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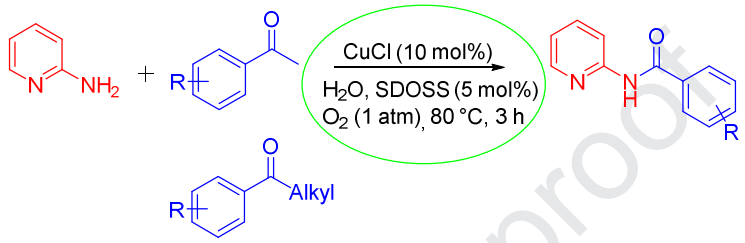

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Singlet Oxygen Mediated One Pot Synthesis of *N*-pyridinylamides via Oxidative Amidation of Aryl Alkyl Ketones

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ABSTRACT

An environmental friendly, efficient protocol has been realized for the synthesis of *N*-pyridinylamides via copper catalyzed oxidative amidation of aryl alkyl ketones with 2-aminopyridines. This one pot protocol involves chemo selective cleavage of C (O)-C bond in the presence of singlet oxygen. The reaction conditions are simple, tolerates wide range of substrates and the products were formed in good to excellent yields. This method offers a moderate improvement over the earlier successful attempts in generating *N*-pyridinylamides.

1. Introduction

Water mediated synthesis of organic building blocks is a topic of current interest.[1] Several organic frameworks are being generated using water as a reaction medium. Such methods have tremendous advantages in terms of green chemistry efforts.[2] This approach is being adopted in the manufacture of drugs, pharmaceuticals and industrial chemicals,[3] because such procedures help in reducing the use of volatile organic solvents. However, the poor solubility of most organic compounds in water reduces the scope on water mediated organic synthesis and this has brought to light the use of surfactants in aqueous organic reactions.[4]

Amide bond formation reactions were also reported in water medium, which showed distinct advantage in terms of low generation of organic waste, high reaction yields, ease of recyclability.[5] However, for the synthesis of N-pyridinylamides such methods are rarely being used. Kaliappan and co-workers reported a biomimetic route for the generation of N-heterocyclic amides.[6] This reaction involves the formation of an imine, imine-enamine tautomerism,[7] copper mediated dioxetane generation and the formation of phenyl glyoxal as initial steps. Subsequently, the reaction follows a biomimetic path which is similar to the luciferin-luciferage path.[6] Huang and co-workers reported a dehydrogenative reaction between aldehydes and 2-aminopyridines to yield N-pyridinylamides using a Cu(I) catalyzed pathway.[8] The p-xylene mediated reaction between aryl acetic acids and 2-aminopyridine as well as the m-xylene mediated reaction between 1,2-diketones and 2-aminopyridines are also known to produce *N*-pyridinylamides.[9] Cerium nitrate catalyzed reaction between nitro olefins and 2-aminopyridines was also known to produce title compounds.[10] (water was used as a co-solvent).

Aqueous oxidizing agents like TBHP and H_2O_2 were also employed to generate *N*-pyridinylamides in an attempt to develop metal free methods.[11] Only one method is reported till now, in which water was used as reaction medium for the preparation of *N*-pyridinylamides (oxidative amidation using Cu(II)). In this approach, use of micellar systems was found to be a requirement to improve the yields. An attempt was made to generate *N*-pyridinylamides in water medium using simpler reagents and reaction conditions, the results are presented below (Figure 2). The salient features of this transformation are (i) water as a greener solvent (ii) shorter reaction time, (iii) good to excellent yields, (iv) wide substrate scope and (v) use of oxygen gas bubbling to facilitate oxidation.

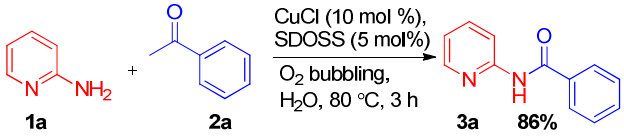


Figure 2. Copper (I) Chloride catalyzed synthesis of N-pyridinylamides via oxidative amidation reaction.

