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·Research report·

Synthesis and Fungicidal Activities of (E)-α-Oxocyclododecanone Oxime Ethers

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Abstract: A series of (E)-α-oxocyclododecanone oxime ethers (**5**) were synthesized by oximation of cyclododecanone followed by etherification in yields of 59%～92%. Their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The (E)-configuration was confirmed by single crystal X-ray diffraction analysis of a representative compound (**5o**). Bioassay results showed that most of the title compounds present good fungicidal activities against Rhizoctonia solani, Cladosporium cucumerinum, Colletotrichum orbiculare, Botrytis cinerea, Fusarium oxysporum and Phomopsis asparagi. For example, the EC_{50} values of **5k** against mentioned-above six fungi were 13, 9, 12, 19, 14, 3 mg/L, respectively.

Key words: (E)-α-oxocyclododecanone oxime ether; synthesis; configuration; fungicidal activity

(E)-α-氧代环十二酮肟醚的合成及其杀菌活性

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摘 要: 由环十二酮先后经肟化和醚化反应合成了一系列(E)-α-氧代环十二酮肟醚, 收率59%～92%。其结构经IR, ^{1}H NMR, ^{13}C NMR确证。以化合物**5o**为代表, 通过单晶X衍射分析确证了其构型为E式。生物测定结果表明, 多数化合物对蔬菜苗期立枯病菌、黄瓜黑星病菌、黄瓜炭疽病菌、瓜类灰霉病菌, 棉花枯萎病菌和芦笋茎枯病菌的生长有良好的抑制活性。如**5k**对上述6种病原菌的EC_{50}值分别为13、9、12、19、14、3 mg/L。

关键词: (E)-α-氧代环十二酮肟醚; 合成; 构型; 杀菌活性
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In recent years, the pesticidal activities of 12-membered ring derivatives have been studied systematically and more than ten series of cyclododecanone derivatives have been synthesized in our laboratory. Previous results showed that most of them exhibited good pesticidal activities. For example, compounds in series **1**[1] and **2**[2] have good fungicidal activities and compounds in series **3**[3] and **4**[4] have good herbicidal activities.

It is also known that oxime ethers present fungicidal or antiviral activity[5～8]. In this paper we report the synthesis of a series of (E)-α-oxocyclododecanone oxime ethers (**5**) and their fungicidal activities against some economically important fungal species. **5**

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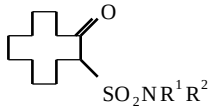
was synthesized by oximation of cyclododecanone followed by etherification (**Scheme 1**).



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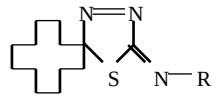

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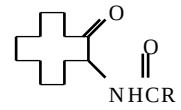

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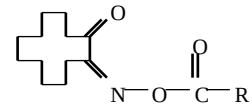

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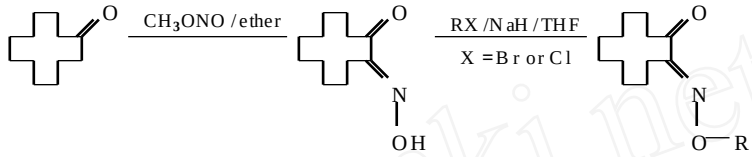
Scheme 1



5a **5b～5s**

1 Experimental

1.1 Apparatus and material

Shimadzu IR-435 spectrophotometer (KBr disk or liquid films); Bruker DPX300 spectrometer (TMS as internal standard, $CDCl_3$ or CD_3COCD_3 as solvent); ST-02 Elementary analyzer; Yanagimoto melting-point apparatus (The melting point was uncorrected). The solvents and reagents were used as received or dried prior to use as needed.

1.2 Synthesis of (E)-α-oxocyclododecanone oxime (5a)

Compound **5a** was prepared according to references[4,9].

1.3 Typical synthetic procedure for compounds 5b～5s

To a solution of NaH (0.013 mol) in THF (10 mL) was added a solution of **5a** (0.01 mol) in THF (10 mL) with stirring at room temperature and the mixture was then stirred at the same temperature for 1.5 h. A solution of alkyl halide (0.01 mol) in THF (12 mL) was added dropwise via a dropping funnel and the mixture was stirred for another 12 h. The solvent was removed under vacuum and the residue was treated with water (20 mL) and chloroform (20 mL). The organic phase was separated and washed with water, dried over anhydrous $MgSO_4$, and concentrated under vacuum to yield the crude product. Purification by silica gel column chromatography with hexane + ethyl acetate (1∶10 by volume) gave the target compounds of series 5.

