香胺	产物	收率/%
1			32.8
2			36.2
3			23.6
4			30
5			27
6			79
7			40
8			38

a:分离收率.

1:8 - (1 - (4,5 - 二甲基咪唑基)) - 喹啉:棕黑色固体; m. p. :124～126 ℃; IR (KBr) :3 431 (w),3 118 (m),2 924 (m),1 661 (m),1 589 (m),1 495 (s),1 399 (s),1 205 (m),831 (m),798 (m) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) : δ = 8. 95 (1H, dd, J = 1. 8 Hz, 1. 8 Hz), 8. 26 (1H, d, J = 1. 8 Hz, 1. 8 Hz), 7. 94 (1H, dd, J = 3. 0 Hz, 3. 0 Hz), 7. 65 (1H, s), 7. 61 (2H, t), 7. 49 (1H, dd, J = 3. 0 Hz, 3. 0 Hz), 2. 29 (3H, s, CH_3), 1. 96 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 151. 59, 144. 04, 136. 64, 136. 29, 134. 48, 133. 25, 129. 34, 129. 11, 127. 99, 126. 14, 124. 99, 122. 17, 12. 82, 9. 23; GC - MS: (m/z) :2 4. 2 (M^+ + 1, 17 %), 223. 2 (M^+, 100 %), 222. 1 (61), 208. 1 (25), 197. 2 (12), 181. 1 (9), 169. 1 (9), 155. 1 (22), 129. 1 (32), 101. 0 (13).

2:2 - (1 - 咪唑基) - 吡啶:黄色液体; IR (KBr) :3 128 (w), 1 592 (s), 1 487 (s), 1 440 (m), 1 400 (s), 1 306 (s), 1 260 (m), 1 056 (m), 780 (m) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) : δ = 8. 39 (1H, t), 8. 28 (1H, d), 7. 57 (1H, t), 7. 65 (1H, q), 7. 57 (1H, t), 7. 26～7. 29 (1H, dd, J = 7. 8 Hz, 7. 8 Hz), 7. 14 (2H, q); ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 149. 25, 139. 15, 135. 1, 130. 82, 122. 14, 116. 28, 112. 45; GC - MS: (m/z) :146. 1 (M^+ + 1, 14 %), 145. 0 (M^+, 100 %), 118. 1 (45), 91. 0 (43), 78. 0 (28), 51. 0 (27).

3:2 - (1 - (4,5 - 二甲基咪唑基)) - 吡啶,棕色固体; m. p. :70～71 ℃; IR (KBr) :3 388 (w), 3 123 (m), 3 056 (m), 1 668 (m), 1 594 (s), 1 479 (s), 1 440 (s), 1 400 (s), 1 311 (m), 1 250 (m), 1 198 (m), 1 154 (m) cm^{-1};^{1}H NMR (300 MHz, $CDCl_3$) : δ = 8. 48 (1H, q), 7. 78 (2H, t), 7. 23 (1H, s), 7. 21 (1H, t), 2. 24 (3H, s, CH_3), 2. 16 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 149. 49, 138. 77, 135. 75, 134. 89, 122. 37, 117. 14, 113. 0; GC - MS: (m/z) : 174. 1 (M^+ + 1, 11 %), 173. 0 (M^+, 100 %), 172. 0 (42), 158. 0 (21), 145. 0 (26), 131. 1 (16), 119. 1 (3), 105. 0 (6), 95. 1 (20), 79. 0 (20), 78. 0 (37), 51. 0 (19), 44. 0 (7), 40. 0 (13).

4:3 - (1 - 咪唑基) - 吡啶,淡黄色固体;m. p.:49～51 ℃; IR(KBr):3 411(w),3 127(w),1 641(m),1 584(m),1 505(s),1 400(s),1 309(m),1 270(m),1 192(m),1 110(m),1 062(m),811(m),706(m) cm^{-1};^1H NMR(300 MHz,$CDCl_3$):δ = 8.58(1H,d),8.45(1H,d),7.75(1H,s),7.60(1H,t),7.58(1H,d),7.26～7.30(1H,dd,J = 4.5 Hz,4.5 Hz),7.17(1H,s),7.07(1H,s);^{13}C NMR(75 MHz,$CDCl_3$):δ = 148.40,142.49,135.22,133.57,130.78,128.44,124.00,117.75; GC - MS:(m/z):146.1(M^+ + 1,14 %),145.0(M^+,100 %),119.1(24),118.1(40),91.0(11),79.0(12),78.0(53),52.0(12),51.0(23).

