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Silver mediated synthesis of 4*H*-benzoxazin-4-ones by intramolecular decarboxylative O-acylation reactions with α-oxocarboxylic acid

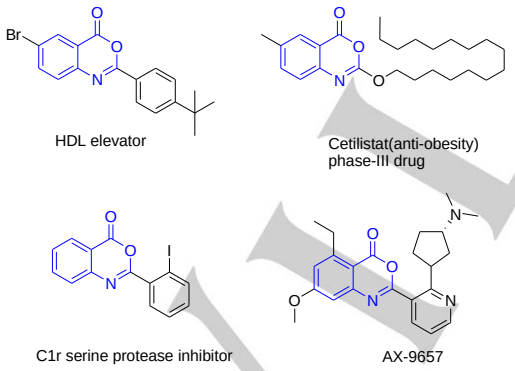
Kuppusamy Bharathimohan,[a,b] Thanasekaran Ponpandian,[b] and Ahamed A Jafar*[a]

Abstract: The first example of intramolecular decarboxylative acylation reaction with α-oxocarboxylic acid has been described. This method offers a mild and rapid synthesis of 4*H*-benzoxazin-4-ones derivatives in high yields with silver salt.

Introduction

Transition metal catalyzed decarboxylative cross coupling reaction is an effective and attractive method for the generation of carbon-carbon or carbon-heteroatom bond.[1] In the recent years, the decarboxylative acylation reactions has generated considerable attention for accessing aryl ketone by using α-oxocarboxylic acid as an acyl surrogates, which was accomplished by several metal directing groups via sp^2 C-H activation.[2] However, besides these fruitful accomplishments, all those reports provide the facile access of aryl ketones by intermolecular decarboxylative acylation and this methodology further not extended to intramolecular acylation reaction. Moreover, the decarboxylative O-acylation has also not been addressed so far in the literature with α-oxocarboxylic acid. Recently, Luo et al reported the radical pathway synthesis of phenanthridinones through intramolecular decarboxylative amidation reaction.[3]

Figure 1 Selected bioactive molecules of 4*H*-benzoxazin-4-one



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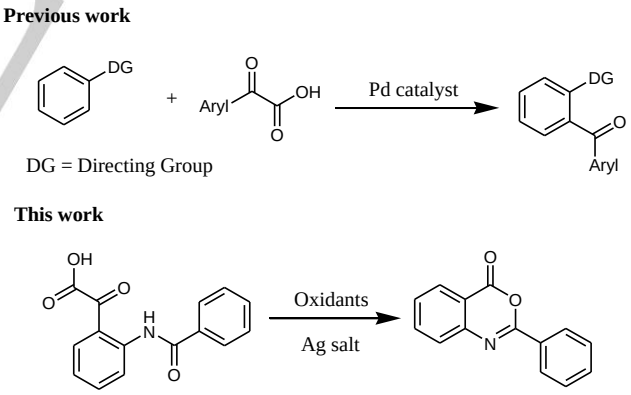
The 4*H*-benzoxazin-4-ones represent a class of important scaffolds displaying a wide range of application in pharmaceuticals[4] (Figure 1). Particularly, 2-substituted 4*H*-benzoxazin-4-one derivatives show remarkable biological activity such as chymotrypsin inactivators,[4c] C1r protease inhibitor,[4d] HDL elevators[4e] and pancreatic lipase inhibitor.[4f] In addition, 2-substituted 4*H*-benzoxazin-4-ones are used as a key raw material for the synthesis of quinazolinone analogues and its derived pharmaceuticals.[5] Therefore, demand to devise versatile methodologies for the construction of 4*H*-benzoxazin-4-ones is growing. The cyclisation of anthranilic acid, N-acyl anthranilic acid and isotoic anhydride[6] are commonly used methods to contruct 4*H*-benzoxazin-4-ones. Other improved methods include the electrochemical cyclisation of o-trichloroacetylanilide[6] and imine cyclisation using hypervalent iodine (PIDA).[7] They are also synthesized by palladium catalyzed carbonylative reactions of N-(o-haloaryl)amides using CO gas[8a-8e] or CO surrogates such as paraformaldehyde,[8f] phenylformate[8g,8h] and oxalylchloride.[8i]

Scheme 1 Approach of decarboxylative acylation reaction



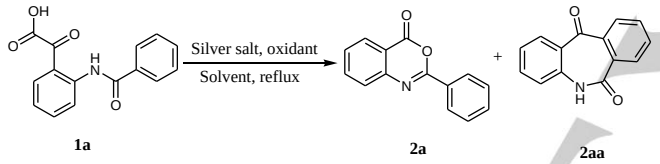
Other notable methods are TM-catalyzed or TM-free synthesis of 4*H*-benzoxazin-4-ones from 2-azidoalkynylbenzene,[9] 2-aryl indole[10] and N-benzoyl-2-iodobenzamide.[11] Very recently, Du et al[12] described the $CoCl_2$/TBHP mediated intramolecular oxidative cyclisation of *N*-(2-formylphenyl)amides. Thus, catalytic aza-Wittig reaction of 2-azido phenyl anhydride described by Huang and Ding groups.[13] During the preparation of this manuscript Gogai group[14] published the copper catalyzed C-N, C-O coupling reaction of aryl glyoxylicacid with isatins. Earlier, we demonstrated that a sequential decarboxylative coupling reaction for the synthesis of polycyclic triazoles.[15] Leveraging from our previous experience on the decarboxylative coupling reactions, we describe herein

development of a new approach to the synthesis of 4*H*-benzoxazin-4-ones via intramolecular decarboxylative O-acylation reactions with α-oxocarboxylic acid (Scheme 1). The distinctive features of this work include, first intramolecular decarboxylative acylation, inexpensive reagents, broad substrate scope and one pot sequence from *N*-aroyl isatin.

