Preparation of Alkyl Substituted 1,3,4-Oxadiazin-6-ones by the DCC Induced Cyclization of 2-Oxoalkanoic Acid Acylhydrazones

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A series of 2,5-disubstituted 1,3,4-oxadiazin-6-ones were prepared by treating *syn*-2-oxoalkanoic acid acylhydrazones with dicyclohexylcarbodiimide. The isomeric *anti* isomers produced acylureas when treated with DCC. The cycloaddition reaction of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one with norbornene was studied and found to give a nitrogen deficient 1:1-cycloadduct. The formation of the product can be rationalized in terms of a Diels-Alder cycloaddition followed by nitrogen extrusion and cyclization of the resulting γ-ketoketene intermediate.

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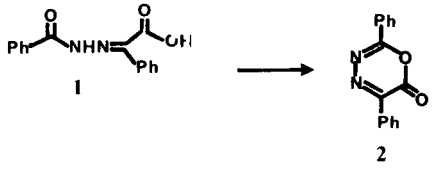
The recent availability of highly functionalized dienes has considerably widened the scope of the Diels-Alder reaction [1-6]. Dienes substituted with two nitrogen atoms have attracted interest because of their value in natural product synthesis [7-9]. There are numerous reports in the literature indicating that 1,2- 1,3- and 1,4-diazabutadienes can act as 4π-components in Diels-Alder reactions [10]. On the other hand, there are few examples of 2,3-diazabutadienes participating in 4+2-cycloadditions [11-16]. The 2,3-diazabutadiene unit is incorporated in the structure of 1,3,4-oxadiazin-6-ones. Recently, the preparation and cycloaddition behaviour of the first member of this class of heterocycles has been described by Steglich and coworkers [17]. These workers found that the treatment of 2-phenyl-2-oxoethanoic acid benzoylhydrazone **1** with trifluoroacetic anhydride or dicyclohexylcarbodiimide affords the oxadiazinone ring system. This method appears to be limited only to the availability of the prerequisite 2-oxoalkanoic acid acylhydrazone analogs. As part of a general program designed to study the cycloaddition behavior of unusual heterocyclic ring systems [18], we decided to prepare a series of alkyl substituted oxadiazinones *via* the DCC induced cyclization of 2-oxoalkanoic acid acylhydrazones. We report here the results of these studies.



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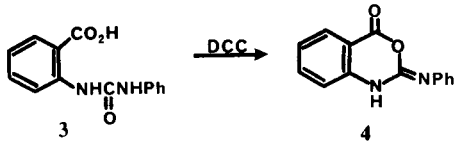
Results and Discussion.

As a consequence of its ready accessibility coupled with its chemical properties, dicyclohexylcarbodiimide has been extensively used as a condensing agent [19]. In general, reaction occurs rapidly with a variety of carboxylic acids and, in the absence of competitive reagents such as amine compounds, leads to the formation of anhydrides [20]. The structure of the products derived from the reaction of DCC with carboxylic acids containing an additional functionality frequently corresponds to a cyclized product. For example, treatment of the *o*-acylaminocarboxylic acid **3** with DCC gave rise to the *O*-acylisourea structure **4** [21].



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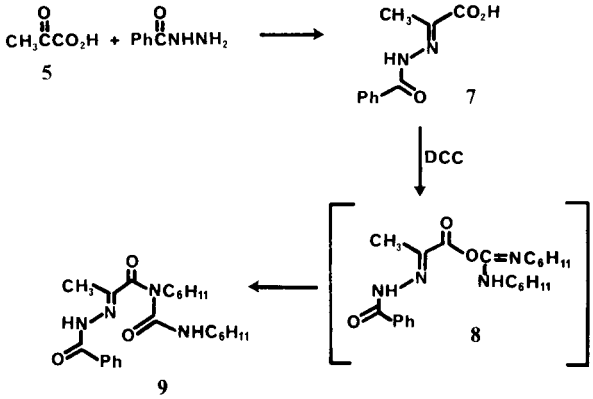
The first approach we investigated for the synthesis of the 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one (**6**) ring system involved treating 2-oxopropanoic acid benzoylhydrazone (**7**) with trifluoroacetic anhydride in trifluoroacetic acid according to the method of Steglich [17]. The required hydrazone **7** was prepared from the reaction of benzoylhydrazine with 2-oxopropanoic acid. Unfortunately, all attempts to convert **7** into oxadiazinone **6** with trifluoroacetic anhydride failed. At this point we decided to investigate the dicyclohexylcarbodiimide induced cyclization reaction. Treatment of **7** with DCC gave acylurea **9** in quantitative yield. This reaction probably involves formation of the very reactive *O*-acylisourea **8** which undergoes a subsequent intramolecular migration of the acyl group from oxygen to nitrogen. The exclusive formation of **9** suggests that the initially formed benzoylhydrazone **7** possesses the