5:3 - (1 - (4,5 - 二甲基咪唑基)) - 吡啶,无色晶体;m. p.:83～85 ℃; IR(KBr):3 239(w),3 109(w),2 920(w),1 970(m),1 879(m),1 584(s),1 489(s),1 440(s),1 343(m),1 275(m),1 235(m),1 126(m),1 100(m),1 021(m),940(m),815(s),714(m) cm^{-1};^1H NMR(300 MHz,$CDCl_3$):δ = 8.64～8.66(1H,dd,J = 1.4 Hz,1.4 Hz),8.58(1H,d),7.58(3H,t),7.48(1H,s),7.43(1H,q),2.20(3H,s,CH_3),2.09(3H,s,CH_3);^{13}C NMR(75 MHz,$CDCl_3$):δ = 149.28,146.65,135.43,135.13,133.50,132.82,124.06,122.50,12.89,9.13; GC - MS:(m/z):174.2(M^+ + 1,12 %),173.1(M^+,100 %),172.1(60),158.0(18),145.0(15),131.1(18),119.1(4),105.0(12),91.05(20),79.0(4),78.0(24),51.0(15),39.0(4).

6:2 - (1 - 咪唑基) - 4 - 甲基 - 嘧啶,白色固体;m. p.:94 ～ 96 ℃; IR(KBr):3 450(w),3 134(w),1 978(m),1 592(s),1 553(s),1 469(w),1 401(w),1 319(m),1 253(m),1 158(m),1 099(m),1 049(m),1 008(m),835(m),775(m) cm^{-1};^1H NMR(300 MHz,$CDCl_3$):δ = 8.59(1H,s),8.49(1H,s),8.47(1H,s),7.86(2H,d),7.12(1H,t),7.00(1H,d),2.52(3H,s,CH_3);^{13}C NMR(75 MHz,$CDCl_3$):δ = 170.03,158.44,154.89,136.59,130.85,118.80,116.91,24.51; GC - MS:(m/z):1 161.2(M^+ + 1,15 %),160.2(M^+,100 %),159.1(24),134.2(68),133.1(27),113.1(29),66.1(26),53.1(13),40.1(19),39.1(22).

7:2 - (1 - (4,5 - 二甲基咪唑基)) - 4 - 甲基 - 嘧啶,黄色晶体;m. p.:63～65; IR(KBr):3 126(w),2 928(m),1 578(s),1 487(m),1 436(s),1 402(s),1 211(m),1 142(m),946(m) cm^{-1};^1H NMR(300 MHz,$CDCl_3$):δ = 8.47(1H,d,J = 5.1 Hz),8.41(1H,s),6.99(1H,d,J = 5.1 Hz),2.50(3H,d),2.48(3H,s,CH_3),2.18(3H,s,CH_3);^{13}C NMR(75 MHz,$CDCl_3$):δ = 169.48,158.17,156.42,136.44,136.12,123.24,118.20,111.52,24.50,12.99,12.29; GC - MS:(m/z):189.2(M^+ + 1,12 %),188.2(M^+,100 %),187.1(53),173.1(31),160.1(18),146.1(10),95.1(20),94.1(16),66.1(11).

8:2 - (1 - (4,5 - 二乙基咪唑基)) - 4 - 甲基 - 嘧啶,黄色液体;IR(KBr):3 133(m),2 973(s),2883(m),1 701(m),1 589(s),1 492(m),1 402(w),1 315(m),1 197(m),1 037(m),994(m),951(m),831(m) cm^{-1};^1H NMR(300 MHz,$CDCl_3$):δ = 8.44(1H,d),8.37(1H,s),6.95(1H,d),2.98(2H,q,5 Hz),2.52(2H,q,J = 7.5 Hz),2.46(3H,s),1.20(3H,t,CH_3),1.08(3H,t,CH_3),5.59(1H,d,s);^{13}C NMR(75 MHz,$CDCl_3$):δ = 169.12,157.90,155.94,141.74,136.20,128.26,117,80,24.1,20.27,18.23,15.03,14.53; GC - MS:(m/z):217.3(M^+ + 1,15 %),216.2(M^+,84 %),215.2(15),202.2(24),187.2(24),174.2(26),172.0(15),172.0(15),152.1(12),123.1(15),107.1(14),93.0(45),66.1(27),41.0(23),39.1(19).