Results and Discussion

In our initial study, 2-(2-benzamido)phenyl)-2-oxoacetic acid (**1a**) was selected as a modal substrate for the optimization of intramolecular decarboxylative acylation reaction. Here, two types of acylation reactions are possible such as O-acylation or sp^2 C-H acylation which may leads to either 4*H*-benzoxazin-4-ones (**2a**) or 5*H*-dibenzo [b,e]azepine-6-11-dione (**2aa**) respectively. The reaction was first investigated with Ag_2O (1 eq.) and TBHP (2 eq.) as an oxidant in acetonitrile (ACN) at reflux condition led to the formation of **2a** in 25% yield (Table 1, Entry 1) and formation of **2aa** was not observed. The product **2a** was confirmed by NMR, Mass and IR spectroscopy. With this result, next we screened the reaction with different oxidant,

Table 1 Optimization of reaction conditions[a]



1a **2a** **2aa**

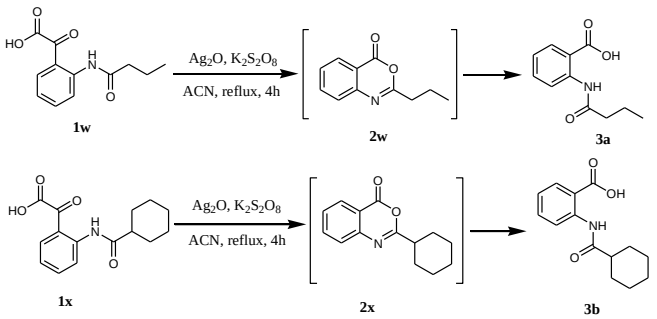
Entry	Silver salt (1 eq.)	Oxidant (1 eq.)	solvent	Time (h)	Yield[b] **2a** (%)
1[c]	Ag_2O	TBHP	ACN	12	25
2	Ag_2O	PIDA	ACN	12	40
3	Ag_2O	Oxone	ACN	12	28
4	Ag_2O	$(NH_4)_2S_2O_8$	ACN	12	65
5	**Ag_2O**	**$K_2S_2O_8$**	ACN	**3**	**88**
6[d]	Ag_2O	$K_2S_2O_8$	ACN	12	50
7[e]	Ag_2O	$K_2S_2O_8$	ACN	3	87
8	Ag_2O	$K_2S_2O_8$	DCE	8	20
9	Ag_2O	$K_2S_2O_8$	DME	8	-
10	Ag_2O	$K_2S_2O_8$	Dioxane	8	10
11	Ag_2O	$K_2S_2O_8$	Toluene	8	35
12[f]	Ag_2O	$K_2S_2O_8$	DMF	8	45
13	$AgNO_3$	$K_2S_2O_8$	ACN	3	40
14	AgOAc	$K_2S_2O_8$	ACN	3	15
15	Ag_2CO_3	$K_2S_2O_8$	ACN	5	81
16	Ag_2O	-	ACN	12	trace
17	-	$K_2S_2O_8$	ACN	12	-

[a] **1a** (0.2 g), silver salt (1 eq.), oxidant (1 eq.), solvent (5 mL), reflux. [b] Isolated yield. [c] 2 eq. of TBHP. [d] 0.5 eq. Ag_2O. [e] 1.5 eq. Ag_2O [f] Reaction at 100°C

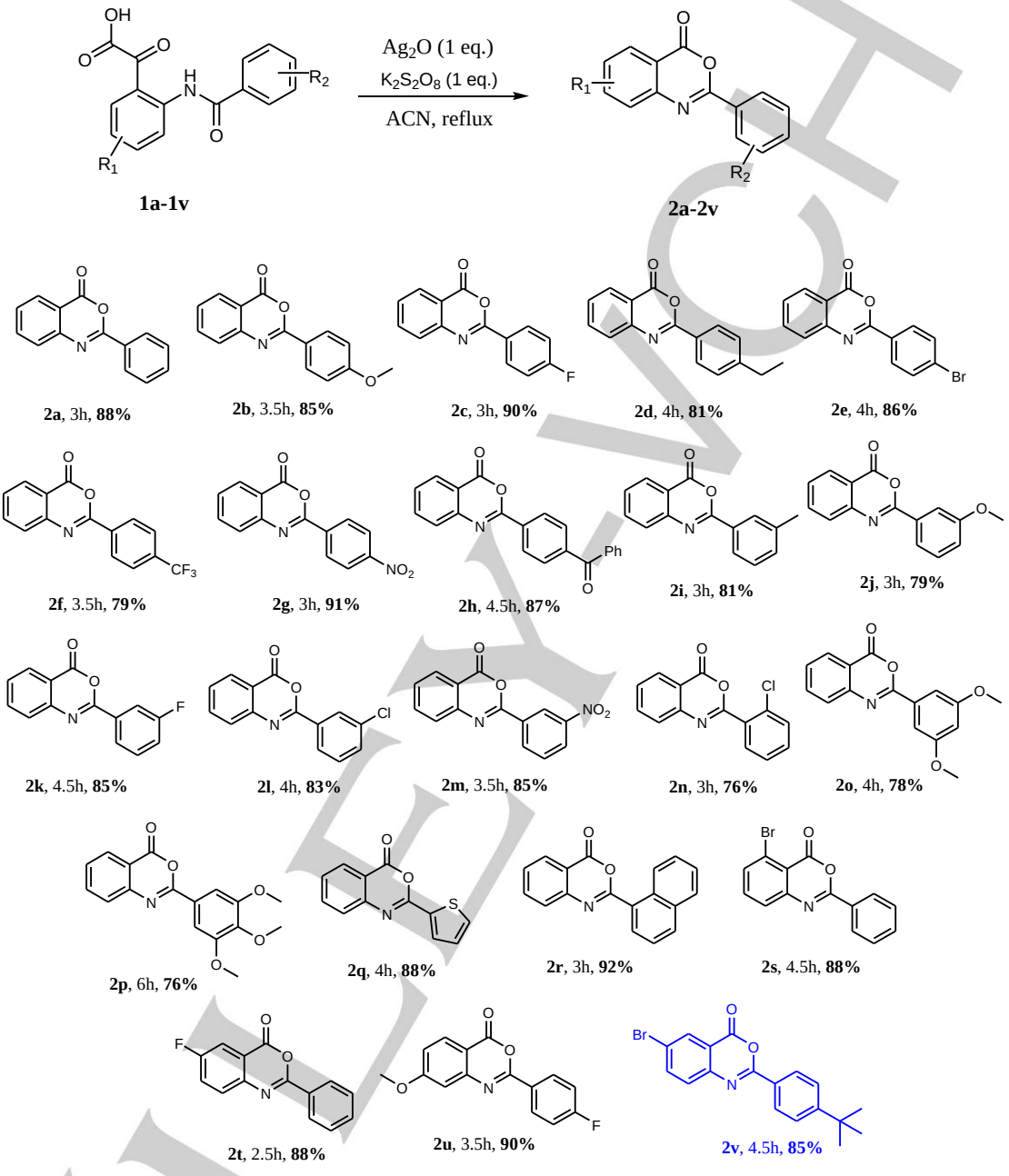
such as PIDA, oxone and $(NH_4)_2S_2O_8$, affording **2a** in 40%, 28% and 65% yield respectively (Table 1, Entries 2-4). To our delight the use of $K_2S_2O_8$ as oxidant showed clean conversion to desired product and the **2a** was isolated in 88% yield within 3h (Table 1, Entry 5). Efforts to decrease the amount of silver salts showed inconvincing results while use of excess silver salt led to similar results (Table 1, Entry 6 and 7). Use of other solvents such as 1,2-DCE, DME, dioxane, toluene and DMF were failed to improve the product yield (Table 1, Entries 8-12), while acetonitrile found to be more suitable solvent for this reaction. We have subjected various silver salts in the reaction by replacing Ag_2O with $AgNO_3$, AgOAc and Ag_2CO_3 which provided 40%, 15% and 81% of **2a** respectively (Table 1, Entries 13-15). As control experiments, no product formation was observed, if only Ag_2O or $K_2S_2O_8$ were used (Table 1, Entries 16 and 17). The formation of **2aa** was not observed under the optimized reaction condition.

