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Ebrahim Kianmehr, Azin Pakbaznia, Nasser Faghih

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Graphical Abstract

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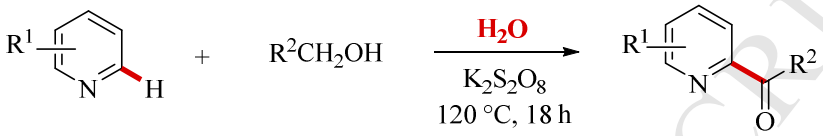
Ebrahim Kianmehr, Azin Pakbaznia, Nasser Faghih
School of Chemistry, College of Science, University of Tehran, Tehran 1417614411, Iran



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School of Chemistry, College of Science, University of Tehran, Tehran 1417614411, Iran
kianmehr@khayam.ut.ac.ir

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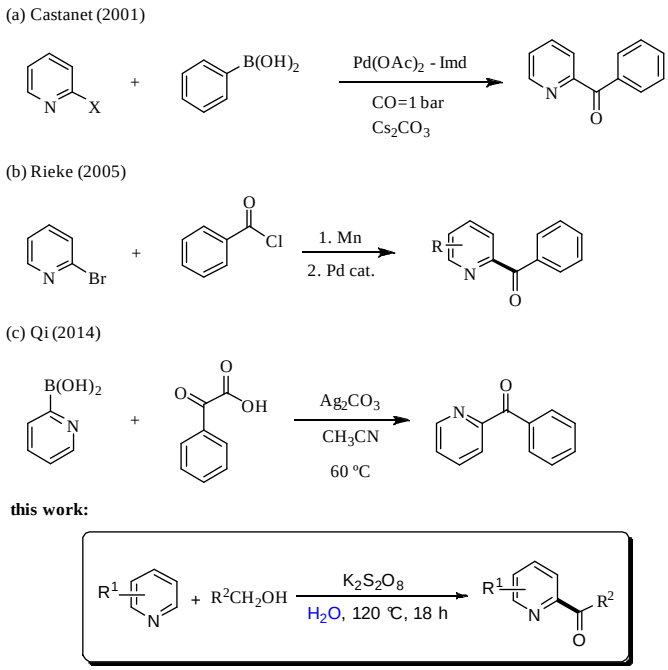
ABSTRACT

A straightforward acylaltion of pyridine derivatives has been developed using $K_2S_2O_8$ as the oxidant and water as a green solvent. The corresponding 2-acylpyridines were synthesized with high chemo- and regioselectivity in good to high yields. This efficient and practical method could serve as a new tool for the convenient synthesis of 2-benzoylpyridines of interest for future pharmaceutical and chemical applications.

1. Introduction

Pyridine nuclei are ubiquitous scaffolds that occupy a central role in many medicinally relevant compounds, ligands, and agrochemicals.[1] Due to the importance of pyridine motifs, significant efforts have been devoted to develop various methods to construct 2-acylpyridines in the last decade. Acylation of electron-rich heteroarenes is facile and numerous synthetic methods are available for this transformation such as the Friedel–Crafts reaction.[2] Acylation of electron-deficient heterocycles such as pyridines is more challenging however several methods have been reported to achieve the synthesis of 2-alkanoyl- and 2-benzoylpyridines.[3] Castanet and co-workers reported palladium-catalyzed carbonylative cross-coupling reactions of pyridine halides and aryl boronic acids to access α-pyridyl ketones (Scheme 1-a).[3a] In 2001, Sato and co-workers described acylation of bromopyrazines and 2-bromopyridine via a copper co-catalytic Stille reaction.[3b] Various 2- and 3-acyl heteroaryls were obtained by using highly active manganese and heteroaryl halides reported by Rieke in 2005 (Scheme 1-b).[3c] Wang developed a metal-free catalytic system for the oxidation of benzylic methylenes to ketones.[3d] Oxidation of heterobenzylic methylenes to access 2-acyl heteroarenes has also been reported.[3e,f] Murai and co-workers developed another route for the synthesis of 2-acyl pyridines as a single product with elemental sulphur.[3g] Organocatalytic C–H bond arylation of aldehydes to bis-heteroaryl ketones was developed by the Gaunt group[3h] as a new approach to the titled products. The Au(III)-catalyzed coupling reactions between alcohols and *N*-heterocycles *via* C–H bond activation was reported by Zhu.[3i] In 2014, Qi and co-workers reported the silver-catalyzed coupling of arylboronic acids with arylglyoxylic acids as an efficient route for the synthesis of unsymmetrical diaryl ketones (Scheme 1-c).[3j] Nakazawa described dehydrogenation of 2-pyridylmethanol derivatives catalyzed by an iron complex to yield the corresponding ketones in the same year .[3k]



Scheme 1. Selected approaches to 2-acylpyridines.

