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Title: Palladium-Catalyzed Decarboxylative Synthesis of 5H-Benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6aH)-diones using 2-Phenyl-4H-benzo[d][1,3]oxazin-4-ones and α-Oxo Carboxylic Acids

Authors: Ram Sunil Kumar Lalji, Prashant Kumar, Mohit Gupta, Virinder Parmar, and Brajendra Singh

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Palladium-Catalyzed Decarboxylative Synthesis of 5*H*-Benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones using 2-Phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones and α-Oxo Carboxylic Acids

Ram Sunil Kumar Lalji,[a,b,#] Prashant Kumar,[a,c,#] Mohit Gupta,[a,d] Virinder S. Parmar,[a,e] Brajendra K. Singh[a]*

a Bioorganic Laboratory, Department of Chemistry, University of Delhi, Delhi 110 007, India

b Department of Chemistry, Kirori Mal College, University of Delhi, Delhi 110007, India

c Department of Chemistry, SRM University, Delhi-NCR Sonepat, Haryana-131029, India

d Department of Chemistry, L.N.M.S. College, Birpur, B.N. Mandal University, Bihar-854340, India

e Department of Chemistry and Environmental Science, Medgar Evers College, The City University of New York, Brooklyn, NY 11225, USA

#These authors contributed equally to this work

*Corresponding-Author. Tel: +91-11-27666646, Ext: 136, Fax: +91-11-27667206, E-mail address: singhbk@chemistry.du.ac.in (Dr. Brajendra Kumar Singh)

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Abstract. A Pd-catalyzed novel and efficient protocol has been developed for the direct functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with α-oxo carboxylic acids resulting in 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones using $(NH_4)_2S_2O_8$ as effective oxidant and $AgNO_3$ as co-oxidant. All the explored substrates were found to be compatible for this transformation and delivered the corresponding desired products in moderate to excellent yields.

Keywords: Cyclized product, Control experiments, Pd-catalyzed, Free-radical, Discreet assessment

Introduction

Isoindolinones are an important class of heterocycles in organic chemistry. This moiety forms an essential structural motif of many biologically significant molecules,[1] natural products[2] and useful intermediates in the synthesis of several drug like molecules.[3] Nevertheless, isoindolinones and their derivatives have shown various pharmaceutical properties such as anti-ulcer,[4] anti-fungal,[5] anti-hypertensive,[2j] vasodilatory,[6] anti-psychotic,[7] anti-inflammatory[8] and anti-leukemic activities.[9] Broad range applicability of isoindolinones in therapeutic industries has drawn the attention of the organic chemists worldwide and several elegant methods for their synthesis have been developed.[10] Recently, our group has also developed a radical-induced, Pd(II)-catalyzed strategy for the synthesis of 2-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones from 4*H*-benzo[*d*][1,3]oxazin-4-ones using readily available toluenes, aldehydes and benzyl alcohols as reaction partners [**Scheme 1(i)**].[11]

In recent years, transition metal-catalyzed decarboxylative cross-coupling has proven to be an attractive approach for the selective C-C and C-heteroatom bond formations.[12] In this context, α-oxo carboxylic acids have been exploited to a great extent as convenient sources for the functionalization of numerous important organic molecules and remarkable success has been achieved.[13] It has also been established that the α-oxo carboxylic acids have a tendency to behave as aroyl surrogates in the presence of radical inducer oxidants as that of aldehydes and toluenes.[14]

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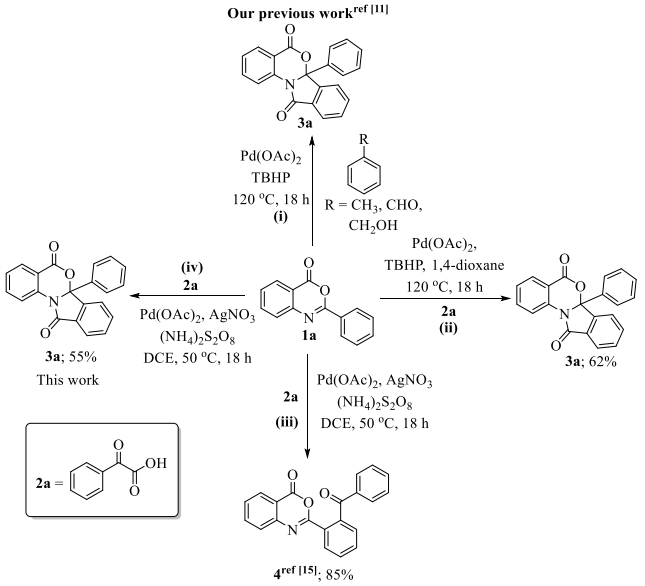
In continuation of our work[11] and to explore the expedient behavior of α-oxo carboxylic acids for the synthesis of isoindolinones, reaction between 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) employing α-oxo carboxylic acid (**2a**) was examined. Initially, we performed the reaction between 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one and α-oxo carboxylic acid with our previously reported conditions in a sealed reaction vial,[11] the anticipated product 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-dione (**3a**) was obtained in 62 % yield [**Scheme 1(ii), Table 1, entry 1**]. However, to our surprise B C Ranu and his group have reported the formation of the acylated product **4** [**Scheme 1(iii)**] with the same reaction substrates.[15] On the contrary, with the same substrates and under identical reaction conditions, we obtained **3a** in 55 % yield [**Scheme 1(iv), Table 1, entry 2**].

This result prompted us to explore the compatibility of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones and α-oxo carboxylic acids for this transformation. Herein, we are reporting a Pd-catalyzed decarboxylative free radical approach for the synthesis of 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones from 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones and α-oxo carboxylic acids. To the best of our knowledge, this is the first report for the synthesis of 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones through selective functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with α-oxo carboxylic acids.