We next explored the scope of this reaction with various substituted 2-benzamidophenyl-2-oxoacetic acid under the optimized reaction conditions and the results are summarized in Scheme 2. Both electron donating (OMe, Me, Et) and electron withdrawing (F, Cl, NO_2, benzoyl) substitution in 4th or 3rd position of benzamide ring does not affect the product yield which gave the corresponding benzoxazinones in 79-91% (**2b-2m**). Whereas, the benzamide ring substituted with 2-chloro (**2n**) 3,5-dimethoxy (**2o**) and 3,4,5-trimethoxy (**2p**) afforded the product in 76%-78% yield. Replacing benzamide ring with 2-thiophene (**2q**) and 1-naphthyl (**2r**) also showed good reactivity which gave 88% and 92% respectively. To extent the substrate scope of 2-amidophenyl glyoxalic acid ring, substituted with Br, F and OMe were all provided excellent yield of corresponding cyclized product (**2s-2u**). Notably, the compound **2v** is HDL elevator was synthesized in 85% yield in our reaction condition. The aliphatic amides **1w** and **1x** were examined under our reaction condition (Scheme 3). Surprisingly, the instability of corresponding cyclized product **2w** and **2x** were observed, it converted into 2-amido anthranilic acid derivatives **3a** and **3b** respectively. Mass analysis and TLC R_f value (near with **2a**) of crude reaction mixture confirmed the formation of **2w** and **2x** but failed to isolate and thus led to ring opening reaction with water during isolation, which produces **3a** and **3b** respectively. The key starting material **1** was synthesized from isatin derivative (Scheme 4)

Scheme 3 Decarboxylative acylation of aliphatic amides

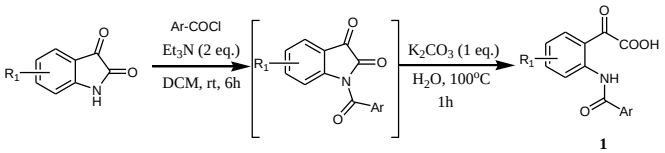


Scheme 2 Synthesis of 4*H*-benzoxazin-4-ones derivatives



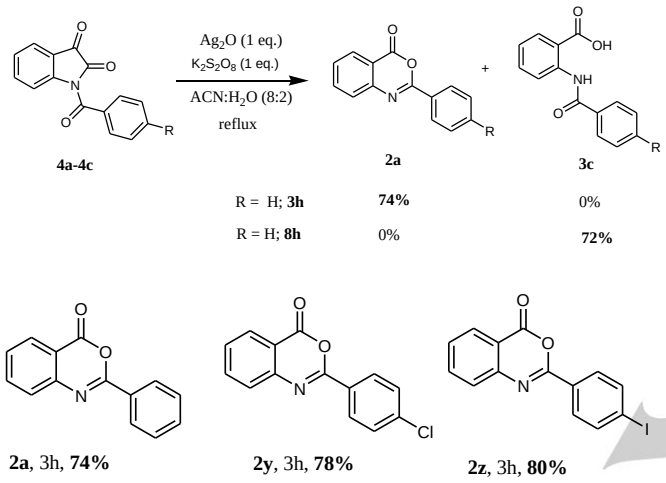
This methodology was further extended to synthesize 4*H*-benzoxazin-4-ones from *N*-aroyl isatins by one pot fashion via in-situ hydrolysis followed by decarboxylative O-acylation sequence (Scheme 5). Water included into this reaction condition as a hydrolytic agent which produces the α-oxocarboxylic acid **1** from N-aroyl isatins**.** The one-pot conversion of **4a** to **2a** was achieved with Ag_2O (1 eq), $K_2S_2O_8$ (1 eq), ACN:H_2O (8:2) at reflux for 3h in 74% yield. But, prolonged reaction maintenance for 8h led to the formation of **3c** in **72%** due to the hydrolysis of **2a** with water present in the reaction medium.

Scheme 4 Synthesis of 2-(2-substituted benzamido)phenyl)-2-oxoacetic acid



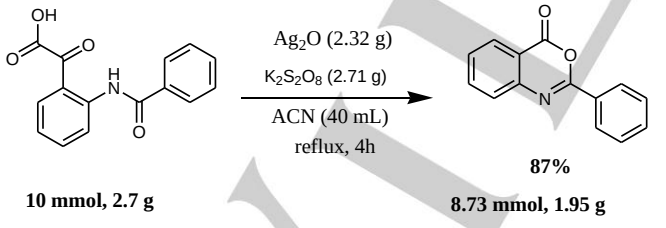
No reaction was observed in the absence of water, meanwhile we found that $K_2S_2O_8$ acts as a base for the hydrolysis of **4** to **1**. It is noted that $K_2S_2O_8$ serves as an oxidant as well as base for this one-pot reaction. With these observations, the methodology was extended to 4-chloro benzoyl isatin (**4b**) and 4-iodo benzoyl isatin (**4c**) under these conditions which provided corresponding benzoxazinones (**2y** & **2z**) 78% and 80% respectively in 3h (Scheme 5).