Finally, Liu reported metal-free oxidative cross-dehydrogenative coupling (CDC) of *N*-heterocycles with various

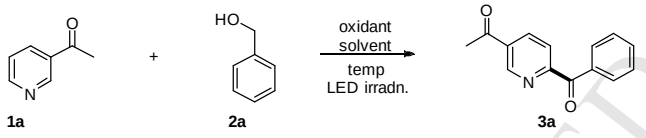
aldehydes in the presence of TBHP/TFA as one of the more recent attempts in this area.[3l]

Cross dehydrogenative coupling (CDC) reactions have emerged as an important tool for the synthesis of a variety of useful organic compounds according to its atom economical shorter routes.[4] Metal-free CDC acylation of electron-deficient heterocycles like pyridine derivatives is a demanding area in organic synthesis. Towards addressing these issues and in continuation of our interest in CDC reactions,[5] herein, we describe a convenient protocol to prepare 2-acylpyridines from pyridines and benzylic and aliphatic alcohols through CDC reactions under metal-free conditions in water for the first time (Scheme 1).

2. Results and discussion

This new strategy provides an alternative to the previous methods by using alcohols as the coupling partner and without limitations such as low regio- and chemo-selectivity and harsh conditions. This new protocol represents an environmentally benign, practical and cost-effective method for acylation of pyridines. The reaction is compatible with accessible aliphatic alcohols and benzyl alcohols as the acylation sources and provides a new route to both alkanoyl- and aroylpyridines. Furthermore, the reaction is carried out in one pot under metal-free conditions in water as a green solvent. Initially, 3-acetylpyridine (**1a**) and benzyl alcohol (**2a**) were used as the model substrates to optimize the reaction conditions (Table 1).

Table 1. Optimization of the reaction conditions.[a]



1a 2a 3a

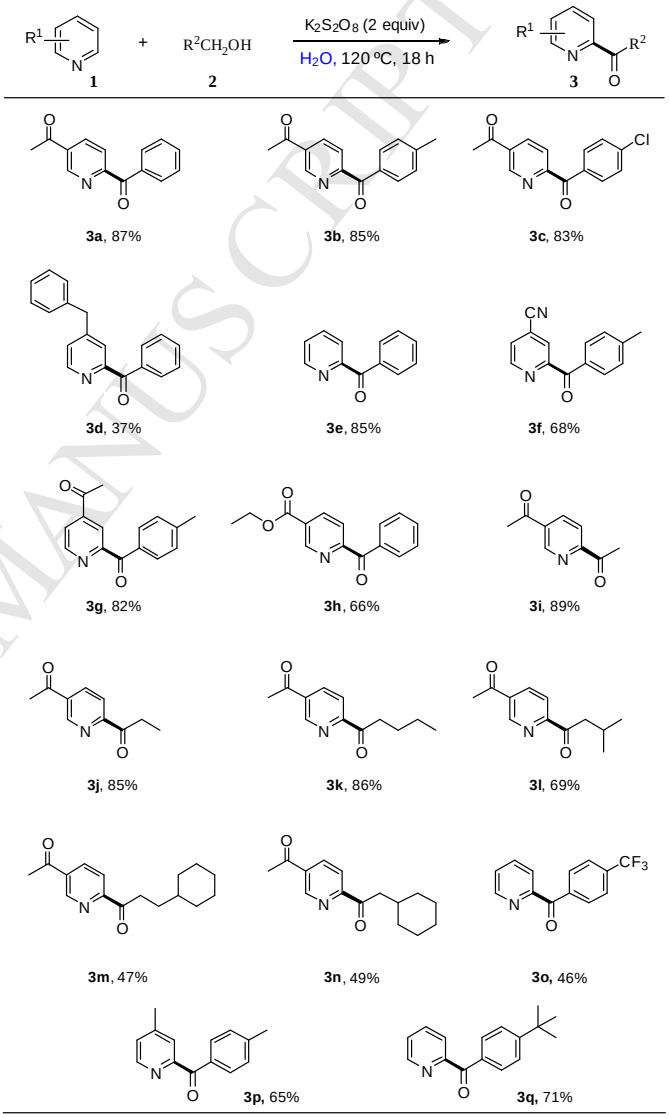
Entry	Oxidant (equiv)	Solvent	Temp (°C)	Time (h)	Yield(%)
1	$K_2S_2O_8$(2)	DMSO	120	18	trace
2	$K_2S_2O_8$(2)	PhCl	120	18	65
3	$K_2S_2O_8$(2)	CH_3CN	120	18	63
4	$K_2S_2O_8$(2)	DCE	120	18	82
5	**$K_2S_2O_8$(2)**	**H_2O**	**120**	**18**	**87**
6	TBHP(2)	H_2O	120	18	33
7	DTBP(2)	H_2O	120	18	trace
8	$(NH_4)_2S_2O_8$ (2)	H_2O	120	18	51
9	Ag_2CO_3(2)	H_2O	120	18	trace
10	$K_2S_2O_8$(2)	H_2O	120	18	23
11	-	H_2O	120	18	-
12	$K_2S_2O_8$(2)	H_2O	25	18	trace
13	$K_2S_2O_8$(2)	H_2O	80	18	25
14	$K_2S_2O_8$(2)	H_2O	100	18	38
15	$K_2S_2O_8$(2)	H_2O	140	18	66
16	$K_2S_2O_8$(2)	H_2O	120	8	11
17	$K_2S_2O_8$(2)	H_2O	120	24	83

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (2.0 mmol) in solvent (2.0 mL) were stirred at 120 °C for 18 h.

