

·研究简报·

新型脲类衍生物的合成及其生物活性

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摘要:利用 3-(N-甲基-N-甲氧基氨基)-1-芳基-1-丙酮脲与酰氯反应, 合成了 14 个新型 N-酰基-3-(N-甲基-N-甲氧基氨基)-1-芳基-1-丙酮脲化合物, 其化学结构经 ¹H 核磁共振和元素分析确证。初步的生物活性测试结果表明, 部分化合物在 50 mg/L 时对淡色库蚊 *Culex pipiens pallens* 的致死率为 95% ~ 100%; 化合物 **6** 在 1 000 mg/L 时对粘虫 *Leucania separata* Walke 的致死率达 100%。

关键词:酰化反应; 芳基丙酮脲; 合成; 生物活性

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Synthesis and Bioactivity of a Series of Novel Hydrazone Derivatives

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Abstract: In search of novel pesticide compound with high bioactivity, fourteen new N-3-(N-methoxy-N-methyl-amino)-1-aryl-propylidene-hydrazone derivatives have been designed and synthesized by the reaction of N-[3-hydrazono-propyl]-O, N-dimethyl-hydroxylamine with different acyl chlorides. Their structures have been confirmed by ¹H NMR and elemental analysis. The preliminary biological activity showed that some compounds possessed insecticidal activities against *Culex pipiens pallens* and *Leucania separata* Walke. The mortality ratio of some compounds against *C. pipiens pallens* coquillett were 95% ~ 100% at concentration of 50 mg/L. The mortality ratio of **6** against *L. separata* was 100% at 1 000 mg/L.

Key words: acylation; hydrazone; synthesis; bioactivity

脲基团 (—C(=O)—N—N—) 是医药和农药化合物中的重要结构, 不少含脲结构的化合物具有抑菌、消炎止痛、抗肿瘤和治疗肺结核等作用^[1-4]。1973 年杜邦公司首次介绍了某些结构简单的二苯

甲酮脲的杀虫活性, 其后此类化合物引起了众多农药公司与科研工作者的兴趣。含脲结构的化合物作为农药具有制备简单、活性优良、作用谱广、毒性小等优点, 目前已商品化的品种有伏蚊脲

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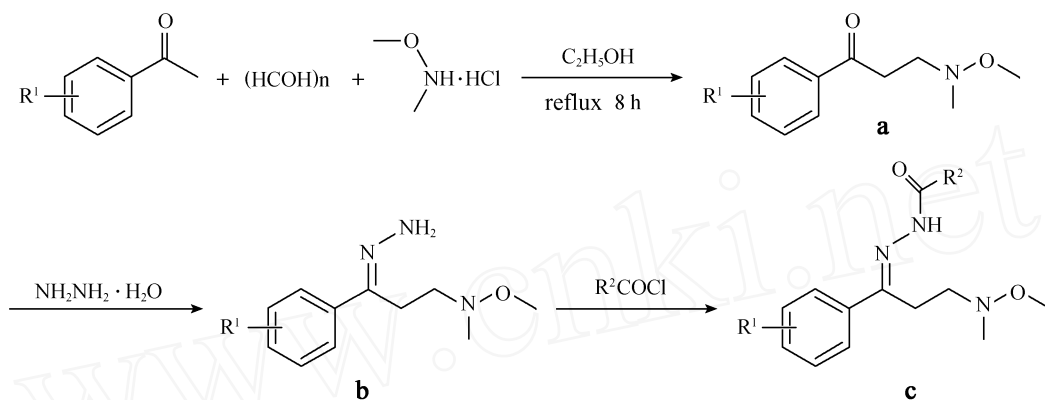
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(hydram ethyl non)、噻菌脲 (ferim zone)和氟吡草脲 (diflufenzopyr)等^[5]。作者等曾经制备了取代苯丙酮脲衍生物,部分具有很好的杀菌活性^[6]。在此基础上保留其基本化学结构,将其中的脲醚演变为脲进行结构改造,并通过酰化反应引入烷基、

取代芳基等,合成了一系列未见文献报道的 N 酰基-3-(N-甲基-N-甲氧基氨基)-1-芳基-1-丙酮脲化合物 (c),其结构经元素分析和核磁共振氢谱确证,并初步测试了其生物活性。

合成路线如下:



1 合成实验

1.1 仪器与试剂

Bruker AC200型核磁共振仪 (TMS为内标, CDCl_3 为溶剂); Carloerba EA 1110元素分析仪; WRS-1A型数字熔点仪 (温度计未经校正); 100~200目硅胶; 试剂均为化学纯或分析纯。