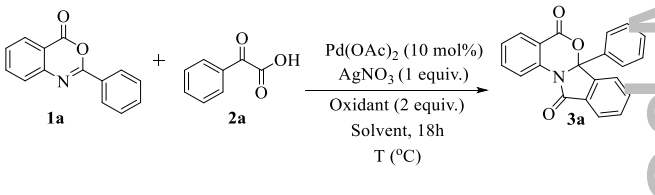


Scheme 1. Preliminary studies and functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one with α-oxocarboxylic acid.

Results and Discussion

After preliminary examination of the reaction protocol and to assess the feasibility of α-oxo carboxylic acids for the synthesis of 5*H*-benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones in better yields, reaction conditions were optimized (**Table 1**). The reaction between 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) and α-oxo carboxylic acid (**2a**) resulted in the formation of the desired product in 55 % yield (**Table 1, entry 2**) using $Pd(OAc)_2$ (10 mol %) in the presence of oxidant $(NH_4)_2S_2O_8$ (2 equivalent) and co-oxidant $AgNO_3$ (1 equivalent) in 1,2-dichloroethane (DCE) solvent at 50 °C. However, replacement of $(NH_2)_2S_2O_8$ with other oxidants like $K_2S_2O_8$ and $Na_2S_2O_8$ yielded inferior product yields (**Table 1, entries 3** and **4**). Inferior product yield was also observed when the reaction was carried out at lower temperature of 30 °C (**Table 1, entry 5**), whereas improvement in product yield was observed when the reaction was carried out at elevated temperature (**Table 1, entries 6-8**) and the best product yield (96 %) was observed when the reaction was performed at 120 °C (**Table 1, entry 8**). However, further increase in the temperature above 120 °C was found unsuitable for this transformation (**Table 1, entry 9**).

Table 1. Optimization of reaction conditions.[a]



Entry	Catalyst	Oxidant	Co-Oxidant	Solvent	Temp. [°C]	Yield [%][b]
1	$Pd(OAc)_2$	TBHP	-	1,4-dioxane	120	62[c]
2	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	50	55
3	$Pd(OAc)_2$	$K_2S_2O_8$	$AgNO_3$	DCE	50	50
4	$Pd(OAc)_2$	$Na_2S_2O_8$	$AgNO_3$	DCE	50	26
5	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	30	39
6	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	80	62
7	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	100	71
8	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	120	96
9	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	130	87
10	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	-	DCE	120	63
11	$Pd(OAc)_2$	-	$AgNO_3$	DCE	120	64
12	-	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	120	ND
13	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	120	81[d]
14	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	120	26[e]
15	$Pd(OAc)_2$	$(NH_4)_2S_2O_8$	$AgNO_3$	DCE	120	94[f]

[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**1a**) (0.5 mmol), α-oxo carboxylic

acid **2a** (1.5 mmol), catalyst $Pd(OAc)_2$ (10 mol%), oxidant $(NH_4)_2S_2O_8$ (2 equivalent) and co-oxidant $AgNO_3$ (1 equivalent) was treated in DCE solvent (2 mL) at the given temperature for 18h; [b]isolated yields; [c]5 mmol of TBHP was used; [d]7 mol% of $Pd(OAc)_2$ was used; [e]5 mol% of $Pd(OAc)_2$ was used; [f]2 equivalent of $AgNO_3$ was used.

Absence of either of the oxidant $(NH_4)_2S_2O_8$ or the co-oxidant $AgNO_3$ deterred the product yield (**Table 1, entries 10** and **11**). In a blank experiment, without the catalyst $Pd(OAc)_2$, no product formation was observed (**Table 1, entry 12**). Additionally, different catalyst concentrations were screened and it was perceived that the lower catalyst loading yielded inferior product yields, and merely 26 % yield could be obtained with 5 mol % of $Pd(OAc)_2$ (**Table 1, entries 13** and **14**). However, higher $AgNO_3$ concentration did not improve the product yield (**Table 1**, **entry 15**).

The success of this strategy was subsequently applied towards the reactions of various substituted 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones **1** with α-oxo carboxylic acids **2** as shown in **Table 2**. All the tried substrates yielded the desired products in moderate to good yields (**Table 2**). Both the electron releasing and electron withdrawing substituents on the 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones **1**, as well as on the α-oxo carboxylic acids **2** were well tolerated and resulted in formation of the targeted products in good yields (**Table 2**). Unsubstituted substrates provided the highest product yield of 96 % (**Table 2, entry 3a**). α-Oxo carboxylic acids bearing electron releasing substituents (-CH_3, -OCH_3) delivered better product yields as compared to those containing the electron withdrawing substituents (-Cl, -Br) (**Table 2, entries 3b-3e**).

Nitro-substituted 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones delivered the products in moderate yields and that could be attributed to the strong electron withdrawing nature of the nitro group (**Table 2**, **entries 3n** and **3o**). Furthermore, treatment of the substituted 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with substituted α-oxo carboxylic acids provided the desired products in good yields, irrespective of the position and electronic nature of the substituents; however, relatively longer time was required in some cases (**Table 2**).