Various solvents such as DMSO, PhCl, CH_3CN, DCE, and water were screened (Table 1, entries 1-5). To our delight, the reaction proceeds successfully in water and the yield was improved to 87% which is very important from a green chemistry view point (Table 1, entry 5). The effect of changing oxidant was investigated (Table 1, entries 5–11), whereby it was found that the best results are obtained with 2.0 equiv of $K_2S_2O_8$ (Table 1, entry 5). The yield of the reaction was decreased with lower amounts of oxidant and finally the reaction did not occur in the absence of the oxidant (Table 1, entry 11). The reaction was also tested at different temperatures and times and the best result was obtained at 120 °C in 18 hours (Table 1, entries 12-17).

With the optimal conditions identified, we proceeded with examining the substrate scope and the results are summarized in Table 2.

Table 2. Scope of direct 3-acylation of pyridines with alcohols[a]



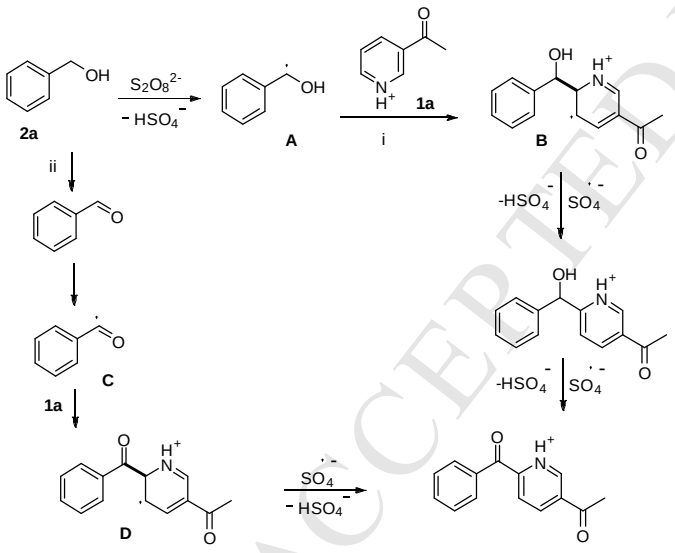
[a] Reaction conditions: **1** (1.0 mmol), **2** (2.0 mmol), $K_2S_2O_8$ (2 equiv), H_2O (2.0 mL) at 120 °C for 18 h.

Surprisingly, the reaction proceeded smoothly with both aromatic and aliphatic alcohols. The chemoselectivity of the reaction is interestingly high and the reaction doesn't suffer from double acylation. With pyridine, 2-benzoylpyridine was obtained exclusively (Table 2, **3e**). 4-chlorobenzyl alcohol, which could be easily further functionalized, was also well tolerated under the reaction conditions, affording the desired product in good yield (Table 2, **3c**). The reactions with aliphatic alcohols proceeded successfully and

the best result was obtained with 3-acetylpyridine and ethanol as the substrates (Table 2, **3i**).

To prove the role of the $K_2S_2O_8$ as a radical agent, a control reaction was performed. When the reaction of **1a** was performed in the presence of 2,6-di-*tert*-butyl-4-methylphenol (BHT) as a radical-scavenger, no desired product **3a** was obtained.

On the basis of the above results and previous reports, a plausible mechanism for the reaction is shown in Scheme 2. Intermediate **A** is generated *in situ* through hydrogen-atom abstraction from the benzyl alcohol in the presence of sulfate radical anion which is produced from $K_2S_2O_8$ under the reaction conditions.[6] Next, radical addition of **A** to pyridine **1a,** which is protonated under the reaction conditions, gives species **B** (path i) which leads to the formation of **3a** by elimination followed by oxidation. Path ii is also possible for this acylation reaction using benzyl alcohols as the acylation sources. Benzyl alcohol is oxidized to benzaldehyde under the reaction conditions.[8] Hydrogen-atom abstraction from benzaldehyde in the presence of sulfate radical anion gives intermediate **C**. The obtained free radical attacks the C-2 position of 3-acetylpyridine which is protonated under the reaction conditions, producing the corresponding free radical **D**.[7] Finally, a hydrogen atom abstraction from **D** affords the desired product **3a.** This pathway is confirmed by the observations that benzylalcohol is oxidised to benzaldehyde in the absence of pyridines under the reaction conditions and also the reaction proceeds successfully with benzaldehydes as the coupling partners instead of benzyl alcohols. When we considered the reaction scope with benzaldehyde derivatives as the coupling partners it was found that the efficiency of the reaction was decreased in comparison with the corresponding benzyl alcohols.



