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Synthesis and Fungicidal Activity of Novel 2-Oxocycloalkylsulfonylureas

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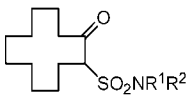
A series of 2-oxocycloalkylsulfonylureas (**2**) have been synthesized in a six-step, three-pot reaction sequence from readily available cyclododecanone, cycloheptanone, and cyclohexanone. Their structures were confirmed by IR, ^{1}H NMR, and elemental analysis. The bioassay indicated that some of them possess certain fungicidal activity against *Gibberella zeae* Petch. In general, compounds containing a 12-membered ring (**2A**) are more active than those containing a 6- or 7-membered ring (**2B**, **2C**). In the series **2A**, the compounds in which R is a disubstituted phenyl or pyrimidyl showed better activity than those in which R is a monosubstituted phenyl or pyrimidyl, and aryl-substituted compounds have somewhat higher activity than those substituted by pyrimidyl. The further bioassay showed that the representative of **2A**, **2A$_{15}$**, has good fungicidal activities against not only *G. zeae* Petch but also *Botrytis cinerea* Pers, *Colletotrichum orbiculare* Arx, *Pythium aphanidermatum* Fitzp, *Fusarium oxysporum* Schl. f. sp. Vasinfectum, etc.

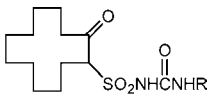
KEYWORDS: 2-Oxocycloalkylsulfonylurea; synthesis; fungicidal activity

1. INTRODUCTION

In the searching for potential pesticides, more than 10 series of cyclododecanone derivatives have been synthesized and their biological activities evaluated. Among them, 2-oxocyclododecylsulfonamides (**1**) were found to be active against *Gibberella*



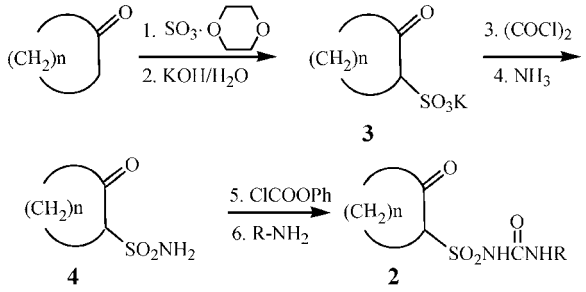
1



2A

zeae Petch (*1*). To our surprise, QSAR study (CoMFA) (*2*) showed that 2-oxocyclododecylsulfonylureas (**2A**) may have higher predicted activity. It is known that some types of sulfonylureas are highly efficient chemical herbicides and hypoglycemic agents such as glimepiride (*3*). However, very little of their fungicidal activities was studied. It was of interest for us to synthesize and evaluate their fungicidal activity. Meanwhile, to study the relationship between the size of the ring and their activity, 2-oxocycloheptylsulfonamides (**2B**) and 2-oxocyclohexylsulfonamides (**2C**) were also synthesized. The synthetic route of the title compounds (**2**) is shown in **Scheme**

Scheme 1. Synthetic Route to the Title Compounds **2**



A, n=10 ; B, n=5 ; C, n=4

1. Potassium 2-oxocycloalkylsulfonates (**3**), prepared from readily available cycloalkanones by sulfonation with a sulfur trioxide−dioxane adduct and neutralization with potassium hydroxide, were allowed to react with oxalyl chloride to give corresponding sulfonyl chlorides, which were converted into sulfonamides (**4**) using NH_3. The reaction of **4** with phenyl chloroformate and amines successively afforded title compounds 2-oxocycloalkylsulfonylureas (**2**).

Fungicidal activities of compounds **2** against some economically important fungus species were evaluated, and one of the compounds **1**, *N*-(4-chlorophenyl)-2-oxocyclododecylsulfonamide (**1c**), was synthesized and used as a control in the bioassay.

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Table 1. Physical and Elemental Data of Compounds **2**