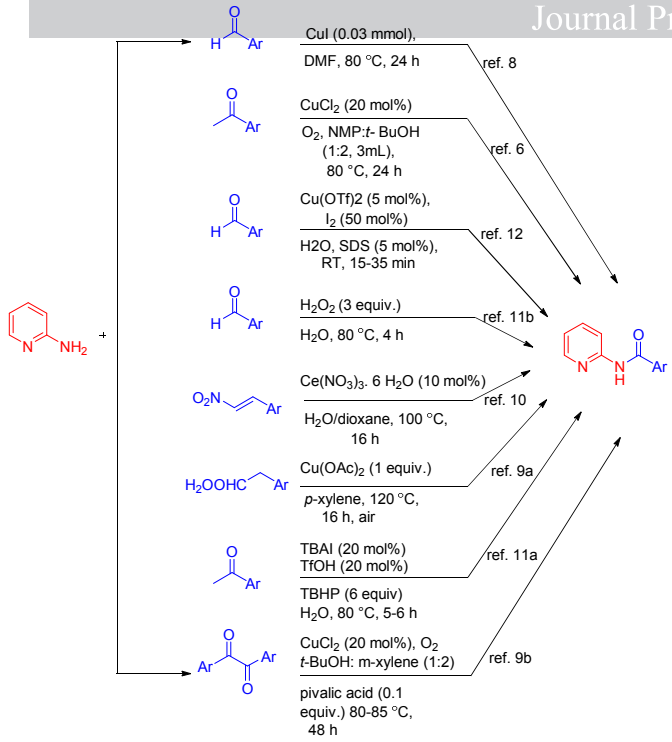


Figure 1. Various reported methods for the generation of *N*-pyridinylamides.

Table 1. Solvent and catalyst optimization studies.[a]

Entry	Catalyst (mol %)	Temp. (°C)	Time (h)	Surfactant	Solvent	% Yield
1	Cu-Mn B (5)	rt	12	-	DMSO	n.r
2	Cu-Mn B (5)	rt	12	-	CH_3CN	n.r
3	$[RhCl(CO)_2]_2$ (5)	rt	12	-	CH_3CN	n.r
4	$[Ru(p\text{-}cp)Cl_2]_2$ (5)	rt	12	-	CH_3CN	n.r
5	CuBr (5)	rt	12	-	CH_3CN	trace
6	$CuCl_2$ (5)	rt	12	-	CH_3CN	15
7	$CuCl_2$ (10)	rt	12	-	CH_3CN	20
8	$Cu(OTf)_2$ (10)	rt	12	-	CH_3CN	25
9	CuI (5)	rt	12	-	CH_3CN	10
10	CuCl (5)	rt	12	-	DMSO	trace
11	CuCl (5)	rt	12	-	Iso-propanol	20
12	CuCl (5)	rt	12	-	CH_3CN	35
13	CuCl (5)	rt	12	-	DCE	trace
14	CuCl (5)	80	12	-	CH_3CN	50
15	CuCl (5)	80	12	-	Toluene	58
16	CuCl (10)	80	12	-	Toluene	69
17	CuCl (10)	rt	12		Water	trace
18	CuCl (10)	80	12	-	Water	26
19	CuCl (10)	rt	12	SDOSS	Water	72
20[b]	CuCl (10)	rt	12	SDOSS	Water	73
21	CuCl (10)	rt	12	Tween 80	Water	60
22[c]	CuCl (10)	80	12	SDOSS	Water	82
23[d]	**CuCl (10)**	80	3	SDOSS	Water	**86**
24	CuCl (10)	80	3	SLS	Water	75
25[e]	CuCl (10)	80	12	-	Water	20
26[f]	-	80	12	SDOSS	Water	n.r

[a]Reagents and conditions: 2-aminopyridine **1a** (1.2 equiv.), acetophenone **2a** (1 equiv.) was treated with CuCl (10 mol%), SDOSS (5 mol%) in water (2 mL) at 80 °C (oil bath) under O_2 bubbling for 3 h, [b] With 20 mol% SDOSS, [c]The reaction was performed under oxygen atmosphere using a ballon filled with oxygen, [d]Optimized reaction conditions, [e]without O_2 ballon; [f] without CuCl; n.r = No reaction. All the reactions were performed under oxygen atmosphere using a ballon filled with oxygen unless otherwise specified (d, e).

2. Results and discussions

Our initial attempt was to synthesize *N*-pyridinylamides from 2-aminopyridine (**1a**) and acetophenone (**2a**), with the aim to generate acyl group from the acetophenones. After getting insights from the literature (Figure 1) for the synthesis of *N*-pyridinylamides, a model reaction of 2-aminopyridine and acetophenone in the presence of CuCl at room temperature for 12 h using MeCN as a solvent was tried, the desired product **3a** was formed in 35% yield (Table 1, entry 12). When the same model reaction was refluxed at 80 °C, an improvement in yield up to 50% was observed (Table 1, entry 14). Based on these results, various copper salts were screened and CuCl in 10 mol% was found to be the most efficient catalyst for such transformation. Rhodium catalyst (Table 1, entry 3) as well as ruthenium catalyst (Table 1, entry 4) were found to be ineffective. When $CuCl_2$ was used as the catalyst (Table 1, entry 7), the desired product was obtained in only 20% yield. Various solvents were screened and toluene was found to provide better yields of the desired product in 69% (Table 1, entry 16).

