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$Ru(bpy)_2Cl_2$: a catalyst able to shift the course of the photorearrangement in the Boulton–Katritzky reaction

Maurizio D'Auria [a,*], Vincenzo Frenna [b], Magda Monari [c], Antonio Palumbo-Piccionello [b], Rocco Racioppi [a], Domenico Spinelli [c], Licia Viggiani [a]

[a] Dipartimento di Scienze, Università della Basilicata, Viale dell'Ateneo Lucano 10, 85100 Potenza, Italy
[b] Dipartimento di Scienze e Tecnologie Biologiche, Chimiche e Farmaceutiche, Università di Palermo, Viale delle Scienze, Ed. 17, 90128 Palermo, Italy
[c] Dipartimento di Chimica 'G. Ciamician', Alma Mater Studiorum—Università di Bologna, Via F. Selmi 2, 40126 Bologna, Italy

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ABSTRACT

The Boulton–Katritzky reaction represents one of the most popular and efficient strategies used to realize azole-into-azole conversions. For example, under different experimental conditions, it allows the rearrangement of *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazoles (**1**) into 2-aryl-4-benzoylamino-5-phenyl-2*H*-1,2,3-triazoles (**2**) in very high yields. Moreover, we have recently realized this conversion also by UV-photostimulation. Now we have enlarged the scope of the reaction irradiating with visible or UV light an acetonitrile solution of some *Z*-arylhydrazones (**1a–e**) in the presence of catalytic amounts of $Ru(bpy)_2Cl_2$. We have observed the unexpected formation of the 1-aryl-5-benzoylamino-3-phenyl-1,2,4-triazoles (**3a–e**) eventually together with the expected **2a–d** in high yields.

Introduction

The use of Ruthenium complexes in organic synthesis has received great attention in recent years.[1] $Ru(bpy)_3Cl_2$, after excitation, is able to give a single electron transfer (SET) process that can be used for both oxidation and reduction reactions. Thus, it can reduce a C–Br bond to give an electron deficient radical able to add with high stereoselectivity to chiral enamines.[2] The same complex was used to catalyze [2+2] cycloaddition reactions with high diastereoselectivity.[3] Some reviews cover the recent acquisitions in this field,[4] but, on the whole, the use of $Ru(bpy)_2Cl_2$ in organic synthesis has not been significantly investigated.

$Ru(bpy)_2Cl_2$ shows an absorption at λ_{max} = 538 nm (ε 9890 in *N*-methylformamide)[5] and is able to give photosubstitution reactions with molecules possessing a lone pair,[6] because of its ability to give reactive adducts.

In the framework of our interest in the study of azole reactivity,[7a–d] we have recently reported that the irradiation of some arylhydrazones of 3-benzoyl-1,2,4-oxadiazole **1** gave the corresponding triazoles **2** (Scheme 1)[8] furnishing a photochemical version of the Boulton–Katritzky reaction (BKR).[7]

In this Letter we like to report the effect of the presence of $Ru(bpy)_2Cl_2$ on the course of the BKR: we shall offer a methodology unexpectedly able to change regioselectivity in a photostimulated reaction. We think that this result can exceed the interest in the chemistry of azoles and could open the way to further applications thus becoming of general interest and utility in organic syntheses.[9]

The regioselectivity that we have observed in the BKR of *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in different solvents in the absence of photostimulation[7a–d] (via a SN_i process)[7c] or by photostimulation in acetonitrile in the absence of catalysts,[8] has been related to the fact that the attack of the arylhydrazonic NH on the N-2 atom of the 1,2,4-oxadiazole ring gave a heterocyclic system (the 1,2,3-triazole), much more aromatic of the starting 1,2,4-oxadiazole,[10] while the eventual attack on the N-4 atom of the above ring seems not able to furnish a stable heterocyclic compound.

Results and discussion

We have observed that the irradiation of an acetonitrile solution of some *Z*-arylhydrazones (**1a–e**: see Scheme 2 and entries 1, 3, 5, 7 and 9 of Table 1) in the presence of catalytic amounts of $Ru(bpy)_2Cl_2{\cdot}3H_2O$ with visible light gives in high yields (60–95%) unexpected reaction products, whose structures have been ascertained by ^1H, ^{13}C NMR, and ESI-MS spectra and definitively supported by

* Corresponding author. Tel.: +39 0971 205480; fax: +39 0971 205678.
E-mail address: maurizio.dauria@unibas.it (M. D'Auria).