				elemental analysis (%)		
compd	R	yield (%)	mp (°C)	C (calcd)	H (calcd)	N (calcd)
2A$_1$	4-methyl-2-pyrimidyl	47	147–148	54.03 (54.52)	7.04 (7.12)	13.73 (14.13)
2A$_2$	4-chloro-6-methoxy-2-pyrimidyl	58	134–136	47.89 (48.37)	6.34 (6.09)	12.76 (12.54)
2A$_3$	4,6-dimethoxy-2-pyrimidyl	74	164–166	51.20 (51.57)	7.28 (6.83)	12.68 (12.66)
2A$_4$	4,6-dimethyl-2-pyrimidyl	47	131–132	55.58 (55.59)	7.40 (7.37)	13.62 (13.65)
2A$_5$	4,6-diethyl-2-pyrimidyl	67	136–138	53.32 (53.60)	7.46 (7.28)	11.47 (11.91)
2A$_6$	4,6-dipropyl-2-pyrimidyl	58	120–122	55.23 (55.40)	7.88 (7.68)	11.10 (11.24)
2A$_7$	4,6-diisopropyl-2-pyrimidyl	60	158–160	54.97 (55.40)	7.75 (7.68)	10.79 (11.24)
2A$_8$	*p*-tolyl	51	134–136	60.49 (60.89)	8.19 (7.66)	7.21 (7.10)
2A$_9$	*p*-methoxyphenyl	52	102–104	58.52 (58.51)	7.40 (7.37)	6.82 (6.82)
2A$_{10}$	*p*-chlorophenyl	56	148–149	54.80 (55.00)	6.71 (6.56)	6.86 (6.75)
2A$_{11}$	*o*-chlorophenyl	50	142–144	54.96 (55.00)	7.03 (6.56)	6.77 (6.75)
2A$_{12}$	5-oxa-6-oxocyclohexadec-1-yl	36	150–152	61.71 (61.96)	9.64 (9.29)	5.53 (5.16)
2A$_{13}$	*p*-fluorophenyl	43	147–149	57.12 (57.27)	7.09 (6.83)	6.83 (7.03)
2A$_{14}$	3,4-dichlorophenyl	63	163–164	50.70 (50.78)	5.83 (5.83)	6.16 (6.23)
2A$_{15}$	2,5-dichlorophenyl	67	150–152	50.65 (50.78)	6.23 (5.83)	6.56 (6.23)
2A$_{16}$	*m*-tolyl	33	144–146	60.84 (60.89)	7.62 (7.66)	7.08 (7.10)
2A$_{17}$	3,4-xylyl	58	148–150	61.75 (61.74)	8.00 (7.89)	6.90 (6.86)
2A$_{18}$	*m*-nitrophenyl	60	162–164	53.69 (53.63)	6.42 (6.40)	9.88 (9.88)
2A$_{19}$	*m*-chlorophenyl	54	146–148	55.46 (55.00)	6.47 (6.56)	6.58 (6.75)
2A$_{20}$	*p*-acetylphenyl	46	137–139	59.91 (59.69)	7.51 (7.16)	6.82 (6.63)
2B$_1$	2,5-dichlorophenyl	57	152–153	44.28 (44.34)	4.27 (4.25)	7.28 (7.39)
2B$_2$	2,4-xylyl	50	120–121	56.85 (56.78)	6.61 (6.55)	8.24 (8.28)
2B$_3$	4,6-dimethoxy-2-pyrimidyl	62	147–148	45.20 (45.15)	5.49 (5.41)	15.06 (15.04)
2B$_4$	*p*-chlorophenyl	55	161–162	49.24 (48.77)	5.07 (4.97)	8.10 (8.12)
2B$_5$	*p*-tolyl	52	138–139	55.54 (55.54)	6.27 (6.21)	8.67 (8.64)
2B$_6$	3,4-dichlorophenyl	43	150–151	44.40 (44.34)	4.29 (4.25)	7.28 (7.39)
2C$_1$	2,5-dichlorophenyl	30	145–146	43.05 (42.75)	3.91 (3.86)	7.59 (7.67)
2C$_2$	2,4-xylyl	35	140–141	55.85 (55.54)	6.27 (6.21)	8.66 (8.64)
2C$_3$	4,6-dimethoxy-2-pyrimidyl	60	141–143	43.66 (43.57)	5.10 (5.06)	15.62 (15.63)
2C$_4$	4-chlorophenyl	43	154–155	47.10 (47.20)	4.59 (4.57)	8.38 (8.47)
2C$_5$	*p*-tolyl	33	146–147	54.22 (54.18)	5.91 (5.85)	8.96 (9.03)
2C$_6$	3,4-dichlorophenyl	36	161–162	42.99 (42.75)	3.89 (3.86)	7.53 (7.67)

2. MATERIALS AND METHODS

2.1. General. Infrared spectra were recorded in potassium bromide disks on a Shimadzu IR-435 spectrophotometer; NMR spectra were recorded in $CDCl_3$, CD_3COCD_3, or DMSO-d_6 unless otherwise indicated with a Bruker DPX300 spectrometer, using TMS as internal standard; elemental analysis was performed by the analytical center at the Institute of Chemistry (Beijing), Chinese Academy of Science; melting points were measured on a Yanagimoto melting-point apparatus and are uncorrected. The solvents and reagents were used as received or were dried prior to use as needed.

2.2. Chemical Synthesis. *2.2.1. N-(4-Chlorophenyl)-2-oxocyclododecylsulfonamide (**1c**).* Compound **1c** was prepared according to the method given in ref *1*.

*2.2.2. Potassium 2-Oxocyclododecylsulfonate (**3A**).* Compound **3A** was prepared according to the method given in ref *1*.

*2.2.3. Potassium 2-Oxocycloheptylsulfonate (**3B**).* To a solution of cycloheptanone (11.5 g, 0.10 mol) in 1,2-dichloroethane (40 mL) at 5 °C under a nitrogen atmosphere was added sulfur trioxide−dioxane adduct (20.7 g, 0.12 mol) portion by portion within 15 min. The mixture was stirred for 3 h in an ice−water bath. Water (40 mL) was poured into the mixture. The aqueous layer was separated, and the organic layer was extracted with water (10 mL × 3). The combined aqueous layer was treated with $Ba(OH)_2 \cdot 8H_2O$ until no $BaSO_4$ precipitate could be observed, then filtered, and the filtrate was neutralized to pH 7−8 with potassium hydroxide. The aqueous solution was concentrated to dryness at reduced pressure. The resulting yellow solid was recrystallized in methanol to give 15 g of white solid (66%): mp 268−270 °C; ^{1}H NMR (D_2O) δ 1.07−1.39 (m, 3H), 1.75−1.98 (m, 4H), 2.22−2.31 (m, 1H), 2.38−2.45 (m, 1H), 2.72−2.81 (m, 1H), 3.80 (dd, 1H, $J_{\alpha,\beta1}$ = 11.5 Hz, $J_{\alpha,\beta2}$ = 5.0 Hz).

