EurJOC
European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.202100716

Link to VoR: https://doi.org/10.1002/ejoc.202100716

WILEY-VCH

10.1002/ejoc.202100716

Iron Promoted Ring Opening and Ring Closing Cascade (ROCC) Reaction of Ortho-Carboxy-Isoxazole leading to Isoindolinone Derivatives

Ramakrishna Gudipati[a,b], Vankudoth Jayaram[a], Karri Raghavulu[a, b] , Dinesh Bhoot[a], Keloth Basavaiah[b], Satyanarayana Yennam[a], Manoranjan Behera*[a]

Abstract: An efficient and convenient route for the synthesis of various functionalized 3-alkylidene isoindolin-1-ones is presented. The synthesis involves the ring opening and ring Closing Cascade (ROCC) reaction of ortho-carboxy-isoxazole using Fe/NH_4Cl. This is the first report for the synthesis of 3-alkylidene isoindolin-1-one using Fe/NH_4Cl.

Introduction

N-containing heterocycles are highly demanded structural motifs and they are found in nature with a numerous biological activities.[1] Among the vast family of *N*-containing heterocycles, isoindolinones (**Fig 1**) such as, chileninc, pictonamine[2], lennoxamine, D4 dopamine receptor ligand (S)-PD 172938, Pagoclone (Cl-1043) and Pazinaclone (DN-2327) are very important boiological active compounds.[3-6] Due to their great significance, many powerful synthetic methodologies have been reported for the synthesis of alkylidene Isoindolin-1-ones in last decades.These methods mainly involved the traditional condensation reaction of phthalimides with stabilized phosphoranes[7] or addition of organometallic reagents followed by dehydration of the resulting 3-hydroxyphthalimidines[8]. Also, the Horner condensation of 3-(diphenylphosphinoyl)isoindolin-1-ones with aldehydes,[9] ortho lithiation–anionic cyclization of N-acyl-2-bromobenzamides,[10] electrophilic cyclizations of 2-alkynylbenzamides[11] (**Scheme 1**) and metal-catalyzed cascade reactions[12] are reported in literature. However, most of these procedures suffer from one or more drawbacks such as the use of expensive metal reagents or palladium catalyzed reactions, availability of starting materials like alkyne ketone. So, there is an urgent need to develop new method for the synthesis of isoindoline using less expensive regents.

Isoxazoles have recently emerged as valuable precursors for the synthesis of various other scaffolds.[13] One of the key structural elements of isoxazole which attracts attention of synthetic chemist is the relatively labile N-O bond, which is easy to cleave into heterocyclic compounds.[14] There are many examples found in the literature where isoxazoles have been employed as the starting materials.[15-17] Recently, many research groups used isoxazoles as substrates to react with alkynes in the presence of gold[18], platinum[19], $Zn(OTf)_2$ [20] and Tf_2NH as catalysts[21], affording various nitrogen containing heterocycles.The application of iron salts as catalysts in organic synthesis has attracted much attention[22] owing to their environmentally benign, low cost, and the abundance of elemental iron.[23] However, it is still a challenge to form other heterocycles from isoxazoles catalyzed by iron salts. There are few examples reported for prepration of N-heterocycles using iron salts as catalysts. For example, domino transformation of isoxazoles to 2,4-dicarbonylpyrroles under Fe/Ni relay catalysis has been reported by Khlebnikove and co-workers.[24] The same group have also reported Fe(II)-Catalyzed isomerization of 4-vinylisoxazoles into pyrroles[25] and Fe(II)/Au(I) relay catalyzed propargylisoxazole to pyridine isomerization: access to 6-halonicotinates.[26] Chen et al. has reported iron-mediated Ring-Opening and Rearrangement Cascade synthesis of polysubstituted pyrroles from 4-alkenylisoxazoles. [27]

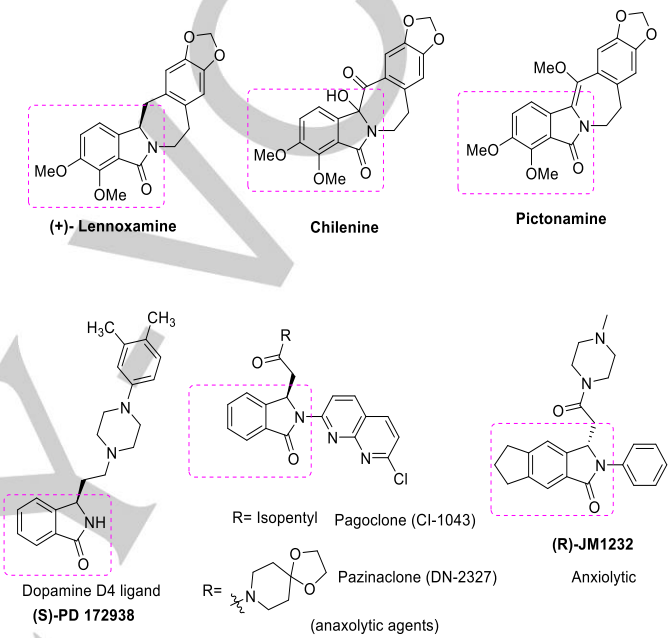

Figure 1. Selected examples of biologically active compounds with the isoindolin-1-one skeleton.

[a] R. Gudipati, V. Jayaram, K. Raghavulu, Dinesh Bhoot, S. Yennam, Dr. M. Behera, Chemistry Services, Aragen Life Sciences (Formerly known as GVK Biosciences),
Plot No. 125 (part)&126, IDA, Mallapur, Hyderabad, Telangana, India, 500076.
E-mail: Manoranjan.Behera@aragen.com
[b] R. Gudipati, K. Raghavulu, Dr.K. Basavaiah
Department of Inorganic & Analytical Chemistry, Andhra University, Waltair Junction, Visakhapatnam, Andhra Pradesh, India, 530003.

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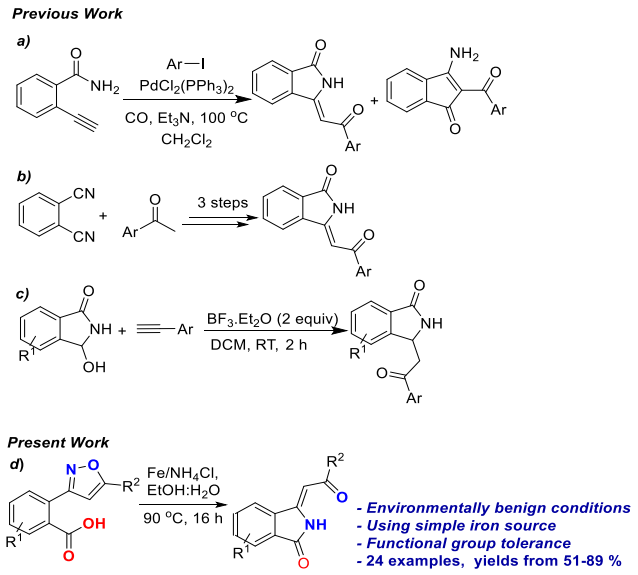
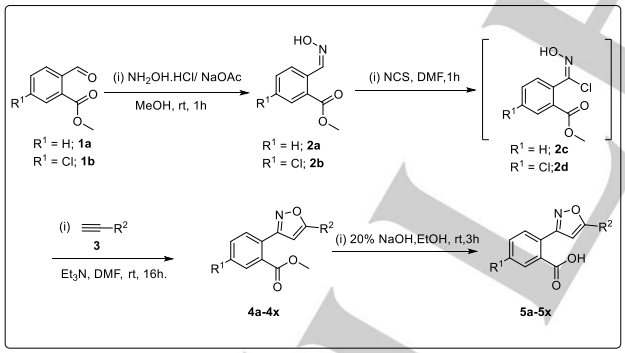
Recently we have reported Fe/NH_4Cl mediated conversion of isoxazole to substituted pyridine derivatives via ROCC mechanism.[28] In our continuous effort to prepare natural product hybrids [29], we were interested to prepare few isoindoline derivatives. Here in we report, the preparation of alkylidene Isoindolinone derivatives from ortho-carboxy isoxazole via ROCC mechanism.