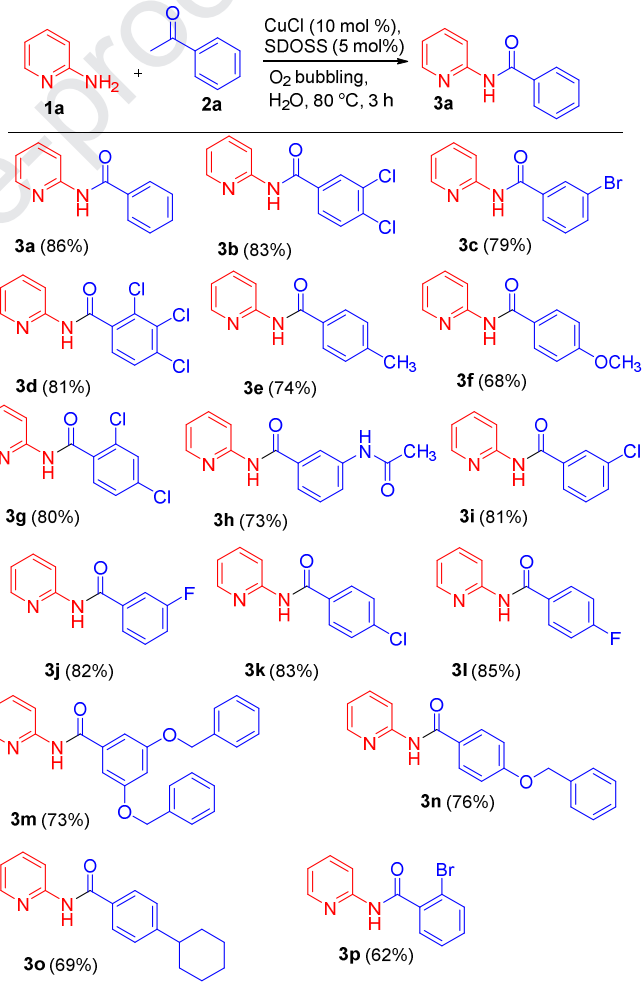


Figure 3. Substrate scope with aryl methyl ketones and 2-aminopyridine. Reaction conditions: The magnetically stirred mixture of **1a** (1.2 equiv), **2a** (1 eqiv) was treated with CuCl (10 mol%) in the presence of SDOSS (5 mol%) in water at 80 °C under O_2 bubbling condition for 3 h (yields of the isolated products).

But, when toluene was replaced with water as greener reaction medium and in the presence of sodium dioctyl sulfosuccinate (SDOSS), the reaction provided better yield 72% (Table 1, entry 19). Then various surfactants were screened for improvement of yield, but SDOSS was found to be most effective (Table 1, entry 23). This may be attributed due to the reduction of interfacial tension and formation of aqueous micellar system.[12, 14] The greater efficiency of SDOSS can be accounted for the capability of maximum oxygen uptake compared to other surfactants.[13] Increase in the concentration of SDOSS from 5 mol% to 20 mol%, did not produce improved yields (Table 1, entry 20). Next, oxygen gas bubbling into the reaction mixture was considered – for a period of 1h, 2h and 3h, improvement of yields was noticed in the order 52%, 67% and 86% respectively. Thus, passing oxygen gas into the reaction mixture (O_2 bubbling), instead of performing the reaction under oxygen atmosphere using a balloon filled with oxygen, provided added advantage in terms of reducing the reaction time from 12 h to 3 h. These results led to the following optimized reaction conditions: **1a** (1.2 equiv), **2a** (1 equiv), CuCl (10 mol%), SDOSS (5 mol%) in water (2 ml) at 80□ under oxygen bubbling (1 atm.) for 3 h.

Having the optimized reaction conditions in hand, substrate scope of reaction was explored for various substituted aryl methyl ketones, reaction works well with all substituted aryl methyl ketones bearing electron withdrawing (Figure 3, entry, **3b**, **3c**, **3d**, **3g**, **3i**, **3j**, **3k**, **3l** and **3p**) as well as electron donating groups (Figure 3, entry, **3e**, **3f** and **3m**). Yields in case of ketones with electron withdrawing groups are slightly higher than in case of ketones with electron donating groups. Ketones bearing substituents in meta position (Figure 3, entry **3c**, **3i** and **3j**) gave slightly lower yield in comparison to ketones with substituents at para position (Figure 3, entry **3k** and **3l**). Also, disubstituted aryl methyl ketones (Figure 3, entry **3b**, **3g** and **3n**) as well as trisubstituted aryl methyl ketones (Figure 3, entry **3d**) work well, giving corresponding products in good yield.

The scope of the reaction was further established by using various aryl alkyl ketones (Figure 4). To our pleasant surprise, the corresponding products were formed in moderate yields. These results points to the chemoselective cleavage of C(CO)-C(alkyl) bond for synthesis of the title compounds.