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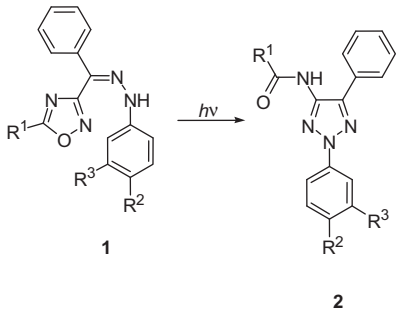
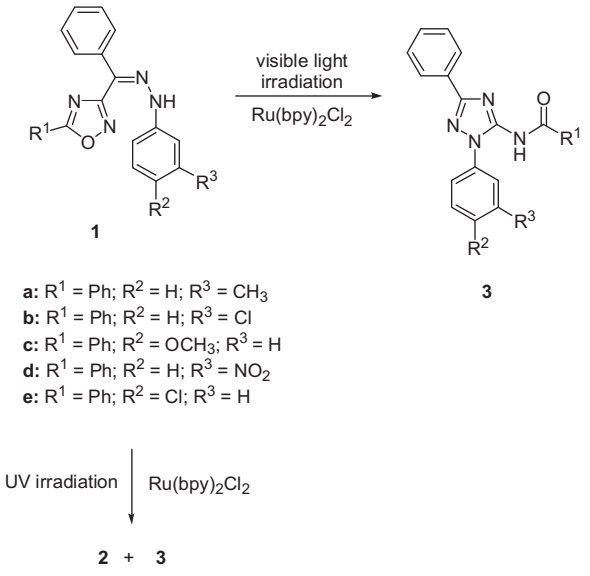


Scheme 1. Photochemical rearrangement of 1,2,4-oxadiazoles **1** to give 1,2,3-triazoles **2**.

X-ray analysis (Fig. 1): they are the unknown 1-aryl-5-benzoylamino-3-phenyl-1,2,4-triazoles (**3a–e**). Of course independent experiments (blank tests) have shown that compounds **1a–e** in acetonitrile under visible-stimulation at 20 °C stay practically unchanged in the absence of $Ru(bpy)_2Cl_2{\cdot}3H_2O$. It is interesting to know that the presence of a nitro group in *meta* position on the arylhydrazonic aromatic group induced a marked decrease of the reactivity of starting material. The *E*-isomer of **3d** showed the same behavior.

For the sake of comparison we have carried out in parallel the reaction under UV-stimulation and we have observed the formation of compound **3a–e** (main products) and of the expected products of BKR, that is, compounds **2a–d** (see Scheme 2 and entries 2, 4, 6, and 8 of Table 1). Only compound **1e** gave only **3e** as the reaction product in both the reaction conditions tested. Probably the formation of **2a–d** occurs because of the UV-stimulation (see above).[8]

The role of Ruthenium complex in this reaction can be understood on the basis of some previous results[6] and is supported by calculations. We have optimized the structure of two possible adducts between $Ru(pby)_2Cl_2$ and the *Z*-phenylhydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole in acetonitrile. On the basis of the previous reported work,[6] we can formulate the hypothesis that a chloride is substituted by acetonitrile, while the other chloride can be substituted by the 1,2,4-oxadiazole derivative.



Scheme 2. Photochemical reaction of 1,2,4-oxadiazoles **1a–e** in the presence of $Ru(bpy)_2Cl_2{\cdot}3H_2O$.

Table 1
Photochemical reaction of *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazoles **1a–c** in the presence of $Ru(bpy)_2Cl_2{\cdot}3H_2O$

Entry	Substrate	Irradiation condition	Irradiation time (h)	Product **2**[13] (Yield, %)	Product **3**[13] (Yield, %)
1	**1a**	Visible[11]	48		**3a** (95)
2	**1a**	UV[12]	120	**2a** (30)	**3a** (60)
3	**1b**	Visible[11]	48		**3b** (93)
4	**1b**	UV[12]	48	**2b** (45)	**3b** (45)
5	**1c**	Visible[11]	48		**3c** (75)
6	**1c**	UV[12]	48	**2c** (25)	**3c** (44)
7	**1d**	Visible[11]	216		**3d** (60)
8	**1d**	UV[12]	216	**2d** (25)	**3d** (34)
9	**1e**	Visible[11]	48		**3e** (85)
10	**1e**	UV[12]	48		**3e** (60)