Scheme 1. Synthetic strategies toward the isoindolin-1-ones framework

Results and discussion

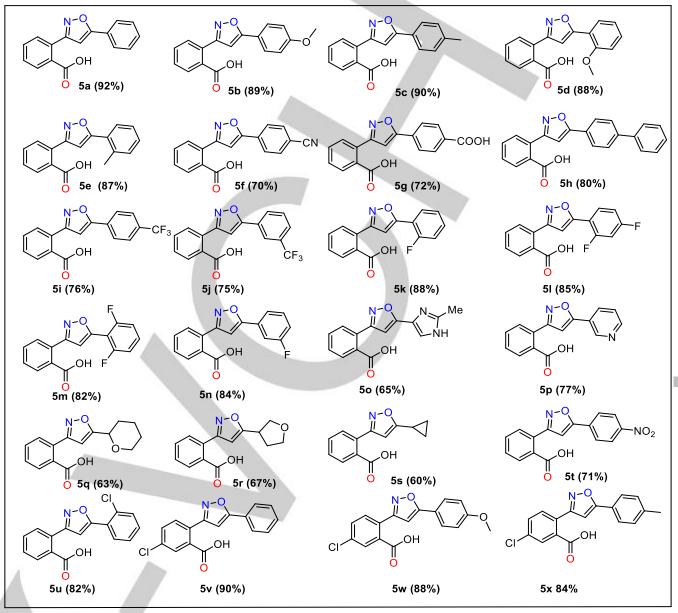
We initiated our studies with 2-carboxy isoxazoles **5a as** model substrate**,** which was easily prepared from the commercially available methyl 2-formylbenzoate *via* a three steps[30] synthetic sequence (**Scheme 2**).



Scheme 2: Synthesis of Ortho-Carboxy-Isoxazoles

The reaction involved the condensation of hydroxylamine with methyl 2-formylbenzoate to give oxime derivatives **2a-2b** which upon treatment with N-chlorosuccinimide gave the methyl 2-(chloro(hydroxyimino)methyl) benzoate **2c-2d**. The key 3+2 cycloaddition reaction was performed with substituted acetylenes to afford various methyl 2-(isoxazol-3-yl) benzoate derivatives **4a-4x**. This was employed for basic hydrolysis without purification to afford the 2-carboxy isoxazole derivatives **5a-5x** with moderate to good yields (**Table1**) (60-92%).

Table1: Various Ortho-Carboxy-Isoxazoles Prepared[a]

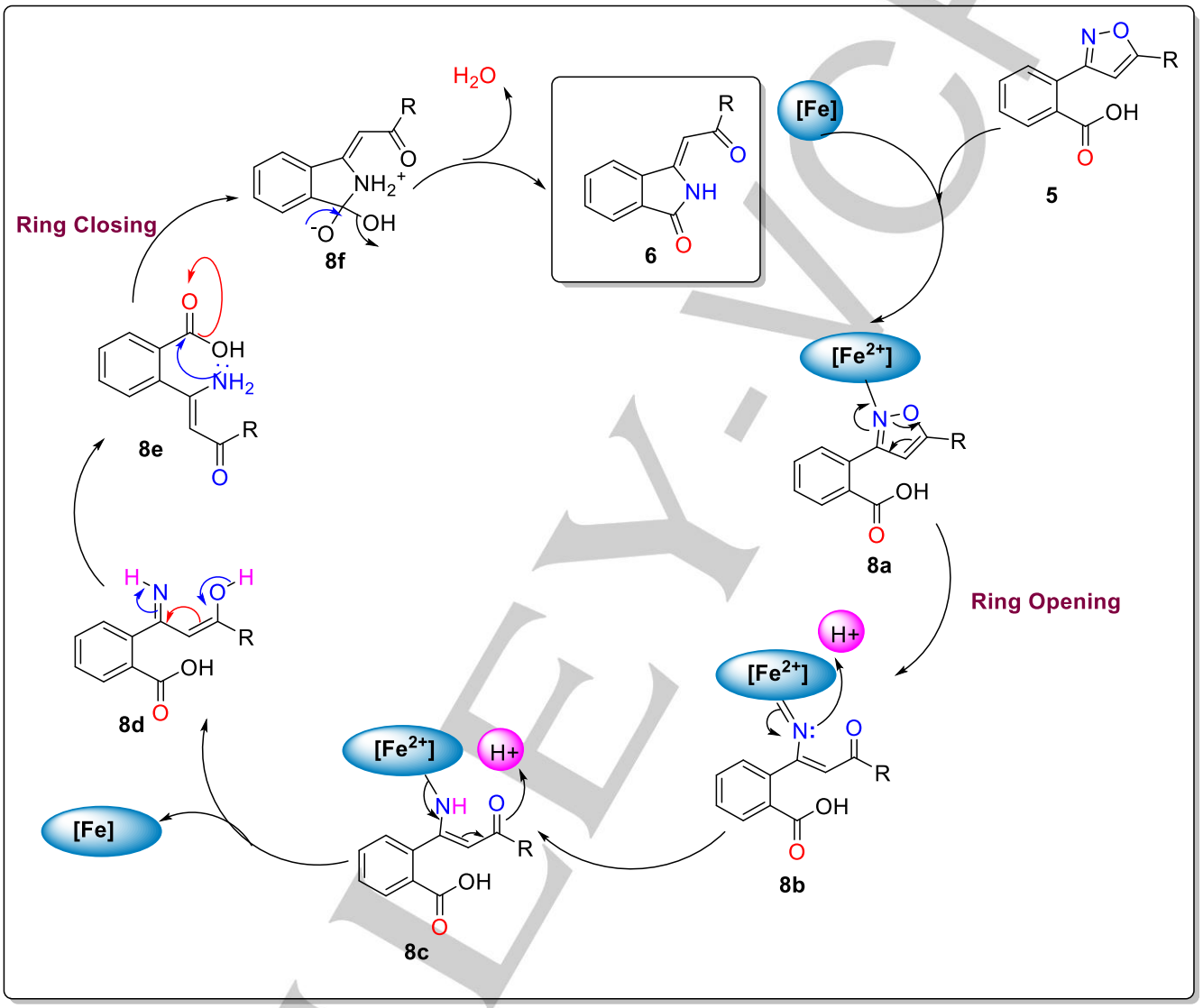


[a]Yields of isolated products in parenthesis

With our previous work based on isoxazole opening, we started to explore the ring opening ring closing cascade reaction of 5 with Fe/ NH_4Cl condition. Initially we conducted the optimization reaction by using Fe (10 equiv) and NH_4Cl (6 equiv.) in EtOH: H_2O (2:1) at 120 ^{0}C for 24 h and we observed the N-cyclized product 6 as a single (*Z*)-isomer **6** in 45% yield The structure was ascertained by NMR spectroscopy 2D conformation (**Table 2, entry 1**). Further reducing the temperature to 90 ^{0}C and reaction time to 16 h led to the improvement of the product yield (**Table 2, entry 2**). Then decreasing the amount of catalyst loading Fe (5 equiv) and NH_4Cl (3 equiv) resulted the product formation with improved yield to 89% (**Table 2, entry 3**). When the reactions were performed in other solvents such as MeOH (**Table 2, entry 4**), IPA (**Table 2, entry 5**), DMF (**Table 2, entry 6**), Dioxane (**Table 2, entry 7**), yield of the product could not be further improved. Notably, EtOH was most favourable reaction media. In a similar manner, presence of EtOH (**Table 2 entry 8**) and H_2O (**Table 2 entry 9**) was critical for the product formation**.**When the reaction was performed in the absence of NH_4Cl (**Table 2**, **entry 10**) very less product formation was observed. Similarly, without Fe (**Table 2**, **entry 11**) the reaction gave poor yield. The lowering of catalyst loading and reaction time (**Table 2**, **entries 12-15**) resulted in reduction of the product yield. No improvement was found by switching of solvent and with the addition of AcOH **(Table 2, entries 16-17).** The reaction was failed with the use of other catalyst Fe and NH_4OAc (**Table 2**, **entry 18**). Therefore, the optimum reaction conditions for the transformation was found to be taking 5 equiv of Fe, 3 equiv NH_4Cl in EtOH: H_2O (2:1) ration and refluxing the reaction mixture at 90 ^{o}C for 16 h which gave 89% yield **(Table 2, Entry 3)**.