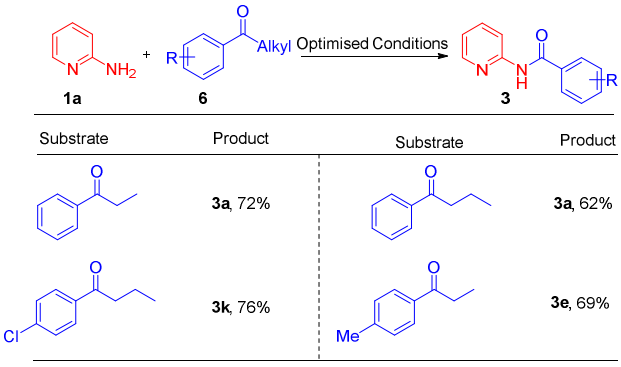


Figure 4. Substrate scope with aryl alkyl ketones and 2-aminopyridine. Reaction conditions: The magnetically stirred mixture of **6** (1 equiv), **1a** (1.2 eqiv) was treated with CuCl (10 mol%) in the presence of SDOSS (5 mol%) in water at 80° C under O_2 bubbling condition for 3 h (yields of the isolated products).

Many control experiments were carried out to probe the mechanism of the reaction. The non-radical pathway of the reaction was established by performing the reaction of **1a** and **2a** in the presence of TEMPO (2 equiv) used as the radical scavenger[15] with the formation of desired product **3a** (Figure 5, entry 1). Next, when the reaction of **1a** with **2a** was tried under the optimized reaction condition, but in the presence of DABCO as singlet oxygen quencher[16] (Figure 5, entry 2) the desired product was not formed, suggesting that the participation of the singlet oxygen species during the transformation is essential. When the reaction was tried under nitrogen atmosphere, product was not formed thereby suggesting the role of molecular oxygen as the sole oxidant in the reaction (Figure 5, entry 3). Formation of the desired product was not observed in the absence of CuCl, thereby suggesting the crucial role of catalyst in the reaction (Figure 5, entry 4). Similarly, when the reaction was carried out in the absence of SDOSS, **3a** was obtained in 30% yield (Figure 5, entry 5). The surfactant helps in the improvement of yield by two processes – i) the formation of aqueous micellar system thereby allowing the reactants to approach each other and, ii) the surfactant helps in increasing the oxygen content in the aqueous micellar system by having maximum capacity of oxygen reuptake.[13]

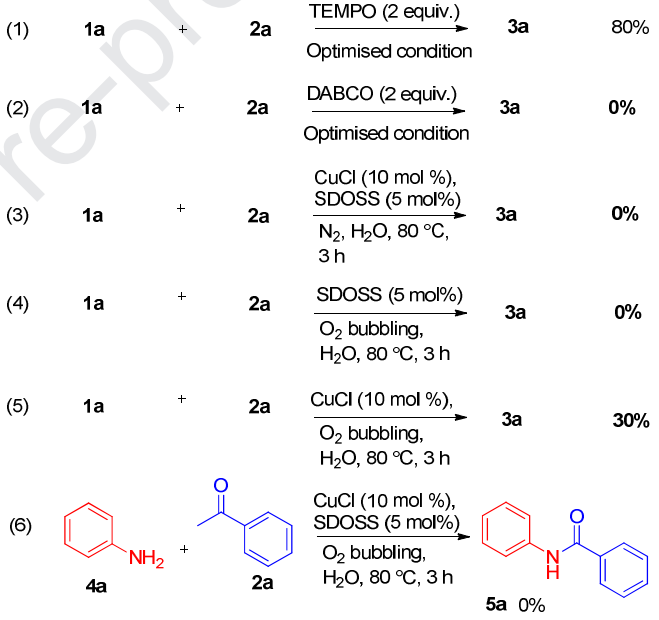
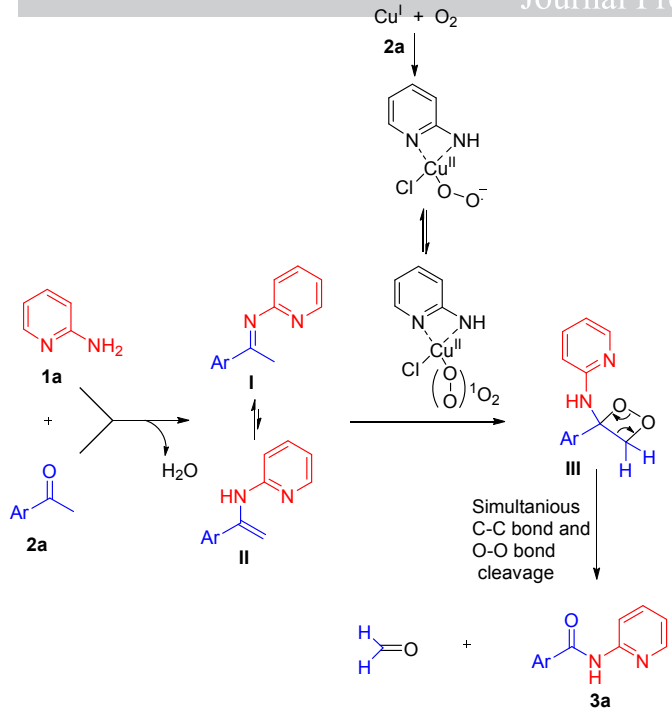


Figure 5. Control experiments.