1.2 化合物的制备

1.2.1 化合物 a和 b的制备 分别参照文献 [7, 8]方法合成。

1.2.2 目标化合物 c的制备 以 N环丙酰基-3-(N-甲氧基-N-甲基氨基)-1-(4-t-丁基苯基)-1-丙酮脲 (c_1)的制备为例。

在 100 mL 三口烧瓶中加入 0.79 g (0.003 mol) 3-(N-甲氧基-N-甲基氨基)-1-(4-t-丁基苯基)-1-丙酮脲, 0.30 g (0.003 mol) 三乙胺, 20 mL 二氯甲烷。冰水浴冷却至 0, 搅拌下滴加 0.31 g (0.003 mol) 环丙酰氯。室温下搅拌反应 4 h。用 NaCl 饱和溶液洗涤, 无水 MgSO_4 干燥, 减压脱溶, 经柱层析 (石油醚-乙酸乙酯 = 2:1, 体积比) 纯化得白色粉末 (c_1), mp: 129~130, 收率 74%。

采用同样的方法制得 $c_2 \sim c_{14}$, 均为白色固体。所有目标化合物的熔点、元素分析和 $^1\text{H NMR}$ 数据分别见表 1 和表 2。

Table 1 Physical constants and elemental analysis data of synthesized compounds c

Compd	R^1	R^2	Mp /	Yield (%)	Elemental analysis (Calcd, %)		
					C	H	N
c_1	4-(t-C ₄ H ₉)-C ₆ H ₄	cyclo-C ₃ H ₅	129~130	74	68.73 (68.85)	8.85 (8.82)	12.62 (12.68)
c_2	4-(t-C ₄ H ₉)-C ₆ H ₄	p-C ₆ H ₄	136~142	82	65.72 (65.74)	7.09 (7.02)	10.43 (10.45)
c_3	4-(t-C ₄ H ₉)-C ₆ H ₄	2-furan	104~105	79	67.12 (67.20)	7.58 (7.61)	11.81 (11.76)
c_4	4-(t-C ₄ H ₉)-C ₆ H ₄	CH ₂ CH ₂ Cl	99~105	72	61.13 (61.09)	8.04 (7.97)	11.78 (11.87)
c_5	4-(t-C ₄ H ₉)-C ₆ H ₄	o-CF ₃ C ₆ H ₄	101~103	65	63.42 (63.43)	6.44 (6.48)	9.81 (9.65)
c_6	4-(t-C ₄ H ₉)-C ₆ H ₄	CF ₃	80~81	63	56.79 (56.81)	6.70 (6.73)	11.75 (11.69)
c_7	2-thiophene	i-C ₃ H ₇	84~85	68	55.13 (55.10)	7.51 (7.47)	14.80 (14.83)
c_8	4-(t-C ₄ H ₉)-C ₆ H ₄	i-C ₃ H ₇	140~141	71	68.49 (68.43)	9.40 (9.37)	12.66 (12.6)
c_9	4-(t-C ₄ H ₉)-C ₆ H ₄	CH ₂ CH ₃	84~85	63	67.62 (67.68)	9.14 (9.15)	13.09 (13.15)

Continued

Compd	R ¹	R ²	Mp /	Yield (%)	Elemental analysis (Calcd, %)		
					C	H	N
c ₁₀	2-thiophene	CH ₂ CH ₃	70 ~ 71	70	53.50 (53.51)	7.15 (7.11)	15.49 (15.60)
c ₁₁	2-thiophene	p-(t-C ₄ H ₉)-C ₆ H ₄	109 ~ 111	58	64.38 (64.31)	7.27 (7.29)	11.26 (11.25)
c ₁₂	2-thiophene	m, p-C ₁₂ H ₆	130 ~ 132	52	49.79 (49.75)	4.40 (4.44)	10.85 (10.88)
c ₁₃	4-(C ₂ H ₅ O)-C ₆ H ₄	i-C ₃ H ₇	120 ~ 121	80	63.50 (63.53)	8.49 (8.47)	13.02 (13.07)
c ₁₄	3, 4-(CH ₃) ₂ -C ₆ H ₄	i-C ₃ H ₇	91 ~ 92	73	66.84 (66.85)	8.88 (8.91)	13.82 (13.76)