*2.2.4. Potassium 2-Oxocyclohexylsulfonate (**3C**).* The reaction was run similarly to that used to synthesize **3B**. After the reaction was completed, water was poured into the reaction mixture. The aqueous layer was separated, and the organic layer was extracted with water. The combined aqueous layer was treated with $Ba(OH)_2 \cdot 8H_2O$ until no $BaSO_4$ precipitate could be observed, then filtered, and the filtrate was neutralized to pH 7−8 with potassium hydroxide. Concentration of the aqueous solution at reduced pressure gave a yellow oil, which was cooled in an ice−water bath to give the first portion of yellow solid (D). To the filtrate was added 4 equivalent volumes of methanol. It was heated and then filtered to give the second portion of yellow solid (E), which was identified as disulfonated product [^{1}H NMR (D_2O) δ 1.87−1.95 (m, 2H), 2.08−2.17 (m, 2H), 2.21−2.37 (m, 2H), 3.98−4.03 (m, 2H)]. The filtrate was concentrated again at reduced pressure and then methanol added. After 24 h of standing, filtration gave the third portion of yellow solid (F). All of D and F were **3C** as identified by ^{1}H NMR, which could be recrystallized from methanol: yield, 56%; mp 235−238 °C; ^{1}H NMR (D_2O) δ 1.52−2.03 (m, 5H), 2.22−2.46 (m, 3H), 3.76 (dd, 1H, $J_{\alpha,\beta1}$ = 6.3 Hz, $J_{\alpha,\beta2}$ = 8.5 Hz).

*2.2.5. 2-Oxocyclododecylsulfonamide (**4A**).* To the slurry of **3A** (12 g, 0.04 mol) and DMF (0.1 mL) in methylene chloride (60 mL) was added oxalyl chloride (3.4 mL, 0.04 mol); the mixture was stirred under reflux for 1.5 h. After the slurry had been cooled in an ice−water bath, it was filtered at reduced pressure before NH_3(g) was introduced into the ice-cold filtrate. Ammonia was added until the pH rose to 7−8. The mixture was treated with water and extracted with methylene chloride. The combined organic layer was washed with water, dried over sodium sulfate, and evaporated to give a white solid, which was recrystallized from benzene to give 6.8 g of **4A** (65%): mp 150−151 °C; ^{1}H NMR ($CDCl_3$) δ 1.22−1.42 (m, 14H), 1.75−1.81 (m, 2H,), 2.02−2.06 (m, 1H), 2.23−2.33 (m, 1H), 2.62−2.71 (m, 1H), 2.94−3.03 (m, 1H), 4.34 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 3.1 Hz), 4.67 (s, 2H); IR ν 3350, 3250, 2920, 2850, 1705, 1315, 1150 cm^{-1}.

*2.2.6. 2-Oxocycloheptylsulfonamide (**4B**).* The reaction was run similarly to that used to synthesize **4A**. A white solid was obtained, and it was recrystallized from benzene/petroleum ether to give **4B** in 61% yield: mp 75−76 °C [lit. (*4*) 76−78 °C].

*2.2.7. 2-Oxocyclohexylsulfonamide (**4C**).* The reaction was run similarly to that used to synthesize **4A**. The crude product was