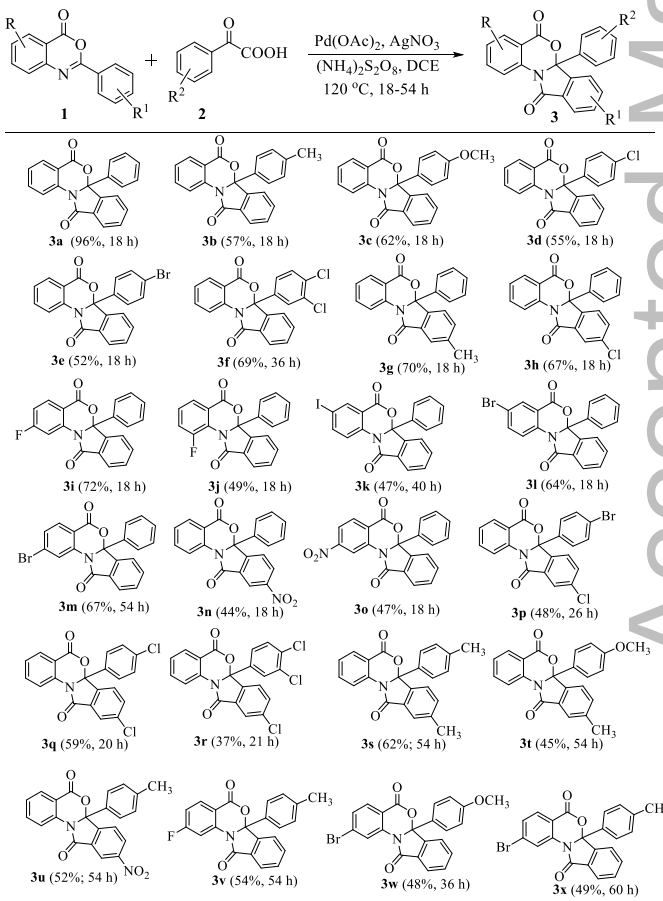
Control experiments

Furthermore, to get an insight into the reaction pathway, controlled experiments were performed and examined (**Scheme 2**). A careful assessment of the reaction condition ascertained the formation of the intermediate **4** after 60 minutes along with the unreacted reactants, which on continuation, were converted into the product **3a** (**Scheme 2a**). Moreover, when this isolated product **4** was treated separately under these conditions, it got fully converted into the cyclized product **3a** (**Scheme 2b**).

These observations suggested that the first step of the reaction involves the acylation of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one providing the intermediate **4** and the second step entails the cyclization of intermediate **4** into the product **3a**.

Furthermore, when compound **4** was allowed to react in the absence of the catalyst $Pd(OAc)_2$, the compound **3a** was obtained (**Scheme 2c**). The conversion of compound **4** into the desired product **3a** in the absence of $Pd(OAc)_2$ ruled out any possible role of this catalyst in the cyclization of compound **4** into product **3a**. Additionally, the role of both the oxidants for the conversion of compound **4** into the product **3a** was examined. It was observed that the oxidant $(NH_4)_2S_2O_8$ yielded the desired product **3a** in absence of $AgNO_3$, whereas, oxidant $AgNO_3$ solely was unable to deliver the product in the absence of $(NH_4)_2S_2O_8$ (**Scheme 2d**). In absence of both the oxidants, no product formation was observed and compound 4 was left unreacted (**Scheme 2g**).

Table 2. Evaluation of substrate scope.[a],[b]



[a]Reaction conditions: a mixture of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (0.5 mmol), phenylglyoxylic acid (1.5 mmol), catalyst $Pd(OAc)_2$ (10 mol%), oxidant $(NH_4)_2S_2O_8$ (2 equivalent) and co-oxidant $AgNO_3$ (1 equivalent) was treated in

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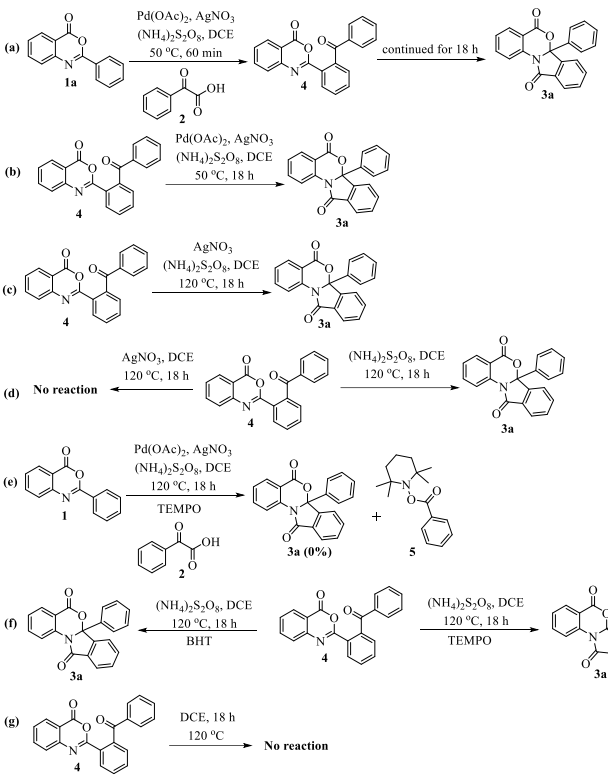
the DCE (1,2-dichloroethane; 2 mL) at 120 °C for different time interval as indicated in parenthesis; [b]isolated yields are given in parentheses.

Finally, the plausible reaction pathway for this reaction was examined. For this purpose, the reaction was run in the presence of the free radical scavenger (2,2,6,6-tertamethylpiperidin-1-yl)oxidanyl (TEMPO) between the reactants **1** and **2** under optimized reaction conditions (**Scheme 2e**) when only the TEMPO-trapped intermediate **5** could be isolated and no desired product formation was observed. This indicated the formation of acyl radical at the outset, which suggests that the first acylation step follows a radical pathway.