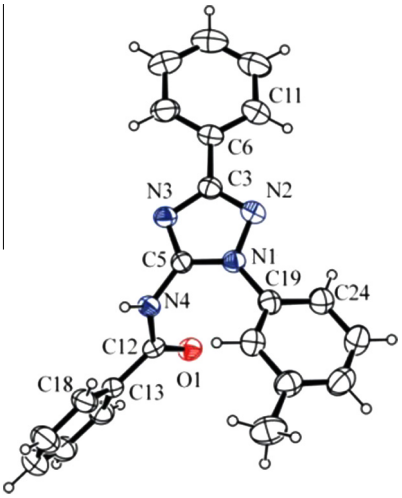


Figure 1. ORTEP drawing of **3a** showing the atom labeling scheme. Displacement ellipsoids are drawn at the 30% probability level. CCDC-1029103 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

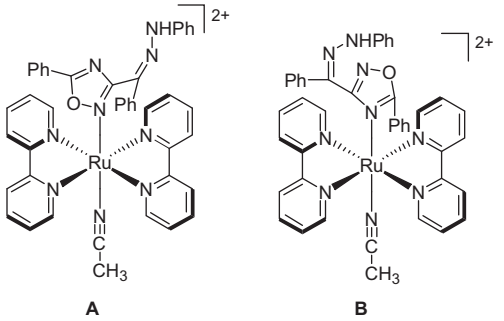


Figure 2. Possible complexes between $Ru(bpy)_2Cl_2$ and an 1,2,4-oxadiazole derivative in acetonitrile.

The complex can derive from an interaction between Ruthenium and the N-2 atom (**A**) or the N-4 one (**B**) (Fig. 2). The structures have been optimized at the DFT/B3LYP/LanL2DZ level of theory on Gaussian 09.[14] The complex **A** appears much more stable than **B** (see Supporting information). Of course, the formation of the complex between Ruthenium and the N-2 atom in the oxadiazole ring inhibits its reactivity toward the normal BKR allowing the possibility of attack on the other nitrogen atom (the N-4 atom) of the ring.

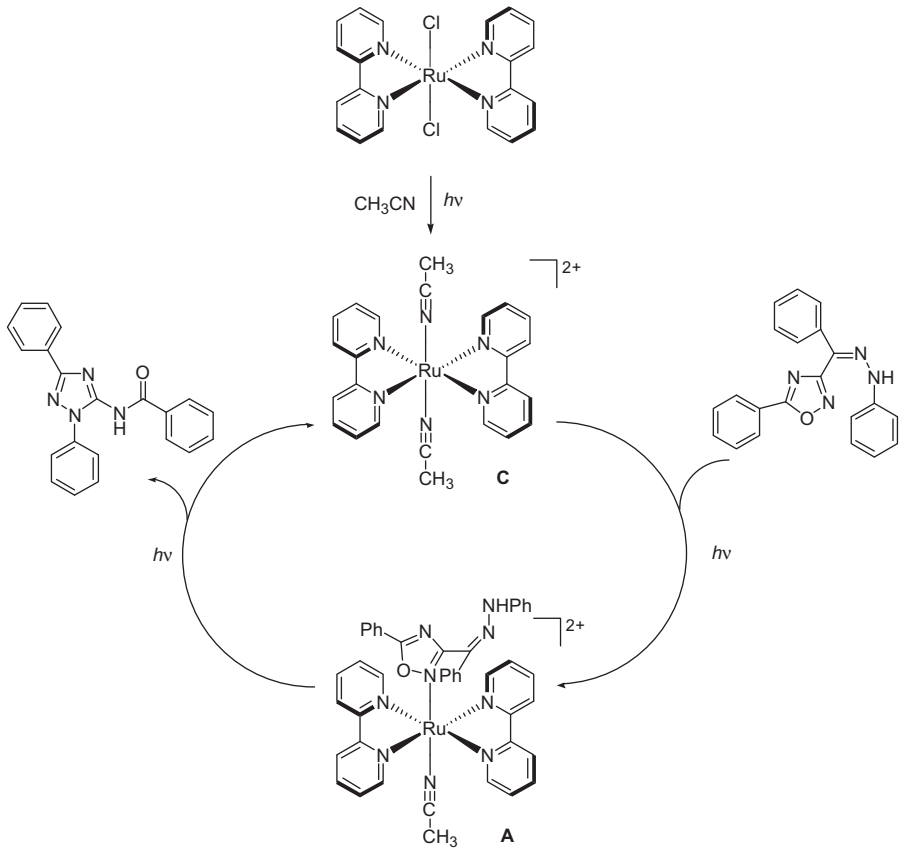
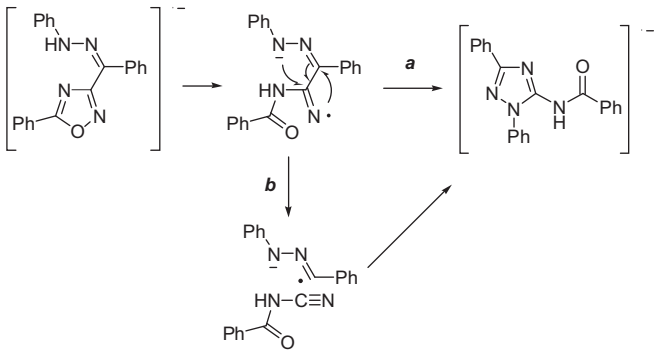