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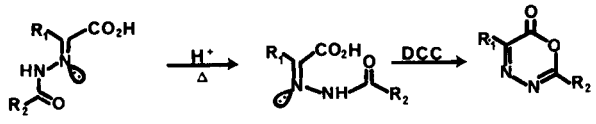
anti configuration. Interconversion of the *syn* and *anti* isomers of imines are a subject of long-standing interest [22].

Recent investigations into the factors influencing the ease of isomerization about the C-N double bond have shown that the interconversion barrier is remarkably sensitive to the attached substituent groups [23]. We found that the initially produced *anti* hydrazone **7** could be isomerized to the thermodynamically more stable *syn* isomer **10**. Treatment of **10** with DCC afforded the desired oxadiazinone **6** in good yield.

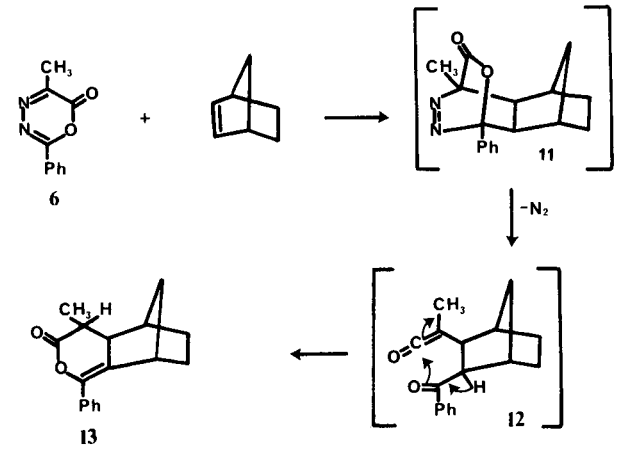


7; R_1=CH_3; R_2=Ph
14; R_1=Ph; R_2=CH_3
17; R_1=Ph; R_2=CH_2Ph

10; R_1=CH_3; R_2=Ph
15; R_1=Ph; R_2=CH_3
18 R_1=Ph; R_2=CH_2Ph

6; R_1=CH_3; R_2=Ph
16; R_1=Ph; R_2=CH_3
19; R_1=Ph; R_2=CH_2Ph

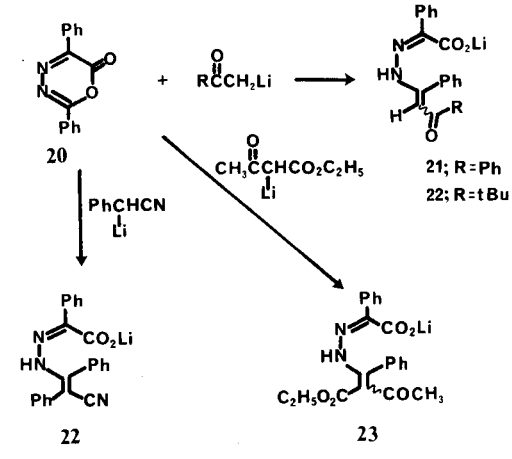
The structure of **6** was assigned on the basis of its spectral and analytical properties. Oxadiazinone **6** displayed uv bands at 375, 356, 292 and 251 nm and showed strong ir bands at 1760 and 1595 cm^{-1}. Its nmr spectrum showed the presence of a methyl group at δ 2.54. Further proof was obtained from its cycloaddition behavior. Heating a sample of **6** and norbornene at 85° affords the nitrogen deficient 1:1-cycloadduct **13** as the exclusive product [nmr (deuteriochloroform, 90 MHz) δ 1.14 (d, 3H, J = 6.5 Hz), 1.33 (brd, 1H), 1.50-1.90 (m, 5H), 2.29 (brs, 1H), 2.66 (brd, 1H), 2.93 (m, 1H), 3.18 (brs, 1H) and 7.30-7.55 (m, 5H)]. Structure **13** can be rationalized in terms of a Diels-Alder cycloaddition followed by nitrogen extrusion to give a ketoketene intermediate (*i.e.* **12**) which undergoes a subsequent cyclization [24].