Table 2. ^{1}H NMR and IR Data of Compounds **2**

compd	^{1}H NMR, δ	IR (ν, cm^{-1})
2A$_1$	1.20–1.40 (m, 14H), 1.62–1.69 (m, 2H), 1.86–2.05 (m, 2H), 2.53 (s, 3H), 2.81–2.98 (m, 2H), 4.88 (dd, 1H, $J_{\alpha,\beta1}$ = 11.9 Hz, $J_{\alpha,\beta2}$ = 2.7 Hz), 6.93 (d, 1H, J = 5.2 Hz), 8.48 (d, 1H, J = 5.0 Hz), 8.50 (s, 1H), 12.53 (s, 1H)	3400, 3150, 3080, 2920, 2860, 1720, 1600, 1340, 1155
2A$_2$	1.21–1.40 (m, 14H), 1.65–1.71 (m, 2H), 1.86–2.07 (m, 2H), 2.81–2.92 (m, 2H), 3.98 (s, 3H), 4.82 (dd, 1H, $J_{\alpha,\beta1}$ = 11.7 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 6.50 (s, 1H), 7.60 (s, 1H), 12.53 (s, 1H)	3250, 3150, 3080, 2920, 2860, 1715, 1590, 1360, 1160
2A$_3$	1.21–1.42 (m, 14H), 1.63–1.85 (m, 2H), 1.99–2.44 (m, 2H), 2.77–2.97 (m, 2H), 3.91 (s, 6H), 4.85 (dd, 1H, $J_{\alpha,\beta1}$ = 11.6 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 5.79 (s, 1H), 7.42 (s, 1H), 12.51 (s, 1H)	3200, 3150, 3030, 2920, 2860, 1720, 1610, 1360, 1150
2A$_4$	1.22–1.43 (m, 14H), 1.63–1.90 (m, 2H), 2.00–2.49 (m, 2H), 2.45 (s, 6H), 2.80–2.98 (m, 2H), 4.88 (dd, 1H, $J_{\alpha,\beta1}$ = 11.9 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 6.78 (s, 1H), 7.97 (s, 1H), 12.40 (s, 1H)	3250, 3180, 2920, 2860, 1710, 1600, 1340, 1155
2A$_5$	1.33–1.41 (m, 20H), 1.66–1.87 (m, 2H), 1.98–2.44 (m, 2H), 2.77–2.98 (m, 2H), 4.29 (q, 4H, J = 7.1 Hz), 4.87 (dd, 1H, $J_{\alpha,\beta1}$ = 11.7 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 5.73 (s, 1H), 7.33 (s, 1H), 12.49 (s, 1H)	3350, 3220, 3150, 2920, 2860, 1720, 1700, 1610, 1340, 1160
2A$_6$	1.02 (t, 6H, J = 7.5 Hz), 1.21–1.41 (m, 14H), 1.65–1.87 (m, 6H), 2.00–2.44 (m, 2H), 2.78–2.93 (m, 2H), 4.18 (t, 4H, J = 6.6 Hz), 4.86 (dd, 1H, $J_{\alpha,\beta1}$ = 11.8 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 5.75 (s, 1H), 7.32 (s, 1H), 12.51 (s, 1H)	3150, 3090, 2920, 2860, 1735, 1710, 1605, 1350, 1150
2A$_7$	1.20–1.41 (m, 26H), 1.66–1.89 (m, 2H), 1.97–2.44 (m, 2H), 2.72–2.99 (m, 2H), 4.89 (dd, 1H, $J_{\alpha,\beta1}$ = 11.8 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 5.05–5.11 (m, 2H), 5.66 (s, 1H), 7.26 (s, 1H), 12.44 (s, 1H)	3240, 3180, 3060, 2920, 2860, 1720, 1700, 1610, 1360, 1155
2A$_8$	1.21–1.41 (m, 14H), 1.73–1.75 (m, 2H), 2.04–2.46 (m, 2H), 2.31 (s, 3H), 2.65–2.98 (m, 2H), 4.58 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 2.9 Hz), 7.12 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.3 Hz), 8.19 (s, 1H), 8.48 (s, 1H)	3350, 3150, 3030, 2920, 2860, 1710, 1695, 1610, 1345, 1140
2A$_9$	1.21–1.40 (m, 14H), 1.74–1.76 (m, 2H), 2.00–2.44 (m, 2H), 2.65–2.98 (m, 2H), 3.79 (s, 3H), 4.57 (d, 1H, J = 9.4 Hz), 6.82–6.87 (m, 2H), 7.25–7.30 (m, 2H), 8.12 (s, 1H), 8.69 (s, 1H)	3350, 3160, 3060, 2920, 2860, 1710, 1690, 1610, 1350, 1140
2A$_{10}$	1.24–1.43 (m, 14H), 1.72–1.76 (m, 2H), 2.03–2.42 (m, 2H), 2.63–2.98 (m, 2H), 4.55 (dd, 1H, $J_{\alpha,\beta1}$ = 11.1 Hz, $J_{\alpha,\beta2}$ = 3.1 Hz), 7.26–7.37 (m, 4H), 8.24 (s, 1H), 8.33 (s, 1H)	3350, 3210, 2920, 2850, 1725, 1705, 1600, 1335, 1150
2A$_{11}$	1.22–1.42 (m, 14H), 1.73–1.79 (m, 2H), 2.05–2.46 (m, 2H), 2.66–3.01 (m, 2H), 4.53 (dd, 1H, $J_{\alpha,\beta1}$ = 11.3 Hz, $J_{\alpha,\beta2}$ = 3.2 Hz), 7.05–7.11 (m, 1H), 7.28–7.31 (m, 1H), 7.37–7.40 (m, 1H), 8.13–8.16 (m, 1H), 7.95 (s, 1H), 8.88 (s, 1H)	3300, 3150, 3050, 2920, 2860, 1720, 1700, 1600, 1355, 1140
2A$_{12}$	1.23–1.77 (m, 38H), 1.97–2.01 (m, 1H), 2.31–2.40 (m, 3H), 2.71–2.75 (m, 1H), 2.86–2.94 (m, 1H), 3.86 (s, 1H), 4.08–4.21 (m, 2H), 4.41 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 2.0 Hz), 6.32 (d, 1H, J = 8.6 Hz), 8.31 (s, 1H)	3300, 3250, 2920, 2860, 1730, 1705, 1690, 1530, 1340, 1155