Based on the literature[31], a plausible mechanism is proposed in **Scheme 3**. The reaction starts with iron coordinating wth isoxaole ring through N atom to form the interemediate 8a which undergo reductive ring opening of isoxazole ring to give the enaminone interemdiate 8b. The lone pair of nitrogen in enaminone intermediate 8b picks up H^+ ion in acidic medium (NH_4Cl in H_2O) to form the intermediate 8c which picks up a second H^+ to facilitate the cleavage of Fe in the mechansism cycle and give the 2-(3-hydroxy-1-imino-3-phenylallyl) benzoic acid 8d. The intermediate 8d undergoes intramolecular rearrangement to give the more stable 2-(1-amino-3-oxo-3-phenylprop-1-en-1-yl) benzoic acid 8e. The nucleophilic attack of nitrogen loan pair towards the carbonyl function gave the ring closure intermediate 8C. Finally, elimination of water takes place to afford the desired product the 3-alkylidene isoindolin-1-one 6.

Scheme 3: Plausible Mechanism for the Formation of 3-alkylidene Isoindolin-1-ones



With the optimized conditions in hand, we then focused on studying the scope of the different substitution in the isoxazole derivatives in the ring opening and ring closing cascade reaction and the results are described below **(Table 3).** Electron donating groups on para/ortho position such as methoxy, methyl, could be well tolerated and their corresponding products **6b-6e** were obtained in comparable yield (74-83%). On the other hand, aryl having electron withdrawing group (-CN, COOH, Phenyl or $–CF_3$) at the para /meta position (**6f-6j)** gave moderate to good yield (51-84%). Interestingly, halogen- substituted isoxazole could also be applied in this methodology to give the products **6k-6n** and **6u** in good yields (77-82%). It was found that hetero aromatics such as 2-methyl-1H-imidazol-5-yle, 3-pyridyl, were also found to be good substrates to furnish **6o**, **6p** (53-65%) yield. In addition, aliphatic side chain also afforded **6q-6s** in synthetically yields (56-64%). It is noteworthy to mention here that ortho-carboxy-isoxazoles having NO_2 group substitution on phenyl ring was also engaged in ROCC mechanism to give isoindoline derivative **6t** with amine functionality in 56% yield. Subsequently, if the R_1 having chloro substitution and the targeted products **6v-6x** were obtained in moderate to good yields (76-85%).

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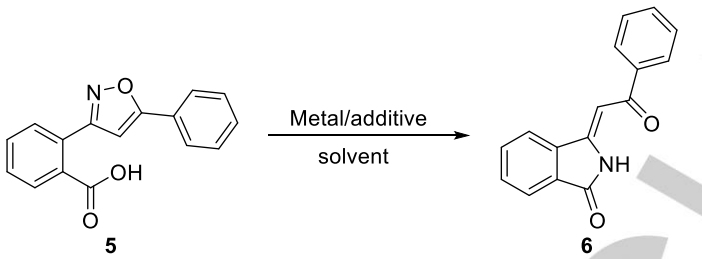
Table 2: Optimization of the Reaction Conditions for the Synthesis of 3-alkylidene Isoindolinone 6