The synthesis of the closely related 2-methyl (**16**) and 5-benzyl (**19**) oxadiazinones was also carried out in a similar manner. In both cases the *syn* hydrazones were found to undergo smooth cyclization whereas the *anti* isomers produced *O*-acylisoureas related to **9**.

As a continuation of our investigations in this area, we became interested in studying the reactivity of an α-carbanion on the 2 or 5-position of the oxadiazinone ring. We suspected that these anions would be easily generated by treating the alkyl substituted oxadiazinones with a number of strong bases, *e.g.*, lithium diisopropylamide, potassium hydride, *t*-butyllithium or potassium bistrimethylsilylamide. Unfortunately, quenching of the resulting carbanion with a variety of electrophiles produced a complex mixture of products and we abandoned further work with these carbanions.

We also undertook a study of the reactivity of oxadiazinone **20** with a variety of carbanions. Treatment of **20** with the lithium enolate derived from acetophenone or pinacolone afforded the ring opened lithium carboxylates **21** and **22**. A related set of reactions occurred with the lithiate anions derived from phenylacetonitrile and ethyl acetoacetate.



Further work dealing with the 4+2-cycloaddition behavior of the oxadiazinone system with enamines and enol ethers will be described elsewhere.

EXPERIMENTAL

Preparation of 5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one (**6**).

To a stirred solution containing 27.2 g of benzoylhydrazine in 700 ml of water at 65° was added 17.6 g of 2-oxopropanoic acid in 50 ml of water. The mixture was kept at this temperature for 2 hours and was then cooled to 0°. The white, crystalline solid that formed was filtered and dried to give 37.0 g (90%) of anti-2-oxopropanoic acid benzoylhydrazone (**7**) which was crystallized from acetone-water, mp 105-106° (lit mp 106° [26]); ir (potassium bromide): 3460, 3360, 1745, 1645, 1525, 1345, 1285, 1225, 915, 810 cm^{-1}; nmr (90 MHz, [acetone-d_6]): mixture of *anti*- and *syn*-isomers δ 2.20, (1.5H), 2.27 (1.5H), 7.40-8.10 (m, 6H), 10.5 (br s, 1H) [26].

A stirred suspension containing 20.0 g of the above solid and a catalytic amount of *p*-toluenesulfonic acid in 200 ml of dry benzene was heated at reflux for 4 hours. After cooling to 0° the resulting solid was filtered, washed with cold benzene and dried to give 19 g (95%) of the *syn* isomer **10** as a white crystalline product, mp 167-168°. A pure sample could be obtained by recrystallization from methanol-ethyl acetate, mp 171-172°; ir (potassium bromide): 2800-3200 (br), 1695, 1650, 1595, 1580, 1515, 1490, 1435, 1270, 1195, 1150, 1090, 915, 795 cm^{-1}.

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.24; H, 4.88; N, 13.58. Found: C, 58.23; H, 4.92; N, 13.59.

To a stirred suspension containing 6.88 g of *syn*-2-oxopropanoic acid benzoylhydrazone (**10**) in 140 ml dry benzene at 85° was rapidly added 6.88 g of dicyclohexylcarbodiimide in 20 ml of dry benzene. The mixture was kept at this temperature for 40 minutes and was then cooled to 0°. After filtering 6.92 g (92%) of dicyclohexylurea, the solvent was removed under reduced pressure. The resulting residue was dissolved in 50 ml of hot benzene and 100 ml of ether was added. The mixture was cooled to 0° and 4.3 g (68%) of a pale yellow solid was filtered and dried. An analytically pure sample of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one (**6**) was obtained by recrystallization from benzene-ether, mp 132-133°; ir (potassium bromide): 1760, 1595, 1575, 1535, 1500, 1455, 1390, 1350, 1275, 1150, 1090, 775, 705 cm^{-1}; nmr (deuteriochloroform, 90 MHz): δ 2.54 (s, 3H), 7.40-8.30 (m, 5H); uv (acetonitrile): 375 (ε 690), 356 (ε 900), 292 (ε 13100), 251 (ε 18600); ms: m/e 188 (M^+), 132, 105 (base), 77.