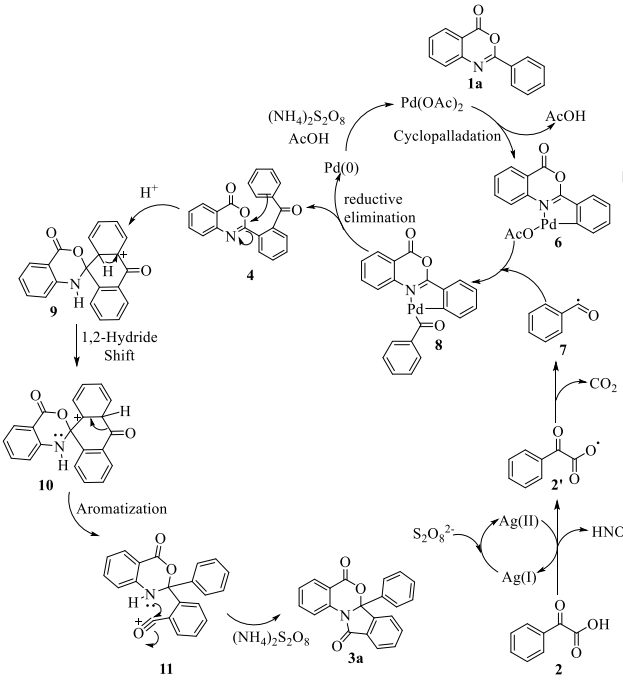
Further, isolated intermediate **4** was reacted with radical scavengers TEMPO and BHT (2,6-di-tert-butyl-4-methylphenol) independently (**Scheme 2f**). To our surprise, no TEMPO-trapped intermediate was observed in the reaction under these conditions, rather a complete conversion of the intermediate into the product **3a** was observed. The absence of any TEMPO-trapped intermediate suggested that the cyclization step is independent of radical mechanism.

Nevertheless, the radical initiator $(NH_4)_2S_2O_8$ did not generate any persulphate radicals that could have been trapped with radical scavengers, TEMPO and BHT. The complete conversion of intermediate **4** into the desired product **3a**, and the absence of any by product indicates that $(NH_4)_2S_2O_8$ does not act as a radical initiator rather as an oxidant for this cyclization step.

On the basis of the results of the control experiments and literature information, [12], [14b], [14g], [14h] a plausible reaction pathway has been proposed (**Scheme 3**). We believe that initially complex **6** is formed by the *ortho*-palladation of compound **1a** with $Pd(OAc)_2$ with the liberation of AcOH.[14e] At the same time, persulphate oxidizes Ag(I) to Ag(II), which then provides the carboxyl radical **2′** by the abstraction of single electron from the α-oxo carboxylic acid **2**. Carboxyl radical **2′** rapidly undergoes decarboxylation and generates the acyl radical **7**. [14b], [14g], [14h] Subsequently, complex **6** reacts with the acyl radical **7** and forms complex **8**. [14i], [16] Thereafter, complex **8** undergoes a reductive elimination process to give compound **4** which on subsequent intramolecular cyclization results in compound **9**. The compound **9** thus produced undergoes 1,2-hydride shift which leads to the formation of the intermediate **10**, which on aromatization affords the final compound **3a**.



Scheme 2. Monitoring of the reaction and controlled experiments.



Scheme 3. Plausible reaction mechanism.

Conclusion

In conclusion, we have developed a new methodology for the selective functionalization of 2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones with α-oxo carboxylic acids using $Pd(OAc)_2$ as a catalyst, $(NH_4)_2S_2O_8$ as an oxidant and $AgNO_3$ as co-oxidant. In this transformation, the cyclized products 5*H*-

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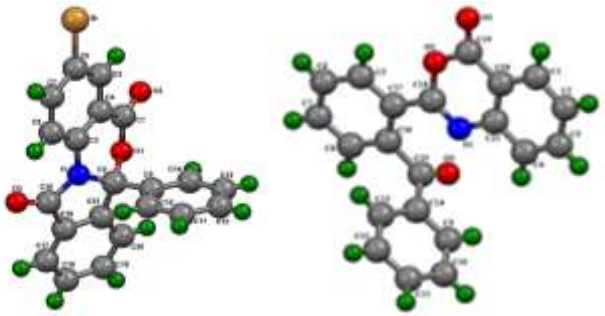
benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones could be obtained in good yields. In total, 23 products have been successfully synthesized and fully characterized by different spectroscopic techniques; the formation of the acylated product **4** and one of the final product **3l** was also confirmed by X-ray crystallographic analysis (**Figure 1**).[17]



3l **4**

Figure 1. Single crystal X-ray structure of final compound **3l** and acylated product **4.**

Experimental Section

All the experiments were performed in a reaction tube under conventional heating conditions. Analytical TLCs were performed on Merck silica gel 60_{F254} plates. IR spectra were recorded using KBr film method. The ^{1}H and ^{13}C NMR spectra (in DMSO or $CDCl_3$) were recorded on a JEOL ECX-400P NMR at 400 MHz and 100 MHz, respectively using TMS as internal standard. The high-resolution mass spectral data was obtained using an Agilent Technology-6530, Accurate mass, Q-TOF LCMS spectrometer. Melting points were recorded on a Buchi M-560 melting point apparatus and are uncorrected. All the chemicals and reagents were purchased from commercial sources and used as received unless otherwise indicated. 48 % $Pd(OAc)_2$ was used as a source of Pd-catalyst.

Experimental procedure for the synthesis of compounds of series 3

An oven dried reaction tube (10 mL) with a small stir bar was charged with a mixture of 4*H*-benzo[*d*][1,3]oxazin-4-ones (**1**, 0.5 mmol), the corresponding phenylglyoxylic acid (1.5 mmol), $Pd(OAc)_2$ (10 mol %), $(NH_4)_2S_2O_8$ (2 equivalent) and $AgNO_3$ (1 equivalent). The tube was capped tightly and heated at 120 °C for appropriate time. The progress of the reaction was monitored by TLC. After completion of the reaction, mixture was cooled to ambient temperature and passed through a short plug of celite and washed with EtOAc (3x10 mL). The combined organic filtrate was further diluted with 30 mL EtOAc and washed with 20 mL saturated $NaHCO_3$ solution 2 times, followed by distilled water (2x15 mL). The organic layer was separated, dried over solid anhydrous Na_2SO_4 and concentrated on a rotary evaporator to obtain the crude product which was purified on a silica gel column using hexane/ethyl acetate as eluent to give the pure targeted product.