Scheme 2. A plausible mechanism for acylation of pyridines with alcohols

For example, using 4-methylbenzaldehyde as the acylation source, **3g** and **3b** were obtained in 64 and 70 % yields, respectively and the reaction failed to proceed with 4-cyanopyridine to afford **3f**. According to the above-mentioned observations the reaction mechanism with benzyl alcohols may be explained by the both path i and path ii. On the other hand, when the same trend was examined with aliphatic alcohols, it was observed that the oxidation of ethanol and propanol to the corresponding aldehydes was not successful under the reaction conditions, in the absence of pyridines. Furthermore the reaction failed to proceed with ethanal and propanal as the coupling partner. With the results obtained with the control experiments, path i may be suggested as the sole reaction mechanism with aliphatic alcohols as the coupling partners.

3. Conclusion

In summary, we have successfully developed an efficient and practical method for the chemo- and regioselective synthesis of 2-acylpyridines using pyridines and a range of aliphatic and benzylic alcohols. The reaction is performed in water and can be applied to numerous substrates with good tolerance of various functional groups, providing a straightforward route to 2-acylpyridines using accessible starting materials. Products of the reaction are interesting targets to explore potential applications in materials science as well as medicinal chemistry.

4. Experimental section

4.1. General

Solvents, $K_2S_2O_8$, pyridine and alcohol derivatives were purchased from Merck. Other reagents were purchased from commercial distributors and used without further purification. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. The products were purified by preparative column chromatography on silica gel (0.063-0.200 mm; Merck). ^{1}H and ^{13}C-NMR Spectra: were recorded on Bruker DRX 500 and 400 Advance instrument in $CDCl_3$ and DMSO-d_6; δ in ppm, *J* in Hz. Mass spectrometry was obtained on Agilent 5975C VL MSD (Ion source: EI+, 70eV, 230 °C). IR spectra were obtained on a Bruker Equinox 55.

4.2. General procedure for 2-acylation of pyridines:

A 10 mL microvawe vial was charged with pyridine derivatives (1 equiv, 1 mmol), alcohol derivatives (2 equiv, 2 mmol), $K_2S_2O_8$ (2 mmol, 540 mg,) and water (H_2O, 2mL). The vial was then sealed and immersed in an oil bath, which was preheated at 120 °C, for 18 h. After this time the reaction mixture was then cooled to room temperature and then diluted with water (3 mL) and the aqueous phase was extracted with dichloromethane (2 × 5 mL). The organic extracts were dried over sodium sulphate and filtered. Concentration of the solution by rotary evaporation under reduced pressure gave a residue which was purified by using column chromatography (n-hexane/EtOAc, 4/1) to yield the desired products.

4.2.1. 1-(6-benzoylpyridin-3-yl) ethanone ***(3a)***

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), benzyl alcohol (2 mmol, 216 mg), $K_2S_2O_8$ (2 mmol, 540 mg,). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3a** (195 mg, 87%) as a purple solid, m.p. 110-113 ºC; IR (KBr) ν_{max} 2918, 1661, 1586, 1378, 1256, 934, 863 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 9.23 (1H, d, *J* 2 Hz, =CHN), 8.40 (1H, dd, *J* 8, 2 Hz, =CH), 8.10 (1H, dd, *J* 8.5, 1 Hz, =CH), 8.06 (2H, dt, *J* 6.5, 1 Hz, =CH), 7.60 (1H, td, *J* 7.5, 1 Hz, =CH), 7.49 (2H, td, *J* 8, 1 Hz, =CH), 2.70 (3H, s, MeCO); δ_C (125 MHz, $CDCl_3$) 196.1, 193.7, 158.0, 148.6, 136.6, 135.7, 133.3, 131.0, 129.7, 128.3, 124.4, 29.6; MS (EI) *m/z* 225 (74, M^+), 210 (8), 197 (57), 182 (27), 169 (15), 155 (21), 105 (100), 77 (77), 43 (33%). Anal. Calcd. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22. Found: C, 74.77; H, 4.95; N, 6.19.

4.2.2.) 1-(6-(4-methylbenzoyl)pyridine-3-yl)ethanone ***(3b)***

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), 4-methyl benzyl alcohol (2 mmol, 244 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3b** (203 mg, 85 %) as a purple solid, m.p. 118-119 ºC; IR (KBr) ν_{max} 2920, 1686, 1653, 1595, 1412, 1382, 1265, 930, 759 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.23 (1H , d, *J* 2 Hz, =CHN), 8.39 (1H , dd, *J* 8.5, 2 Hz, =CH), 8.07 (1H, d, *J* 8.5 Hz, =CH), 7.97 (2H, d, *J* 8.5 Hz, =CH), 7.29 (2H, d, *J* 8 Hz, =CH), 2.70 (3H, s, MeCO), 2.44 (3H, s, Me); δ_C (125 MHz, $CDCl_3$) 195.3, 192.5, 158.4, 148.6, 144.3, 136.5, 133.4, 133.2, 131.2, 129.0, 124.3, 26.9, 21.7; MS (EI) *m/z* 239 (15, M^+), 223 (7), 196 (7), 136 (33), 119 (55), 91 (100), 77 (18), 43 (41%). Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: 75.19; H, 5.51; N, 5.84.