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.88; H, 4.29; N, 14.88. Found: C, 63.71; H, 4.35; N, 14.84.

Preparation of *O*-(2-Benzoylhydrazonopropionyl)-*N,N'*-dicyclohexylisourea (**9**).

A solution containing 1.03 g of *anti*-2-oxopropanoic acid benzoylhydrazone (**7**) and 1.03 g of dicyclohexylcarbodiimide in 50 ml of dry tetrahydrofuran was stirred for 72 hours at 20°. The mixture was filtered to give 0.51 g (46%) of dicyclohexylurea. The mother liquor was concentrated under reduced pressure to leave behind a yellow oil which was dissolved in 5 ml of hot ethyl acetate and 10 ml of ether. The mixture was cooled to -10° and 0.72 g (35%) of a white solid was formed whose structure was assigned as *O*-(2-benzoylhydrazonopropionyl)-*N,N'*-dicyclohexylisourea (**9**). This material was crystallized from dichlormethane-ether, mp 189-190°; ir (potassium bromide): 3300, 2950, 2870, 1765, 1700, 1530, 1430, 1320, 1185, 1130, 900 cm^{-1}; nmr (deuteriochloroform, 360 MHz): δ 1.00-2.40 (m, 20H), 1.49 (s, 3H), 3.10-3.55 (m, 1H), 3.65-4.10 (m, 1H), 5.58 (br d, 1H), 7.30-7.73 (m, 6H).

Anal. Calcd. for $C_{23}H_{32}N_4O_3$: C, 66.96; H, 7.82; N, 13.58. Found: C, 66.88; H, 7.83; H, 13.56.

Preparation of 2-Methyl-5-phenyl-1,3,4-oxadiazin-6-one (**16**).

To a stirred solution containing 5.38 g of acetylhydrazide in 300 ml of water at 50° was added a solution containing 10.9 g of benzoylformic acid in 50 ml water. The mixture was kept at this temperature for 2 hours and was then cooled to 0°. The white solid that precipitated was filtered and dried to give 10.9 g (73%) of *anti*-benzoylformic acid acetylhydrazone (**14**), mp 139-140°; ir (potassium bromide): 3325, 1735, 1690, 1510, 1345, 1250, 805, 730 cm^{-1}; nmr (90 MHz, [acetone-d_6]): (mixture of *anti*- and *syn*-isomers) δ 2.17 (br s, 3H), 7.33-7.60 (m, 6H), 9.20 (br s, 1H) [27].

A stirred suspension containing 7.0 g of the above solid in 100 ml of dry benzene was heated at reflux for 3 hours. After cooling to 0° the white solid that formed was filtered, washed with cold benzene and dried to give 6.0 g (86%) of the *syn*-isomer **15**, mp 156-157°: ir (potassium bromide): 3200, 1700, 1655, 1390, 1345, 1250, 1145, 1030, 790 cm^{-1}.

To a stirred suspension containing 4.36 g of the above solid in 100 ml of dry benzene at 20° was added a solution containing 4.95 g of dicyclohexylcarbodiimide in 20 ml of benzene. The mixture was stirred for 1 hour and the precipitated urea was filtered and the solution was concentrated under reduced pressure. To the residue was added 10 ml of dry ether and the solution was crystallzed at 0° to give 3.0 g (76%) of 2-methyl-5-phenyl-1,3,4-oxadiazin-6-one (**16**) as a very moisture sensitive solid, mp 118-119°; ir (potassium bromide): 2940, 2870, 1763, 1593, 1388, 1245, 1150, 1013, 963, 805, 760, 695 cm^{-1}; nmr (carbon tetrachloride, 90 MHz): δ 2.48 (s, 3H), 7.34-7.61 (m, 3H), 8.18-8.32 (m, 2H).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.88; H, 4.29; N, 14.88. Found: C, 63.88; H, 4.29; N, 14.64.

Preparation of *O*-(2-Acetylhydrazonophenylacetyl)-*N,N'*-dicyclohexylisourea.