6a-Phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3a): White solid; mp: 182-184 °C. 96 % yield. IR (KBr) ν_{max} (cm^{-1}): 3058, 2926, 1752, 1735, 1702, 1607, 1486, 1361, 1068, 1024, 753. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (1H, d, *J* = 8.2 Hz), 8.00-7.97 (2H, m), 7.71-7.67 (1H, m), 7.64-7.56 (2H, m), 7.54-7.51 (3H, m), 7.34-7.28 (3H, m), 7.23 (1H, dd, *J* = 7.7, 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.83, 162.53, 145.01, 137.47, 136.65, 135.95, 134.23, 130.84, 130.81, 129.68, 129.39, 125.71, 125.65, 124.90, 123.68, 121.24, 116.27, 94.54. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{21}H_{13}NO_3$: 328.0968; found: 328.0974.

6a-(*p*-Tolyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3b): White solid, mp: 208-210 °C, 57% yield. IR (KBr) ν_{max} (cm^{-1}): 3026, 2925, 1734, 1723, 1604, 1487, 1375, 1251, 1069, 750. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (1H, d, *J* = 8.0 Hz), 7.99 (2H, t, *J* = 6.4 Hz), 7.71-7.67 (1H, m), 7.63-7.56 (2H, m), 7.51 (1H, d, *J* = 7.0 Hz), 7.40 (2H , d, *J* = 7.4 Hz), 7.23 (1H , d, *J* = 7.4 Hz), 7.11 (2H, d, *J* = 7.5 Hz), 2.26 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$), 165.86, 162.65, 145.20, 139.77, 136.68, 135.90, 134.46, 134.21, 130.79, 130.76, 130.08, 129.36, 125.65, 125.60, 124.86, 123.62, 121.23, 116.36, 94.64, 21.21 HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{22}H_{15}NO_3$: 342.1125; found: 342.1131.

6a-(4-Methoxyphenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3c): White solid; mp: 205-207 °C; 45% yield. IR (KBr) ν_{max} (cm^{-1}): 1728, 1608, 1477, 1365, 1313, 1249, 1166, 1022, 763, 678. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (1H, d, *J* = 8.4 Hz), 7.99 (2H, t, *J* = 7.9 Hz), 7.69 (1H, t, *J* = 7.6 Hz), 7.64-7.55 (2H, m), 7.51 (1H, d, *J* = 7.2 Hz), 7.43 (2H, dd, *J* = 9.0, 1.9 Hz), 7.23 (1H, d *J*=7.6Hz), 6.81 (dd, *J* = 8.9, 1.8 Hz, 2H), 3.72 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.82, 162.66, 160.48, 145.30, 136.62, 135.88, 134.20, 130.74, 130.71, 129.26, 129.19, 127.15, 125.59, 124.84, 123.55, 121.25, 116.40, 114.70, 94.58, 55.39. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{22}H_{15}NO_4$: 358.1074; found: 358.1047.

6a-(4-Chlorophenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3d): Pale yellow solid; mp: 209-211 °C; 55% yield. IR (KBr) ν_{max} (cm^{-1}): 3059, 2924, 1731, 1702, 1606, 1485, 1363, 1252, 1067, 1007, 762. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 8.1 Hz), 8.02-7.99 (2H, m), 7.71 (1H, dd, *J* = 11.0, 4.4 Hz), 7.66-7.59(2H, m), 7.48 (3H, dd, *J* = 11.1, 8.3 Hz), 7.28 (3H, dd, *J* = 7.6, 6.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.71, 162.25, 144.67, 136.51, 136.21, 136.13, 135.93, 134.38, 131.07, 130.92, 129.73, 129.34, 127.23, 125.87, 125.07, 123.60, 121.30, 116.16, 94.15. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{21}H_{12}ClNO_3$: 362.0578; found: 362.0566.

6a-(4-Bromophenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3e): White solid; mp: 226-228 °C. 52% yield. IR (KBr) ν_{max} (cm^{-1}): 3086, 3058, 2925, 1729, 1702, 1606, 1485, 1363, 1252, 1148, 1068, 1016, 761. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (1H , d, *J* = 8.1 Hz), 7.99 (2H, t, *J* = 6.2 Hz), 7.70 (1H, t, *J* = 7.6 Hz), 7.65-7.58 (m, 2H),7.48 (1H, d, *J* = 7.2 Hz) 7.42 (4H, dd, *J* = 20.2, 8.4 Hz), 7.26 (1H, t, *J* = 7.5 Hz,). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.67, 162.21, 144.52, 136.71, 136.44,

136.12, 134.37, 132.65, 131.06, 130.89, 129.28, 127.46, 125.86, 125.05, 124.12, 123.57, 121.27, 116.08, 94.14. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}BrNO_3$: 406.0073; found: 406.0081.

6a-(3,4-Dichlorophenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3f): White solid; mp: 167-169 ^{o}C; 69% yield. IR (KBr) ν_{max} (cm^{-1}): 3067, 2925, 1774, 1736, 1604, 1484, 1466, 1363, 1247, 1064, 1015, 748. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 7.8 Hz, 1H), 8.01 (t, *J* = 7.5 Hz, 2H), 7.73 (t, *J* = 7.1 Hz, 1H), 7.66-7.62 (m, 2H), 7.50 (d, *J* = 6.7 Hz, 1H), 7.40 (s, 2H), 7.31-7.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.60, 161.88, 144.21, 137.98, 136.32, 134.52, 134.37, 134.02, 131.53, 131.28, 131.03, 129.23, 127.81, 126.05, 125.21, 125.14, 123.56, 121.37, 115.91, 93.49. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{11}Cl_2NO_3$: 396.0189; found: 396.0182.