*4.2.3. 1-(6-(4-chlorobenzoylpyridin-3-yl) ethanone (**3c**)*

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), 4-chloro benzyl alcohol (2 mmol, 284 mg), $K_2S_2O_8$ (2 mmol, 540 g). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3c** (216 mg, 83%) as a purple solid, m.p. 137-139 ºC; IR (KBr) ν_{max} 2921, 2542, 1676, 1587, 1546, 1400, 1088, 1014, 931, 846, 771 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.23 (1H, s, =CHN), 8.41 (1H, dd, *J* 8, 2 Hz, =CH), 8.13 (1H, d, *J* 8.5 Hz, =CH), 8.07 (2H, d, *J* 9 Hz, =CH), 7.47 (2H, d, *J* 8.5 Hz, =CH), 2.70 (3H, s, MeCO); δ_C (125 MHz, $CDCl_3$) 195.9, 191.3, 157.5, 148.5, 140.1, 136.7, 134.0, 133.6, 132.4, 128.6, 124.5, 26.9; MS (EI) *m/z* 259 (11, M^+), 216 (7), 155 (41), 139 (100), 111 (70), 76 (15), 43 (26%). Anal. Calcd. for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.99; H, 3.90; N, 5.42.

*4.2.4. (4-benzoylpyridine-2-yl)(phenyl)methanone (**3d**)*

The general procedure was followed using 4-benzyl pyridine (1 mmol, 169 mg), benzyl alcohol (2 mmol, 216 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3d** (101 mg, 37%) as an orange oil; IR (KBr) ν_{max} 2914, 1662, 1592, 1493, 1284, 1076, 844, 700 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 8.58 (1H, d, *J* 5 Hz, =CHN), 8.03 (2H, dd, *J* 8.5, 1 Hz, =CH), 7.89 (1H, s, =CH), 7.56 (1H, td, *J* 8.5, 1 Hz, =CH), 7.45 (2H, t, *J* 7.5 Hz, =CH), 7.32 (2H, t, *J* 7 Hz, =CH), 7.27 (2H, d, *J* 5 Hz, =CH), 7.22 (2H, d, *J* 7.5 Hz, =CH), 4.07 (2H, s, CH_2Ph); δ_C (125 MHz, $CDCl_3$) 193.8, 160.1, 151.0, 148.6, 137.0, 135.0, 132.8, 130.9, 129.0, 128.9, 128.1, 127.0, 126.9, 126.4, 124.9, 41.4; MS (EI) *m/z* 272 (96, MH^+), 244 (100), 182 (34), 167 (14), 105 (58), 77 (83). Anal. Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53; N, 5.12. Found: C, 83.62; H, 5.56; N, 5.15.

*4.2.5. Phenyl(2-pyridyl) methanone (**3e**)*

The general procedure was followed using pyridine (1 mmol, 79 mg), benzyl alcohol (2 mmol, 216 mg), $K_2S_2O_8$ (2 mmol, 540 mg,). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3e** (155 mg, 85%) as a white solid, m.p. 42-44 ºC; IR (KBr) ν_{max} 3057, 1664, 1581, 1442, 1315, 1278, 1237, 1154, 990, 937, 775, 749, 730, 698, 647 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 8.71 (1H, d, *J* 5 Hz, =CHN), 8.06 (1H , dd, *J* 8, 1 Hz, =CH), 8.03 (2H, d, *J* 7.5 Hz, =CH), 7.87 (1H, td, *J* 8, 2 Hz, =CH), 7.57 (1H, td, *J* 8, 1 Hz, =CH), 7.50-7.46 (3H, m, =CH); δ_C (125 MHz, $CDCl_3$) 193.7, 155.1, 148.5, 136.9, 136.3, 132.8, 130.9, 128.1, 126.0, 124.5; MS (EI) *m/z* 183 (41, MH^+), 155 (90), 105 (75), 77 (100), 51 (76%). Anal. Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.81; H, 4.92; N, 7.62.

*4.2.6. 2-(4-methylbenzoyl)pyridine-4-carbonitrile (**3f**)*

The general procedure was followed using 4-cyano pyridine (1 mmol, 104 mg), 4-methyl benzyl alcohol (2 mmol, 244 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3f** (151 mg, 68%) as a yellow solid, m.p. 96-97 ºC; IR (KBr) ν_{max} 3092, 2923, 2859, 1653, 1602, 1295, 1206, 1176, 1072, 762 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 8.88 (1H, d, *J* 5 Hz, =CHN), 8.23 (1H, d, *J* 2.5 Hz, =CH), 7.97 (2H, d, *J* 8.5 Hz, =CH), 7.68 (1H, dd, *J* 4.5, 1.5 Hz, =CH), 7.30 (2H, d, *J* 8.5 Hz, =CH), 2.44 (3H, s, Me); δ_C (125 MHz, $CDCl_3$) 191.1, 156.5, 149.3, 144.6, 132.0, 131.1, 129.1, 126.9, 126.2, 121.0, 115.8, 21.7; MS (EI) *m/z* 222 (25, M^+), 207 (21), 194 (29), 119 (100), 91 (42), 77 (8%). Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.66; H, 4.54; N, 12.60.

