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Structural characterization of new 2-aryl-5-phenyl-1,3,4-oxadiazin-6-ones and their *N*-aroylhydrazone precursors

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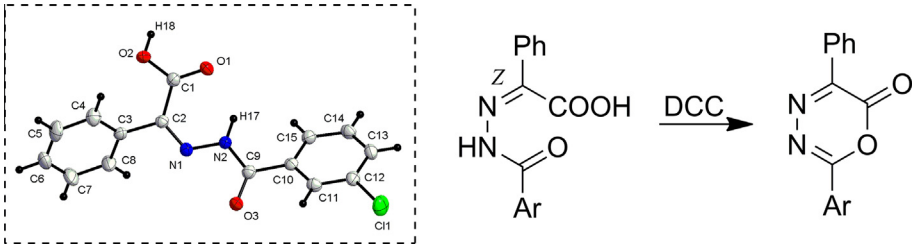
HIGHLIGHTS

- New oxadiazinones by intramolecular cyclization of corresponding *N*-aroylhydrazones.
- Electronic properties of oxadiazinones are mainly influenced by the 2-aryl substituent.
- Isolation of *Z*,*anti* isomer of *N*-aroylhydrazones.
- Strong intermolecular interactions in the solid state revealed for *N*-aroylhydrazones.

GRAPHICAL ABSTRACT



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ABSTRACT

A series of novel 2,5-disubstituted 1,3,4-oxadiazin-6-ones and their *N*-aroylhydrazone precursors were synthesized and characterized by NMR and UV–Vis spectroscopy. The electronic properties of 2-aryl-5-phenyl-1,3,4-oxadiazin-6-ones are mainly dependent on the 2-aryl substituent and their absorption maxima exhibit a red shift in dichloromethane. Single crystal X-ray diffraction on four acylhydrazones indicated the isolation of isomer with *Z* configuration of the C=N double bond. Intermolecular interactions through strong H-bonding and C—H···π contacts serve to link the molecules into a three-dimensional supramolecular network.

1. Introduction

1,3,4-Oxadiazin-6-ones are known as valuable substrates for access to a wide variety of bicyclic and heterocyclic compounds by their [2 + 2] and [4 + 2] cycloaddition reactions with alkynes, alkenes and cycloalkenes [1–20]. The oxadiazinones act as electron deficient 2,3-diaza-1,3-butadienes playing the role of diene in Diels–Alder reactions with reversed electron demand, when γ-ketoketene are formed after loss of nitrogen from the initially produced cycloadduct [6,7,19]. Recently, their reactivity in cycloaddition reaction has found a new application in obtaining organic semiconductors such as polycyclic aromatic hydrocarbons, which are known for their electrical properties. Thus, the Diels–Alder reactions of some 2,5-diaryl-6-oxo-1,3,4-oxadiazine-6-one with benzyne or naphthyne in order to obtain linear polyacenes were reported [21,22]. When cycloaddition is performed under acidic catalysis (trifluoroacetic acid), enol-lactone derivatives are obtained without γ-ketoketene intermediate formation [7]. An exception was reported for 2,5-diphenyl-1,3,4-oxadiazin-6-one, playing the role of dienophile component when reacted with 2,3-dimethyl-1,3-butadiene [9].

The synthesis of the first member of this class of heterocycles, 2,5-diphenyl-1,3,4-oxadiazin-6-one, was reported by Steglich [10], and the first oxadiazinones bearing an alkyl side chain in position 2 or 5 was obtained by Padwa [7]. Later, a considerable number of derivatives with aryl and alkyl substituents were reported by Christl [2,3,6,9,11,12,18,19]. These works describe oxadiazinones

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as versatile substrates in cycloaddition reactions, revealing interesting application in the synthesis of various compounds, such as cyclopenta[*c*]pyrans [17]. An efficient four-step synthetic pathway leading to oxadiazinones was recently developed starting from α-aminoacid esters by a sequence of diazotation, reduction and acylation reactions, followed by cyclization of the resulted *N*-acylhydrazones [23]. A series of 1,3,4-oxadiazinylacetates were obtained in rather low yields as side products along with oxadiazepine derivatives by the condensation reaction of several carbohydrazides with dimethyl but-2-ynediolate [24].