1.4 X-ray diffraction analysis of 5o

A single crystal of compound **5o** was grown from a mixture of n-hexane and ethyl acetate (5∶1, V/V). The X-ray diffraction intensities were collected at room temperature from the single crystal (0.60 mm ×0.45 mm ×0.10 mm) on a Rigaku AFC 6S four circle X-ray diffractometer with Mo Kα radiation (λ = 0.071 073), by using the $\omega/2\theta$ scan technique. The intensities were collected for Lorentz-Polarization effects and empirical absorption. The structure was solved by using the Patterson method with subsequent difference-Fourier synthesis and refined by full-matrix least-squares method with anisotropic thermal factors. All the hydrogen atoms were placed in calculated positions. All the calculations were performed by using the SHELX-97 system of computer programs.

1.5 Bioassay of fungicidal activities

Fungicidal activities of compounds of series **5** against Rhizoctonia solani Kühn, Cladosporium cucumerinum Ell et Arthur, Colletotrichum orbiculare Arx, Botrytis cinerea Pers, Fusarium oxysporum Schl f. sp. and Phomopsis asparagi Bubak were evaluated using mycelium growth rate test according to reference[10]. Fungicidal activities of commercial fungicides carbendazim or procymidone as a control against mentioned-above six fungi were evaluated at the same condition.

2 Discussion and conclusion

2.1 Configuration of compounds in series 5

The physico-chemical and elementary analysis data of compounds in series **5** were shown in Table 1 and spectral data were shown in Table 2.

Selected crystal data of compound **5o** are shown in Table 3, and the crystal structure of compound **5o** is shown in Fig. 1.

Table 1 Physico-chemical and elemental analysis data of compounds **5b～5s**

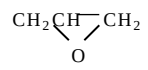
Compd.	R	Mp/℃	Yield (%)	Elemental analysis (Cacld., %)		
				C	H	N
5b	CH_3	/	65	69.68(69.30)	10.47(10.29)	6.23(6.22)
5c	Et	/	70	70.40(7025)	10.67(10.53)	5.84(5.85)
5d	n-Pr	/	63	71.33(71.10)	10.27(10.74)	5.92(5.53)
5e	n-Bu	/	61	71.90(71.86)	11.01(10.93)	5.41(5.24)
5f	$(CH_2)_2Br$	41.0～42.5	59	53.18(52.84)	7.71(7.60)	4.26(4.40)
5g	$CH_2CH=CH_2$	/	68	71.60(71.67)	10.01(10.02)	5.43(5.57)
5h		/	80	67.50(67.38)	9.60(9.42)	5.34(5.24)
5i	$(CH_2)_2CN$	/	84	68.37(68.15)	9.21(9.15)	11.01(10.60)
5j	CH_2CO_2H	100～101	86	62.26(62.43)	8.37(8.61)	4.98(5.20)
5k	$CH_2CO_2CH_3$	42～43	86	63.57(63.58)	8.85(8.89)	4.59(4.94)
5l	CH_2CONH_2	134～135	73	62.89(62.66)	9.13(9.01)	10.39(10.44)
5m	$C_6H_5CH_2$	/	92	75.84(75.71)	9.05(9.03)	4.59(4.65)
5n	4-$ClC_6H_4CH_2$	60～61	81	68.35(67.94)	7.96(7.80)	4.08(4.17)
5o	4-$FC_6H_4CH_2$	120～123	82	71.74(71.44)	8.20(8.20)	4.30(4.38)
5p	2-F-4-Br-$C_6H_3CH_2$	42～42.5	84	57.57(57.29)	6.28(6.33)	3.48(3.52)
5q	3,4-Cl_2-$C_6H_3CH_2$	52～53	82	61.57(61.63)	6.79(6.80)	3.62(3.78)
5r	2-F-6-Cl-$C_6H_3CH_2$	65～67	68	64.81(64.49)	7.21(7.12)	3.76(3.96)
5s	CH_2CONH-$C_6H_3(Me)_2$	36～38	88	71.17(70.94)	8.75(8.66)	7.54(7.52)