Figure 3. Catalytic cycle of Ru complex in the conversion **1** → **3**.



Scheme 3. Evolution of the radical anion of **1** (R^1 = Ph, R^2 = R^3 = H).

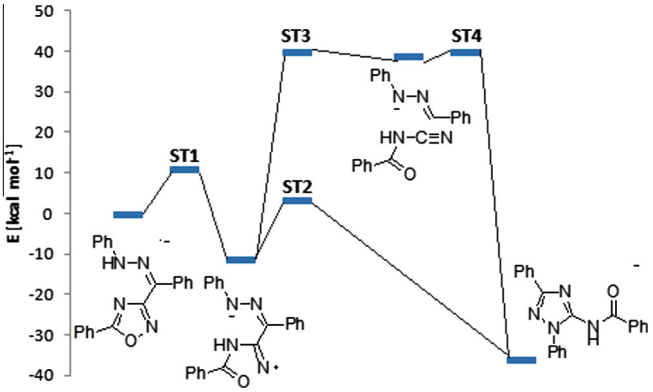


Figure 4. Reaction paths of the mechanism leading to **3**.

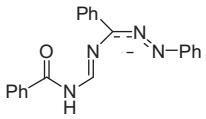


Figure 5. The transition state **ST2**.

The catalytic cycle of the Ruthenium complex can be rationalized as described in Figure 3. Calculations at the DFT/B3LYP/LanL2DZ level of theory of the complex of Ruthenium with the corresponding compound **3** showed that it cannot be formed (see Supporting information).

In a previous work on this type of compounds the absorption of the complexes deriving from a photochemical substitution of the chlorine atoms with acetonitrile (**C**) was identified as charge transfer bands. We can suppose that also **A** gave a charge transfer transition. The evolution of the radical anion of the compound **1** (R^1 = Ph, R^2 = R^3 = H) has been studied on the isolated molecule at the DFT/B3LYP/6-311G+(d,p) level of theory and the results are reported in Scheme 3 and Figure 4.

The transfer on a hydrogen atom from the hydrazonic nitrogen atom to the N-4 in the oxadiazole ring in the radical anion of **1** induces a ring opening with breaking of the O–N bond. Two possible evolution pathways have been tested. In path ***a***, the attack of the hydrazonic N atom on the C-3 of the oxadiazole ring induces a transposition reaction able to give directly product **3**. In the transition state **ST2** the first transposition of the benzylic carbon atom on the nitrogen radical has just occurred (Fig. 5). In pathway ***b***, the cleavage of the C–C bond gave a nitrile and PhN(⁻)-N=C(·)-Ph radical anion able to give a [3+2] cycloaddition reaction to give the product. Path ***b*** showed to present a highly endothermic step

(Fig. 4). These pathways are in agreement with the lower reactivity of *meta* nitro substituted oxadiazole derivative. In fact, the presence of the nitro substituent can increase the delocalization of the negative charge on the nitrogen atom.