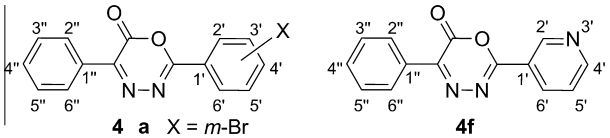
The acylhydrazones are of particular interest due to the various applications, such as electrophilic reagents in many reactions, as well as their biological activity [25–28]. Moreover, acylhydrazones are known for their ability to bind transitional metals forming complexes with antibacterial activity [29–31].

In this context, we focused in this work on the synthesis and investigation of the absorption properties of some new 2,5-diaryl-oxadiazinone derivatives and their corresponding precursors, *N*-acylhydrazones. Single crystal X-ray diffraction on four *N*-acylhydrazones revealed the isolation of the *Z,anti* isomer, stabilized by intramolecular N—H···O hydrogen bonds.

2. Experimental

2.1. General remarks

Chemicals and solvents of commercial grade were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature on Brucker Avance 300 and Brucker Avance 500 spectrometers (δ in ppm, J in Hz); spectra were referenced using the solvent signal as internal standard. The numbering of the compounds used for assigning the NMR spectra signals was done arbitrary (for acylhydrazones **3** the same numbering as in the ORTEP diagrams was used, for oxadiazinones **4** see Chart 1). The EI mass spectra were recorded on a GC–MS Shimadzu QP 2010 spectrometer. HRMS in APCI mode ionization were recorded with an LTQ XL ThermoScientific mass spectrometer. UV–Vis absorption spectra were measured on a Cecil 9500 spectrophotometer using quart cuvettes (1 cm); the solutions for acylhydrazones **3** were 3.0 $\times 10^{-5}$ M and all solutions for oxadiazinones **4** were 4.0 $\times 10^{-5}$ M. Melting points were measured with a Kleinfeld melting point apparatus and are uncorrected. The single crystals were obtained from DMSO:methanol = 1:1 by gel method using agar-agar gel [32]. Data were collected at room temperature on a Bruker SMART APEX diffractometer, using graphite monochromated Mo Kα radiation (λ = 0.71073 Å). For this purpose the crystal was mounted on a cryo-loop with Paratone-N oil. The structure was solved by direct methods (SHELXS-97) [33] and refined by full matrix least-squares procedures based on F^2 with all measured reflections (SHELXL-97) [33]. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were introduced in their idealized positions, except for the hydrogen atom of the carboxyl group which was identified from the electron density map, and refined as riding. Further details on the data collection and refinement methods can be found in Table 1. The drawings were created with the Diamond program [34].



4 **a** X = *m*-Br
b X = *m*-Cl
c X = *m*-OMe
d X = *p*-*t*Bu
e X = *p*-HO

4f

Chart 1. Numbering of oxadiazinones **4a–f.**

2.2. Synthesis of hydrazones **3**

2.2.1. General procedure

A solution of **1** (5.2 mmol) in water (60 mL) was added dropwise (over 1–2 h) under vigorous stirring to a solution of hydrazide **2** (5.2 mmol) in water (60 mL) heated to 50–60 °C. The mixture was stirred for additional 2 h, and then cooled on an ice bath until the complete precipitation of the white solid. After filtration, the solid was successively washed with cold water and cold diethyl ether (or 2-propanol). The hydrazones have been used in the next step without further purification.

2.2.2. 2-(2-(3-Bromobenzoyl)hydrazono)-2-phenylacetic acid (**3a**)

Yield 93%, white solid, m.p. 177–178 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.39–7.49 (overlapped peaks, 3H, H_5, H_6, H_7), 7.53 (t from overlapped dd, 1H, J = 7.8 Hz, H_{14}), 7.62–7.76 (m, 2H, H_4, H_8), 7.84 (overlapped peaks, 2H, H_{13}, H_{15}), 8.02 (d, 1H, J = 0.6 Hz, H_{11}), 12.70 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 121.4, 128.1, 128.3, 128.7, 129.6, 131.0, 134.5, 135.2, 135.5, 164.0, 165.4. UV/Vis (1,4-dioxane) λ_{max} (log ε) = 236 (4.16), 315 (4.21) nm. EI–MS m/z (rel. int.) = 44 (31), 50 (46), 51 (32), 65 (10), 76 (53), 89 (18), 103 (34), 119 (6), 139 (12), 155 (34), 157 (31), 183 (100), 185 (99), 199 (39), 201 (37), 301 (9), 303 (9), 345 (2), 347 (0.2) [M$^+$]. MS (APCI+): 347.0 [M+H]$^+$, 303.0 [M–CO_2]$^+$. HRMS (APCI+): calcd for $C_{15}H_{12}BrN_2O_3$ [M+H]$^+$: 347.0026; found: 347.0023.