Scheme 5 One pot conversion of N-aroyl isatin to 4*H*-benzoxazin-4-ones



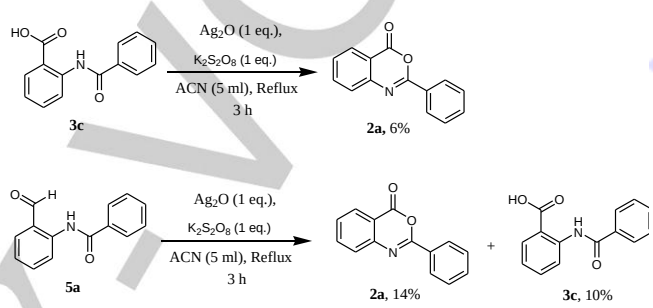
To further examine the synthetic potential of our protocol, we also conducted a gram scale reaction by choosing 2-(2-benzamido)phenyl)-2-oxoacetic acid (10 mmol, 2.7 g) as the substrate under the optimized reaction condition, the desired product (**2a**) could be isolated in 87% yield, which confirms its suitability of large scale reaction (Scheme 6).

Scheme 6 Gram scale reaction of 2-(2-benzamido)phenyl)-2-oxoacetic acid



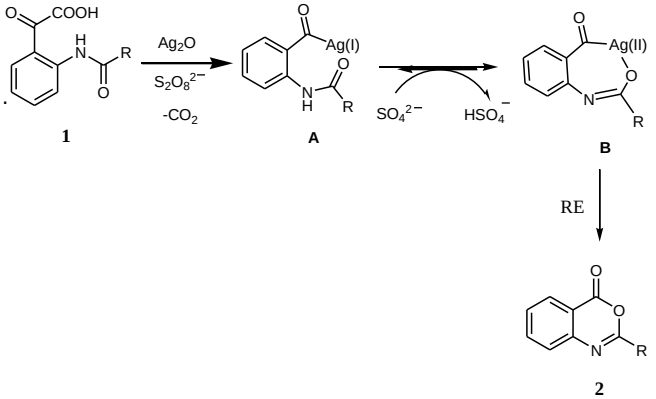
In order to reveal the detailed transformation of this reaction, a stability and reactivity of *α*-keto acids was studied in the literature. In 1983, Cooper *et al*[16] reviewed the synthesis and properties of *α*-keto acids. Here reported that thermal and oxidative decarboxylation of *α*-keto acids produces the corresponding carboxaldehyde and carboxylic acid respectively in the presence of various oxidants or transition metal catalyst (Pd, Os or Ru). Under our reaction condition *α*-keto acids (**1a**) interacted with oxidants (Ag_2O & $K_2S_2O_8$) and suspected that carboxylic acid **3c** or carboxaldehyde **5a** formed as an intermediate, which may undergo subsequent reaction to yield **2a**. The formation of carboxaldehyde and carboxylic acid derivatives were not observed during the preparation of **2** from **1** under this reaction condition. Further, control experiments were conducted to study the reaction pathway . When **3c** and **5a** were exposed to our reaction condition, the desired product **2a** obtained only 6% and 14% respectively (Scheme 7). These results clearly states that the formation of **2a** from **1a** does not proceed through **3c** and **5a** intermediates.

Scheme 7 Control experiments with **3c** and **5a**



Further experiment was conducted to obtain insight into the reaction mechanism, the yield of **2a** was not affected in the presence of radical trapping reagent TEMPO (1.0 eq or 2.0 eq), which suggest that the reaction may not be mediated by radical. Mechanism of the reaction remains unclear on the basis of our experimental results and previous literature[17]. The proposed mechanism of the reaction was shown in Scheme 8. It is believed that this transformation starts with acyl silver species (**A**) from **1** in presence of $Ag_2O/K_2S_2O_8$ and then with additional Ag(I) salt and sulphate anion to produce high valent silver complex (**B**). Reductive elimination of **B** provides the desired product **2.**

Scheme 8 Proposed reaction mechanism of formation of **2**



Conclusions

In summary, we have developed an alternative methodology for the synthesis of 4*H*-benzoxazin-4-ones derivatives through silver mediated intramolecular decarboxylative O-acylation of amide oxygen with *α*-oxocarboxylic acid. This work represents the first example of intramolecular decarboxylative acylation reaction. Our methodology is operationally mild, broad substrate scope, and is amenable to the gram-scale synthesis of 4*H*-benzoxazin-4-ones. Furthermore, the same method has been applicable for the conversion of *N*-aroyl isatin to 4*H*-benzoxazin-4-ones via *insitu* hydrolysis, and decarboxylative cyclisation.

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Experimental Section

General procedure for the preparation of substituted benzamidophenyl-2-oxoacetic acid (1): To a stirred solution of substituted isatins (2.04 mmol) and triethylamine (4.08 mmol) in dichloromethane (10 mL) was added acid chloride (2.24 mmol) at 0 °C. The resulting reaction mixture was warmed to rt and stirred for 6h. Reaction was monitored by TLC. The reaction mixture was distilled under vacuum and obtained residue was mixed with water (10 mL) and K_2CO_3 (2.04 mmol) then heated to 100 °C for 1 h. Cooled to rt and pH was adjusted to 1-2 using aqueous HCl (1:1), obtained solid was filtered and washed with water (20 mL) then dried. Solid was further triturated with diethyl ether (10 mL) to afford pure **1**

General procedure for the preparation of substitituted *N*-aroyl isatin (4): To a stirred solution of isatin (3.40 mmol) and triethylamine (6.80 mmol) in dichloromethane (15 mL) was added acid chloride (4.08 mmol) at 0 °C, and the resulting reaction mixture was slowly brought to rt and stirred for 6h. Reaction was monitored by TLC. Diethyl ether (15 mL) was added to the reaction mixture. Precipitated solid was filtered, washed Et_2O (15 mL), dried to afford pure **4.**

Preparation of benzo[*d*][1,3]oxazin-4-ones (2a-2v): To a stirred solution of 2-(2-benzamido)phenyl)-2-oxoacetic acids **1** (0.2 g, 0.74 mmol) in acetonitrile (5 mL) was added $K_2S_2O_8$ (0.74 mmol) and Ag_2O (0.74 mmol) at rt. The reaction mixture was heated to reflux for 2.5-7h. Reaction was monitored by TLC. Ethyl acetate (20 mL) was added to the reaction mixture under stirring, filtered through a pad of celite, filtrate was distilled under reduced pressure. The obtained residue was purified by silica gel column chromatography using hexane/ethylacetate (2-5%) as eluent to afford pure **2a-2u** (76-92%).