*4.2.7. 1-(2-(4-methylbenzoyl)-4-pyridyl)ethanone (**3g**)*

The general procedure was followed using 4-acetyl pyridine (1 mmol, 121 mg), 4-methyl benzyl alcohol (2 mmol, 244 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3g** (196 mg, 82%) as a purple solid, m.p. 115-117 ºC; IR (KBr) ν_{max} 2921, 1685, 1655, 1598, 1412, 1383, 1265, 931, 759 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.23 (1H, s, =CHN), 8.39 (1H, dd, *J* 8, 2 Hz, =CH), 8.07 (1H, d, *J* 8 Hz, =CH), 7.97 (2H , d, *J* 8 Hz, =CH), 7.29 (2H, d, *J* 8 Hz, =CH), 2.70 (3H, s, MeCO), 2.44 (3H, s, Me); δ_C (100 MHz, DMSO-d_6) 196.1, 192.5, 158.4, 149.6, 148.5, 144.3, 136.5, 133.3, 131.1, 129.0, 124.3, 26.9, 21.7; MS (EI) *m/z* 239 (30, M^+), 224 (15), 211 (24), 196 (11), 136 (26), 119 (100), 91 (91), 76 (30), 65 (31), 43 (15%). Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.14; H, 5.46; N, 5.88.

*4.2.8. Ethyl 6-benzoylpyridine-3-carboxylate (**3h**)*[9]

The general procedure was followed using ethyl-3-pyridylcarboxylate (1 mmol, 151 mg), benzyl alcohol (2 mmol, 216 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3h** (168 mg, 66%) as a white solid, m.p. 106-108 ºC δ_H (500 MHz, $CDCl_3$) 9.34 (1H, s, =CHN), 8.52 (1H, dd, *J* = 8.4, 2 Hz, =CH), 8.09 (2H, dd, *J* 8, 1.6 Hz, =CH), 8.11 (1H, d, *J* 7.5 Hz, =CH), 7.63 (2H, td, *J* 6.8, 1.2 Hz, =CH), 7.51 (1H, t, *J* 7.2 Hz, =CH), 4.47 (2H, q, *J* 7.2 Hz, CH_2), 1.45 (3H, t, *J* 7.2 Hz, Me); δ_C (100 MHz, DMSO-d_6) 193.0, 167.7, 157.9, 149.6, 138.1, 135.7, 133.3, 131.0, 130.9, 128.3, 124.1, 62.0, 38.7; MS (EI) *m/z* 255 (88, M^+), 240 (72), 210 (61), 182 (50), 169 (33), 154 (77), 77 (100), 43 (55%). Anal. Calcd. for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.67; H, 5.12; N, 5.52.

*4.2.9. 1,1'-pyridine-2,5-diyldiethanone (**3i**)*[10]

The general procedure was followed using 3-acethyl pyridine (1 mmol, 121 mg), ethanol (2 mmol, 92 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/ EtOAc, 4/1) gave the desired product **3i** (145 mg, 89%) as a pale yellow solid, m.p. 83-85 ºC; IR (KBr) ν_{max} 2925, 1680, 1586, 1382, 1347, 1261, 1133, 1097, 1017, 951, 849, 754, 643 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.20 (1H, s, =CHN), 8.33 (1H, dd, *J* 8, 2 Hz, =CH), 8.11 (1H, d, *J* 8 Hz, =CH), 2.75 (3H, s, MeCO), 2.69 (3H, s, MeCO); δ_C (125 MHz, $CDCl_3$) 199.8, 196.8, 155.8, 149.1, 136.3, 134.2, 121.3, 26.8, 25.8; MS (EI) *m/z* 163 (100, M^+), 148 (22), 135 (37), 121 (81), 106 (35), 78 (20), 43 (96%). Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 66.42; H, 5.55; N, 8.61.

*4.2.10. 1-(5-acetylpyridin-2-yl)propanone (**3j**)*

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), propanol (2 mmol, 120 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/ EtOAc, 4/1) gave the desired product **3j** (150 mg, 85%) as a yellow solid, m.p. 94-95 ºC; IR (KBr) ν_{max} 2986, 2945, 2913, 1685, 1587, 1558, 1254, 1215, 1014, 959, 868, 807, 740, 710 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.19 (1H, d, *J* 2 Hz, =CHN), 8.32 (1H, dd, *J* 8, 2 Hz, =CH), 8.11 (1H, d, *J* 8 Hz, =CH), 3.24 (2H, q, CH_2), 2.68 (3H, s, Me), 1.21 (3H, t, Me); δ_C (125 MHz, $CDCl_3$) 201.7, 196.1, 155.7, 149.1, 136.4, 134.2, 121.5, 31.4, 26.9, 7.8; MS (EI) *m/z* 177 (37 MH^+), 162 (30), 149 (77), 121 (100), 106 (18), 77 (22), 57 (29), 43 (81%). Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.60; H, 6.24; N, 7.90.