9-Methyl-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3g): White solid; mp: 189-191 ^{o}C. 70% yield. IR (KBr) ν_{max} (cm^{-1}): 3059, 2922, 1746, 1718, 1604, 1486, 1361, 1238, 1041, 759. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 7.8 Hz), 7.98 (1H, d, *J* = 7.3 Hz), 7.86 (1H, d, *J* = 7.4 Hz), 7.67 (1H, t, *J* = 7.1 Hz), 7.53 (2H, d, *J* = 6.2 Hz), 7.37 (1H, d, *J* = 7.4 Hz), 7.30 (4H, s), 7.24-7.20 (1H, m), 2.42 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.93, 162.59, 145.56, 145.42, 137.70, 136.84, 135.89, 131.79, 130.77, 129.60, 129.37, 126.79, 125.75, 125.47, 124.74, 124.10, 121.22, 116.27, 94.43, 22.21. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{22}H_{15}NO_3$: 342.1125; found: 342.1127.

9-Chloro-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3h): White solid; mp: 245-247 ^{o}C. 67% yield. IR (KBr) ν_{max} (cm^{-1}): 3050, 2925, 1748, 1736, 1719, 1602, 1485, 1363, 1248, 1065, 1024, 756. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.7 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.69 (t, *J* = 7.6 Hz, 2H), 7.55-7.48 (m, 4H), 7.32 (d, *J* = 6.6 Hz, 3H), 7.25-7.22 (m, 1H).^{13}C NMR (100 MHz, $CDCl_3$): δ 164.77, 162.04, 146.47, 140.68, 136.82, 136.41, 136.06, 131.47, 130.90, 130.00, 129.60, 127.77, 126.14, 125.88, 125.69, 124.25, 121.21, 116.21, 93.94. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}ClNO_3$: 362.0578; found: 362.0579.

2-Fluoro-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3i): Light grey solid; mp: 205-207 ^{o}C; 72% yield. IR (KBr) ν_{max} (cm^{-1}): 1724, 1608, 1593, 1492, 1456, 1355, 1315, 1257, 1055, 1012, 810, 790, 758, 742, 698, 686, 640, 611. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03-7.99 (2H, m), 7.91 (1H, dd, *J* = 9.4, 2.4 Hz), 7.66-7.58 (2H, m), 7.52 (3H, dd, *J* = 7.1, 5.1 Hz), 7.36-7.30 (3H, m), 6.93 (1H, td, *J* = 8.5, 2.4 Hz).^{13}C NMR (100 MHz, $CDCl_3$): δ 168.43, 165.87, 165.68, 161.72, 144.98, 138.67, 138.54, 137.35, 134.52, 133.60, 133.49, 130.98, 129.84, 129.51, 129.04, 125.62, 125.07, 123.74, 113.60, 113.38, 112.53, 108.71, 108.44, 94.70, . HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}FNO_3$: 346.0874; found: 346.0802.

1-Fluoro-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione(3j): Pale yellow solid; mp: 224-226 ^{o}C; IR (KBr) ν_{max} (cm^{-1}): 2924, 1737, 1612, 1494, 1467, 1346, 1278, 1124, 950, 754, 696. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00 (d, *J* = 7.1 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.65-7.57 (m, 5H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.35 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.60, 161.31, 156.37, 153.82, 145.19, 136.42, 134.25, 131.04, 129.98, 129.50, 127.54, 126.13, 125.81, 125.14, 123.99, 123.37, 123.18, 119.15, 95.38. HRMS (ESI$^+$): m/z [M+H]$^+$ calculated for $C_{21}H_{12}$ FNO_3 : 346.0874; found: 346.0801.

3-Iodo-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3k): Yellow solid; mp: 223-225 ^{o}C; 47% yield. IR (KBr) ν_{max} (cm^{-1}): 1728, 1593, 1477, 1409, 1361, 1222, 1064, 754, 692, 513. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (1H, d, *J* = 1.7 Hz), 8.00-7.93 (3H, m), 7.66-7.58 (2H, m), 7.50 (3H, t, *J* = 8.3 Hz), 7.36-7.31 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.63, 161.13, , 144.88, 144.52, 139.30, 137.13, 136.17, 134.44, 131.00, 129.90, 129.53, 129.10, 125.66, 125.01, 123.71, 122.91, 117.81, 94.55,88.96. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}INO_3$: 453.9935; found: 453.9861.

3-Bromo-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3l): White solid; mp: 185-187 ^{o}C. 64% yield. IR (KBr) ν_{max} (cm^{-1}): 3056, 2925, 1753, 1731, 1690, 1603, 1482, 1364, 1224, 1066, 1016, 756. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (1H, d, *J* = 2.1 Hz), 8.07 (1H, d, *J* = 8.6 Hz), 7.99 (1H, d, *J* = 7.2 Hz), 7.79 (1H, dd, *J* = 8.8, 2.2 Hz), 7.66-7.58 (2H, m), 7.52-7.48 (3H, m), 7.35-7.31 (3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.69, 161.37, 144.85, 138.82, 137.11, 135.59, 134.47, 133.42, 131.02, 129.93, 129.54, 129.11, 125.68, 125.03, 123.75, 122.86, 118.66, 117.76, 94.64. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}BrNO_3$: 406.0073; found: 406.0088.

2-Bromo-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3m): Pale yellow solid; mp: 182-184 ^{o}C; 67% yield IR (KBr) ν_{max} (cm^{-1}): 3062, 2924, 1730, 1593, 1433, 1346, 759, 694. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (1H, s), 8.00 (1H, d *J* = 7.0 Hz), 7.84 (1H, d, *J* = 8.4 Hz), 7.66-7.58 (2H, m), 7.52-7.49 (3H, m), 7.37 (1H, d *J* = 8.7 Hz), 7.32 (3H, t, *J* = 6.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.62, 161.99, 144.95, 137.40, 137.20, 134.50, 131.99, 130.99, 130.95, 129.87, 129.54, 129.10, 129.01, 125.67, 125.10, 124.17, 123.73, 115.01 94.65, 21.22. HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}BrNO_3$: 406.0073; found: 406.0091.