2A$_{13}$	1.22–1.43 (m, 14H), 1.70–1.76 (m, 2H), 2.03–2.43 (m, 2H), 2.64–2.98 (m, 2H), 4.56 (dd, 1H, $J_{\alpha,\beta1}$ = 11.1 Hz, $J_{\alpha,\beta2}$ = 3.2 Hz), 6.99–7.06 (m, 2H), 7.33–7.38 (m, 2H), 8.27 (s, 1H), 8.37 (s, 1H)	3350, 3250, 3080, 2920, 2860, 1720, 1710, 1620, 1330, 1150
2A$_{14}$	1.21–1.41 (m, 14H), 1.65–1.89 (m, 2H), 1.99–2.36 (m, 2H), 2.65–3.03 (m, 2H), 5.04 (dd, 1H, $J_{\alpha,\beta1}$ = 11.7 Hz, $J_{\alpha,\beta2}$ = 3.0 Hz), 7.43 (dd, 1H, J = 8.8 Hz, 2.5 Hz), 7.53 (d, 1H, J = 8.8 Hz), 7.86 (d, 1H, J = 2.5 Hz), 8.66 (s, 1H), 9.70 (s, 1H)	3290, 3200, 2920, 2860, 1708, 1580, 1340, 1148
2A$_{15}$	1.22–1.42 (m, 14H), 1.73–1.80 (m, 2H), 2.02–2.46 (m, 2H), 2.65–3.02 (m, 2H), 4.54 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 3.2 Hz), 7.06 (dd, 1H, J = 8.6, 2.5 Hz), 7.31 (d, 1H, J = 8.6 Hz), 8.26 (d, 1H, J = 2.5 Hz), 8.14 (s, 1H), 8.96 (s, 1H)	3300, 3150, 3080, 2920, 2860, 1715, 1695, 1595, 1360, 1140
2A$_{16}$	1.22–1.43 (m, 14H), 1.74–1.76 (m, 2H), 2.04–2.40 (m, 2H), 2.34 (s, 3H), 2.68–2.97 (m, 2H), 4.55 (dd, 1H, $J_{\alpha,\beta1}$ = 11.1 Hz, $J_{\alpha,\beta2}$ = 2.8 Hz), 6.95–6.98 (m, 1H), 7.21–7.22 (m, 3H), 8.10 (s, 1H), 8.24 (s, 1H)	3350, 3180, 2920, 2860, 1710, 1670, 1615, 1340, 1150
2A$_{17}$	1.21–1.42 (m, 14H), 1.70–1.77 (m, 2H), 1.99–2.07 (m, 1H), 2.20 (s, 3H), 2.29 (s, 3H), 2.33–2.45 (m, 1H), 2.66–2.97 (m, 2H), 4.55 (dd, 1H, $J_{\alpha,\beta1}$ = 11.4 Hz, $J_{\alpha,\beta2}$ = 2.4 Hz), 7.01 (d, 2H, J = 5.5 Hz), 7.53 (s, 1H), 8.11 (s, 1H), 8.50 (s, 1H)	3350, 3150, 3050, 2920, 2860, 1710, 1695, 1605, 1345, 1140
2A$_{18}$	1.22–1.42 (m, 14H), 1.68–2.03 (m, 2H), 2.04–2.37 (m, 2H), 2.67–3.05 (m, 2H), 5.04 (dd, 1H, $J_{\alpha,\beta1}$ = 11.7 Hz, $J_{\alpha,\beta2}$ = 3.0 Hz), 7.61–7.66 (m, 1H), 7.83–7.87 (m, 1H), 7.95–7.99 (m, 1H), 8.54–8.56 (m, 1H), 8.89 (s, 1H), 9.80 (s, 1H)	3300, 3260, 2920, 2860, 1710, 1605, 1350, 1160
2A$_{19}$	1.22–1.42 (m, 14H), 1.67–2.03 (m, 2H), 2.04–2.36 (m, 2H), 2.66–3.04 (m, 2H), 5.05 (dd, 1H, $J_{\alpha,\beta1}$ = 11.7 Hz, $J_{\alpha,\beta2}$ = 3.0 Hz), 7.11–7.72 (m, 4H), 8.63 (s, 1H), 9.68 (s, 1H)	3350, 3250, 3080, 2920, 2860, 1720, 1710, 1600, 1335, 1150
2A$_{20}$	1.23–1.43 (m, 14H), 1.73–1.76 (m, 2H), 2.06–2.39 (m, 2H), 2.59 (s, 3H), 2.66–2.99 (m, 2H), 4.61 (dd, 1H, $J_{\alpha,\beta1}$ = 11.1 Hz, $J_{\alpha,\beta2}$ = 3.1 Hz), 7.54 (d, 2H, J = 8.7 Hz), 7.95 (d, 2H, J = 8.7 Hz), 8.39 (s, 1H), 8.56 (s, 1H)	3370, 3250, 3080, 2920, 2860, 1720, 1680, 1600, 1340, 1150
2B$_1$	1.46–1.53 (m, 3H), 1.89–1.93 (m, 2H), 2.03–2.12 (m, 2H), 2.50–2.58 (m, 2H), 2.76–2.86 (m, 1H), 4.60 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 4.8 Hz), 7.17 (dd, 1H, J = 8.6, 2.2 Hz), 7.50 (d, 1H, J = 8.6 Hz), 8.33 (d, 1H, J = 2.5 Hz), 8.58 (s, 1H), 9.89 (s, 1H)	3200, 3150, 2800, 1700, 1680, 1580, 1345, 1150
2B$_2$	1.39–1.59 (m, 3H), 1.91–1.98 (m, 2H), 2.02–2.10 (m, 2H), 2.20 (s, 3H), 2.28 (s, 3H), 2.47–2.56 (m, 1H), 2.60–2.76 (m, 2H), 4.38–4.40 (d, 1H, J = 7.4 Hz), 6.99 (s, 2H), 7.55 (s, 1H), 8.04 (s, 1H), 8.36 (s, 1H)	3320, 3200, 3080, 2920, 2880, 1700, 1665, 1600, 1330, 1140
2B$_3$	1.35–1.52 (m, 3H), 1.93–1.97 (m, 2H), 2.07–2.19 (m, 2H), 2.53–2.61 (m, 2H), 2.77–2.85 (m, 1H), 3.90 (s, 6H), 4.56 (dd, 1H, $J_{\alpha,\beta1}$ = 11.5 Hz, $J_{\alpha,\beta2}$ = 4.7 Hz), 5.78 (s, 1H), 7.51 (s, 1H), 12.48 (s, 1H)	3250, 3200, 3100, 3020, 2920, 2850, 1720, 1620, 1340, 1150
2B$_4$	1.27–1.45 (m, 3H), 1.79–2.03 (m, 4H), 2.29–2.37 (m, 1H), 2.46–2.52 (m, 1H), 2.67–2.76 (m, 1H), 4.56 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 4.9 Hz), 7.34–7.39 (m, 2H), 7.43–7.48 (m, 2H), 9.00 (s, 1H), 9.98 (s, 1H)	3380, 3200, 2920, 2880, 1710, 1600, 1320, 1140