Conclusion

In the framework of our general interest in the study of the rearrangement of azoles[7a–d,8] and extending the application of UV–visible irradiation as promoter of the reactivity in organic systems we have examined the photorearrangement of some *Z*-arylhydrazones of 3-benzoyl-5-phenyl-1,2,4-oxadiazoles (**1a**–**e**) in the presence of $Ru(bpy)_2Cl_2$, thus obtaining only the unexpected 1-aryl-5-benzoyamino-3-pheny-1,2,4-triazoles (**3a**–**e**) under visible stimulation and in contrast a mixture of **3a**–**e** (main products) and 2-aryl-4-benzoylamino-5-phenyl-2*H*-1,2,3-triazoles (**2a**–**d**) under UV-stimulation.

The observed reactivity allowed us to report a new strategy to obtain 1,2,4-triazole derivatives known for their biological properties as anti-inflammatory, CNS stimulants, sedatives, anti-anxiety, antimicrobial, antimycotic, antitumor, and antiviral properties.[15]

Furthermore, the observed result (the shift of the course of the reaction) represents the first instance of this kind of effect exerted by $Ru(bpy)_2Cl_2$ in an organic reaction and opens the way to new uses and applications of Ruthenium complexes. We think that this observation on the ability of $Ru(bpy)_2Cl_2$ to modify the organic reactivity represents a new and interesting result, which can open the way to further applications of this catalyst in organic syntheses.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.10.030.