Table 2 ¹H NMR data of synthesized compounds c

Compd	¹ H NMR (CDCl ₃ /TMS),
c ₁	0.89 ~ 1.09 (m, 4H, 2CH ₂), 1.33 [s, 9H, C(CH ₃) ₃], 2.62 (s, 3H, NCH ₃), 2.68 ~ 2.73 (m, 1H, CH), 2.85 ~ 2.94 (m, 4H, 2CH ₂), 3.73 (s, 3H, OCH ₃), 7.45 (d, 2H, J = 8.52 Hz, A _H -3, 5), 7.94 (d, 2H, J = 8.52 Hz, A _H -2, 6), 9.92 (s, 1H, NH)
c ₂	1.29 [s, 9H, C(CH ₃) ₃], 2.08 (s, 3H, NCH ₃), 2.83 ~ 2.86 (m, 2H, CH ₂), 3.07 ~ 3.13 (m, 2H, CH ₂), 3.38 (s, 3H, OCH ₃), 7.59 (d, 2H, J = 7.88 Hz, A _H -3, 5), 7.63 (d, 2H, J = 8.42 Hz, A _H -3, 5), 7.79 (d, 2H, J = 8.42 Hz, A _H -2, 6), 7.76 (d, 2H, J = 8.42 Hz, A _H -2, 6), 10.15 (s, 1H, NH)
c ₃	1.33 [s, 9H, C(CH ₃) ₃], 2.69 (s, 3H, NCH ₃), 3.01 ~ 3.06 (m, 4H, 2CH ₂), 3.63 (s, 3H, OCH ₃), 6.56 ~ 7.44 (m, 3H, Furan-H), 7.51 (d, 2H, J = 8.52 Hz, A _H -3, 5), 7.78 (d, 2H, J = 8.52 Hz, A _H -2, 6), 9.89 (s, 1H, NH)
c ₄	1.34 [s, 9H, C(CH ₃) ₃], 3.63 (s, 3H, NCH ₃), 2.85 ~ 2.97 (m, 4H, 2CH ₂), 3.28 (t, J = 6.94 Hz, 2H, CH ₂ CO), 3.68 (s, 3H, OCH ₃), 3.91 (t, J = 6.94 Hz, 2H, CH ₂ Cl), 7.43 (d, 2H, J = 8.50 Hz, A _H -3, 5), 7.68 (d, 2H, J = 8.50 Hz, A _H -2, 6), 10.15 (s, 1H, NH)
c ₅	1.34 [s, 9H, C(CH ₃) ₃], 2.69 (s, 3H, NCH ₃), 3.03 ~ 3.05 (m, 4H, 2CH ₂), 3.41 (s, 3H, OCH ₃), 7.43 (d, 2H, J = 7.90 Hz, A _H -3, 5), 7.68 (d, 2H, J = 7.90 Hz, A _H -2, 6), 7.78 ~ 8.16 (m, 4H, A _H -2, 3, 4, 6), 10.15 (s, 1H, NH)
c ₆	1.34 [s, 9H, C(CH ₃) ₃], 2.71 (s, 3H, NCH ₃), 2.64 ~ 2.70 (m, 2H, CH ₂), 2.83 ~ 2.94 (m, 2H, CH ₂), 3.60 (s, 3H, OCH ₃), 7.44 (d, 2H, J = 7.92 Hz, A _H -3, 5), 7.74 (d, 2H, J = 7.92 Hz, A _H -2, 6), 12.42 (s, 1H, NH)
c ₇	1.22 [d, 6H, J = 6.38 Hz, C(CH ₃) ₂], 2.62 (s, 3H, NCH ₃), 2.86 ~ 2.97 (m, 4H, 2CH ₂), 3.47 ~ 3.49 (m, 1H, CH), 3.68 (s, 3H, OCH ₃), 7.02 (d, d, 1H, J ₁ = 3.42, J ₂ = 4.60 Hz, ThiopheneH-4), 7.24 (d, d, 1H, J ₁ = 3.42, J ₂ = 1.23 Hz, ThiopheneH-5), 7.31 (d, d, 1H, J ₁ = 4.60, J ₂ = 1.23 Hz, ThiopheneH-3), 9.78 (s, 1H, NH)