Procedure for the preparation of 2a, 2y and 2z from N-aroyl isatins: To a stirred solution of *N*-aroyl isatins **4** (0.1 g, 0.39 mmol) in Acetonitrile:Water (4:1, 5 mL) was added $K_2S_2O_8$ (0.39 mmol) and Ag_2O (0.39 mmol) at rt. The resulting reaction mixture was heated to reflux for 3h. Reaction was monitored by TLC. Reaction mixture was diluted with EtOAc (20 mL), and filtered through a pad of celite, filtrate was washed with water (20 mL), brine solution (15 mL) and dried over anhydrous Na_2SO_4. Solvent was removed by distillation under vacuum and the obtained residue was purified by silica gel column chromatography using hexane/ethylacetate (2-5%) as eluent to afford pure product (74-80%).

Characterization data:

2-(2-Benzamidophenyl)-2-oxoacetic acid (1a): White solid; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 11.37 (s, 1H), 8.26 (d, *J* = 8.4 Hz, 1H), 7.94 (t, *J* = 7.2 Hz, 2H), 7.72-7.77 (m, 2H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.57 (t, *J* = 7.2 Hz, 2H), 7.34 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 190.9, 165.9, 165.3, 140.3, 135.8, 134.3, 132.7, 132.6, 129.4, 129.3, 127.8, 124.5, 122.6, 122.4; ESI-MS (M+1) 270.1

1-(Phenylcarbonyl)-1*H*-indole-2,3-dione (3a): Yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.02 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 7.6 Hz, 1H), 7.74-7.77 (m, 3H), 7.65 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 180.6, 168.4, 157.6, 148.5, 137.9, 134.2, 133.4, 130.1, 128.5, 127.8, 125.7, 124.9, 120.4, 116.5; ESI-MS (M+1) 252.1

1-[(4-Chlorophenyl)carbonyl]-1*H*-indole-2,3-dione (3b): Yellow color solid; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.94 (d, *J* = 7.6 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.78 (t, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 180.4, 167.4, 157.6, 148.2 138.3, 137.9, 133.1, 131.9, 129.8, 129.3, 128.7, 125.8, 124.9, 120.5, 116.6; ESI-MS (M+1) 286.2

1-[(4-Iodophenyl)carbonyl]-1*H*-indole-2,3-dione (3c): Yellow color solid; ^{1}H NMR (400 MHz, DMSO-d_6) *δ* 7.89-7.94 (m, 3H), 7.77 (t, *J* = 8.4 Hz, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 7.37 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): 180.4, 167.8, 157.6, 148.2, 138.0, 137.9, 137.5, 133.7, 131.7, 131.5, 125.8, 124.9, 120.5, 116.6, 101.7; ESI-MS (M+1) 378.1

2-Phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (2a):[7] White solid; m.p. 124-126 °C; IR (KBr) 3039, 1764, 1613,1474, 1314, 1259, 1039, 764, 684 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 7.6 Hz, 2H), 8.25 (d, *J* = 8.0 Hz, 1H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.50−7.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.6, 157.1, 146.9, 136.6, 132.6 130.2, 128.7, 128.6, 128.3, 128.2, 127.2, 117.0,; Anal. Calcd. for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27. found C, 75.24; H, 4.11; N, 6.22; ESI-MS (M+1) 224.2

2-(4-Methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2b):[12] White solid; mp 146-148 °C; IR (KBr) 2924, 1759, 1616, 1600, 1566, 1470, 1253, 1170, 1059, 679 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.26-8.29 (m, 2H), 8.22-8.24 (m, 1H), 7.78-7.83 (m, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.5 (t, *J* = 7.24 Hz, 1H), 6.99-7.03 (m, 2H), 3.9 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 163.4, 159.9, 157.2, 147.4, 136.6, 130.4, 128.7, 127.8, 127.0, 122.6, 116.8, 114.3, 55.6; Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. found C, 71.53; H, 4.24; N, 5.61; ESI-MS (M+1) 254.2

2-(4-Fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2c):[7] White solid; m.p. 166-168 °C; IR (KBr) 3072, 2926, 1769, 1623, 1513, 1475, 1322, 1063, 843, 770 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.32-8.36 (m, 2H), 8.24 (d, *J* = 7.84 Hz, 1H), 7.82-7.86 (m, 1H), 7.68 (d, *J* = 8.04 Hz, 1H), 7.53 (t, *J* = 7.24 Hz, 1H), 7.20 (t, *J* = 8.64 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 165.7 (d, *J* = 252.7 Hz), 159.5, 156.4, 147.1, 136.7, 130.8 (d, *J* = 9.1 Hz), 128.8, 128.4, 127.3, 126.7, 117.0, 116.1 (d, *J* = 21.9 Hz); Anal. Calcd. for C14H8FNO$_2$: C, 69.71; H, 3.34; N, 5.81. found C, 69.58; H, 3.25; N, 5.92; ESI-MS (M+1) 242.2

2-(4-Ethylphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2d): White solid; m.p. 148-151 °C; IR (KBr) 3133, 1701, 1661, 1611, 1589, 1273, 755 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.23 (d, *J* = 8.4 Hz, 3H), 7.79-7.83 (m, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.50 (t, *J* = 6.8 Hz, 1H), 7.34(d, *J* = 8.0 Hz, 2H), 2.74 (q, *J* = 7.2 Hz, 2H), 1.28 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.6, 157.3, 149.5, 147.1, 136.4, 128.5, 128.4, 128.2, 127.9,

127.6, 127.1, 116.9, 29.3, 15.1 ; Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. found C, 76.39; H, 5.27; N, 5.59; ESI-MS (M+1) 252.2

2-(4-Bromophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2e):[7] White solid; m.p. 182-184 °C; IR (KBr) 1764, 1620, 1485, 1257, 1008, 834, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.25 (d, *J* = 7.84 Hz, 1H), 8.18 (d, *J* = 8.68 Hz, 2H), 7.83-7.87 (m, 1H), 7.65-7.77 (m, 3H), 7.54 (t, *J* = 7.24 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.4, 156.5, 146.9, 136.8, 132.2, 129.9, 129.3, 128.8, 128.6, 127.8, 127.4, 117.13, Anal. Calcd. for $C_{14}H_8BrNO_2$: C, 55.66; H, 2.67; N, 4.64. found C, 55.13; H, 2.72; N, 4.84; ESI-MS (M+1) 303.2