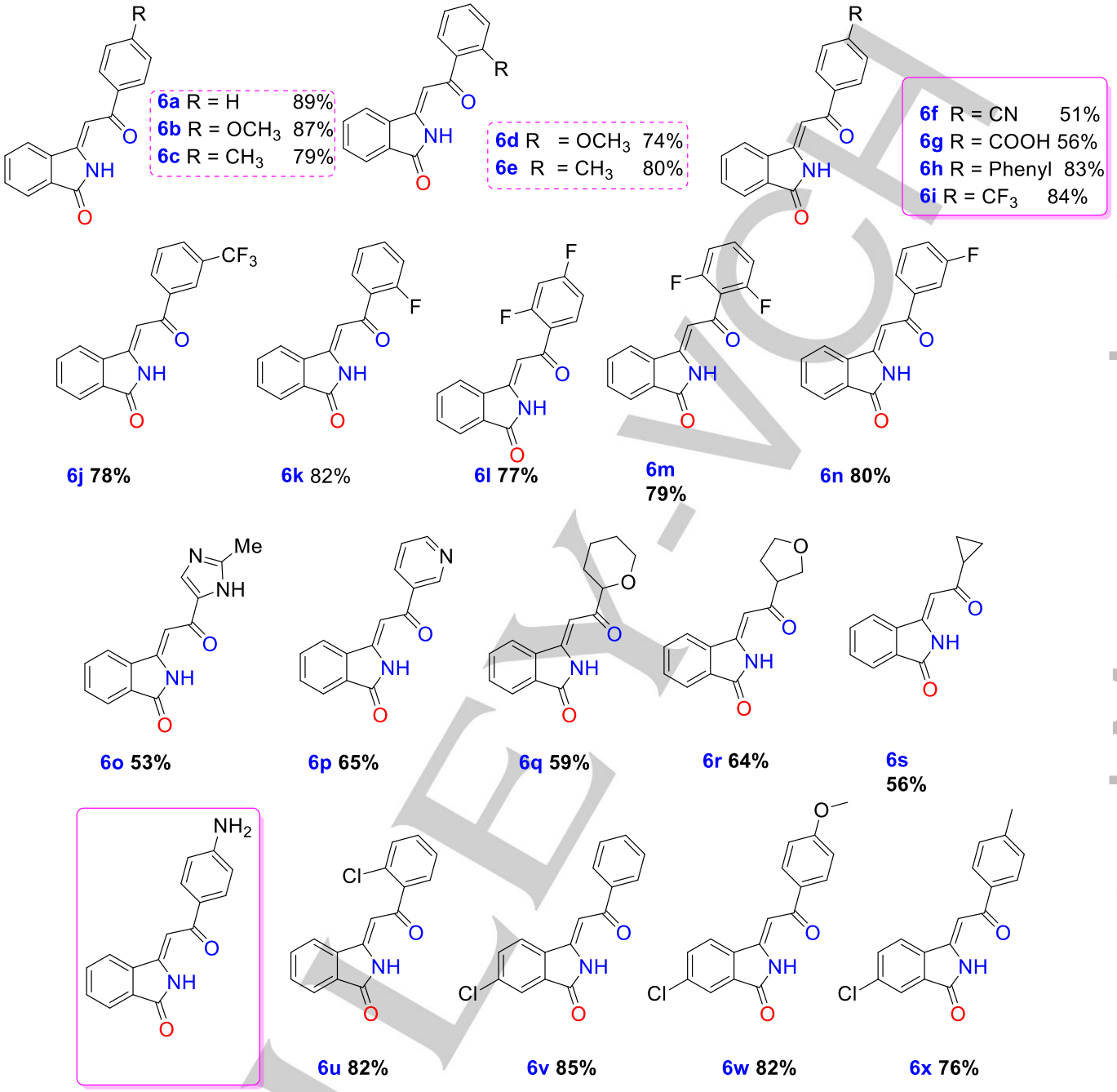


5 6

Entry	Catalyst (x eq)	NH_4Cl (eq)	Temp	Time(h)	Solvent	Yield [a]
1	Fe (10)	6	120 ^0C	24	EtOH/H_2O(2:1)	45
2	Fe (10)	6	90 ^0C	16	EtOH/H_2O(2:1)	67
3	**Fe(5)**	**3**	**90 ^0C**	**16**	**EtOH/H_2O(2:1)**	**89**
4	Fe (5)	3	90 ^0C	16	MeOH/H_2O(2:1)	55
5	Fe(5)	3	90 ^0C	16	IPA/H_2O(2:1)	80
6	Fe(5)	3	90 ^0C	16	DMF/H_2O(2:1)	30
7	Fe(5)	3	90 ^0C	16	Dioxane /H_2O (2:1)	34
8	Fe(5)	3	90 ^0C	16	H_2O	63
9	Fe (5)	3	90 ^0C	16	EtOH	12
10	Fe (5)	-	90 ^0C	16	EtOH/H_2O(2:1)	8
11	-	3	90 ^0C	16	EtOH/H_2O(2:1)	5
12	Fe(2)	1	90 ^0C	16	EtOH/H_2O(2:1)	20
13	Fe (5)	3	90 ^0C	4	EtOH/H_2O(2:1)	15
14	Fe (5)	3	90 ^0C	8	EtOH/H_2O(2:1)	32
15	Fe(5)	3	90 ^0C	12	EtOH/H_2O(2:1)	64
16	Fe (5)	-	90 ^0C	16	AcOH	30
17	Zn (5)	-	90 ^0C	16	AcOH	0
18	Fe(5)	NH_4OAc	90 ^0C	16	EtOH/H_2O(2:1)	0

[a] Yields based on LC-MS analysis

Table 3. Scope of substituted 3-alkylidene Isoindolin-1-ones



[a]General conditions: 5 (1 eq), Iron (5 eq) and NH_4Cl (3 eq), EtOH:H_2O (2:1 mL), 90 ^{0}C, 16 h. [b] Yields of isolated products.

Conclusion:

In conclusion, we have developed a simple and facile synthesis of isoindolinones from easily accessible or commercially available starting materials. The key features of this methodology involve Fe/NH_4Cl, mediated Reductive Ring Opening and Ring Closing cascade (ROCC) mechanism of ortho-carboxy-Isoxazole This general method affords a reasonably broad substrate scope and good functional group compatibility, allowing for the introduction of functionalized organic molecules. We believe that this methodology will be of interest to the synthetic/medicinal chemists and may find applications in the pharmaceutical industry.

General Procedure for the Ring-opening and Ring Closing Cascade (ROCC) of Ortho-Carboxy-Isoxazole (5a-5x). A solution of methyl 2-(isoxazol-3-yl) benzoate 4a-4x (1.79 mmol) in EtOH (10mL) and added 20% NaOH (5.37 mmol) at 0 ^{0}C and the RM was stirred at RT for 2-4 h. TLC analysis in 100 % EtOAc/Pet-ether showed completion of the reaction. Then RM was evaporated and solid was dissolved in water. The aqueous solution was extracted with ethyl acetate and discard. Then the aqueous layer was taken into the RB flask and acidified with Conc.HCl at 0 ^{0}C, solid formed, filtered the solid and dried under vacuum to give the pure compounds **5a-5x** (60-92%) yield.

2-(5-phenylisoxazol-3-yl)benzoic acid (5a). R_f = 0.10 (EtOAc 100). Off-white solid (437 mg, 92%). M.p. 144-147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.08-8.07 (d, 1H, *J* = 7.0 Hz), 7.83-7.80 (dd, 2H, *J* = 8 & 7.2 Hz), 7.66-7.55 (m, 3H), 7.49-7.44 (m, 3H), 6.68(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 266.27.

2-(5-(4-methoxyphenyl)isoxazol-3-yl)benzoic acid (5b) R_f = 0.10 (EtOAc 100). Off-white solid (466 mg, 89%). M.p. 180-183 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.07-8.05(d, 1H, *J* = 7.6 Hz), 7.75-7.73(d, 2H, *J* = 8.8 Hz), 7.64-7.53 (m,3H), 6.99-6.96 (d, 2H, *J* = 8.8 Hz), 6.55(s, 1H), 3.87(s,3H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 296.27.

2-(5-(p-tolyl)isoxazol-3-yl)benzoic acid (5c) R_f = 0.10 (EtOAc 100).Off-white solid (427 mg, 90%). M.p. 152-155°C. ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.08-8.06 (d, 1H, *J* = 7.5 Hz), 7.71-7.70(d, 2H, *J* = 8 Hz), 7.64-7.63 (t, 2H), 7.58-7.56 (d, 1H, *J* = 7.5 Hz), 7.78(s, 2H), 6.62(s, 1H), 2.41 (s,3H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 280.26.

2-(5-(2-methoxyphenyl)isoxazol-3-yl)benzoic acid (5d). R_f = 0.10 (EtOAc 100), Off-white solid (420 mg, 88%). M.p. 175-178 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.07-8.05(d, 1H, *J* = 7.6 Hz), 8.01-7.99 (d, 2H, *J* = 6.8 Hz), 7.64-7.63 (d, 2H, *J* = 4 Hz), 7.56-7.52 (m, 1H), 7.42-7.38(m, 1H), 7.09-7.06(t, 1H), 7.00-6.98(d, 1H, *J* = 8.8 Hz), 6.94(s, 1H), 3.91 (s,3H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 296.27.

2-(5-(o-tolyl)isoxazol-3-yl)benzoic acid (5e). R_f = 0.10 (EtOAc 100), Off-white solid (414 mg, 87%). M.p. 164-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10-8.08(d, 1H, *J* = 8 Hz), 7.75 (d, 1H, *J* = 2 Hz), 7.66 (d, 2H, *J* = 3.6 Hz),7.60-7.57 (m, 1H), 7.35-7.28 (m, 3H), 6.58(s, 1H), 2.52 (s, 3H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 280.30.

2-(5-(4-cyanophenyl)isoxazol-3-yl)benzoic acid (5f). R_f = 0.10 (EtOAc 100). Off-white solid (333mg, 70%). M.p. 172-175 °C.^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.10-8.08 (d, 1H, *J* = 8.5 Hz), 7.93-7.91(d, 2H, *J* = 8.5 Hz), 7.78-7.76(d, 2H, *J* = 8.5 Hz), 7.67-7.66 (t, 1H), 7.62-7.58 (m, 2H), 6.80 (s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 291.25

2-(5-(4-carboxyphenyl)isoxazol-3-yl)benzoic acid (5g). R_f = 0.30 (MeOH/DCM 10:90). Off-white solid (344 mg, 72%). M.p. 207-210 °C.^{1}H NMR (400 MHz, DMSO-d_6): *δ* 13.17 (bs, 2H), 8.11-8.09 (d, 2H, *J* = 8.8 Hz), 8.05-8.03 (d, 2H, *J* = 8.8 Hz), 7.90-7.88 (dd, 1H, *J* = 8 & 8 Hz), 7.70-7.62 (m, 3H), 7.40 (s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 310.

2-(5-([1,1'-biphenyl]-4-yl)isoxazol-3-yl)benzoic acid (5h). R_f = 0.10 (EtOAc 100). Off-white solid (384 mg, 80%). M.p. 183-186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.09-8.07 (d, 1H, *J* = 7.6 Hz), 7.89-7.87(d, 2H, *J* = 8 Hz), 7.72-7.55 (m, 7H), 7.49-7.45(t, 2H), 7.39-7.37(m, 1H), 6.71(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 342.31.

