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Palladium(0) nanoparticle-catalyzed sp^2 C–H activation: a convenient route to alkyl–aryl ketones by direct acylation of aryl bromides and iodides with aldehydes

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ABSTRACT

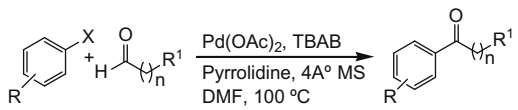
Palladium(0) nanoparticles efficiently catalyze aliphatic aldehyde C–H functionalization by aryl halides to produce alkyl–aryl ketones in good yields. A wide range of substituted aryl and hetero-aryl bromides/iodides and open-chain aldehydes of varied chain length participated in this reaction.

The C–H activation by a transition metal catalyst is a very useful tool in organic synthesis and has wide applications in functionalization of C–H to C–C, C–X, C–O, and C–N bonds.[1] There are also several reports of C–C double and triple bond activations;[2] however, the C=O activation is limited.[3] The direct introduction of carbonyl group into a phenyl ring by aldehyde C–H activation is a very useful proposition. The rhodium-catalyzed activation of aldehydes by organometallic reagents[4a] and addition of aldehyde to alkenes to produce diaryl ketones[4b] are noteworthy among others.[5] The nickel-catalyzed coupling of aryl iodides with aromatic aldehydes[6a] and palladium(II)-catalyzed addition of salicylaldehydes to aryl iodides[6b] for the synthesis of diaryl ketones are of much importance. Recently, Xiao and co-workers reported an elegant synthesis of alkyl–aryl ketone by direct acylation of aryl bromides with aldehydes catalyzed by Pd(II) species[7a] and Cheng[7b] demonstrated an efficient route to diaryl ketones by reaction of 2-aryl pyridine and aryl aldehydes.

The use of metal nanoparticles as efficient catalysts in organic reactions has attracted considerable interest in recent times in the context of green chemistry because of their benign character and ease of preparation.[8] As a part of our continuing activities to explore the novel applications of metal nanoparticles[9] we report here a Pd(0) nanoparticle-catalyzed C–H functionalization of aliphatic aldehyde by aryl halides leading to an easy route to alkyl–aryl ketone (Scheme 1).

Alkyl–aryl ketones are of much importance as useful intermediates in pharmaceutical, fragrance, dye, and agrochemical industries.[10]

To standardize the reaction conditions a series of experiments were carried out with various palladium salts and additives using different solvents and varied reaction parameters for a representative reaction of bromobenzene and octanal. The results are summarized in Table 1. A variety of palladium salts such as $Pd(OAc)_2$, $PdCl_2$, and $Pd(NO_3)_2$ in combination with different additives including K_2CO_3, $KOBu^t$, Et_3N, *n*-$BuNH_2$, *n*-Bu_2NH, and pyrrolidine were investigated in solvents such as DMF, DMSO, H_2O, toluene, and THF to best fit the reaction. It was found that the best results were obtained using $Pd(OAc)_2$ and tetrabutylammonium bromide (TBAB) in combination with pyrrolidine and 4 Å molecular sieves in DMF at 100 °C for 10 h (Table 1, entry 12). The absence of TBAB reduces the yield of product considerably (Table 1, entry 14). It is believed that TBAB acts as a stabilizer for Pd nanoparticles preventing them from fast agglomerization and thus helps in the progress of the reaction.[8d] The preformed Pd nanoparticles are not equally active in this reaction possibly due to their inherent tendency for agglomerization (Table 1, entry 18). No efficient reaction was



Scheme 1. Direct acylation of aryl halides with aldehydes.

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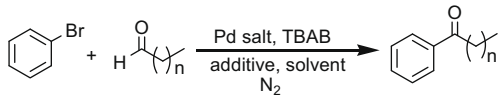
Table 1
Standardization of reaction conditions[a]