Based on the control experiments and previous literature reports,[17-19] the plausible mechanism for the generation of the title compound has been proposed (Scheme 1). Initially condensation reaction of methyl ketone and 2-aminopyridine leads to the generation of imine intermediate **I**. This intermediate **I** undergoes tautomerism (1,3-H shift), leading to the formation of reversible enamine **II**[7] A Cu-peroxy radical (reactive oxygen species) gets generated by the oxidation of Cu(I) in the presence of molecular oxygen with the formation of superoxide radical ($O_2^{\cdot-}$) and Cu(II). Subsequently, superoxide radical ($O_2^{\cdot-}$) delivers electron to the Cu(II) leading to generation of Cu(I) and singlet oxygen species ($^1O_2$). Singlet oxygen species immediately reacts with the enamine leading to formation of aminodioxetane intermediate **III**. Oxidative C-C bond cleavage of dioxetane intermediate leads to the generation of the desired product **3a** and formaldehyde.



Scheme 1. Plausible mechanism for the generation of title compounds.

When 2-aminopyridine was replaced with aniline and subjected to reaction with optimised conditions, the formation of an amide was not observed (Figure 5, entry 6). These results suggest that ring nitrogen in 2-aminopyridine is playing a crucial supportive role in terms of coordination with copper catalyst and thereby assisting in the delivery of singlet oxygen to the enamine intermediate (**II)** as propped in the plausible reaction mechanism.

The reaction has been tried with pyridine-2,3-diamine, 2-aminopyridin-3-ol, 5-chloro-3-nitropyridin-2-amine, 2-aminoisonicotinonitrile, benzo[d]thiazol-2-amine and thiazol-2-amine. In each case the product formation wasn't noticed. This may be due to weak electron donating capability of ring nitrogen to the metal centre as required in the complex (Scheme 1). (See ESI, section 4)

3. Conclusions

In summary, an efficient method for the synthesis of *N*-pyridinylamides by copper (I)-catalyzed oxidative C–C bond cleavage of aryl alkyl ketones using molecular oxygen as an oxidant was developed. The reaction has wide substrate scope, various functional groups are well tolerated and products are formed in good to excellent yields.

4. Experimental

4.1 General

All chemicals were obtained from Sigma-Aldrich Company and used as received. ^{1}H, ^{13}C and DEPT NMR spectra were recorded on Brucker-Avance DPX FT-NMR 500 and 400 MHz instruments. Chemical data for protons are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$, 7.26 ppm; CD_3OD, 3.31 ppm; DMSO-d_6 2.51 ppm). The carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded at 100 MHz: chemical data for carbons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonance of the solvent ($CDCl_3$, 77.16 ppm; CD_3OD, 49.0; DMSO-d_6 39.51 ppm). ESI-MS spectra were recorded on Agilent 1100 LC-Q-TOF. IR spectra were recorded on Perkin-Elmer IR spectrophotometer. Melting points were recorded on digital melting point apparatus.

4.2. Typical procedure for the synthesis of *N*-(pyridin-2-yl)benzamide (3a)

The magnetically stirred mixture of the 2-amino pyridine **1a** (112.9 mg, 1.2 mmol), acetophenone **2a** (120.2 mg, 1 mmol, 1equiv), CuCl (10 mol%, 9.9 mg), sodium dioctylsulphosuccinate (SDOSS, 5 mol%, 22.2 mg) in water (2 mL) was heated at 80 ^{o}C while oxygen gas was bubbled into the mixture for 3 h. After completion of the reaction (TLC), the mixture was cooled to room temperature and diluted with EtOAc (10 mL), filtered by ordinary filter paper to recover the catalyst. The organic layer was washed with brine and dried over anhydrous Na_2SO_4. The filtrate was concentrated under rotary vacuum evaporation, and the residue was charged on to chromatography (100-200 mesh silica gel) column and eluted with EtOAc-hexane to afford pure **3a** (170.4 mg, 86%). All the remaining reactions were performed following this general procedure. The spectral data of the synthesized compounds are provided below.

4.2.1 *N-(pyridin-2-yl) benzamide* **(3a)** compound **3a** was prepared using typical experimental procedure shown in section 4.2. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.89 (bs, 1H), 8.44 (d, *J* = 8Hz, 1H), 8.29 (d, J = 4Hz, 1H), 7.98-7.95 (m, 2H), 7.81-7.77 (m, 1H), 7.61-7.50 (m, 3H), 7.11-7.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 150.6, 146.7, 137.6, 133.2, 131.2, 127.8, 126.2, 118.9, 113.3; IR (CH_2Cl_2) 3749.9, 3245.1, 3064.1, 2924.7, 2853.5, 1674.6, 1595.9, 1576.5, 1522.3, 1492.9, 1431.2, 1303.5, 1261.5, 1237.5, 1181.5, 1150.0, 1092.7, 1074.1, 1051.9, 1027. 7 cm^{-1} ; ESI-MS (LTQ) : $[M+H]^+$ 199.10