9-Nitro-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3n): Yellow solid; mp: 205-207 ^{o}C; 44% yield. IR (KBr) ν_{max} (cm^{-1}): 2924, 2854, 1734, 1600, 1529, 1487, 1346, 1253, 1014,765, 696. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.51-8.46 (1H, m), 8.36 (1H, d, *J* = 13.5 Hz), 8.29-8.15 (2H, m), 8.02 (1H, d, *J* = 7.5 Hz), 7.91-7.72 (2H, m), 7.62-7.53 (2H, m), 7.37-7.29 (3H, m) ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.44, 161.47, 151.59, 146.10, 137.06, 136.24, 135.99, 134.50, 131.09, 130.41, 129.87, 129.40, 127.81, 126.42, 126.18, 125.68, 124.04, 121.21, 119.42, 116.28, 94.18 HRMS (ESI$^+$): m/z [M+H] $^+$ calculated for $C_{21}H_{12}N_2O_5$: 373.0819; found: 373.0748.

2-Nitro-6a-phenyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3o): White solid; mp: 256-258 ^{o}C; 46% yield. IR (KBr) ν_{max} (cm^{-1}): 2924, 1737, 1612, 1494, 1467, 1346, 1278, 1124, 754, 696. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.01 (1H, d, *J* = 2.0 Hz), 8.19 (1H, d, *J* = 8.6 Hz), 8.06-8.03 (2H, m), 7.71-7.63 (2H, m), 7.56-7.50

(3H, m), 7.38-7.31(3H, m). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.56, 160.94, 152.14, 144.69, 137.50, 136.67, 134.86, 132.28, 131.29, 130.17, 129.71, 128.63, 125.73, 125.35, 123.85, 120.68, 119.90, 116.59, 94.94. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{21}H_{12}N_2O_5$: 373.0819; found: 373.0745.

6a-(4-Bromophenyl)-9-Chloro-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3p): White solid; mp: 131-133 ºC; 48% yield. IR (KBr) ν_{max} (cm^{-1}): 2926, 1730, 1604, 1487, 1363, 1249, 1066, 1014, 966, 769, 752, 677. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.4 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.71 (t, *J* = 8.1 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 1H), 7.48 (d, *J* = 8.4 Hz, 3H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.57, 148.40, 138.90, 136.50, 135.28, 134.70, 131.95, 128.91, 128.11, 127.57, 127.41, 121.80, 116.66, 94.48 HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{21}H_{11}BrClNO_3$: 439.9684; found: 439.9612.

9-Chloro-6a-(4-chlorophenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3q): White solid; mp: 179-181 ºC; 59% yield. IR (KBr) ν_{max} (cm^{-1}): 1734, 1606, 1481, 1365, 1311, 1244, 1016, 759, 671, 601. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, *J* = 8.1 Hz, 1H), 8.00 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.92 (d, *J* = 8.1 Hz, 1H), 7.73-7.69 (m, 1H), 7.57 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 3H), 7.38 (d, *J* = 8.6 Hz, 2H), 7.29 (d, *J* = 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$):`1 δ 164.60, 161.71, 146.02, 140.88, 136.23, 136.07, 132.87, 131.69, 131.00, 127.69, 127.43, 126.27, 126.06, 124.51, 124.14, 121.25, 116.04, 93.55.HRMS (ESI+): m/z $[M+H]^+$ calculated for $C_{21}H_{11}Cl_2NO_3$: 396.0189; found: 396.0117.

9-Chloro-6a-(3,4-dichlorophenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3r): Pale yellow solid; mp: 216-218oC; 37% yield. IR (KBr) ν_{max} (cm^{-1}): 3076, 2924, 2854, 1732, 1602, 1485, 1361, 1246, 1022,763, 677. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (1H, d, *J* = 8.2 Hz), 8.03 (1H, d, *J* = 7.1 Hz), 7.93 (1H, d, *J* = 8.1 Hz), 7.73 (1H, t, *J* = 7.2 Hz), 7.60-7.56 (2H, m), 7.46-7.37 (3H, m), 7.30 (1H, t, *J* = 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.52, 161.38, 145.68, 141.05, 137.29, 136.42, 136.08, 134.78, 134.25, 131.90, 131.73, 131.12, 127.72, 127.60, 126.41, 125.12, 124.16, 121.34, 115.84, 92.89. HRMS (ESI+): m/z $[M+H]^+$ calculated for $C_{21}H_{11}Cl_3NO_3$: 429.9799; found: 429.9722.

9-Methyl-6a-(p-tolyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3s): White solid; mp: 181-183 ºC. 62% yield. IR (KBr) ν_{max} (cm^{-1}): 1722, 1606, 1487, 1465, 1363, 1064, 1022, 767, 754. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 8.5 Hz), 7.98 (1H, d, *J* = 7.9 Hz), 7.85 (1H, d, *J* = 7.8 Hz), 7.69-7.65 (1H, m), 7.38 (3H, dd, *J* = 14.2, 7.9 Hz), 7.30 (1H, s), 7.22 (1H, t, *J* = 7.7 Hz), 7.12 (2H, d, *J* = 8.3 Hz), 2.41 (3H, s), 2.26 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.94, 162.70, 145.58, 145.52, 139.69, 136.86, 135.84, 134.68, 131.71, 130.75, 130.07, 126.76, 125.68, 125.42, 124.70, 124.03, 121.20, 116.33, 94.51, 22.22, 21.22. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{23}H_{17}NO_3$: 356.1281; found: 356.1268.

6a-(4-Methoxyphenyl)-9-methyl-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3t): White solid; mp: 157-159ºC; 45% yield. IR (KBr) ν_{max} (cm^{-1}): 1728, 1608, 1477, 1365, 1249, 1166, 1022, 763. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (1H, d, *J* = 8.1 Hz), 7.99 (1H, dd, *J* = 7.8, 1.1 Hz), 7.85 (1H, d, *J* = 7.8 Hz), 7.70-7.66 (1H, m), 7.44-7.42 (2H, m), 7.37 (1H, d, *J* = 7.8 Hz), 7.30 (1H, s), 7.23 (1H, t, *J* = 7.6 Hz), 6.82 (2H, d, *J* = 8.9 Hz), 3.73 (3H, s), 2.42 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.93, 162.73, 160.48, 145.73, 145.52, 136.83, 135.84, 131.68, 130.73, 129.45, 127.19, 126.71, 125.43, 124.69, 123.99, 121.25, 116.41, 114.71, 94.48, 55.40, 22.24. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{23}H_{17}NO_4$: 372.1230; found: 372.1154.