Entry	Pd salt	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	$Pd(OAc)_2$	—	DMF	100	24	0
2	$Pd(OAc)_2$	K_2CO_3	DMF	120	18	0
3	$Pd(OAc)_2$	$KOBu^t$	DMF	120	18	0
4	$Pd(OAc)_2$	Et_3N	DMF	120	18	0
5	$Pd(OAc)_2$	n-$BuNH_2$	DMF	120	18	<5
6	$Pd(OAc)_2$	n-Bu_2NH	DMF	120	18	12
7	$Pd(OAc)_2$	Pyrrolidine	DMF	100	10	30
8	$Pd(OAc)_2$	Pyrrolidine	DMSO	130	18	70
9	$Pd(OAc)_2$	Pyrrolidine	H_2O	100	22	0
10	$Pd(OAc)_2$	Pyrrolidine	Toluene	110	24	0
11	$Pd(OAc)_2$	Pyrrolidine	THF	70	24	0
12	**$Pd(OAc)_2$**	**Pyrrolidine, 4 Å MS**	**DMF**	100	10	**83**
13[b]	$Pd(OAc)_2$	Pyrrolidine, 4 Å MS	DMF	130	24	43
14[c]	$Pd(OAc)_2$	Pyrrolidine, 4 Å MS	DMF	100	10	50
15	$Pd(OAc)_2$	4 Å MS	DMF	100	24	0
16	$PdCl_2$	Pyrrolidine, 4 Å MS	DMF	100	10	54
17	$Pd(NO_3)_2$	Pyrrolidine, 4 Å MS	DMF	100	10	60
18	PdNPs[d]	Pyrrolidine, 4 Å MS	DMF	100	10	48

[a] Reaction conditions: a mixture of bromobenzene (1 mmol), octanal (1.2 mmol), Pd salt (4 mol %), TBAB (1 mmol), additive (2 mmol), and solvent (4 mL) was heated.
[b] Undesired tarry material was obtained.
[c] Reaction was carried out in the absence of TBAB.
[d] Pd nanoparticles were prepared separately.

observed in the absence of 4 Å molecular sieves (Table 1, entry 7). The amount of $Pd(OAc)_2$ was also optimized to 4 mol %.

Thus, in a typical experimental procedure,[11] a mixture of aryl bromide, aldehyde, $Pd(OAc)_2$, TBAB, pyrrolidine, and 4 Å molecular sieves in DMF was heated at 100 °C for a certain period of time as required to complete the reaction (TLC). The standard work-up and purification by column chromatography provided the pure product.

To determine the active catalytic species in this reaction, an extract from the reaction mixture of bromobenzene and octanal after 4 h from the start of the reaction showed the formation of nanoparticles of 5–8 nm size by TEM (Transmission Electron Microscope) image (Fig. 1). The identity of these particles as palladium was confirmed by the selected area electron diffraction (SAED) pattern (Fig. 2) which exhibited four diffused rings due to (1 1 1), (2 0 0), (2 2 0), and (3 1 1) reflections of fcc Pd and indicated the crystalline nature of nanoparticles. The study of this reaction by UV (DMF) spectroscopy showed a peak at 415 nm corresponding to Pd(II) before the start of the reaction and disappearance of this peak with the progress of the reaction by 4 h indicated the formation of Pd(0) (Fig. 3).

A series of diversely substituted aryl halides underwent acylation with a variety of aliphatic aldehydes by this procedure to produce the corresponding alkyl–aryl ketones. The results are summarized in Table 2. Although the aryl iodides and bromides are highly reactive, the corresponding chlorides are considerably less reactive (Table 2, entry3). Thus chloro and fluoro groups present in aryl iodides and bromides remained unaffected during acylations. Both electron-donating and electron-withdrawing substituted aryl bromides participated in this reaction although electron-donating substituents led to marginally higher yield.

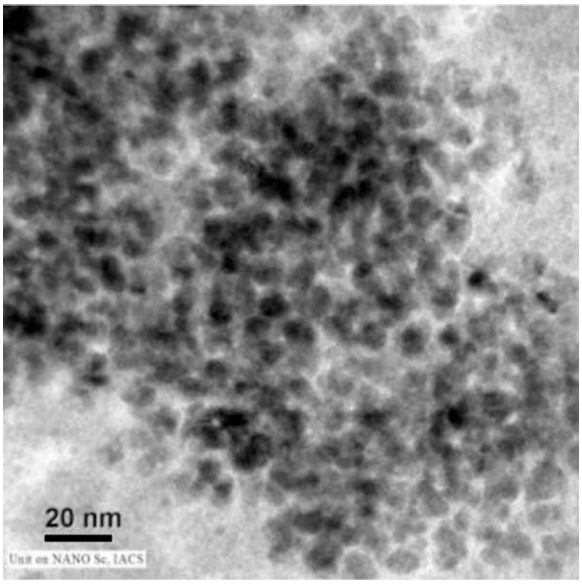


Figure 1. TEM image of Pd-nanoparticles formed in the reaction mixture.