A solution containing 1.03 g of benzoylformic acid acetylhydrazone, 1.2 g of dicyclohexylcarbodiimide and 20 mg of *p*-toluenesulfonic acid in 40 ml of dry tetrahydrofuran was heated at reflux for 3 hours. After cooling to room temperature, the precipitated dicyclohexylurea was filtered and the solvent was concentrated under reduced pressure. The resulting oil was taken up in 10 ml of ether and the solution was cooled to 0° to give 0.99 g (48%) of *O*-(2-acetylhydrazonophenylacetyl)-*N,N'*-dicyclohexylisourea, mp 210-211°; ir (potassium bromide): 3370, 3260, 2945, 2865, 1772, 1710, 1670, 1530, 1430, 1195, 1135, 1110, 910, 740 cm^{-1}; nmr (deuteriochloroform, 90 MHz): δ 0.75-2.4 (m, 20H), 1.81 (s, 3H), 2.8-3.3 (m, 1H), 3.7-4.3 (m, 1H), 5.18 (br d, 1H), 7.03 (br d, 1H), 7.38-7.43 (m, 5H).

Anal. Calcd. for $C_{23}H_{32}N_4O_3$: C, 66.96; H, 7.82; N, 13.58. Found: C, 66.77; H, 7.89; N, 13.49.

Preparation of 2-Benzyl-5-phenyl-1,3,4-oxadiazin-6-one (**19**).

To a stirred solution containing 7.5 g of phenylacetic acid hydrazide in 250 ml of water at 55° was added 7.5 g of benzoylformic acid in 50 ml of water. The mixture was kept at this temperature for 2 hours and was then cooled to 0°. The solid that formed was filtered and dried. Recrystallization from isopropanol afforded 9.3 g (66%) of benzoylformic acid phenylacetylhydrazone as a white solid, mp 138-130°; ir (potassium bromide): 3220, 1695, 1655, 1480, 1480, 1410, 1250, 1165, 1060, 1030, 980, 890 cm^{-1}; nmr (90 MHz, acetone-d_6): 4.09 (br s, 2H), 7.17-7.83 (m, 11H), 11.6 (br s, 1H); uv (methanol): 285 nm (ε 14370).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.01; H, 5.03; N, 9.91.

To a stirred suspension containing 5.65 g of the above solid in 100 ml of dry benzene at 20° was added 4.54 g of dicyclohexylcarbodiimide in 10 ml dry benzene. After stirring for 1.5 hours at room temperature, the precipitated dicyclohexylurea was filtered and the mother liquor was concentrated under reduced pressure at a temperature below 30°. To the resulting residue was added 30 ml of dry ether and the solution was cooled to 0° to give 4.2 g (79%) of a yellow crystalline product whose structure was assigned as 2-benzyl-5-phenyl-1,3,4-oxadiazin-6-one (**19**), mp 95-96°; ir (potassium bromide): 1760, 1580, 1495, 1440, 1345, 1315, 1255, 1160, 1130, 995, 970, 810, 735, 700, cm^{-1}; nmr (90 MHz, carbon tetrachloride): δ 3.94 (s, 2H), 7.20-8.33 (m, 10H); uv (acetonitrile): 303 (ε 11300), 226 (ε 7500).

Anal. Calcd. for $C_{16}H_{12}N_2O_2$: C, 72.72; H, 4.58; N, 10.60. Found: C, 72.60; H, 4.59; N, 10.57.

Reaction of 5-Methyl-2-phenyl-1,3,4-oxadiazin-6-one (**6**) with Norbornene.

A solution containing 0.565 g of 5-methyl-2-phenyl-1,3,4-oxadiazin-6-one (**6**) and 0.29 g of norbornene in 15 ml of tetrachloromethane was heated at reflux for 22 hours. The cooled reaction mixture was concentrated under reduced pressure and 5 ml of ether was added. The resulting precipitate contained 0.48 g (63%) of 6-methyl-3-phenyl-4-oxatricyclo[4.4.1.$0^{2,7}$]undec-2-en-5-one (**13**) as a colorless solid, mp 131-132°; ir (potassium bromide): 2960, 2880, 1760, 1495, 1450, 1235, 1230, 1205, 1065, 775, 705 cm^{-1}; nmr (deuteriochloroform, 90 MHz): δ 1.14 (d, J = 6.5 Hz, 3H), 1.33 (br d, 1H), 1.50-1.90 (m, 5H), 2.29 (br s, 1H), 2.66 (br d, 1H), 2.93 (m, 1H), 3.18 (br s, 1H), 7.30-7.55 (m, 5H).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13; Found: C, 80.39; H, 7.23.

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (**20**) with Metalated Pinacolone.