c ₈	1.19 [d, 6H, J = 6.48 Hz, C(CH ₃) ₂], 1.31 [s, 9H, C(CH ₃) ₃], 2.64 (s, 3H, NCH ₃), 2.83 ~ 2.86 (m, 2H, CH ₂), 2.91 ~ 2.94 (m, 2H, CH ₂), 3.63 ~ 3.65 (m, 1H, CH), 3.69 (s, 3H, OCH ₃), 7.41 (d, 2H, J = 8.48 Hz, A _H -3, 5), 7.69 (d, 2H, J = 8.48 Hz, A _H -2, 6), 9.59 (s, 1H, NH)
c ₉	1.22 (t, J = 6.72 Hz, 3H, CH ₃), 1.33 [s, 9H, C(CH ₃) ₃], 2.61 (s, 3H, NCH ₃), 2.70 ~ 2.82 (m, 4H, 2CH ₂), 2.85 ~ 2.93 (m, 2H, CH ₂ CO), 3.64 (s, 3H, OCH ₃), 7.41 (d, 2H, J = 8.50 Hz, A _H -3, 5), 7.68 (d, 2H, J = 8.50 Hz, A _H -2, 6), 9.70 (s, 1H, NH)
c ₁₀	1.21 (t, J = 6.75 Hz, 3H, CH ₃), 2.63 (s, 3H, NCH ₃), 2.62 ~ 2.72 (m, 2H, CH ₂), 2.80 ~ 2.88 (m, 2H, CH ₂), 2.90 ~ 2.92 (m, 2H, CH ₂ CO), 3.64 (s, 3H, OCH ₃), 7.02 (d, d, 1H, J ₁ = 3.36, J ₂ = 4.63 Hz, ThiopheneH-4), 7.23 (d, d, J ₁ = 3.36, J ₂ = 1.21 Hz, 1H, ThiopheneH-5), 7.31 (d, d, J ₁ = 4.63, J ₂ = 1.21 Hz, 1H, ThiopheneH-3), 9.84 (s, 1H, NH)
c ₁₁	1.33 [s, 9H, C(CH ₃) ₃], 2.67 (s, 3H, NCH ₃), 2.95 ~ 3.09 (m, 4H, 2CH ₂), 3.46 (s, 3H, OCH ₃), 7.03 (d, d, 1H, J ₁ = 3.40, J ₂ = 4.61 Hz, ThiopheneH-4), 7.31 (d, 2H, J = 8.48 Hz, A _H -3, 5), 7.45 (d, d, 1H, J ₁ = 3.40, J ₂ = 1.21 Hz, ThiopheneH-5), 7.49 (d, d, 1H, J ₁ = 4.61, J ₂ = 1.21, ThiopheneH-3), 7.83 (d, 2H, J = 8.48 Hz, A _H -2, 6), 9.78 (s, 1H, NH)
c ₁₂	2.66 (s, 3H, NCH ₃), 2.86 ~ 3.01 (m, 4H, 2CH ₂), 3.73 (s, 3H, OCH ₃), 6.97 (d, d, 1H, J ₁ = 3.45, J ₂ = 4.56 Hz, ThiopheneH-4), 7.24 (d, d, 1H, J ₁ = 3.45, J ₂ = 1.24 Hz, ThiopheneH-5), 7.31 (d, d, 1H, J ₁ = 4.56, J ₂ = 1.24 Hz, ThiopheneH-3), 7.33 ~ 7.58 (m, 3H, A _H -3, 5, 6), 9.72 (s, 1H, NH)
c ₁₃	1.25 [d, 6H, J = 6.49 Hz, C(CH ₃) ₂], 1.44 (t, J = 7.42 Hz, 3H, CH ₃), 2.62 (s, 3H, NCH ₃), 2.76 ~ 2.93 (m, 4H, 2CH ₂), 2.49 ~ 2.56 (m, 1H, CH), 3.68 (s, 3H, OCH ₃), 4.09 ~ 4.15 (m, 2H, CH ₂), 6.89 (d, 2H, J = 8.50 Hz, A _H -3, 5), 7.74 (d, 2H, J = 8.50 Hz, A _H -2, 6), 9.53 (s, 1H, NH)
c ₁₄	1.26 [d, 6H, J = 6.52 Hz, C(CH ₃) ₂], 2.31 (s, 6H, 2CH ₃), 2.65 (s, 3H, NCH ₃), 2.78 ~ 2.85 (m, 2H, CH ₂), 2.90 ~ 2.96 (m, 2H, CH ₂), 3.49 ~ 3.57 (m, 1H, CH), 3.64 (s, 3H, OCH ₃), 7.17 ~ 7.49 (m, 3H, A _H -3, 5, 6), 9.60 (s, 1H, NH)