*4.2.11. 1-(5-acetylpyridin-2-yl)pentanone (**3k**)*

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), pentanol (2 mmol, 176 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/ EtOAc, 4/1) gave the desired product **3k** (176 mg, 86%) as a yellow oil; IR (KBr) ν_{max} 2958, 2869, 2913, 1691, 1588, 1560, 1383, 1261, 1017, 958, 855, 731, 640 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.19 (1H, dd, *J* 2, 0.5 Hz, =CHN), 8.32 (1H, dd, *J* 8, 2.5 Hz, =CH), 8.10 (1H, dd, *J* 8, 0.5 Hz, =CH), 3.22 (2H, t, *J* 7 Hz, CH_2), 2.68 (3H, s, MeCO), 1.75-1.69 (2H, m, CH_2), 1.39 (2H, m, *J* 7 Hz, CH_2), 0.96 (3H, t, *J* 7 Hz, Me); δ_C (125 MHz, $CDCl_3$) 201.4, 196.1, 155.9, 149.1, 136.4, 134.2, 121.5, 37.7, 26.9, 26.0, 22.4, 13.8; MS (EI) *m/z* 205 (52, M^+), 190 (37), 186 (16), 176 (20), 162 (44), 148 (37), 121 (74), 78 (29), 69 (37), 57 (37), 43 (100%). Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.39; H, 7.39; N, 6.81.

*4.2.12. 1-(5-acetylpyridin-2-yl)-3-methylbutanone (**3l**)*

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), 3-methyl butanone (2 mmol, 176 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3l** (141 mg, 69%) as a brown oil; IR (KBr) ν_{max} 2958, 2872, 1691, 1588, 1560, 1260, 1214, 1013, 957, 849, 734 (cm^{-1}); δ_H (500 MHz, $CDCl_3$) 9.19 (1H, d, *J* 1.5 Hz, =CHN), 8.32 (1H, dd, *J* 8, 2 Hz, =CH), 8.11 (1H, d, *J* 8 Hz, =CH), 3.11 (2H, d, *J* 7 Hz, CH_2), 2.68 (3H, s, MeCO), 2.27 (1H, m, *J* 6.5 Hz, CH), 1.00 (6H, d, *J* 7 Hz, 2 Me; δ_C (100 MHz, DMSO-d6) 196.8, 193.1, 156.0, 149.0, 144.4, 136.4, 121.5, 46.6, 26.9, 24.8, 22.4; MS (EI) *m/z* 205 (51, M^+), 190 (31), 175 (25), 162 (17), 148 (17), 121 (100), 77 (16), 43 (89%). Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.10; H, 7.35; N, 6.84.

4.2.13. 1-(5-acetylpyridin-2-yl)-3-cyclohexylpropanone (3m)

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), 3-cyclohexylpropanole (2 mmol, 284 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3m** (122 mg, 47%) as a yellow oil; IR (KBr) ν_{max} 2922, 2851, 1692, 1531, 1350, 1253, 1084; δ_H (500 MHz, $CDCl_3$) 9.19 (1H, d, *J* = 2 Hz, =CHN), 8.32 (1H, dd, *J* 8, 2 Hz, =CH), 8.10 (1H , d, *J* 8 Hz, =CH), 3.23 (2H, t, *J* 7.5, CH_2CO), 2.67 (3H, s, MeCO), 1.78-1.60 (5H, m), 1.28-1.14 (7H, m, Cyclohexyl), 0.98 (1H, m, Cyclohexyl); δ_C (125 MHz, $CDCl_3$) 196.7, 193.7, 161.1, 153.3, 149.1, 136.5, 121.7, 37.4, 35.6, 33.1, 31.3, 29.6, 26.5, 26.3; MS (EI) *m/z* 259 (52, M^+), 231 (15), 203 (37), 176 (57), 164 (91), 148 (81), 135 (46), 121 (94), 77 (22), 55 (74), 43 (100%). Anal. Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.26; H, 8.15; N, 5.41.