Table 2 (Continued)

compd	^{1}H NMR, δ	IR (ν, cm^{-1})
2B$_5$	1.41–1.52 (m, 3H), 1.89–2.09 (m, 4H), 2.30 (s, 3H), 2.49–2.51 (m, 1H), 2.64–2.71 (m, 2H), 4.43 (dd, 1H, $J_{\alpha,\beta1}$ = 10.8 Hz, $J_{\alpha,\beta2}$ = 3.9 Hz), 7.10 (d, 2H, J = 8.3 Hz), 7.27 (d, 2H, J = 8.1 Hz), 8.14 (s, 1H), 8.34 (s, 1H)	3270, 3320, 2920, 2850, 1710, 1600, 1330, 1140
2B$_6$	1.24–1.45 (m, 3H), 1.79–2.03 (m, 4H), 2.29–2.38 (m, 1H), 2.46–2.52 (m, 1H), 2.67–2.76 (m, 1H), 4.56 (dd, 1H, $J_{\alpha,\beta1}$ = 11.2 Hz, $J_{\alpha,\beta2}$ = 4.9 Hz), 7.37 (dd, 1H, J = 8.9, 2.6 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.81 (d, 1H, J = 2.5 Hz), 9.18 (s, 1H), 10.79 (s, 1H)	3350, 3200, 3110, 2920, 2850, 1710, 1610, 1580, 1370, 1130
2C$_1$	1.72–1.88 (m, 2H), 2.05–2.23 (m, 3H), 2.37–2.47 (m, 1H), 2.47–2.74 (m, 2H), 4.24 (dd, 1H, $J_{\alpha,\beta1}$ = 11.8 Hz, $J_{\alpha,\beta2}$ = 5.4 Hz), 7.04 (dd, 1H, J = 8.6, 2.4 Hz), 7.30 (d, 1H, J = 8.6 Hz), 8.26 (d, 1H, J = 2.4 Hz), 8.04 (s, 1H), 8.98 (s, 1H)	3320, 3205, 2920, 2860, 1720, 1680, 1580, 1345, 1150
2C$_2$	1.82–1.88 (m, 2H), 1.96–2.06 (m, 3H), 2.21–2.29 (m, 7H), 2.48–2.54 (m, 2H), 4.63 (dd, 1H, $J_{\alpha,\beta1}$ = 9.3 Hz, $J_{\alpha,\beta2}$ = 5.8 Hz), 6.97–7.01 (m, 2H), 7.60–7.64 (m, 1H), 8.00 (s, 1H), 9.30 (s, 1H)	3380, 3300, 3160, 2920, 2860, 1705, 1680, 1600, 1355, 1160
2C$_3$	1.85–2.06 (m, 4H), 2.29 (m, 1H), 2.42–2.56 (m, 3H), 3.95 (s, 6H), 4.57 (dd, 1H, $J_{\alpha,\beta1}$ = 9.4 Hz, $J_{\alpha,\beta2}$ = 5.9 Hz), 5.86 (s, 1H), 9.42 (s, 1H), 12.49 (s, 1H)	3250, 3200, 3100, 3030, 2950, 2880, 1710, 1615, 1355, 1155
2C$_4$	1.82–2.08 (m, 4H), 2.23–2.28 (m, 1H), 2.48–2.55 (m, 3H), 4.65 (dd, 1H, $J_{\alpha,\beta1}$ = 9.5 Hz, $J_{\alpha,\beta2}$ = 5.8 Hz), 7.31–7.36 (m, 2H), 7.50–7.55 (m, 2H), 8.57 (s, 1H), 8.29 (s, 1H)	3360, 3240, 3080, 2950, 2880, 1710, 1600, 1320, 1140
2C$_5$	1.83–2.08 (m, 4H), 2.25–2.28 (m, 4H), 2.48–2.54 (m, 3H), 4.64 (dd, 1H, $J_{\alpha,\beta1}$ = 9.40 Hz, $J_{\alpha,\beta2}$ = 5.9 Hz), 7.10–7.14 (m, 2H), 7.34–7.38 (m, 2H), 8.37 (s, 1H), 9.15 (s, 1H)	3350, 3250, 2950, 2880, 1710, 1600, 1320, 1135
2C$_6$	1.68–1.96 (m, 4H), 2.11–2.16 (m, 1H), 2.33–2.58 (m, 3H), 4.64 (dd, 1H, $J_{\alpha,\beta1}$ = 8.8 Hz, $J_{\alpha,\beta2}$ = 6.0 Hz), 7.35 (dd, 1H, J = 8.8, 2.5 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.81 (d, 1H, J = 2.46 Hz), 9.16 (s, 1H), 10.70 (s, 1H)	3360, 3200, 2920, 2860, 1715, 1695, 1530, 1320, 1140