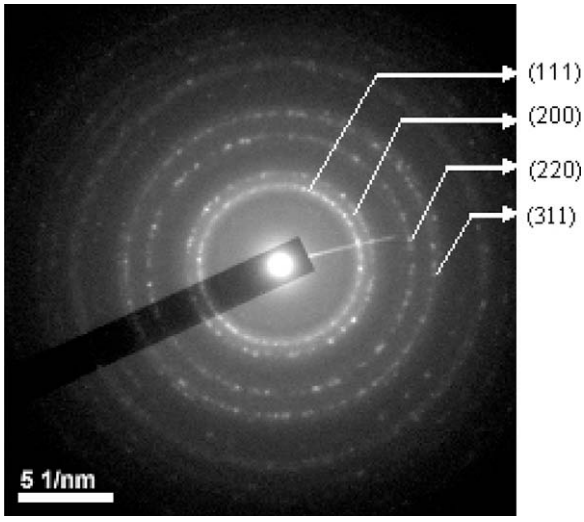


Figure 2. SAED pattern of crystalline Pd-nanoparticles.

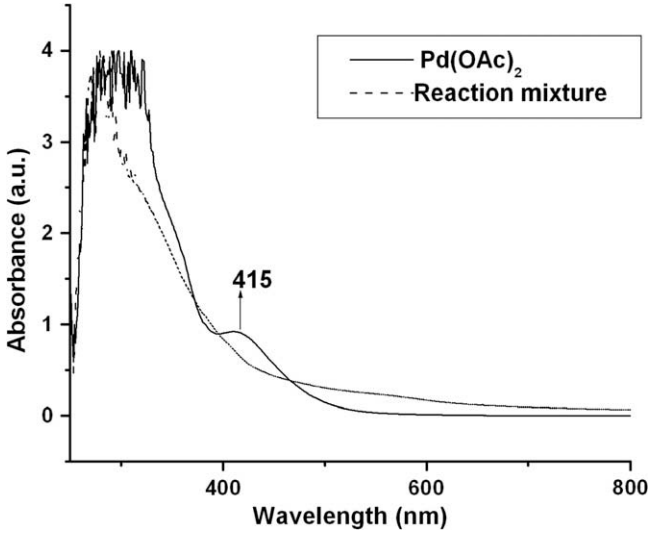
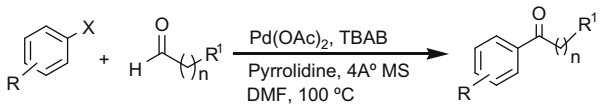


Figure 3. UV spectra of Pd at the initial and in the reaction mixture after the reaction.

Table 2
Palladium nanoparticle-catalyzed acylation of aryl and heteroaryl halides with aldehydes



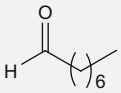
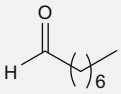
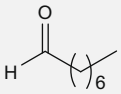
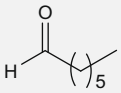
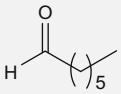
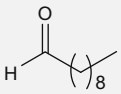
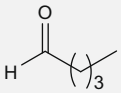
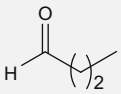
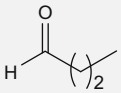
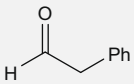
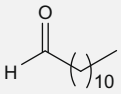
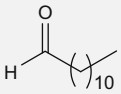
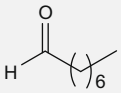
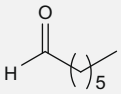
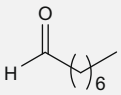
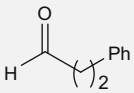
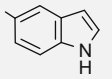
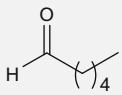
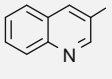
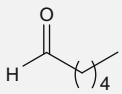
Entry	R	X	Aldehyde	Time (h)	Yield[a] (%)	Ref.
1	H	I		7.0	90	13
2	H	Br		8.5	83	13
3	H	Cl		15	32	13
4	*p*-OMe	I		8	84	7a
5	*p*-OMe	Br		10	76	7a
6	*p*-Me	Br		9	80	14
7	*p*-Cl	Br		12	70	15
8	*p*-COCH3	I		10	68	
9	*p*-COCH3	Br		13	62	
10	*m*-OMe	Br		15	59	16
11	*m*-F	Br		9.0	72	
12	*m*-NH_2	Br		12	88	
13	*p*-OH	Br		12	64	
14		Br		10	80	
15		Br		10	78	
16		I		18	54	17