2-(4-Trifluoromethylphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2f):[12] White solid; m.p. 126-128 °C; IR (KBr) 3435, 1762, 1617, 1605, 1568, 1473, 1260, 1179, 1065, 854, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.37 (d, *J* = 8.2 Hz, 2H), 8.19-8.21 (m, 1H), 7.78-7.82 (m, 1H), 7.67-7.72 (m, 3H), 7.48-7.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.1, 155.9, 146.7, 136.8, 133.7, 129.0, 128.9, 128.7, 127.6, 125.8 (q, *J* = 3.6 Hz), 117.3, Anal. Calcd. for $C_{15}H_8F_3NO_2$: C, 61.86; H, 2.77; N, 4.81. found C, 61.79; H, 2.71; N, 4.89; ESI-MS (M+1) 292.1

2-(4-Nitrophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2g):[8g] Light yellow color solid; m.p. 190-193 °C; IR (KBr) 1763, 1618, 1593, 1517, 1354, 1317, 1065, 1035, 773, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.51 (d, *J* = 8.68 Hz, 2H), 8.36 (d, *J* = 8.64 Hz, 2H), 8.28 (d, *J* = 7.76 Hz, 1H), 7.89 (t, *J* = 7.48 Hz, 1H), 7.75 (d, *J* = 8.08 Hz, 1H), 7.61 (t, *J* = 7.72 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.8, 155.0, 150.3, 146.4, 137.0, 136.0, 129.4, 129.3, 128.9, 127.8, 124.0, 117.2, Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. found C, 62.58; H, 3.12; N, 10.09; ESI-MS (M+1) 269.2

2-(4-Benzoylphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2h): White solid; m.p. 182-185 °C; IR (KBr) 1764, 1740, 1651, 1474, 1306, 1064, cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.44 (d, *J* = 8.48 Hz, 2H), 8.28 (d, 7.88 Hz, 1H), 7.93 (d, *J* = 8.48 Hz, 2H), 7.82-7.89 (m, 3H), 7.74 (d, *J* = 8.0, 1H), 7.64 (t, *J* = 7.36 Hz, 1H), 7.52-7.59 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 195.9, 159.2, 156.2, 146.7, 140.9, 137.0, 136.7, 133.5, 132.9, 130.2, 130.1, 128.8, 128.7, 128.5, 128.2, 127.5, 117.1; Anal. Calcd. for $C_{21}H_{13}NO_3$: C, 77.05; H, 4.0; N, 4.28. found C, 77.10; H, 4.24; N, 4.29; ESI-MS (M+1) 328.2

2-(3-Methylphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2i):[12] White solid; m.p. 108-110 °C; IR (KBr) 1747, 1607, 1578, 1495, 1446, 1307, 836, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.25 (dd, *J* = 7.88 Hz, 1.12 Hz, 1H), 8.12 (t, *J* = 6.2 Hz, 2H), 7.81-7.86 (m, 1H), 7.7 (d, *J* = 7.96 Hz, 1H), 7.50-7.54 (m, 1H), 7.41 (t, *J* = 6.04 Hz, 2H), 2.46 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.7, 157.4, 147.1, 138.7, 136.6, 133.6, 130.2, 128.8, 128.7, 128.6, 128.2, 127.3, 125.6, 117.1, 21.4; Anal. Calcd. for C15H11NO_2: C, 75.94; H, 4.67; N, 5.90. found C, 75.86; H, 4.61; N, 5.81; ESI-MS (M+1) 238.2

2-(3-Methoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2j):[10a] White solid; m.p. 114-116 °C; IR (KBr) 2971, 1604, 1567, 1506, 1305, 1285, 1176, 1047, 831, 781 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.17-8.19 (m, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.74-7.79 (m, 2H), 7.63 (d, *J* = 8.04 Hz, 1H), 7.46 (t, *J* = 7.24 Hz, 1H), 7.35 (t, *J* = 7.96 Hz, 1H), 7.04-7.07 (m, 1H), 3.8 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 160.0, 159.6, 157.1, 147.0, 136.7, 131.6, 129.9, 128.7, 128.4, 127.4, 121.0, 119.5, 117.1, 112.7, 55.7; Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 71.14; H, 4.38; N, 5.53. found C, 71.48; H, 4.21; N, 5.69; ESI-MS (M+1) 254.2

2-(3-Fluorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2k):[9] White solid; m.p. 138-142 °C; IR (KBr) 1759, 1607, 1588, 1446, 1325, 1278, 1008, 948, 768, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.25 (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 7.6Hz, 1H), 8.02 (d, *J* = 9.6 Hz, 1H), 7.85 (t, *J* = 7.6 Hz, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.46-7.56 (m, 2H), 7.27-7.30 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 162.9 (d, *J* = 245.4 Hz), 159.2, 156.0, 146.7, 136.8, 132.5(d, *J* = 8.1 Hz), 130.5 (d, *J* = 7.8 Hz), 128.7, 127.4, 124.1 (d, *J* = 3.2 Hz), 119.7 (d, *J* = 21.2 Hz), 117.1, 115.3 (d, *J* = 24 Hz); Anal. Calcd. for $C1_4H_8FNO_2$: C, 69.71; H, 3.34; N, 5.81. found C, 69.52; H, 3.29; N, 5.95; ESI-MS (M+1) 242.2

2-(3-Chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2l):[8g] White solid; m.p. 153-155 °C; IR (KBr) 1767, 1626, 1605, 1488, 1405, 1325, 1259, 1223, 1095, 1024, 838, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.32 (s, 1H), 8.25 (d, *J* = 7.72 Hz, 1H), 8.2 (d, *J* = 7.84 Hz, 1H), 7.85 (t, *J* = 7.88 Hz, 1H), 7.71 (d, *J* = 8.08 Hz, 1H), 7.55 (t, *J* = 6.16 Hz, 2H), 7.46 (t, *J* = 7.88 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.1, 155.8, 146.6, 136.7, 134.9, 132.6, 132.0, 130.0, 128.7, 128.6, 128.3, 127.3, 126.3, 117.0; Anal. Calcd. for $C_{14}H_8ClNO_2$: C, 65.26; H, 3.13; N, 5.44. found C, 65.23; H, 3.15; N, 5.43; ESI-MS (M+1) 258.2