Table 3. Inhibition Rate of Compounds **2** against *G. zeae*

compd	inhibition rate (%)	compd	inhibition rate (%)	compd	inhibition rate (%)	compd	inhibition rate (%)
2A$_1$	18.1	**2A$_{10}$**	49.0	**2A$_{19}$**	42.0	**2C$_1$**	26.5
2A$_2$	34.5	**2A$_{11}$**	49.0	**2A$_{20}$**	9.3	**2C$_2$**	26.5
2A$_3$	26.5	**2A$_{12}$**	26.1	**1c**	72.6	**2C$_3$**	18.1
2A$_4$	18.1	**2A$_{13}$**	18.1	**2B$_1$**	18.1	**2C$_4$**	18.1
2A$_5$	55.6	**2A$_{14}$**	55.6	**2B$_2$**	9.3	**2C$_5$**	18.1
2A$_6$	34.5	**2A$_{15}$**	81.6	**2B$_3$**	18.1	**2C$_6$**	18.1
2A$_7$	55.6	**2A$_{16}$**	34.5	**2B$_4$**	18.1		
2A$_8$	34.5	**2A$_{17}$**	77.3	**2B$_5$**	18.1		
2A$_9$	18.1	**2A$_{18}$**	18.1	**2B$_6$**	18.1		

recrystallized from water to give **4C** in 52% yield: mp 114−116 °C [lit. (*4*) 118−119 °C].

2.2.8. General Synthetic Procedure for 2-Oxocycloalkylsulfonylureas (2). To a solution of **4** (5.7 mmol) and triethylamine (1.7 mL, 12.0 mmol) in acetonitrile (20 mL) at 20 °C under a nitrogen atmosphere was added dropwise phenyl chloroformate (0.86 mL, 6.9 mmol) within 2 min. The mixture was further stirred at 20−25 °C for 30 min, and to the suspension were added methanesulfonic acid (0.38 mL, 6.0 mmol) and then amine (6.9 mmol). The resulting mixture was stirred at 60 °C for 20 min. After cooling, the title compounds were obtained by filtration. The physical and elemental data of the title compounds are listed in **Table 1** and the ^{1}H NMR and IR data in **Table 2**.

2.3. Bioassay of Fungicidal Activities. *2.3.1. Method.* Fungicidal activities of the title compounds against *G. zeae* Petch, *B. cinerea* Pers, *C. orbiculare* Arx, *P. aphanidermatum* Fitzp, *F. oxysporum* Schl. f. sp. Vasinfectum, *R. solani* Kuhn, and *Verticillium dahliae* Kled were evaluated using the mycelium growth rate test (*5*). The culture media, with known concentration of the test compounds, were obtained by mixing the solution of compounds **2** in acetone with potato dextrose agar (PDA), on which fungus cakes were placed. The blank test was made using acetone. The culture was carried out at 24 ± 0.5 °C. Three replicates were performed. After the mycelia grew completely, the diameter of the mycelia was measured and the inhibition rate calculated according to the formula

$$I = \frac{\bar{D}_1^{\,2} - \bar{D}_0^{\,2}}{\bar{D}_1^{\,2}} \times 100\%$$

in which I is the inhibition rate, $\bar{D}_1$ is the average diameter of mycelia in the blank test, and $\bar{D}_0$ is the average diameter of mycelia in the presence of compounds **2**.

2.3.2. Fungicidal Activities of Compounds 2. The inhibition rate of compounds **2** against *G. zeae* Petch at 50 μg/mL was determined first, and the results are given in **Table 3**. The most active compounds were **2A$_{15}$** and **2A$_{17}$**, and their inhibition rates against seven fungi were further determined at the concentrations of 100, 50, 25, 12.5, and 6.25 μg/mL, respectively. EC_{50} and EC_{90} values were estimated using logit analysis (*6*). The results were shown in **Table 4**. Compound **1c** and commercial fungicides carbendazim or procymidone were used as a control in the above bioassay.

3. RESULTS AND DISCUSSION

3.1. Synthesis. The preparation of 2-oxocyclododecylsulfonamides by reaction of cyclododecanone with phosphorus pentachloride and amines successively was reported in our previous paper (*1*). In this paper we explored the use of oxalyl chloride as chlorinating agent for the preparation of 2-oxocycloalkylsulfonyl chloride and discovered that oxalyl chloride plus DMF as a catalyst gave a somewhat higher yield of 2-oxocycloalkylsulfonyl chloride (*7*), which was converted into 2-oxocycloalkylsulfonamides by ammoniation.