Table 2 Spectral data of compound **5b～5s**

Compds	^{1}H NMR, δ	^{13}C NMR, δ
5b	1.14～1.26(m, 12H), 1.43～1.53(m, 2H), 1.71～1.76(m, 2H), 2.60～2.64(m, 2H), 2.77～2.82(m, 2H), 4.02(s, 3H)	22.3, 23.1, 23.3, 23.4, 23.8, 24.5, 24.9, 26.1, 26.2, 38.0, 62.8, 158.6, 200.7
5c	1.21～1.36(m, 15H), 1.46～1.53(m, 2H), 1.72～1.76(m, 2H), 2.61～2.65(m, 2H), 2.78～2.82(m, 2H), 4.27(q, 2H, J=7.2 Hz)	14.8, 22.3, 23.1, 23.29, 23.31, 23.9, 24.5, 24.8, 26.1, 26.2, 38.1, 70.8, 158.3, 201.0
5d	0.98(t, 3H, J=7.5 Hz), 1.21～1.26(m, 12H), 1.43～1.51(m, 2H), 1.68～1.80(m, 4H), 2.61～2.66(2H, m), 2.77～2.81(m, 2H), 4.18(t, 2H, J=6.6 Hz)	10.2, 22.1, 22.5, 23.0, 23.2, 23.8, 24.5, 24.8, 26.0, 26.1, 37.9, 76.8, 158.1, 200.8
5e	0.96(t, 3H, J=7.4 Hz), 1.21～1.26(m, 12H), 1.39～1.51(m, 4H), 1.66～1.75(m, 4H), 2.61～2.65(m, 2H), 2.77～2.81(m, 2H), 4.22(t, 2H, J=6.6 Hz)	13.8, 19.0, 22.2, 23.1, 23.31, 23.33, 23.9, 24.5, 24.9, 26.0, 26.2, 31.3, 38.0, 75.1, 158.1, 200.9
5f	1.22～1.26(m, 12H), 1.49～1.53(m, 2H), 1.71～1.75(m, 2H), 2.64～2.69(m, 2H), 2.77～2.81(m, 2H), 3.60(t, 2H, J=6.2Hz), 4.49(t, 2H, J=6.2 Hz)	22.6, 23.1, 23.3, 23.8, 24.5, 25.0, 26.1, 26.2, 29.4, 38.2, 74.2, 159.6, 200.5
5g	1.22～1.26(m, 12H), 1.48～1.54(m, 2H), 1.71～1.75(m, 2H), 2.63～2.67(m, 2H), 2.77～2.81(m, 2H), 4.70～4.73(m, 2H), 5.23～5.37(m, 2H), 5.94～6.08(m, 1H)	22.4, 23.2, 23.34, 23.35, 23.8, 24.6, 24.9, 26.1, 38.2, 76.0, 118.0, 133.7, 158.8, 200.9
5h	1.22～1.26(m, 12H), 1.49～1.53(m, 2H), 1.72～1.76(m, 2H), 2.65～2.69(m, 3H), 2.78～2.82(m, 2H), 2.87(dd, 1H, J_1=4.8 Hz, J_2=4.2 Hz), 3.25～3.30(m, 1H), 4.20(1dd, H, J_1=12.0 Hz, J_2=5.9 Hz), 4.40(dd, 1H, J_1=12.0 Hz, J_2=3.6 Hz)	22.5, 23.1, 23.25, 23.31, 23.7, 24.5, 24.8, 26.1, 26.2, 38.2, 44.7, 50.0, 75.8, 159.3, 200.5
5i	1.23～1.28(m, 12H), 1.49～1.53(m, 2H), 1.67～1.73(m, 2H), 2.65～2.69(m, 2H), 2.76～2.82(m, 4H), 4.43(t, 2H, J=6.2 Hz)	22.6, 22.9, 23.1, 23.5, 24.4, 24.8, 25.9, 26.1, 38.1, 60.2, 69.0, 116.9, 160.2, 199.9