9-Nitro-6a-(p-tolyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3u): Pale yellow solid; mp: 185-187 ºC; 52% yield. IR (KBr) ν_{max} (cm^{-1}): 2924, 2852, 1732, 1604, 1537, 1487, 1367, 1344, 1244, 1064, 1020, 854, 767, 671. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46 (1H, dd, *J* = 8.3, 1.9 Hz), 8.33 (1H, d, *J* = 1.7 Hz), 8.16 (2H, d, *J* = 8.2 Hz), 8.03 (1H, d, *J* = 7.8 Hz), 7.73 (1H, t, *J* = 7.1 Hz), 7.41 (2H, d, *J* = 8.3 Hz), 7.30 (1H, t, *J* = 7.6 Hz), 7.16 (2H, d, *J* = 8.1 Hz), 2.28 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.45, 161.56, 151.63, 146.34, 142.00, 140.67, 136.15, 135.05, 134.49, 133.00, 131.07, 130.55, 126.41, 126.31, 126.12, 125.63, 121.21, 119.39, 116.41, 94.04, 27.06, HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{22}H_{14}N_2O_5$: 387.0975; found: 387.0901.

2-Fluoro-6a-(p-tolyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3v): White solid; mp: 193-195 ºC; 54% yield. IR (KBr) ν_{max} (cm^{-1}): 1728, 1608, 1492, 1458, 1357, 1315, 1257, 1184, 1056, 748, 680, 642. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04-7.98 (2H, m), 7.91-7.88 (1H, m), 7.66-7.58 (2H, m), 7.53-7.51 (1H, m), 7.38 (2H, d, *J* = 7.4 Hz), 7.13 (2H, d, *J* = 8.1 Hz), 6.96-6.91 (1H, m), 2.27 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.49, 166.04, 162.30, 145.06, 140.09, 138.47, 134.67, 134.04, 133.66, 130.99, 130.23, 128.82, 125.50, 125.09, 123.71, 113.73, 112.51, 108.77, 94.96, 21.22. HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{22}H_{14}FNO_3$: 360.1030; found: 360.0954.

2-Bromo-6a-(4-methoxyphenyl)-5*H*-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6a*H*)-dione (3w): White solid; mp: 132-134 ºC; 48 % yield. IR (KBr) ν_{max} (cm^{-1}): 3072, 2922, 2852, 1726, 1591, 1514, 1467, 1431, 1342, 1242, 1033, 883, 754, 675, 599, 555. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (1H, d, *J* = 1.8 Hz), 7.99 (1H, d *J* = 6.9 Hz), 7.85 (1H, d, *J* = 8.4 Hz), 7.66-7.57 (2H, m), 7.51 (1H , d, *J* = 7.4 Hz), 7.44-7.33 (3H, m), 6.83 (2H, d, *J* = 8.9 Hz), 3.74 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.62, 161.14, 159.68, 144.26, 136.38, 133.48, 130.93, 129.87, 128.06, 127.90, 126.13, 124.04, 123.20, 122.62, 114.15 113.87, 93.71, 55.44, HRMS (ESI^+): m/z $[M+H]^+$ calculated for $C_{22}H_{14}BrNO_4$: 436.0179; found: 436.0107.

2-Bromo-6a-(p-tolyl)-5H-benzo[4,5][1,3]oxazino[2,3-a]isoindole-5,11(6aH)-dione (3x): Light pink solid; mp 221-223 ºC; 49 % yield. IR (KBr) ν_{max} (cm^{-1}): 1732, 1602, 1473, 1435, 1350, 756, 671, ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.36 (1H, d, *J* = 1.8 Hz), 7.99 (1H, dd *J* = 7.3, 0.9 Hz),

7.84 (1H, d, *J* = 8.4 Hz), 7.65-7.57 (2H, m), 7.51 (1H , d, *J* = 7.4 Hz), 7.38-7.35 (3H, m), 7.13 (2H, d, *J* = 8.01 Hz), 3.74 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.64, 162.11, 145.10, 140.02, 137.40, 134.48, 134.16, 131.96, 130.91, 130.21, 129.05, 128.97, 125.60, 125.04, 124.16, 123.66 115.07, 94.74, 21.22, HRMS (ESI$^+$): m/z $[M+H]^+$ calculated for $C_{22}H_{12}BrNO_3$: 420.0230; found: 420.0217

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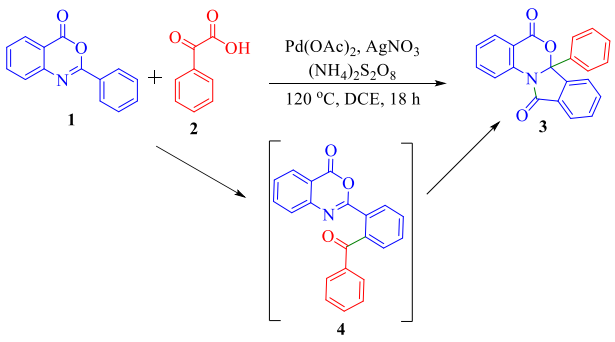
FULL PAPER

Palladium-Catalyzed Decarboxylative Synthesis of 5*H*-Benzo[4,5][1,3]oxazino[2,3-*a*]isoindole-5,11(6a*H*)-diones using 2-Phenyl-4*H*-benzo[*d*][1,3]oxazin-4-ones and α-Oxo Carboxylic Acids



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