2.2.3. 2-(2-(3-Chlorobenzoyl)hydrazono)-2-phenylacetic acid (**3b**)

Yield 96%, white solid, m.p. 178–179 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 7.41–7.48 (overlapped peaks, 3H, H_5, H_6, H_7), 7.60 (t from overlapped dd, 1H, J = 7.8 Hz, H_{14}), 7.66–7.73 (overlapped peaks, 3H, H_4, H_8, H_{13}), 7.80 (d, 1H, J = 7.8 Hz, H_{15}), 7.86–7.88 (br. s, 1H, H_{11}), 12.75 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 127.4, 128.2, 128.3, 128.8, 129.7, 130.8, 132.1, 134.5, 135.1, 135.3, 164.0, 165.4. UV/Vis (1,4-dioxane) λ_{max} (log ε) = 236 (4.14), 316 (4.23) nm. EI–MS m/z (rel. int.) = 39 (3), 44 (10), 50 (12), 51 (10), 65 (6), 75 (23), 76 (23), 89 (4), 103 (60), 111 (45), 113 (15), 139 (100), 141 (34), 155 (53), 157 (18), 257 (10), 302 (0.2) [M$^+$]. MS (APCI+): 303.1 [M+H]$^+$, 259.1 [M–CO_2]$^+$. HRMS (APCI+): calcd for $C_{15}H_{12}ClN_2O_3$ [M+H]$^+$: 303.0531; found: 303.0525.

2.2.4. 2-(2-(3-Methoxybenzoyl)hydrazono)-2-phenylacetic acid (**3c**)

Yield 94%, white solid, m.p. 173–174 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 3.83 (s, 3H, OCH_3), 7.22 (d, 1H, J = 8.1 Hz, H_{13}), 7.40–7.52 (overlapped peaks, 6H, H_5, H_6, H_7, H_{11}, H_{14}, H_{15}), 7.64–7.74 (m, 2H, H_4, H_8), 12.87 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 55.4, 112.8, 118.2, 119.5, 128.2, 128.4, 129.4, 130.2, 134.3, 134.9, 159.5, 164.1, 165.4. UV/Vis (1,4-dioxane) λ_{max} (log ε) = 235 (4.19), 315 (4.21) nm. EI–MS m/z (rel. int.) = 39 (4), 44 (8), 63 (12), 64 (14), 76 (13), 77 (25), 92 (21), 103 (50), 107 (45), 121 (7), 135 (100), 151 (74), 253 (11), 298 (0.3) [M$^+$]. MS (APCI+): 299.1 [M+H]$^+$, 255.1 [M–CO_2]$^+$. HRMS (APCI+): calcd for $C_{16}H_{15}N_2O_4$ [M+H]$^+$: 299.1026; found: 299.1022.

2.2.5. 2-(2-(4-tert-Butylbenzoyl)hydrazono)-2-phenylacetic acid (**3d**)

Yield 92%, white solid, m.p. 175–176 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 1.32 (s, 9H, C(CH_3)$_3$), 7.40–7.47 (overlapped peaks, 3H, H_5, H_6, H_7), 7.59 (d, 2H, J = 8.4 Hz, H_{12}, H_{14}), 7.65–7.72 (m, 2H, H_4, H_8), 7.80 (d, 2H, J = 8.4 Hz, H_{11}, H_{15}), 13.02 (s, 1H, N*H*). ^{13}C NMR (75 MHz, DMSO-d_6) δ ppm: 30.9, 34.8, 125.8, 127.4, 128.1, 128.4, 129.3, 130.1, 135.0, 155.4, 164.1. UV/Vis