To a solution containing 0.22 g of pinacolone in 5 ml of dry tetrahydrofuran at -78° was added 1.5 ml of a 1.48*M* solution of *n*-butyllithium in hexane. Stirring was continued at this temperature for 20 minutes, after which time 0.5 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (**20**) dissolved in 10 ml of dry tetrahydrofuran was added. After stirring for 1 hour, the solution was warmed to room temperature and was concentrated under reduced pressure. The resulting mixtue was cooled to -8° for 12 hours and was then filtered to give 0.43 g (60%) of the product **22** as a pale yellow solid; mp 270-271°; ir (potassium bromide): 3060, 2960, 1585, 1520, 1490, 1430, 1380, 1360, 1290, 1135, 1050, 700 cm^{-1}; nmr (DMSO-d_6, 90 MHz): δ 1.07 (s, 9H), 5.38 (s, 1H), 7.20-8.20 (m, 10H); uv (methanol): 385 nm (ε 15365).

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (**20**) with Metalated Ethyl Acetoacetate.

To a solution containing 0.35 g of ethyl acetoacetate in 5 ml of dry tetrahydrofuran at -78° was added 1.9 ml of a 1.48*M* solution of *n*-butyllithium in hexane. After stirring for 20 minutes, a solution containing 0.6 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (**20**) in 10 ml of dry tetrahydrofuran was added and stirring was continued for 30 minutes. The mixture was warmed to room temperature and the solvent was removed under reduced pressure to leave behind a foam whose structure was assigned as **23** on the basis of its spectral data: ir (neat): 3060, 2980, 1645, 1605, 1515, 1380, 1280, 1240, 1160, 1095, 1070, 700 cm^{-1}; nmr (DMSO-d_6, 90 MHz): δ 0.91 (t), 1.17 (t), 1.66 (s), 2.22 (s), 3.63-3.85 (m), 7.20-7.90 (m), 10.0 (br s); uv (methanol): 385 (ϵ 600), 294 nm (ϵ 13520).

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (**20**) with Phenylacetonitrile in the Presence of Base.

To a solution containing 0.24 g of phenylacetonitrile in 5 ml of tetrahydrofuran at -78° was added 1.4 ml of a 1.48*M* solution of *n*-butyllithium in hexane. After stirring for 20 minutes a solution containing 0.5 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (**20**) was added and stirring was continued for 20 minutes. The reaction mixture was warmed to room temperature and 10 ml of ethyl acetate were added. After cooling to -8° for 12 hours, 0.22 g (30%) of structure **22** was isolated as a yellow solid, mp 270-271°; ir (potassium bromide): 3350, 3055, 2195, 1665, 1625, 1580, 1520, 1475, 1430, 1360, 1270, 1050, 700 cm^{-1}; nmr (DMSO-d_6, 90 MHz): δ 7.0-8.05 (m), 14.40 (br s); uv (methanol): 360 (sh, ϵ 4280), 296 nm (ϵ 21230).

Reaction of 2,5-Diphenyl-1,3,4-oxadiazin-6-one (**20**) with Acetophenone in the Presence of Base.

To a solution containing 0.26 g of acetophenone in 5 ml of tetrahydrofuran at -78° was added 1.55 ml of a 1.48*M* solution of *n*-butyllithium in hexane. After stirring for 20 minutes, a solution containing 0.5 g of 2,5-diphenyl-1,3,4-oxadiazin-6-one (**20**) in 8 ml of dry tetrahydrofuran was added. The mixture was allowed to warm to room temperature and stirring was continued for 12 hours. After addition of 10 ml of ether, the fine yellow precipitate which had formed was filtered and dried to give 0.25 g (33%) of structure **21** as a bright yellow solid; mp 270-271°; ir (potassium bromide): 3060, 1625, 1585, 1520, 1425, 1365, 1270, 1050, 700 cm^{-1}; uv (methanol): 408 (ϵ 9150), 298 nm (ϵ 16210).

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[25] All melting points and boiling points are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA. The infrared absorption spectra were determined on a Perkin-Elmer 467 infrared spectrophotometer. The ultraviolet absorption spectra were measured with a Cary Model 14 recording spectrophotometer, using 1-cm matched cells. The proton magnetic resonance spectra were determined at 90 MHz by using a Varian EM-390 spectrometer. Mass spectra were determined with a Finnigan 4000 mass spectrometer at an ionizing voltage of 70 eV.

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