2-(5-(4-(trifluoromethyl)phenyl)isoxazol-3-yl)benzoic acid (5i). R_f = 0.10 (EtOAc 100). Off-white solid (365 mg, 76%). M.p.181-184°C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10-8.08(d, 1H, *J* = 7.6 Hz), 7.93-7.91 (d, 2H, *J* = 8.4Hz), 7.74-7.72(d, 2H, *J* = 8.4 Hz), 7.69-7.57(m, 3H), 6.77(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 334.26.

2-(5-(3-(trifluoromethyl)phenyl)isoxazol-3-yl)benzoic acid (5j). R_f = 0.10 (EtOAc 100). Off-white solid (360mg, 75%). M.p.123-126 °C.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.82(s, 1H), 7.73-7.68(t, 2H), 7.55-7.53(d, 1H, *J* = 7.6 Hz), 7.42-7.40 (d, 2H, *J* = 6 Hz), 7.38-7.28(m, 2H), 6.61(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 334.18.

2-(5-(2-fluorophenyl)isoxazol-3-yl)benzoic acid (5k). R_f = 0.10 (EtOAc 100). Off-white solid (419 mg, 88%). M.p. 156-159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10-8.00(m, 2H), 7.66-7.56 (m, 3H), 7.45-7.41(t, 1H), 7.31-7.30 (d, 2H, *J* = 7.6 Hz), 7.22-7.17(t, 1H), 7.31-6.88-6.87 (d, 1H, *J* = 3.6 Hz). LC-MS (ESI+): *m/z* $(M+H)^+$ found 284.26.

2-(5-(2,4-difluorophenyl)isoxazol-3-yl)benzoic acid(5l): R_f = 0.10 (EtOAc 100). Off-white solid (406 mg, 85%). M.p. 159-162 °C.^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.07-8.06(d, 1H, *J* = 7.5 Hz), 8.01-7.96(dd, 1H, *J* = 8.5 Hz), 7.66-7.55 (m, 3H), 7.05-7.01(m, 1H),6.96-6.91(m, 1H), 6.80-6.79(d, 2H, *J* = 3.5 Hz). LC-MS (ESI+): *m/z* $(M+H)^+$ found 301.9.

2-(5-(2,6-difluorophenyl)isoxazol-3-yl)benzoic acid (5m) R_f = 0.10 (EtOAc 100). Off-white solid (391 mg, 82%). M.p. 191-194 °C.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10-8.08(d, 1H, *J* = 8 Hz), 7.68-7.65(d, 2H, *J* = 13.2 Hz), 7.59-7.51(m, 1H), 7.44-7.37(m, 1H), 7.07-7.03(t, 2H), 6.87(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 302.3.

2-(5-(3-fluorophenyl)isoxazol-3-yl)benzoic acid (5n): R_f = 0.10 (EtOAc 100). Off-white solid (400 mg, 84%). M.p. 176-179 °C.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.08-8.06(d, 1H, *J* = 7.6 Hz), 7.67-7.55(m, 4H), 7.52-7.49 (d, 1H, J = 9.2 Hz), 7.47-7.41(m, 1H), 7.16-7.12(m, 1H), 6.69 (s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 284.20.

2-(5-(2-methyl-1H-imidazol-4-yl)isoxazol-3-yl)benzoic acid (5o): R_f = 0.10 (EtOAc 100). Off-white solid (309 mg, 65%). M.p. 159-162 °C.^{1}H NMR (500 MHz, DMSO-d_6): *δ* 13.4(bs, 1H), 8.66-8.61 (t, 1H), 8.02-7.99(t, 1H), 7.91-7.89(d, 1H, *J* = 7.5 Hz), 7.72-7.58(m, 3H), 7.23-7.21(t, 1H), 3.96(d, 3H, *J* = 2 Hz). LC-MS (ESI+): *m/z* $(M+H)^+$ found 270.09.

2-(5-(pyridin-3-yl)isoxazol-3-yl)benzoic acid (5p): R_f = 0.10 (EtOAc 100). Off-white solid (365 mg, 77%). M.p. 226-229 °C.^{1}H NMR (500 MHz, $CDCl_3$): *δ* 9.1(s, 1H), 8.67(s, 1H), 8.20-8.19(d, 1H, *J* = 8 Hz), 8.11-8.10(d, 1H, *J* = 7 Hz), 7.67-7.60 (m, 3H), 7.48-7.46(d, 1H, J = 7.5Hz), 6.89 (s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 267.26.

2-(5-(tetrahydro-2H-pyran-2-yl)isoxazol-3-yl)benzoic acid (5q): R_f = 0.10 (EtOAc 100). Semi solid (299 mg, 63%).^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.05-8.04(d, 1H, *J* = 7.5 Hz), 7.63-7.53(dd, 1H, *J* = 8.5&15 Hz), 7.56-7.53(t, 2H), 6.36(s, 1H), 4.36-4.60 (dd, 1H, *J* = 2&10.5 Hz), 4.11-4.09 (d, 1H, J = 11.5Hz), 3.66(t, 1H), 2.08-2.05(d, 1H, J = 13.5Hz), 1.98-1.97(d, 1H, J = 3.5Hz), 1.81-1.6 (m, 4H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 274.34.

2-(5-(tetrahydrofuran-3-yl)isoxazol-3-yl)benzoic acid (5r): R_f = 0.10 (EtOAc 100). Semi solid (450 mg, crude 82% purity as such for used for next step LC-MS (ESI+): *m/z* $(M+H)^+$ found 260.19.

2-(5-cyclopropylisoxazol-3-yl)benzoic acid (5s): R_f = 0.10 (EtOAc 100). Semi solid (282 mg, 60%). ^{1}H NMR (500 MHz, $CDCl_3$): *δ* 8.06 (d, 1H, *J*=2), 7.63-7.59 (m, 1H), 7.55-7.52 (m, 2H), 6.09 (s, 1H), 2.10-2.07 (m, 1H), 1.12-1.06 (m, 4H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 230.19

2-(5-(4-nitrophenyl)isoxazol-3-yl)benzoic acid (5t): R_f = 0.10 (EtOAc 100). Off-white solid (339 mg, 71%). M.p. 227-230 °C.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.36-8.34 (d, 2H, *J* = 8.8 Hz), 8.11-8.10 (d, 1H, *J* = 7.2 Hz), 8.00-7.98(d, 2H, *J* = 8.8 Hz), 7.68-7.61(m, 3H), 6.86 (s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 311.26.

2-(5-(2-chlorophenyl)isoxazol-3-yl)benzoic acid (5u): R_f = 0.10 (EtOAc 100). Off-white solid (391mg, 82%). M.p. 173-178 °C.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.10-8.02 (dd, 2H, *J* = 7.2 & 6.8 Hz), 7.66-7.59(m, 3H), 7.52-7.50 (d, 1H, *J* = 7.2 Hz), 7.42-7.38(t, 2H), 7.13(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 300.23.

5-chloro-2-(5-phenylisoxazol-3-yl)benzoic acid (5v): R_f = 0.10 (EtOAc 100). Off-white solid (429 mg, 90%). M.p. 210-213 °C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.05(s, 1H), 7.82-7.80 (d, 2H, *J* = 6.8 Hz), 7.62-7.59 (d, 2H, *J* = 10.8 Hz), 7.48-7.46(d, 3H, *J* = 5.6 Hz), 7.67(s, 1H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 300.23.

5-chloro-2-(5-(4-methoxyphenyl)isoxazol-3-yl)benzoic acid (5w): R_f = 0.10 (EtOAc 100). Off-white solid (422mg, 88%). M.p. 172-175°C. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.03(s, 1H), 7.74-7.73 (d, 2H, *J* = 8.5 Hz), 7.61-7.56 (dd, 2H, *J* = 17.5Hz), 6.99-6.97(d, 2H, *J* = 8.5Hz), 7.54(s, 1H), 3.87(s, 3H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 330.27.