2-(3-Nitroophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2m): Light yellow color solid; m.p. 162-165 °C; IR (KBr) 1766, 1621, 1595, 1519, 1356, 1319, 1067, 1035, 774, 686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 9.18 (s, 1H) 8.64 (d, *J* = 7.8 Hz, 2H), 8.43 (d, *J* = 8.24 Hz, 1H), 8.28 (d, *J* = 7.84 Hz, 1H), 7.87-7.91 (m, 1H), 7.71-7.77 (m, 2H), 7.6 (t, *J* = 7.24 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.8, 154.9, 148.8, 146.4, 137.0, 133.7, 132.3, 130.0, 129.2, 128.9, 127.6, 126.9, 123.4, 117.2; Anal. Calcd. for $C_{14}H_8N_2O_4$: C, 62.69; H, 3.01; N, 10.44. found C, 62.51; H, 3.16; N, 10.02; ESI-MS (M+1) 269.2

2-(2-Chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2n):[8g] White solid; m.p. 136-138 °C; IR (KBr) 1768, 1625, 1475, 1440, 1315, 1272, 1223, 1092, 1029, 1003, 761cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.28 (d, *J* = 7.6 Hz, 1H), 7.90 (d, *J* = 6.4 Hz, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.53(d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 6.0 Hz, 1H), 7.40 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.3, 156.7, 146.6, 136.7, 133.3, 132.6, 131.6, 131.2, 130.5, 129.1, 128.7, 127.6, 127.0, 117.1; Anal. Calcd. for $C_{14}H_8ClNO_2$: C, 65.26; H, 3.13; N, 5.44. found C, 65.21; H, 3.18; N, 5.49; ESI-MS (M+1) 258.2

2-(3,5-Dimethoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2o): white solid; m.p. 174-176 °C; IR (KBr) 2972, 1752, 1603, 1568, 1478, 1301, 1178, 1025, 832, 783 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.24 (dd, *J* = 6.8 Hz, 1.2 Hz, 1H), 7.81-7.85 (m, 1H), 7.72 (t, *J* = 7.2 Hz, 1H), 7.51-7.54 (m, 1H), 7.47 (d, *J* = 2.0 Hz, 2H), 6.67 (t, *J* = 2.4 Hz, 1H), 3.89 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): *δ* 161.2, 159.2, 156.4, 146.5, 137.4, 132.4, 129.2, 128.5, 127.4, 117.4, 105.9, 105.3, 56.1; Anal. Calcd. for $C_{16}H_{13}NO_4$: C, 67.84; H, 4.63; N, 4.94. found C, 67.79; H, 4.69; N, 4.91; ESI-MS (M+1) 284.2

2-(3,4,5-Trimethoxyphenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2p):[11] white solid; m.p. 178-180 °C; IR (KBr) 2974, 1755, 1605, 1566, 1475, 1303, 1175, 1027, 832, 785 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.24 (d, *J* = 7.88 Hz, 1H), 7.81-7.86 (m, 1H), 7.7 (d, *J* = 7.96 Hz, 1H), 7.50-7.57 (m, 3H), 3.99 (s, 6H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.7, 156.9, 153.4, 147.1, 142.2, 136.7, 128.7, 128.2, 127.2, 125.3, 116.8, 105.6, 104.8, 61.1, 56.1; Anal. Calcd. for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. found C, 65.09; H, 4.94; N, 4.41; ESI-MS (M+1) 314.2

2-(Thiophen-2-yl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2q):[12] White solid; m.p. 128-130 °C; IR (KBr) 1775, 1619, 1600, 1473, 1424, 1221, 1026, 777, 716 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 8.22 (d, 7.88 Hz, 1H), 7.97 (d, *J* = 2.92 Hz, 1H), 7.79-7.83 (m, 1H), 7.61-7.65 (m, 2H), 7.49 (t, *J* = 7.28 Hz, 1H), 7.18 (t, *J* = 4.68 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$): *δ*

158.9, 153.7, 147.1, 136.6, 134.2, 132.3, 131.7, 128.7, 128.3, 127.9, 126.8, 116.7; Anal. Calcd. for $C_{12}H_7NO_2S$: C, 62.87; H, 3.08; N, 6.11; S, 13.99. found C, 62.82; H, 3.01; N, 6.17; S, 13.88; ESI-MS (M+1) 230.2

2-(Naphthalen-1-yl)-4H-3,1-benzoxazin-4-one (2r):[11] Yellow solid; m.p. 118-120 °C; IR (KBr) 1755, 1609, 1563, 1395, 1272, 1095, 1048, 1019, 758, 696, 684 cm^{-1}; ^1H NMR (400 MHz, DMSO- d_6) δ 8.97 (d, J = 8.4 Hz, 1H), 8.19 (d, *J* = 7.6 Hz, 3H), 8.05 (d, *J* = 8 Hz, 1H), 7.98 (t, *J* = 7.2 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.60-7.7 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.6, 157.6, 146.8, 134.0, 133.1, 130.7, 130.0, 128.8, 128.5, 127.8, 127.4, 126.9, 126.4, 125.8, 124.8, 116.9; Anal. Calcd. for $C_{18}H_{11}NO_2$: C, 79.11; H, 4.06; N, 5.13. found C, 79.19; H, 4.12; N, 5.18; ESI-MS (M+1) 274.2

5-Bromo-2-phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (2s): White solid; m.p. 172-174 °C; IR (KBr) 1753, 1615, 1578, 1496, 1299, 1256, 1059, 838, 776, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.6 Hz, 2H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.56-7.60 (m, 2H), 7.50-7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.6, 156.37, 149.3, 136.0, 134.4, 132.9, 129.7, 128.7, 128.4, 126.9, 123.5, 116.1; Anal. Calcd. for $C_{14}H_8BrNO_2$: C, 55.66; H, 2.67; N, 4.64. found C, 55.59; H, 2.65; N, 4.67; ESI-MS (M+1) 302.2

6-Fluoro-2-phenyl-4H-benzo[*d*][1,3]oxazin-4-one (2t):[11] White solid; m.p. 138-140 °C; IR (KBr) 1752, 1625, 1578, 1495, 1297, 1054,1040, 841, 773, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 7.6 Hz, 2H), 7.89 (dd, *J* = 7.6 Hz, *J* = 3.2 Hz, 1H), 7.72 (dd, *J* = 8.8 Hz, *J* = 4.8 Hz, 1H), 7.50-7.60 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (d, *J* = 249.5 Hz), 158.72 (d, *J* = 3.1 Hz), 143.5 (d, *J* = 2.3 Hz), 132.6, 129.9, 129.5 (d, *J* = 8.5 Hz), 128.7, 128.3, 124.6 (d, *J* = 24.1Hz), 118.2, 113.8 (d, *J* = 24.0 Hz); Anal. Calcd. for $C_{14}H_8FNO_2$: C, 69.71; H, 3.34; N, 5.81 found C, 69.69; H, 3.37; N, 5.78; ESI-MS (M+1) 242.2