*4.2.14. 1-(5-acetylpyridin-2-yl)-2-cyclohexylethanone (**3n**)*

The general procedure was followed using 3-acetyl pyridine (1 mmol, 121 mg), 2-cyclohexyl ethanol (2 mmol, 256 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3n** (120 mg, 49%) as a yellow oil; IR (KBr) ν_{max} 2922, 2851, 1692, 1531, 1350, 1253, 1084; δ_H (500 MHz, $CDCl_3$) 9.19 (1H, d, *J* 2 Hz, =CHN), 8.31 (1H, dd, *J* 8.5, 2.5 Hz, =CH), 8.09 (1H, dd, *J* 3, 0.5 Hz, =CH), 3.10 (2H, d, CH_2), 2.67 (3H, s, MeCO), 1.76-1.70 (1H, m, Cyclohexyl),1.68-1.64 (5H, m, Cyclohexyl), 1.19-1.06 (5H, m, Cyclohexyl); δ_C (125 MHz, $CDCl_3$) 201.7, 196.1, 155.7, 149.0, 136.4, 134.2, 121.6, 45.2, 34.2, 33.3, 26.9, 26.2, 26.1; MS (EI) *m/z* 245 (52, M^+), 231 (15), 203 (37), 176 (57), 164 (91), 148 (81), 135 (46), 121 (94), 77 (22), 55 (74), 43 (100%). Anal. Calcd. for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.53; H, 7.80; N, 5.73.

*4.2.15. 2-pyridyl(4-(trifluoromethyl)phenyl)methanone (**3o**)*[11]

The general procedure was followed using pyridine (1 mmol 79 g), 4-(trifluoromethyl)phenyl methanol (2 mmol, 352 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc, 4/1) gave the desired product **3o** (115 mg, 46%) as a yellow oil; IR (KBr) ν_{max} 2925, 2857, 1728, 1672, 1580, 1408, 1320, 1167, 1127, 1066, 936, 856, 631; δ_H (400 MHz, $CDCl_3$) 8.75 (1H, d, *J* 4.4 Hz, =CHN), 8.20 (2H, d, *J* 8 Hz, =CH), 8.16 (1H, d, *J* 2 Hz, =CH), 7.95 (1H, td, *J* 8, 2 Hz, =CH), 7.77 (2H, d, *J* 8 Hz, =CH), 7.56 (1H, td, *J* 4.8, 1.2 Hz, =CH); δ_C (100 MHz, $CDCl_3$) 192.8, 154.1, 148.6, 139.3, 137.3, 134.1, 133.8, 131.2, 126.8, 125.14, 125.10, 77.3, 77.0, 76.7; MS (EI) *m/z* 251 (64, M^+), 182 (10), 145 (100), 106 (30), 78 (43), 69 (80%). Anal. Calcd. for $C_{13}H_8F_3NO$: C, 62.16; H, 3.21; N, 5.58. Found: C, 62.07; H, 3.23; N, 5.57.

*4.2.16. (4-methylpyridin-2-yl)(p-tolyl)mathanone (**3p**)*

The general procedure was followed using 4-methylpyridine (1 mmol, 93 mg), 4-methyl benzyl alcohol (2 mmol, 244 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/EtOAc 4:1) gave the desired product **3p** (137 mg, 65%) as a dark green oil; IR (KBr) ν_{max} 2922, 1659, 1598, 1445, 1408, 1292, 1216, 1179, 997, 967, 831, 768; δ_H (400 MHz, $CDCl_3$) 8.58 (1H , d, *J* 5.2 Hz,=CHN), 7.97 (2H, d, *J* 8.4 Hz, =CH), 7.85 (1H , s, =CH), 7.29 (2H, d, *J* 8 Hz, =CH), 7.29 (1H, s, =CH), 2.48 (3H, s, Me), 2.45 (3H, s, Me); δ_C (100 MHz, $CDCl_3$) 194.0, 155.3, 148.39, 148.36, 143.7, 133.8, 131.1, 128.9, 126.9, 125.3, 21.7, 21.1; MS (EI) *m/z* 211 (51, M^+), 196 (48), 119 (53), 91 (100), 76 (25), 57 (83), 43 (77%). Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.41; H, 6.23; N, 6.61.

*4.2.17. (4-(tert-butyl)phenyl)(2-pyridyl)methanone (**3q**)*[12]

The general procedure was followed using pyridine (1 mmol, 79 mg), 4-tertbutyl benzylalcohol (2 mmol, 328 mg), $K_2S_2O_8$ (2 mmol, 540 mg). Purification by column chromatography (silica gel, n-hexane/ EtOAc, 4/1) gave the desired product **3q** (169 mg, 71%) as a dark green oil; IR (KBr) ν_{max} 2958, 2924, 2856, 1663, 1462, 1274, 746; δ_H (400 MHz, $CDCl_3$) 8.75 (1H , d, *J* 4.4 Hz, =CHN), 8.01 (2H , d, *J* 8.4 Hz, =CH), 7.91 (1H, td, J 7.6, 1.6 Hz, =CH), 7.72 (1H , dd, *J* 5.6, 3.2 Hz, =CH), 7.52 (2H , d, *J* 8.4 Hz, =CH), 1.38 (9H , s, 3Me); δ_C (100 MHz, $CDCl_3$) 193.6, 156.7, 155.2, 148.5, 137.1, 133.4, 132.4, 130.9, 128.8, 125.2, 35.1, 31.1; MS (EI) *m/z* 240 (63, MH^+), 225 (50), 210 (51), 195 (100), 183 (88), 57 (81), 43 (74%). Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.36; H, 7.13; N, 5.84.

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