5-chloro-2-(5-(p-tolyl)isoxazol-3-yl)benzoic acid (5x): R_f = 0.10 (EtOAc 100). Off-white solid (402 mg, 84%). M.p. 253-256 °C.^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.72-7.70 (d, 2H, *J* = 8 Hz), 7.56-7.54 (d, 1H, *J* = 8.5Hz), 7.36-7.34(d, 3H, *J* = 8.5Hz), 7.09 (s, 1H), 2.37(s, 3H). LC-MS (ESI+): *m/z* $(M+H)^+$ found 314.26.

General Procedure for the synthesis *isoindolin-1-one* (6a-6x). A mixture of Ortho-Carboxy-Isoxazole 5a-5x (0.75 mmol), Fe (3.77 mmol), NH_4Cl (2.26 mmol) in EtOH (5mL) and water (2.5 mL) was stirred at 90 ^{0}C for 16h, then the reaction mixture cooled to room temperature, passed through celite pad and diluted with water and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was purified by combi-flash column chromatography (60-120 mesh Silica gel, EtOAc in pet ether) to give the corresponding ROCC products 6a-6x**.**

(Z)-3-(2-oxo-2-phenylethylidene)isoindolin-1-one(6a). 167 mg (89%), off-white solid M.p. 160-163 °C, R_f = 0.6 (EtOAc/Hexane 30:70). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.60 (bs, 1H), 8.05-8.03 (d, 2H, *J* = 7.0 Hz), 7.91 (d, 1H, *J* = 6.5Hz), 7.87(d, 1H, *J* = 6.5Hz), 7.68-7.50 (m, 3H) 7.59 (t, 2H), 6.88(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.07, 169.08, 148.4, 138.4, 137.1, 133.0, 132.9, 131.9, 129.3, 128.7, 124.2, 121.1, 94.7, HRMS (ESI+): *m/z* $(M+H)^+$calculated for $C_{16}H_{12}O_2N$ 250.0862, found 250.0858.

(Z)-3-(2-(4-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one (6b). 164 mg (87%), pale yellow solid M.p. 161-164 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (500 MHz, $CDCl_3$): δ 10.63 (bs, 1H), 8.05 -8.04(d, 2H, *J* = 9 Hz), 7.92-7.90 (d, 1H, *J* = 7.5Hz), 7.84-7.82(d, 1H, *J* = 7.5Hz), 7.70-7.62(m, 2H) 7.01-6.99(d, 2H, *J* = 8.5Hz), 6.86(s, 1H), 3.90(s, 3H). ^{13}C NMR (101MHz, $CDCl_3$): δ 189.4, 168.9, 163.5, 147.7, 137.1, 132.7, 131.7, 131.2, 130.2, 129.3, 124.1, 120.9, 113.9, 94.7, 55.4. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{14}O_3N$ 280.0968 , found 280.0962

(Z)-3-(2-oxo-2-(p-tolyl)ethylidene)isoindolin-1-one (6c). 149 mg (79%), off-white solid M.p. 323-326 °C, R_f = 0.6 (EtOAc/Hexane 30:70).^{1}H NMR (500 MHz, $CDCl_3$): δ 10.62 (bs, 1H), 7.96-7.94(d, 2H, *J* = 7.0 Hz), 7.90-7.90(d, 1H, *J* = 6.5Hz), 7.84-7.83(d, 1H, *J* = 6.5Hz), 7.70-7.63(m, 2H) 7.33-7.31(d, 2H, *J* = 6.5Hz), 6.87(s, 1H), 2.45(s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.6, 169.0, 148.0, 143.8, 137.1, 135.8, 132.8, 131.8, 129.4, 129.3, 128.0, 124.1, 121.0, 94.8, 21.6. HRMS (ESI+): *m/z* $(M+H)^+$calculated for $C_{17}H_{14}O_2N$ 264.1019, found 264.1014.

(Z)-3-(2-(2-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one (6d). 140 mg (4%), off-white solid M.p. 138-141 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): δ 10.49 (bs, 1H), 7.89-7.88 (, 1H, *J* = 7.2 Hz), 7.76 -7.73 (t, 2H), 7.66-7.59 (m, 2H), 7.51-7.47 (t, 1H) 7.07-7.00(m, 2H), 6.94(s, 1H), 3.96 (s, 3H).^{13}C NMR (101MHz, $CDCl_3$): δ 192.3, 169.1, 158.1, 146.4, 137.4, 133.5, 132.6, 131.5, 130.6, 129.3, 129.2, 124.0, 121.0, 120.9, 111.6, 100.2, 55.7. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{14}O_3N$ 280.0968 , found 280.0962.

(Z)-3-(2-oxo-2-(o-tolyl)ethylidene)isoindolin-1-one (6e).150 mg (80%), off-white solid M.p. 148-151 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (500 MHz, $CDCl_3$): δ 10.6 (bs, 1H), 7.92-7.91(d, 1H, *J* = 2Hz), 7.88 -7.76 (d, 1H, *J* = 6 Hz), 7.68-7.62(m, 3H), 7.41-7.40(t, 1H) 7.38-6.28(m, 2H), 6.6 (s, 1H), 2.53 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.5, 169.1, 147.7, 139.6, 137.4, 137.1, 132.9, 131.9, 131.7, 131.0, 129.2, 127.9, 125.7, 124.2, 121.1, 98.3, 20.5. HRMS (ESI+): *m/z* $(M+H)^+$calculated for $C_{17}H_{14}O_2N$ 264.1019,found 264.1014.

(Z)-4-(2-(3-oxoisoindolin-1-ylidene)acetyl)benzonitrile (6f). 96 mg (51%), off-white solid M.p. 271-274 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): δ 10.56(bs, 1H), 8.13-8.11(d, 2H, *J* = 8.4 Hz), 7.94-7.81(m, 4H), 7.77-7.66(m, 2H), 6.81(s, 1H). ^{13}C NMR (101MHz, CDCl3): δ 189.3, 168.9, 150.0, 141.6, 136.7, 133.1, 132.5, 132.4, 129.9, 129.1, 128.3, 127.8, 124.4, 121.2, 117.9, 116.0, 93.8. LC-MS (ESI+): *m/z* $(M+H)^+$ found 275.27.

(Z)-4-(2-(3-oxoisoindolin-1-ylidene)acetyl)benzoic acid (6g). 105 mg (56%), off-white solid M.p. 330-333 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, DMSO-D6): δ 13.3(bs,1H), 10.96 (bs, 1H), 8.38-8.36(d, 1H, *J* = 7.6 Hz), 8.30-8.28 (d, 2H, *J* = 8.4 Hz) 8.12-8.10 (d, 2H, *J* = 8.4 Hz), 7.87 -7.81 (q, 2H), 7.76-7.72 (t, 1H), 7.43(s, 1H). ^{13}C NMR (101MHz, DMSO-d6): δ 189.2, 168.8, 166.7, 148.1, 140.9, 137.1, 134.5, 133.3, 132.2, 129.5, 128.4, 128.12, 123.4, 122.6, 95.6. LC-MS (ESI+): *m/z* $(M+H)^+$ found 294.30.

(Z)-3-(2-([1,1'-biphenyl]-4-yl)-2-oxoethylidene)isoindolin-1-one (6h). 158 mg (83%), off-white solid M.p.209-212 °C R_f = 0.6 (EtOAc/Hexane 30:70).^{1}H NMR (500 MHz, $CDCl_3$): *δ* 10.64 (bs, 1H), 8.12-8.11(d, 2H, *J* = 8.5 Hz), 7.92 -7.85 (dd, 2H, *J* = 7.5 & 27 Hz), 7.76-7.63 (m, 6H), 7.50-7.40 (m, 3H) 6.92 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 190.5, 169.1, 148.3, 145.6, 139.7, 137.1, 137.1,

134.3, 132.9, 131.9, 129.3, 128.9, 128.6, 128.3, 127.3, 127.2, 124.2, 121.1, 94.8. LC-MS (ESI+): *m/z* $(M+H)^+$ found 326.24.