2 生物活性测定

2.1 杀虫活性

2.1.1 杀淡色库蚊 *Culex pipiens pallens* 活性 参照文献 [9] 方法测定。

2.1.2 杀粘虫活性 采用国家南方农药创制中心生测标准程序之 SOP 叶片浸渍法测定。从温室剪下 2~4 叶期的玉米植株,在稀释好的药液中充分浸渍 5 s,取出后悬挂在通风柜中;放置 2~3 h 后,剪下 30 mm 左右长的叶段,置于小试管中,每支试管约放 6~8 片叶段。用毛笔取 10 只 3 龄粘虫 *Leucania separata* 幼虫放入试管中,纱布封口,以不含药剂的溶剂为空白对照。以触动虫体不能正常爬行为死亡标准,非正常的个体(爬行不自然、

半死、全死等)均计为死亡个体。

2.2 结果与讨论

该类化合物具有一定的杀虫活性(见表 3),其中化合物 c_1 、 c_3 、 c_6 和 c_9 在 50 mg/L 时对淡色库蚊的致死率达到 100%, c_2 和 c_6 达到 95% 以上;化合物 c_7 在 1 000 mg/L 时对粘虫的致死率达到 100%。化合物对淡色库蚊的活性与 R^1 为对叔丁基苯基有关,这符合许多杀虫剂的特点,如吡蚜灵、虫酰肼等;同时 R^2 为环丙基或异丙基时,化合物表现出较好的生物活性。

此外,对化合物还进行了杀菌和除草活性的印鉴测试,但均无活性。

Table 3 Effects of compounds **c** on different kinds of insect

Compd	Mortality (%)		Compd	Mortality (%)	
	<i>Culex pipiens pallens</i> * (50 mg/L)	<i>Leucania separata</i> ** (1 000 mg/L)		<i>Culex pipiens pallens</i> * (50 mg/L)	<i>Leucania separata</i> ** (1 000 mg/L)
c_1	100	0	c_8	100	0
c_2	97.3	0	c_9	100	0
c_3	100	0	c_{10}	0	79.2
c_4	52.5	0	c_{11}	0	0
c_5	87.9	0	c_{12}	0	0
c_6	96.8	0	c_{13}	85.7	0
c_7	0	100	c_{14}	0	50.0

* n=4, ** n=3.

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参考文献:

- [1] HUANG Ming-zhi (黄明智), HUANG Ke-long (黄可龙), CHEN Can (陈灿), et al 2-甲硫基-1-苯基乙酮苯甲酰脲类化合物的合成和生物活性[J]. *Chin J Pestic Sci* (农药学报), 2004, 6(3): 67-70.
- [2] Loncle C, Brunel JM, Vidal N, et al Synthesis and antifungal activity of cholesterol-hydrazone derivatives [J]. *Euro J Med Chem*, 2004, (49): 1067-1071.
- [3] Boger M, Durr D, Gsell L, et al Synthesis and structure-activity relationships of benzophenone hydrazone derivatives with insecticidal activity [J]. *Pest Manag Sci*, 2001, (57): 191-202.
- [4] MA Hai-jun (马海军), LI Jie (李捷), JIANG Mu-geng (蒋木庚), et al -(1, 2, 4-三唑-1-基)-乙酰苯-2-基脲类化合物的合成和生物活性[J]. *Zhejiang Chem Ind* (浙江化工), 2000, 31 (Suppl): 24-25.
- [5] WU Xia (吴霞), XU Jin (徐进), ZHANG Yi-bin (张一宾). 含脲结构的农药及其开发方向 [J]. *Modern Agrochemicals* (现代农药), 2004, 3(2): 32-35.
- [6] YUAN Li-ping (袁莉萍), CHEN Li-ang (陈亮), SHEN Zhou (沈宙), et al 取代苯丙酮脲衍生物及其制备方法和应用 [P]. CN 1640868 A, 2004-01-07.
- [7] Kost A N, Ershov V V. Reactions of hydrazine derivatives. Synthesis of pyrazolines by the Mannich reaction [J]. *Zhurnal Obshchei Khimii*, 1957, 27: 1072-1075.
- [8] Newkome G R, Fishel D L. Preparation of hydrazones: acetophenone hydrazone [J]. *Organic Synthesis*, 1970, 50: 102-104.
- [9] WANG Yuan-guang (王远光), YUAN Li-ping (袁莉萍), CHEN Li-ang (陈亮), et al 对氯苯丙酮脲衍生物的合成及生物活性 [J]. *Chin J Pestic Sci* (农药学报), 2005, 7(2): 114-118.

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