4.2.2. *3,4-dichloro-N-(pyridin-2-yl)benzamide* **(3b)** compound **3b** was prepared using typical experimental procedure**.** White powder; m.p 100-102 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (bs, 1H), 8.38 (d, *J* = 8Hz, 1H), 8.32-8.31 (m, 1H), 8.07(d, *J* = 4Hz, 1H), 7.82-7.76 (m, 2H), 7.61 (d, *J* = 8Hz, 1H), 7.15-7.11 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 158.1.0, 142.4, 138.7, 136.9, 134.0, 133.4, 131.7, 130.9, 129.6, 126.2, 120.4, 114.3; IR (CH_2Cl_2) 3006.9, 1528.8, 1433.4, 1308.5, 1275.1, 1261.5 cm-1; ESI-MS (LTQ) : $[M+H]^+$ 267.40

4.2.3. *3-bromo-N-(pyridin-2-yl) benzamide* **(3c)** compound **3c** was prepared using typical experimental procedure**.** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.58 (bs, 1H), 8.39 (d, *J* = 8Hz, 1H), 8.34 (d, *J* = 4Hz, 1H), 8.11 (s, 1H), 7.88 (d, *J* = 8Hz, 1H), 7.82 (t, *J* =8Hz, 1H), 7.74 (d, *J* = 8Hz, 1H), 7.43 (t, *J* = 8Hz, 1H), 7.14 (t, *J* = 4Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5, 150.6, 147.1, 137.6, 134.2, 129.1, 124.7, 122.3, 119.2, 113.2; IR (CH_2Cl_2) 3378.8, 1433.0, 1275.9, 1267.3, 1261.7 cm^{-1} ; ESI-MS (LTQ) : $[M+H]^+$ 279.04

4.2.4. *2,3,4-trichloro-N-(pyridin-2-yl)benzamide* (**3d**) compound **3d** was prepared using typical experimental procedure. Yellow

semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.69 (bs, 1H), 8.37 (d, *J* = 8Hz, 1H), 8.24 (d, *J* = 4Hz, 1H), 7.83-7.79 (m, 1H), 7.55-7.51 (m, 2H), 7.14-7.11 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.9, 151.1, 147.4, 138.8, 136.3, 135.9, 133.0, 131.3, 128.7, 127.1, 120.4, 114.7; IR (CH_2Cl_2) 2961.4, 2921.5, 2850.3, 1686.9, 1574.9, 1537.5, 1463.5, 1435.5, 1363.6, 1309.6, 1261.7, 1179.1, 1152.9, 1105.0, 1088.2, 1047.7, 1023.4 cm^{-1} ; ESI-MS (LTQ) : $[M+H]^+$ 301.15

4.2.5. *4-methyl-N-(pyridin-2-yl) benzamide* (**3e**) compound **3e** was prepared using typical experimental procedure. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (bs, 1H), 8.43 (d, *J* = 8Hz, 1H), 8.29 (d, *J* = 4Hz, 1H), 7.87 (d, *J* = 8Hz, 2H), 7.80-7.75 (m, 1H), 7.32 (t, *J* = 8Hz, 2H), 7.10-7.06 (m, 1H), 2.45 (s, 3H) ; ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.9, 151.6, 148.1, 142.7, 138.3, 131.5, 130.1, 127.1, 119.9, 114.4, 21.3; IR (CH_2Cl_2) 2959.6, 2925.1, 2854.8, 1682.6, 1673.9, 1578.8, 1537.0, 1524.8, 1520.2, 1504.7, 1455.6, 1434.7, 1303.2, 1261.9, 1110.5, 1091.7, 1020.1 cm-1 ; ESI-MS (LTQ) : $[M+H]^+$ 213.10

4.2.6. *4-methoxy-N-(pyridin-2-yl) benzamide* (**3f**) compound **3f** was prepared using typical experimental procedure. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.76 (bs, 1H), 8.42 (d, *J* = 8Hz, 1H), 8.30 (d, *J* = 4Hz, 1H), 7.95 (d, *J* = 12Hz, 2H), 7.79 (t, *J*= 12Hz, 1H), 7.09-7.06 (m, 1H), 7.01(d, *J*= 8Hz, 2H) 3.90 (s, 3H) ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2, 162.8, 151.6, 147.9, 138.6, 129.1, 126.4, 119.6, 114.2, 114.0, 55.6; IR (CH_2Cl_2) 2925.1, 1676.1, 1606.8, 1577.8, 1505.1, 1431.9, 1275.8, 1267.1, 1259.3, 1175.1, 1029.6 cm^{-1} ; ESI-MS (LTQ) : $[M+H]^+$ 229.12