(Z)-3-(2-oxo-2-(4-(trifluoromethyl)phenyl)ethylidene)isoindolin-1-one (6i). 160 mg (84%), off-white solid M.p.230-233 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): δ 10.57 (bs, 1H), 8.14-8.12(d, 2H, *J* = 8 Hz), 7.93 -7.91 (d, 1H, *J* = 6.8 Hz), 7.86-7.84(d, 1H, *J* = 8 Hz), 7.79-7.77 (d, 2H, *J* = 8 Hz) 7.73-7.65(m, 2H), 6.84(s, 1H). ^{13}C NMR (101MHz, $CDCl_3$): δ 189.9, 169.0, 149.5, 141.2, 136.8, 134.3, 134.0, 133.0, 132.3, 129.2, 128.2, 125.7, 125.7, 124.9, 124.4, 121.2, 94.1. LC-MS (ESI+): *m/z* $(M+H)^+$ found 318.23.

(Z)-3-(2-oxo-2-(3-(trifluoromethyl)phenyl)ethylidene)isoindolin-1-one (6j).150 mg (78%), off-white solid M.p. 171-174 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (500 MHz, $CDCl_3$): δ 10.58 (bs, 1H), 8.27(s, 1H), 8.23-8.22(d, 1H, *J* = 7.5 Hz), 7.93-7.84(m, 3H), 7.73 -7.65 (m, 3H), 6.85(s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.5, 169.0, 149.5, 138.9, 136.9, 133.1, 132.3, 131.4, 131.2, 129.4, 129.3, 129.2, 129.2, 124.8, 124.4, 121.3, 93.9. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{11}O_2NF_3$ 318.0736, found 318.0727.

(Z)-3-(2-(2-fluorophenyl)-2-oxoethylidene)isoindolin-1-one (6k). 154 mg (82%), off-white solid M.p.120-123 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): δ 10.49 (bs, 1H), 7.93-7.90(m, 2H), 7.82 -7.80 (d, 1H, *J* = 6.8 Hz), 7.70-7.64(m, 2H), 7.56-7.54 (d, 1H, *J* = 8 Hz) 7.30-7.28(d, 1H, *J* = 7.6 Hz), 7.21-7.16(m, 1H), 6.86(d, 1H, *J* = 8 Hz). ^{13}C NMR (101MHz, $CDCl_3$): δ 188.6, 169.1, 162.4, 159.9, 148.3, 137.1, 134.4, 132.9, 132.0, 131.0, 129.2, 127.1, 124.7, 121.3, 116.7, 98.8. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{16}H_{11}O_2NF$ 268.0768, found 268.0764.

(Z)-3-(2-(2,4-difluorophenyl)-2-oxoethylidene)isoindolin-1-one (6l). 146 mg (77%), off-white solid M.p. 318-321 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (500 MHz, $CDCl_3$): *δ* 10.47 (bs, 1H), 7.99-7.97(dd, 1H, *J* = 2 & 8.5 Hz), 7.92 -7.90 (d, 1H, *J* = 1 Hz), 7.82-7.80(d, 1H, *J* = 7 Hz), 7.70-7.65 (m, 2H), 7.03-6.00 (t, 1H), 6.94 -6.90 (m, 1H), 6.82 (d, 1H, *J* = 7 Hz). ^{13}C NMR (125MHz, $CDCl_3$): *δ* 187.0, 169.1, 166.7, 162.9, 160.9, 148.7, 137.0, 132.9, 132.1, 129.1, 124.2, 123.4, 121.3, 112.4, 104.9, 98.3. LC-MS (ESI+): *m/z* $(M+H)^+$ found 286.19.

(Z)-3-(2-(2,6-difluorophenyl)-2-oxoethylidene)isoindolin-1-one(6m). 150 mg (79%), off-white solid M.p. 188-191 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.37 (bs, 1H), 7.91-7.90(d, 1H, *J* = 6 Hz), 7.76 -7.74 (d, 3H, *J* = 5.6 Hz), 7.67-7.65 (t, 1H), 7.47-7.40 (m, 2H), 6.48(s, 1H). ^{13}C NMR (101MHz, $CDCl_3$): *δ* 186.6, 169.0, 161.5, 159.0, 148.4, 136.8, 134.2, 133.0, 132.6, 129.1, 124.3, 123.5, 121.4, 118.7, 112.3, 99.5. LC-MS (ESI+): *m/z* $(M+H)^+$ found 286.19.

(Z)-3-(2-(3-fluorophenyl)-2-oxoethylidene)isoindolin-1-one(6n). 150 mg (80%), off-white solid M.p. 189-192°C, R_f = 0.6 (EtOAc/Hexane 30:70).^{1}H NMR (500 MHz, $CDCl_3$): δ 10.57 (bs, 1H), 7.93-7.92(d, 1H, *J* = 7 Hz), 7.85 -7.82 (t, 2H), 7.73-7.66(m, 3H), 7.53-7.50 (t, 1H) 7.32-6.03(m, 1H), 6.81(s, 1H). ^{13}C NMR (101MHz, $CDCl_3$): δ 189.6, 168.9, 164.1, 149.0, 140.5, 136.9, 133.0, 132.1, 130.4, 129.2, 124.3, 123.6, 121.1, 120.0, 114.9, 94.2. LC-MS (ESI+): *m/z* $(M+H)^+$ found 268.16.

(Z)-3-(2-(2-methyl-1H-imidazol-5-yl)-2-oxoethylidene) isoindolin-1-one(6o).100 mg (53%), off-white solid M.p. 221-223 °C, R_f = 0.6 (EtOAc/Hexane 30:70). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.44 (bs, 1H), 7.91-7.81(dd, 3H, *J* = 7.6 & 32 Hz), 7.71-7.62(m, 3H), 6.59(s, 1H), 4.01(s, 3H). ^{13}C NMR (101MHz, $CDCl_3$): δ 181.2, 168.8, 147.4, 136.8, 132.8, 131.8, 129.1, 124.1, 121.1, 96.1, 34.9. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{12}O_2N_3$ 254.0924, found 254.0918.

(Z)-3-(2-oxo-2-(pyridin-3-yl)ethylidene)isoindolin-1-one(6p). 122 mg (65%), off-white solid M.p. 160-163 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.58 (bs, 1H), 9.28(s, 1H), 8.82-8.79(t, 1H), 8.33-8.31(d, 1H, *J* = 8Hz),7.93-7.91(d, 1H, *J* = 5.6Hz), 7.86-7.85(d, 1H, *J* = 7.2 Hz), 7.73-7.65 (m, 2H), 7.50-7.46 (q, 1H), 6.84(s, 1H). ^{13}C NMR (101MHz, CDCl3): δ 189.4, 169.0, 153.2, 149.4, 149.1, 136.8, 135.4, 133.7, 133.1, 132.3, 129.1, 124.3, 123.7, 121.2, 94.0. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for C15 H11 O2 N2 = 251.0815, found 251.0810.

Z)-3-(2-oxo-2-(tetrahydro-2H-pyran-2-yl)ethylidene)isoindolin-1-one(6q).110 mg (59%), off-white solid M.p.127-129 °C, R_f = 0.6 (EtOAc/Hexane 30:70).^{1}H NMR (400 MHz, $CDCl_3$): δ 10.30 (bs, 1H), 7.88-7.86 (dd, 1H, *J* = 2 & 6.4 Hz), 7.79-7.77(d, 1H, *J* = 1.2 & 6 Hz), 7.66-7.59(m, 2H), 6.59 (s, 1H), 4.15-4.11(dd, 1H, *J* = 1.2 & 11.6 Hz), 3.95-3.92 (dd, 1H, *J* = 2.4 & 10.8Hz), 3.59-3.52(dd, 1H, *J* = 2.8 & 11.6 Hz), 2.02 -1.93(m, 2H), 1.69-1.51(m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 201.0, 169.0, 148.1,137.1, 132.8, 131.8, 129.2, 124.1, 123.5, 121.4, 93.9, 82.3, 68.3, 25.5, 23.1. HRMS (ESI+): *m/z* $(M+H)^+$ calculated forC15 H16 O3 N 258.1124, found 258.1119.