Irie et al. (*8*) reported that Lewis acids, such as boron trifluoride−diethyl ether, catalyzed the synthesis of arylsulfonylureas by the reaction of arylsulfonamides with alkyl isocy-

Table 4. Fungicidal Activity of Compounds **2A$_{15}$** and **2A$_{17}$** against Seven Fungus Species

fungus	compd	regression eq	r	EC_{50} (μg/mL)	EC_{90} (μg/mL)
Botrytis cinerea	**2A$_{15}$**	$Y = 3.20 + 2.02x$	0.9884	7.8	33.75
	2A$_{17}$	$Y = 2.81 + 2.23x$	0.9967	9.57	35.88
	1c	$Y = 3.41 + 1.81x$	0.9559	7.62	39.05
	procymidone	$Y = 3.46x + 3.66$	0.9920	2.45	5.75
Colletotrichum orbiculare	**2A$_{15}$**	$Y = 2.86 + 1.89x$	0.9882	13.52	64.32
	2A$_{17}$	$Y = 1.45 + 2.39x$	0.9943	30.45	104.53
	1c$_1$	$Y = 2.57 + 2.14x$	0.9975	13.76	54.80
	carbendazim	$Y = 1.81x + 2.11$	0.9873	39.81	199.52
Pythium aphanidermatum	**2A$_{15}$**	$Y = 1.71 + 2.69x$	0.9910	16.66	49.88
	2A$_{17}$	$Y = 1.56 + 2.26x$	0.9900	33.53	123.84
	1c	$Y = 1.09 + 2.42x$	0.9956	17.60	59.57
	carbendazim	$Y = 2.08 + 2.24x$	0.9755	20.42	75.86
Fusarium oxysporum	**2A$_{15}$**	$Y = 1.24 + 2.91x$	0.9989	19.54	53.82
	2A$_{17}$	$Y = 2.10 + 2.10x$	0.9999	24.01	97.98
	1c	$Y = 3.34 + 1.19x$	0.9992	24.60	293.1
	carbendazim	$Y = 5.46 + 1.72x$	0.9436	0.54	2.98
Rhizoctonia solani	**2A$_{15}$**	$Y = 0.31 + 2.95x$	0.9973	38.93	105.80
	2A$_{17}$	$Y = 1.23 + 1.84x$	1.0000	111.79	556.10
	1c	$Y = 3.84 + 1.39x$	0.9995	6.82	57.00
	carbendazim	$Y = 4.40 + 4.16x$	0.9737	1.41	2.82
Verticillium dahliae	**2A$_{15}$**	$Y = 2.87 + 1.58x$	0.9937	22.03	142.17
	2A$_{17}$	$Y = 3.31 + 1.11x$	0.9995	33.69	483.93
	1c	$Y = 3.24 + 1.75x$	0.9903	10.21	55.28
	carbendazim	$Y = 2.72 + 1.80x$	0.9580	18.20	93.33
Gibberella zeae	**2A$_{15}$**	$Y = 2.37 + 1.35x$	0.9934	31.47	169.20
	2A$_{17}$	$Y = 1.88 + 2.00x$	0.9963	39.01	176.08
	1c	$Y = 3.34 + 1.13x$	0.9990	30.05	413.54
	carbendazim	$Y = 3.65x + 3.93$	0.9767	1.95	4.46

anates. However, no product can be obtained in the case of 2-oxocycloalkylsulfonamides instead of arylsulfonamides, perhaps owing to its lower chemical reactivity. Finally, the title compounds were obtained in acceptable yield by the reaction of **4** with phenyl chloroformate and amines successively (*9*).

3.2. Biological Assay. As shown in **Table 3**, title compounds **2** exhibited some fungicidal activity against *G. zeae*. Among them, compounds containing a 12-membered ring (**2A**) are more active than those containing a 6- or 7-membered ring (**2B**, **2C**), which indicated that 2-oxocyclododecyl may be an active group showing pesticidal activities and merits our attention in the research and development of novel pesticides. On the other hand, for the structure−activity of **2A**, it can be seen in **Table 3** that the ureas in which R is a disubstituted phenyl or pyrimidyl showed better activity than those in which R is a monosubstituted phenyl or pyrimidyl, and aryl-substituted ureas have somewhat higher activity than those substituted by pyrimidyl. Further study on their QSAR has been planned.

Precise bioassay (**Table 4**) showed that among compounds **2A**, **2A$_{15}$** has better fungicidal activity against *F. oxysporum* and *G. zeae* than **1c**, almost the same fungicidal activities against *B. cinerea*, *C. orbiculare*, and *P. aphanidermatum* as **1c**, and lower activity against *R. solani* and *V. dahliae* than **1c**; these results do not fully agree with the prediction of CoMFA. The result indicates that the process should be further perfected for using CoMFA to predict the activities of pesticides. In addition, although the activity of **2A$_{15}$** against most of the seven fungal species is lower than that of the commercial fungicides carbendazim or procymidone, the activity against *C. orbiculare* and *P. aphanidermatum* is better than that of carbendazim. All of the results in this paper will be very useful for later research.

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