Continued

Compds	^{1}H NMR, δ	^{13}C NMR, δ
5j	1.22～1.27 (m, 12H), 1.47～1.51 (m, 2H), 1.69～1.74 (m, 2H), 2.67～2,71 (m, 2H), 2.74～2.79 (m, 2H), 4.81 (s, 2H)	22.8, 23.1, 23.2, 23.2, 23.3, 23.7, 24.5, 24.8, 26.2, 26.3, 38.5, 70.8, 160.1, 174.9, 200.4
5k	1.22～1.26 (m, 12H), 1.47～1.52 (m, 2H), 1.70～1.74 (m, 2H), 2.67～2.70 (m, 2H), 2.71～2.75 (m, 2H), 3.79 (s, 3H), 4.76 (s, 2H)	22.7, 23.09, 23.11, 23.2, 23.6, 24.5, 24.7, 26.1, 26.3, 38.5, 51.9, 71.4, 159.7, 169.6, 200.4
5l	1.22～1.26 (m, 12H), 1.54～1.58 (m, 2H), 1.70～1.74 (m, 2H), 2.70～2.74 (m, 2H), 2.77～2.81 (m, 2H), 4.72 (s, 2H), 5.65 (s, 1H), 6.05 (s, 1H)	23.0, 23.09, 23.12, 23.6, 24.4, 25.2, 26.1, 26.3, 38.3, 73.8, 160.7, 171.4, 199.9
5m	1.10～1.18 (m, 12H), 1.43～1.47 (m, 2H), 1.61～1.65 (m, 2H), 5.23 (m, 2H), 7.31～7.41 (m, 5H)	22.3, 23.1, 23.15, 23.17, 23.7, 24.4, 24.8, 26.0, 26.1, 38.0, 77.2, 128.0, 128.3, 128.5, 137.2, 158.7, 200.6
5n	1.10～1.18 (m, 12H), 1.42～1.46 (m, 2H), 1.58～1.62 (m, 2H), 2.61～2.65 (m, 2H), 2.73～2.77 (m, 2H), 5.19 (s, 2H), 7.30～7.34 (m, 4H)	22.5, 23.08, 23.13, 23.8, 24.4, 24.8, 26.0, 26.2, 38.2, 76.4, 128.6, 130.0, 134.1, 135.8, 159.1, 200.6
5o	1.08～1.18 (m, 12H), 1.42～1.46 (m, 2H), 1.60～1.64 (m, 2H), 2.61～2.65 (m, 2H), 2.73～2.78 (m, 2H), 5.19 (s, 2H), 7.02～7.07 (m, 2H), 7.34～7.39 (m, 2H)	22.4, 23.11, 23.14, 23.8, 24.4, 24.8, 26.03, 26.10, 76.4 (d, J_{C-F} = 0.5 Hz), 115.2 (d, J_{C-F} = 21.5 Hz), 130.5 (d, J_{C-F} = 8.2 Hz), 133.1 (d, J_{C-F} = 3.2 Hz), 158.9, 162.7 (d, J_{C-F} = 246.6 Hz), 200.6
5p	1.06～1.17 (m, 12H), 1.38～1.47 (m, 2H), 1.56～1.60 (m, 2H), 5.24 (s, 2H), 7.24～7.33 (m, 3H)	22.4, 23.01, 23.048, 23.054, 23.8, 24.4, 24.6, 26.0, 26.1, 38.2, 70.0 (d, J_{C-F} = 2.9 Hz), 119.1 (d, J_{C-F} = 24.8 Hz), 122.7 (d, J_{C-F} = 9.5 Hz), 123.8 (d, J_{C-F} = 14.9 Hz), 127.4 (d, J_{C-F} = 3.7 Hz), 132.3 (d, J_{C-F} = 4.8 Hz), 159.3 (d, J_{C-F} = 2.0 Hz), 162.6, 200.5
5q	1.06～1.20 (m, 12H), 1.41～1.45 (m, 2H), 1.49～1.60 (m, 2H), 2.61～2.64 (m, 2H), 2.72～2.76 (m, 2H), 5.17 (s, 2H), 7.12～7.26 (m, 1H), 7.42～7.50 (m, 2H)	22.5, 22.9, 23.0, 23.1, 23.7, 24.3, 24.8, 26.0, 26.2, 38.2, 75.6, 127.9, 130.4, 130.7, 132.3, 132.6, 137.6, 159.4, 200.4
5r	1.05～1.13 (m, 12H), 1.35～1.44 (m, 2H), 1.49～1.59 (m, 2H), 2.57～2.61 (m, 2H), 2.73～2.77 (m, 2H), 5.43 (s, 2H), 6.98～7.04 (m, 1H), 7.20～7.31 (m, 2H)	22.2, 22.9, 23.0, 23.1, 23.9, 24.37, 24.44, 26.0, 26.1, 38.2, 67.1 (d, J_{C-F} = 2.6 Hz), 114.1 (d, J_{C-F} = 22.9 Hz, 123.4 (d, J_{C-F} = 17.6 Hz), 125.3 (d, J_{C-F} = 3.5 Hz), 130.6 (d, J_{C-F} = 9.8 Hz), 136.7 (d, J_{C-F} = 5.3 Hz), 158.9, 162.3 (d, J_{C-F} = 252 Hz), 200.8
5s	1.21～1.25 (m, 12H), 1.54～1.58 (m, 2H), 1.72～1.76 (m, 2H), 2.23 (s, 6H), 2.75～2.79 (m, 2H), 2.81～2.85 (m, 2H), 4.90 (s, 2H), 2.81～2.85 (m, 2H), 4.90 (s, 2H), 7.07～7.16 (m, 2H), 7.26～7.32 (m, 1H)	18.4, 23.0, 23.1, 23.2, 23.3, 23.7, 24.4, 25.3, 26.0, 26.3, 38.2, 74.1, 127.7, 128.3, 132.6, 135.2, 161.2, 167.2, 199.8