Z)-3-(2-oxo-2-(tetrahydrofuran-3-yl)ethylidene)isoindolin-1-one(6r). 120 mg (64%), off-white solid M.p. 90-92 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (400 MHz, $CDCl_3$): δ 10.28 (bs, 1H), 7.89-7.88 (d, 1H, *J* = 2 Hz), 7.74 -7.73 (d, 1H, *J* = 5.2 Hz), 7.68-7.61(m, 2H), 6.16(s, 1H), 4.05-4.01(m, 3H), 3.86-3.81 (m, 1H), 3.39-3.32(m, 1H), 2.26-2.18(m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 200.8, 168.8, 147.6, 136.7, 132.8, 132.0, 129.3, 124.2, 121.1, 96.7, 69.9, 68.4, 51.7, 29.4. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{14}H_{14}O_3N$ 244.0968, found 244.0964.

(Z)-3-(2-cyclopropyl-2-oxoethylidene)isoindolin-1-one (6s) .106 mg (57%), off-white solid M.p. 149-52 °C, R_f = 0.6 (EtOAc/Hexane 30:70). ^{1}H NMR (500 MHz, CDCl3): δ 10.31 (bs, 1H), 7.88-7.86 (d, 1H, *J* = 7 Hz), 7.74-7.72(d, 1H, J = 7.5 Hz), 7.66-7.59 (m, 2H), 6.82 (s, 1H), 2.10-2.05 (m, 1H), 1.18-1.17(q, 2H), 1.01-0.99 (q, 2H). 13C NMR (125 MHz, CDCl3): δ 200.9, 168.8, 145.5, 137.0, 132.7, 131.6, 129.5, 124.1, 120.9, 98.3, 22.4, 11.59. LC-MS (ESI+): *m/z* $(M+H)^+$ found 214.18

(Z)-3-(2-(4-aminophenyl)-2-oxoethylidene)isoindolin-1-one(6t).100 mg (56%), off-white solid M.p. 218-221 °C, R_f = 0.6 (EtOAc/Hexane 30:70). ^{1}H NMR (400 MHz, DMSO-D6): *δ* 10.82 (bs, 1H), 8.32-8.30 (d, 1H, *J* = 7.6 Hz), 7.97-7.95 (d, 2H, *J* = 8.8 Hz), 7.84-7.81(m, 2H), 7.79 -7.77(dd, 1H), 7.29(s, 1H), 6.65-6.63(d, 2H, J = 8.8 Hz), 6.21(s, 2H). ^{13}C NMR (101MHz, DMSO-d6): *δ* 187.4,

168.3, 159.5, 154.0, 145.3, 137.3, 132.9, 131.5, 130.8, 129.8, 128.5, 125.6, 123.2, 122.2, 112.7, 112.5, 96.3. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for$C_{16}H_{13}O_2N_2$ 265.0971, found 265.0964.

(Z)-3-(2-(2-chlorophenyl)-2-oxoethylidene)isoindolin-1-one(6u). 153 mg (81%), off-white solid M.p. 163-166 °C. ^{1}H NMR (500 MHz, CDCl3): *δ* 10.31 (bs, 1H), 7.92-7.90 (d, 1H, *J* = 6.5 Hz), 7.76-7.75 (d, 1H, J = 6.5 Hz), 7.68-7.63 (m, 3H), 7.47-7.36 (m, 3H), 6.64(s, 1H). 13C NMR (125 MHz, CDCl3): *δ* 192.8, 169.0, 147.9, 139.6, 136.9, 133.0, 132.1, 131.9, 131.2, 130.5, 129.6, 129.2, 127.1, 124.3, 121.3, 98.7. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{16}H_{11}O_2NCl$ 284.0472, found 284.0467

(Z)-6-chloro-3-(2-oxo-2-phenylethylidene)isoindolin-1-one(6v).160 mg (85%), off-white solid M.p. 208-210 °C, R_f = 0.6 (EtOAc/Hexane 30:70). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 10.64 (bs, 1H), 8.04-8.02 (d, 1H, *J* = 7.6 Hz), 7.88 (s, 1H), 7.78-7.76 (d, 1H, *J* = 8 Hz), 7.66-7.59 (m, 2H), 7.55-7.51 (t, 2H), 6.86 (s, 1H). ^{13}C NMR (125 MHz, CDCl3): *δ* 190.9, 167.6, 147.3, 138.2, 138.2, 135.2, 133.1, 133.0, 130.9, 128.7, 127.9, 124.5, 122.3, 95.2. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{16}H_{11}O_2N$ Cl 284.0472, found 284.0465.

(Z)-6-chloro-3-(2-(4-methoxyphenyl)-2-oxoethylidene)isoindolin-1-one(6w).156 mg (82%), off-white solid M.p.218-221 °C, R_f = 0.6 (EtOAc/Hexane 30:70). ^{1}H NMR (500 MHz, DMSO-d6): δ 10.98 (bs, 1H), 8.40-8.38 (d, 1H, *J* = 8 Hz), 8.21-8.19(d, 2H, *J* = 8.5 Hz), 7.90-7.87(t, 2H), 7.42(s, 1H), 7.11-7.10 (d, 2H, *J* = 8.5 Hz), 3.88(s, 3H). 13C NMR (125 MHz, CDCl3): δ 188.2, 167.3, 163.3, 145.7, 136.5, 135.9, 133.0, 130.7, 130.6, 124.3, 123.2, 114.0, 96.6, 55.6. HRMS (ESI+): *m/z* $(M+H)^+$ calculated for $C_{17}H_{13}O_3NCl$ 314.0578, found 314.0569.

(Z)-6-chloro-3-(2-oxo-2-(p-tolyl)ethylidene)isoindolin-1-one (6x). 144 mg (76%), off-white solid M.p. 226-229 °C, R_f = 0.6 (EtOAc/Hexane 30:70)^{1}H NMR (500 MHz, $CDCl_3$): *δ* 10.65 (bs, 1H), 7.94-7.84(m, 4H), 7.76-7.32 (m, 2H), 6.85 (s, 1H), 2.45 (s, 3H).^{13}C NMR (125 MHz, CDCl3): *δ* 190.4, 167.5, 146.9, 144.1, 138.1, 135.6, 135.2, 132.9, 130.9, 129.4, 128.1, 124.5, 122.2, 95.3, 21.6. LC-MS (ESI+): *m/z* $(M+H)^+$ found 298.25

Conflicts of interest

There are no conflicts to declare**.**

Acknowledgments:

G. Ramakrishna is grateful to Aragen Life Sciences (Formerly known as GVK Biosciences) for giving the opportunity to pursue the Ph. D. work as per Higher Education Policy of the Organization. Help from the analytical department is highly appreciated. We thank Dr Somesh Sharma for his invaluable support and encouragement**.**

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10.1002/ejoc.202100716

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Layout 1:

COMMUNICATION

Ramakrishna Gudipati[a,b] , Vankudoth Jayaram[a], K.Raghavulu[a,b], Dinesh Bhoot[a], K.Basavaiah[b], Satyanarayana Yennam[a] , Manoranjan Behera[a*]

An efficient and convenient route for the synthesis of various functionalized 3-alkylidene isoindolin-1-ones is presented. The synthesis involves the ring opening and ring Closing Cascade (ROCC) reaction of ortho-carboxy-isoxazole using Fe/NH_4Cl. This is the first report for the synthesis of 3-alkylidene isoindolin-1-one using Fe/NH_4Cl.