7-Methoxy-2-(4-(fluoro)phenyl)-4H-benzo[d][1,3]oxazin-4-one (2u): White solid; m.p. 182-186 °C; IR (KBr) 1754, 1626, 1576, 1494, 1295, 1053, 843, 775, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31 (q, *J* = 5.2 Hz, 2H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.19 (t, *J* = 8.4 Hz, 2H),3.96 (s, 3H), 7.06 (t, *J* = 5.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 166.53 (d, *J* = 203.0 Hz), 158.9, 157.0, 149.3, 130.5, 128.7, 126.5(d, *J* = 3.1 Hz), 117.2, 116.0, 115.8, 109.6, 108.7, 55.8; Anal. Calcd. for $C_{15}H_{10}FNO_3$: C, 66.42; H, 3.72; N, 5.16. found C, 66.48; H, 3.79; N, 5.1; ESI-MS (M+1) 272.2

6-Bromo-2-(4-(tert-butyl)phenyl)-4H-benzo[d][1,3]oxazin-4-one (2v):[4e] White solid; m.p. 142-144 °C; IR (KBr) 1753, 1627, 1579, 1497, 1298, 1045, 841, 773, 685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, *J* = 2.0 Hz, 1H), 8.21 (d, *J* = 8.8 Hz, 2H), 7.89 (dd, *J* = 8.4 Hz, *J* = 2.0 Hz, 1H), 7.57(s, 1H), 7.53(t, *J* = 5.6 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.4, 157.6, 156.7, 146.1, 139.5, 131.0, 128.8, 128.3, 127.1, 125.8, 121.1, 118.3, 35.1, 31.1; Anal. Calcd. for $C_{18}H_{16}BrNO_2$: C, 60.35; H, 4.50; N, 3.91. found C, 60.31; H, 4.49; N, 3.93; ESI-MS (M+1) 358.2

2-(4-Chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2y):[12] White solid; m.p. 188-190 °C; IR (KBr) 1769, 1624, 1603, 1489, 1403, 1323, 1259, 1223, 1095, 1058, 1024, 838, 761 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24-8.27 (m, 3H), 7.83 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.48-7.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.2, 156.2, 146.7, 139.1, 136.6, 129.6, 129.1, 128.7, 128.6, 128.4, 127.2, 116.9; Anal. Calcd. for $C_{14}H_8ClNO_2$: C, 65.26; H, 3.13; N, 5.44. found C, 65.19; H, 3.11; N, 5.47; ESI-MS (M+1) 258.2

2-(4-Iodophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (2z): White solid; m.p. 168-170 °C; IR (KBr) 1765, 1621, 1605, 1485, 1321, 1257, 1224, 1056, 1021, 835, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 2H), 7.81-7.88 (m, 3H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 159.1, 156.4, 146.5, 138.4, 137.3, 130.1, 129.9, 129.2, 128.5, 127.4, 117.4, 101.3; Anal. Calcd. for $C_{14}H_8INO_2$: C, 48.16; H, 2.31; N, 4.01. found C, 48.11; H, 2.29; N, 4.05; ESI-MS (M+1) 350.1

2-Butyramidobenzoic acid (3a): White solid; m.p. 116-118 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 13.53 (s, 1H), 11.09 (s, 1H) 8.48 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.0 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 2.34 (t, *J* = 7.6Hz, 2H), 1.58-1.67 (m, 2H), 0.91 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.6, 169.9, 141.4, 134.5, 131.5, 122.9, 120.3, 116.8, 18.7, 13.9; ESI-MS (M+1) 208.1

2-(Cyclohexanecarboxamido)benzoic acid (3b): White solid; m.p. 176-178 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 13.52 (s, 1H), 11.17 (s, 1H) 8.50 (d, *J* = 8.0 Hz, 1H), 7.96 (dd, *J* = 7.6 Hz, *J* = 1.6 Hz, 1H), 7.52-7.56(m, 1H), 7.11 (t, *J* = 7.2 Hz, 1H), 2.25-2.30 (m, 1H), 1.87-1.90 (m, 2H), 1.71-1.74 (m, 2H), 1.61-1.64 (m, 1H), 1.15-1.45 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 174.5, 170.0, 141.6, 134.4, 131.5, 122.8, 120.3, 116.8, 46.3 29.5, 25.8, 25.5; ESI-MS (M+1) 248.1

2-[(Phenylcarbonyl)amino]benzoic acid (3c): White solid; ^1H NMR (400 MHz, DMSO-d_6) δ 13.89 (s, 1H), 12.15 (s, 1H) 8.69 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.2 Hz, 2H), 7.55-7.67 (m, 4H), 7.19 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 170.4, 165.1, 141.5, 135.0, 134.7, 132.5, 131.7, 129.6, 129.4, 128.9, 127.4, 123.3, 120.3, 116.9; ESI-MS (M+1) 242.1

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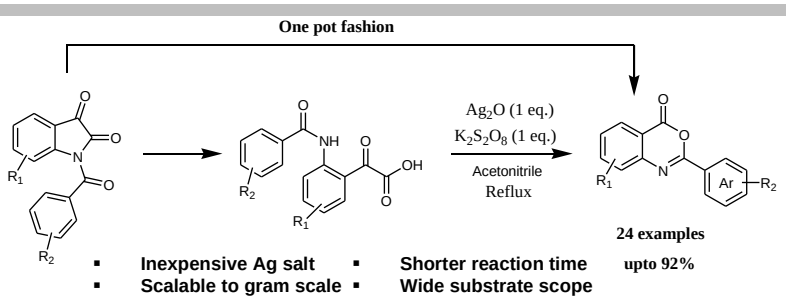

Key Topic*

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Title

Silver mediated synthesis of 4*H*-benzoxazin-4-ones by intramolecular decarboxylative O-acylation reaction with *α*-oxocarboxylic acid

* First report of intramoleculer decarboxylative acylation and more convenient method to prepare 4*H*-benzoxazin-4-ones.