4.2.7. *2,4-dichloro-N-(pyridin-2-yl)benzamide* (**3g**) compound **3g** was prepared using typical experimental procedure. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.03 (bs, 1H), 8.38 (d, *J* = 8Hz, 1H), 8.17 (d, *J* = 4Hz, 1H), 7.81-7.77 (m, 1H), 7.72 (d, *J* = 8Hz, 1H), 7.50 (d, *J* = 4Hz, 1H), 7.40-7.37 (m, 1H), 7.11-7.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.0, 162.8, 151.0, 147.9, 138.7, 137.5, 133.3, 131.8, 131.2, 130.3, 127.9, 120.5, 114.3; IR (CH_2Cl_2) 3182.9, 2925.3, 1688.6, 1579.4, 1532.6, 1471.6, 1435.6, 1375.2, 1281.7, 1239.0, 1150.1, 1096.7, 1050.4 cm^{-1}; ESI-MS (LTQ) : $[M+H]^+$ 267.18

4.2.8. *3-acetamido-N-(pyridin-2-yl) benzamide* (**3h**) compound 3g was prepared using typical experimental procedure. Brown semisolid; ^{1}H NMR (CDCl3 + MeOD), 400 MHz) δ 9.22 (bs, 1H), 8.69 (s, 1H), 8.33 (d, *J* = 8Hz, 1H), 8.19 (s, 1H), 7.99 (s, 1H), 7.89 (d, *J* = 8Hz, 1H), 7.74 (t, *J* = 8Hz, 1H), 7.59 (d, *J* = 8Hz, 1H); 7.37 (t, *J* = 8Hz, 1H), 7.04 (t, *J* = 4Hz, 1H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$ + MeOD), 100 MHz) δ 175.3, 169.2, 165.9, 158.4, 151.6, 138.9, 138.4, 134.8, 129.4, 123.7, 122.7, 119.9, 118.8, 114.5; 24.3; IR (CH_2Cl_2) 3304.9, 3007.2, 2922.0, 1670, 1592.8, 1526, 1486.7, 1433.4, 1372.3, 1274.6, 1261.8 cm^{-1}; ESI-MS (LTQ) : $[M+H]^+$ 256.35

4.2.9. *3-chloro-N-(pyridin-2-yl) benzamide* (**3i**) compound **3i** was prepared using typical experimental procedure. White powder; m.p 95-97 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.64 (bs, 1H), 8.40 (d, *J* = 12Hz, 1H), 8.33 (d, *J* = 4Hz, 1H), 7.96 (s, 1H), 7.82 (t, *J* = 8Hz, 2H), 7.58 (d, *J* = 8Hz, 1H), 7.49 (t, *J* = 8Hz, 1H), 7.14 (t, *J* = 8Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.3, 151.3, 148.1, 138.5, 135.9, 135.3, 132.5, 130.3, 127.9, 125.1, 120.3, 114.1; IR (CH_2Cl_2) 3373.0, 3016.6, 2931.0, 2854, 1678.3, 1576.5, 1526, 1433.5, 1307.3, 1261.1, 1048.7 cm^{-1}; ESI-MS (LTQ) : $[M+H]^+$ 231.18

4.2.10. *3-fluoro-N-(pyridin-2-yl) benzamide* (**3j**) compound 3i was prepared using typical experimental procedure. Cream powder; m.p 62-64 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.90 (bs, 1H), 8.40 (d, *J* = 8Hz, 1H), 8.27-8.25 (m, 1H), 7.81-7.77 (m, 1H), 7.72-7.66 (m, 2H), 7.51-7.46 (m, 1H), 7.31-7.26 (m, 1H), 7.12-7.08 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 163.5 (^{1}*J*CF = 249 Hz) 160.6, 150.3, 146.9, 137.5, 129.5, 121.7, 119.2, 118.4, 113.9, 113.7, 113.3; IR (CH_2Cl_2) 3391.5, 3007.2, 1524.9, 1434.9, 1274.8, 1261.6, 1046.6 cm-1; ESI-MS (LTQ) : $[M+H]^+$ 231.18

4.2.11. *4-chloro-N-(pyridin-2-yl) benzamide* (**3k**) compound **3k** was prepared using typical experimental procedure. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.07 (bs, 1H), 8.41 (d, *J* = 8Hz, 1H), 8.22 (s, 1H), 7.91 (d, *J* = 8Hz, 2H), 7.80 (t, *J* = 8Hz, 1H), 7.48 (d, *J* = 8Hz, 2H), 7.10 (t, *J* = 8Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.8, 160.6, 151.5, 147.8, 138.6, 132.7, 129.1, 128.8, 120.1, 114.4; IR (CH_2Cl_2) 3347.4, 2923.7, 2853.6, 1658.7, 1577.2, 1524.5, 1488.6, 1432.2, 1308.4, 1261.5, 1094 cm^{-1}; ESI-MS (LTQ) : $[M+H]^+$ 233.34