2.3　生物活性测试　灰霉病(Botrytis cinerea Pers)是近年来随着保护地(大棚和日光温室)种植面积的不断增加而日趋严重的真菌病害.是保护地发生最普遍、损失最严重的病害之一,病原为半知菌亚门葡萄孢属真菌[10].西瓜炭疽病(Colletotrichum Lagenarium)是西瓜果实上最易发生的病害,严重影响了西瓜的质量[11].我们选取了化合物 1,6,7,8 测定了其对灰霉病和西瓜炭疽病的抑制作用,以 96 %咪鲜胺原药 10 mg/L 为对照药剂,清水处理为空白对照.结果表明 4 个咪唑化合物均在对灰霉病和西瓜炭疽病有不同程度的抑制作用(表 2,3).

表 2 4 个咪唑化合物对月季灰霉病菌抑制作用测定结果

Tab. 2 Biological activity to the botrytis cinerea pers of the four com p ounds

药剂	质量浓度/ (mg·L⁻¹)	第 1 天		第 2 天		第 3 天	
		菌落直径/	抑制率/ %	菌落直径/	抑制率/ %	菌落直径/	抑制率/ %
1	5	13.50	10.63	39.00	5.74	68.00	4.31
6	5	9.81	45.32	21.19	53.71	34.81	53.93
7	5	12.50	20.04	37.75	9.10	65.43	7.86
8	5	13.50	10.63	37.25	10.45	65.75	7.67
咪鲜胺	10	4	100	4	100	4	100
CK	-	14.63	-	41.3	-	70.88	-

表 3 4 个咪唑化合物对西瓜炭疽病菌抑制作用测定结果

Tab. 3 Biological activity to the colletotrichum lagenarium of the four com p ounds

药剂	质量浓度/ (mg·L⁻¹)	第 3 天		第 5 天		第 7 天	
		菌落直径/	抑制率/ %	菌落直径/	抑制率/ %	菌落直径/	抑制率/ %
1	50	9.13	18.00	14.63	15.87	19.50	12.68
	100	8.75	24.00	13.88	21.81	18.88	16.20
6	50	13.63	4.99	16.50	1.03	22.30	- 3.10
	100	13.13	9.92	15.50	8.95	21.30	2.54
7	50	18.75	- 45.61	24.25	- 60.33	34.00	- 69.01
	100	17.63	- 34.50	23.00	- 50.44	32.63	- 61.27
8	50	8.38	30.00	12.88	29.73	18.00	21.13
	100	5.00	84.00	6.63	79.22	8.75	73.24
咪鲜胺	10	0.00	100.00	0.00	100.00	0.00	100.00
CK	-	10.25	-	16.63	-	21.75	-

表 2 中 4 个咪唑化合物均对月季灰霉病菌有一定的抑制作用,其中 1,7,8 对月季灰霉病菌的生物活性较低,6 的 5 mg/L 溶液对月季灰霉病菌的生物活性较高.

表 3 中咪唑化合物 1,6,8 均对西瓜炭疽病菌有一定的抑制作用,其中 1,6 对西瓜炭疽病菌的生物活性较低,8 的 100 mg/L 溶液对西瓜炭疽病菌的生物活性较高. 7 对西瓜炭疽病菌没有抑制活性,相反对菌丝的生长起到一定的促进作用.

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Establishment of rice oligonucleotide microarray in rice inflorescence development

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Abstract: Fifty rice inflorescence related genes from Internet, references were chosen. After probes of the 50 genes were designed and screened by BLAST analysis in the Internet, they were synthesized, purified and micro-arrayed onto the microscope sliders. Total RNA from 3 kinds of rice inflorescence tissues was extracted and labeled by fluorescent dye. The labeled probes were then hybridized with the oligonucleotide arrays. Expression patterns of 50 genes from rice inflorescence in different development were obtained by detection using ScanArray3000. It showed analyzed pots with uniformity background and clear signal. The plots of the images were acquired after the acquired gene expression patterns were analyzed by ImaGene4.0 software. The scatter plots and scale maps show that there existed a significant difference in the expression of these candidate genes in rice inflorescences with different development phase. Then, a foundation for the preparation of rice oligonucleotide microarray and farther application was layed.

Key words: oligonucleotide microarray; rice inflorescence genes; gene expression profile

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Studies on synthesis and biological activity of 1-Alrylimidazoles

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Abstrsct: A series of 1-alrylimidazoles were synthesized, their biological activities about to Botrytis cinerea Pers and Colletotrichum Lagenarium were tested.

Key words: imidazole; 1-alrylimidazole; synthesis; biological activity