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11. Typical experimental procedure for irradiation with visible light. Compound **1a**[16] (0.42 mmol, 150 mg) was dissolved in acetonitrile (60 ml) in the presence of $Ru(bpy)_2Cl_2{\cdot}3H_2O$ (5×10^{-4} mmol). The mixture was deoxygenated by nitrogen bubbling and irradiated with a solar simulator (Suntest CPS+, Heraeus) equipped with a Xenon lamp (1.1 KW), protected by a quartz plate. The irradiation chamber was maintained at 20 °C by both circulating water from a thermostatic bath and a conditioned airflow. After 2 days the solvent was evaporated and the crude mixture was chromatographed on silica gel (9:1 hexanes/ethyl acetate).
12. Typical experimental procedure for irradiation with UV light. Compound **1a**[16] (0.42 mmol, 150 mg) was dissolved in acetonitrile (60 ml) in the presence of Ru $(bpy)_2Cl_2{\cdot}3H_2O$ (5×10^{-4} mmol). The mixture was deoxygenated by nitrogen bubbling and irradiated with a Photochemical Multirays Reactor (Helios-Italquartz, Milan, Italy) equipped with ten 15 W lamps whose output was centered at 366 nm. After 5 days the solvent was evaporated and the crude mixture was chromatographed on silica gel (9:1 hexanes/ethyl acetate).
13. Compound **2a**: mp 213 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.95–7.90 (m, 5H), 7.81 (d, J = 6.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 8 Hz, 2H), 7.42–7.38 (m, 4H,), 7.17 (d, J = 8 Hz, 1H), and 2.42 ppm (s, 3H); ^{13}C NMR, $CDCl_3$, δ: 142.4, 139.5, 133.2, 132.6, 129.0, 128.7, 127.5, 127.1, 127.0, 119.2, 115.8; MS (EI) m/z: 354, 105, 77. Compound **2b**: mp 205 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.16 (s, 1H), 8.09 (t, J = 2 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 7.5 Hz, 2H), 7.79 (d, J = 7.5 Hz, 2H), 7.59 (t, J = 7.5 Hz, 1H), 7.44–7.38 (m, 6H), and 7.32 ppm (d, J = 10 Hz, 1H); ^{13}C NMR, $CDCl_3$, δ:140.6, 140.3, 135.1, 133.0, 132.6, 130.3, 129.3, 129.1, 128.9, 127.6, 127.4, 127.0, 118.8, and 116.5 ppm. Compound **2c**: mp 178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.04 (s, 1H), 7.96 (d, J = 9.2 Hz, 2H), 7.89 (d, J = 7.2 Hz, 2H), 7.77 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.6 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 7.41–7.34 (m, 3H), 6.96 (d, J = 9.2 Hz, 2H), and 3.84 ppm (s, 3H); ^{13}C NMR, $CDCl_3$, δ: 159.3, 142.3, 139.9, 133.6, 133.5, 132.7, 129.9, 129.1, 129.1, 127.7, 127.2, 120.3, 114.5, and 55.8 ppm. MS (ESI) m/z: 371 (M^++H). Compound **2d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.30 (s, 1H), 8.25 (d, J = 1.5 Hz, 1H), 7.96 (d, J = 8.5 Hz, 1H), 7.60 (t, J = 2 Hz, 1H,), 7.78 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 2H), and 7.66–7.43 ppm (m, 9H); ^{13}C NMR, $CDCl_3$, δ: 135.3, 134.2, 133.9, 132.1, 129.6, 129.0, 127.3, 127.0, 126.4, 122.5, 121.9, and 120.5 ppm. MS (EI) m/z: 385. Compound **3a**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.00 (br s, 1H), 8.03 (s, 2H), 7.90 (s, 2H), 7.60–7.10 (m, 10H), and 2.35 ppm (s, 3H); ^{13}C NMR and DEPT, $CDCl_3$, δ: 144.0 (C), 141.9 (C), 137.6 (C), 137.1 (CH), 134.4 (CH), 133.7 (CH), 133.6 (CH), 133.2 (CH), 133.2 (CH), 132.6 (CH), 130.9 (CH), 128.4 (CH), 124.6 (CH), and 25.5 ppm (CH_3). MS (EI) m/z: 354, 277, 207, 105, 77. Compound **3b**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 9.2 (br s, 1H), 8.10–7.90 (m, 6H), and 7.50–7.27 ppm (m, 8H); ^{13}C NMR and DEPT, $CDCl_3$, δ: 138.3 (C), 135.1 (C), 132.9 (CH), 130.6 (C), 130.6 (CH), 130.4 (C), 129.1 (CH), 128.8 (CH), 127.7 (CH), 127.3 (CH), 126.5 (CH), 123.1 (C), 120.7 (C), 119.0 (C), and 116.8 ppm (C). MS (EI) m/z: 374, 207, 105, 77, 51. Compound **3c**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.90 (br s, 1H), 8.06 (br s, 2H), 8.01–7.90 (m, 2H), 7.69–7.60 (m, 2H), 7.59–7.50 (m, 2H), 7.49 (br s, 4H), 6.99 (d, 2H, J = 8 Hz), and 3.83 ppm (s, 3H); ^{13}C NMR, $CDCl_3$, δ: 159.4, 132.6, 130.4, 129.9, 128.7, 128.7, 128.1, 127.5, 126.2, 124.8, 114.4, 114.3, and 55.5 ppm. MS (EI) m/z: 370, 342, 293, 247, 207. Compound **3d**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 9.55 (br s, 1H), 8.91 (t, J = 2.5 Hz, 1H), 8.40 (dd J_1 = 1.0 Hz, J_2 = 7.5 Hz, 1H), 8.18 (dd, J_1 = 8.5 Hz, J_2 = 2. Hz, 1H), 7.93 (d, J = 7.5 Hz, 2H,), 7.80 (d, J = 7.5 Hz, 2H), 7.64 (dd, $J_1 = J_2$ = 8.5 Hz, 1H), 7.57 (dd, $J_1 = J_2$ = 7.0 Hz, 1H), 7.52 (dd, $J_1 = J_2$ = 7.5 Hz, 2H), 7.48–7.38 (m, 3H); ^{13}C NMR, $CDCl_3$, δ: 166.3, 148.9, 143.5, 141.4, 130.9, 130.4, 130.2, 129.1, 129.0, 128.9, 127.6, 127.5, 127.2, 127.0, and 123.9 ppm. MS (EI) m/z: 385. Compound **3e**: ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 8.8 (br s, 1H), 8.2–7.6 (m, 4H), 7.60 (s, 2H), and 7.50 ppm (br s, 8H). ^{13}C NMR, $CDCl_3$, δ: 136.1, 132.6, 130.4, 129.3, 128.9, 128.6, 126.2, and 124.0 ppm. MS (EI) m/z: 374.
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