4.2.12. *4-fluoro-N-(pyridin-2-yl) benzamide* (**3l**) compound **3l** was prepared using typical experimental procedure. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.64 (bs, 1H), 8.43 (d, *J* = 8Hz, 1H), 8.32 (d, *J* = 4Hz, 1H), 7.89 (d, *J* = 8Hz, 2H), 7.80-7.76 (m, 1H), 7.37 (d, *J* = 8Hz, 2H), 7.10-7.07 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.6 (^{1}JCF = 249 Hz), 160.6, 152.9, 151.7, 147.9, 138.5, 131.7, 127.3, 127.2, 119.8, 114.1; IR (CH_2Cl_2) 3369, 2924.1, 2851.5, 1676.9, 1600.7, 1578.5, 1530.2, 1503.9, 1461.7, 1433.3, 1274.8, 1261.5, 1230.7, 1158.4, 1093.1 cm^{-1}; ESI-MS (LTQ): $[M+H]^+$ 217.23

4.2.13. *3,5-bis(benzyloxy)-N-(pyridin-2-yl)benzamide* (**3m**) compound **3m** was prepared using typical experimental procedure. Yellow semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.10 (bs, 1H), 8.43 (d, *J* = 8Hz, 1H), 8.23-8.22 (m, 1H), 7.79-7.74 (m, 1H), 7.46-7.34 (m, 10H), 7.19 (d, *J* = 4Hz, 2H), 7.08-7.05 (m, 1H); 6.82 (t, *J* = 4Hz, 1H); 5.08 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 160.1, 151.6, 147.9, 138.5, 136.5, 136.4, 128.7, 128.2, 127.6, 119.9, 114.3, 106.4, 106.1, 70.3; IR (CH_2Cl_2) 3007.1, 2872, 1678.5, 1593.6, 1520.3, 1433.6, 1275.1, 1261.6, 1158.7, 1054.7 cm-1; ESI-MS (LTQ) : $[M+H]^+$ 411.41

4.2.14. 4-(benzyloxy)-*N*-(pyridin-2-yl)benzamide (**3n**) compound **3n** was prepared using typical experimental procedure. White semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.55 (bs, 1H), 8.41 (d, *J* = 8Hz, 1H), 8.32 (d, *J* = 4Hz, 1H), 7.93 (d, *J* = 8Hz, 2H), 7.79 (t, *J* = 8Hz, 1H), 7.48-7.37 (m, 5H), 7.10 (d, *J* = 8Hz, 3H), 5.17 (s, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.0, 162.1, 151.7, 147.9, 138.4, 136.3, 129.1, 128.7, 128.1, 127.4, 126.7, 119.8, 115.0, 114.1, 69.9; IR (CH_2Cl_2) 3393.2, 2958.5, 2925.6, 2860.1, 1736.7, 1679.3, 1601.4, 1507, 1432.9, 1298, 1261.0, 1024.4 cm^{-1};

4.2.15. 4-cyclohexyl-*N*-(pyridin-2-yl)benzamide (**3o**) compound **3o** was prepared using typical experimental procedure. cream semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.94 (bs, 1H), 8.31 (d, *J* = 8Hz, 1H), 8.13 (s, 1H), 7.90-7.86 (m, 2H), 7.70 (t, *J* = 8Hz, 1H), 7.10 (t, *J* = 8Hz, 2H), 7.00-6.97 (m, 1H), 1.18 (s, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4, 164.8, 163.9, 151.6, 147.8, 138.6, 130.5, 129.8, 120.0, 116.0, 115.8, 114.3, 31.9, 29.9, 22.7, 14.1 IR (CH_2Cl_2) 3013.4, 2924.5, 2855.8, 1679.82, 1574, 1432.8, 1304.3, 1274.9, 1261.5, 1028.2 cm-1; ESI-MS (LTQ) : $[M+H]^+$ 281.41

4.2.16. 2-bromo-*N*-(pyridin-2-yl)benzamide (**3p**) compound **3p** was prepared using typical experimental procedure. Brown

semisolid; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (bs, 1H), 8.20 (t, *J* = 8Hz, 2H), 7.71 (d, *J* = 8Hz, 2H), 7.46 (t, *J* = 8Hz, 1H), 7.25-7.19 (m, 2H), 6.86 (t, *J* = 8Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 151.8, 145.4, 132.9, 128.9, 128.5, 128.3, 127.9, 125.1, 124, 118, 113.1; IR (CH_2Cl_2) 2925.7, 2852, 1470.2, 1261.7, 1105, 1019.1 cm-1; ESI-MS (LTQ) : $[M+H]^+$ 279.04

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Supplementary Material

Supplementary material that may be helpful in the review process should be prepared and provided as a separate electronic file. That file can then be transformed into PDF format and submitted along with the manuscript and graphic files to the appropriate editorial office.

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Highlights

- A greener protocol for the synthesis of *N*-pyridinylamides, was achieved with the cheap and easily available oxygen as an oxidant.

- Generation of singlet oxygen in the presence of copper (I) salt is the key feature of this transformation.

- Method for the chemo selective cleavage of C(O)-C(alkyl) bond in long chain alkyl aryl ketones.