Table 3 Selected crystal data for compound **5o**

Crystal system	Space group	Unit cell dimensions	v	Dc
Triclinic	P-1	a = 0.892 3(2) nm, α = 94.05(2) b = 1.256 3(3) nm, β = 91.49(1) c = 0.807 2(2) nm, γ = 89.81(1)	0.902 3(4) nm^3	1.176 g/cm^3

Configuration of α-oxocyclododecanone oxime (**5a**) was studied by Beckmann reaction. The result indicated that **5a** has an E-configuration[4]. In this paper, the Ycrystal structure of a derivative of **5**, O-(4-fluorobenzyl)-α-oxocyclododecanone oxime (**5o**) was determined, which not only confirmed the E-configuration of **5a** but also showed that the configuration of **5a** was not changed during the etherification. Thus other compounds in series **5** can also be assumed to have an E-configuration.

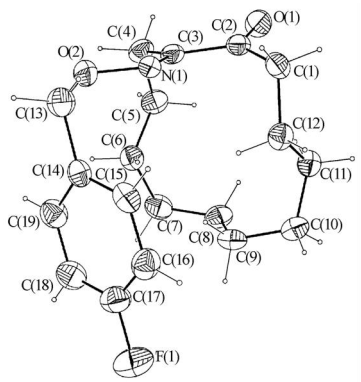


Fig. 1 Crystal structure of compound **5o**

2.2 Fungicidal activities

As shown in Table 4, most of the compounds in series **5** exhibit good fungicidal activities against six fungal species. Although their activities against R. solani, C. cucumerinum, B. cinerea, F. oxysporum and P. asparagi were lower than commercial fungicides carbendazim or procymidone, but the activity of **5k, 5p** and **5q** against C. orbiculare is higher than that of carbendazim. These results will be useful for the next designing step.

Table 4 Toxicity of compounds **5b**～**5s** against six fungal species [EC_{50}/(mg/L)]

Compds	Rhizoctonia solani	Cladosporium cucumerinum	Colletotrichum orbiculare	Botrytis cinerea	Fusarium oxysporum	Phomopsis asparagi
5b	15	32	50	/	60	18
5c	22	9	25	65	11	16
5d	12	16	76	12	/	39
5e	/	23	/	68	/	48
5f	67	39	39	30	/	15
5g	22	28	45	80	/	15
5h	12	9	33	25	6	11
5i	13	24	19	38	18	10
5j	69	17	/	25	54	/
5k	13	9	12	19	14	3
5l	43	/	/	20	/	/
5m	/	/	/	/	/	/
5n	/	/	/	/	/	/
5o	/	35	/	/	/	/
5p	/	39	14	28	40	17
5q	/	/	14	14	/	/
5r	/	/		/		/
5s	/	34	/	15	61	/
Carbendazim	2	1	17	/	2	1
Procymidone	/	/	/	3	/	/

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