Table 2 (*continued*)

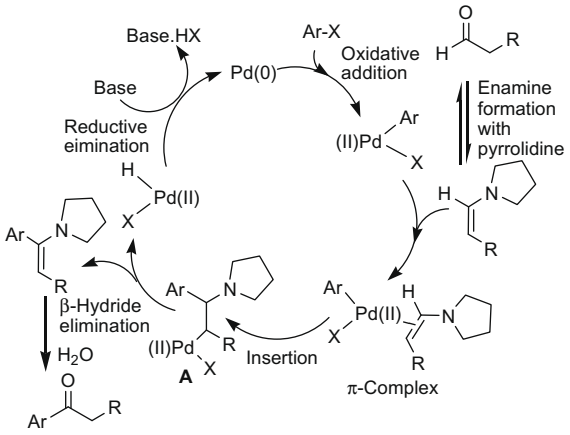
Entry	R	X	Aldehyde	Time (h)	Yield[a] (%)	Ref.
17		Br		12	80	
18		Br		15	62	

[a] Isolated yields of pure products.

The substituents at *m*- or *p*- position did not make much difference in reactivity although *o*-substituted aryl halides did not undergo acylation possibly due to steric factors. The aldehydes are uniformly reactive irrespective of their chain length. The most significant feature of this Pd(0) nanoparticle-catalyzed procedure is efficient participation of heteroaryl bromides and iodides. Thus, several heteroaryl units bearing thiophenyl, pyridyl, indolyl, and quinolinyl moieties produced the corresponding alkyl ketones in moderate to good yields. The direct acylation of heteroaryl halides by aliphatic aldehydes has not been addressed earlier except one report demonstrating only one reaction of thiophenyl bromide in lower yield (58%).[7a]

The reactions are generally clean, although in a few reactions small amounts (2–5%) of dimeric products from self-coupling of aryl halides are formed. These were easily separated during purification of product by column chromatography. Several functionalities such as OMe, F, Cl, COMe, NH_2, and OH were compatible with the reaction conditions. Interestingly when this reaction was performed under identical conditions in the presence of tetrakis(triphenylphosphine)palladium(0), no acylation was observed. Cheng and co-workers[7b] also reported that Pd(0) was totally ineffective for their C–H functionalization by aryl pyridines and to the best of our knowledge we are not aware of any aldehyde C–H functionalization by aryl halides using Pd(0). This demonstrates the importance of Pd(0) nanoparticles for this aldehyde C–H activation. Furthermore, it was reported that palladium nanoparticle-catalyzed reaction of aryl bromides and aliphatic aldehydes in the presence of tetrabutyl ammonium salt, ionic liquid, and potassium carbonate led to biaryl formation by Ullmann reaction without any acylation of aldehyde.[12] Thus, this combination of palladium nanoparticles, pyrrolidine, and molecular sieves in DMF is a best fit for aldehyde C–H activation by aryl halides.

It is suggested that the reaction follows a similar reaction pathway as proposed by Xiao and co-workers[7a] As outlined in



Scheme 2. Probable mechanism of acylation reaction.

Scheme 2, in situ-generated Pd nanoparticles undergo oxidative addition with the aryl halide followed by Heck coupling with the enamine, formed in situ by the reaction of aldehyde and pyrrolidine, to provide an intermediate **A** with the insertion of aryl group at the α-position of the heteroatom. The intermediate **A** on β-hydride elimination followed by hydrolysis furnished the product, alkyl–aryl ketone. Reductive elimination of HX from the catalyst surface releases Pd(0).

In conclusion, we have developed an efficient procedure for aldehyde C–H functionalization by aryl halides catalyzed by palladium nanoparticles. A wide range of substituted aryl and heteroaryl iodides and bromides underwent acylations by a variety of aliphatic aldehydes providing an easy access to alkyl–aryl ketones. The significant advantage of this protocol is successful application to several diverse heteroaryl halides. Furthermore, this work demonstrates the potential and clear distinction of palladium(0) nanoparticles over palladium(0).

Acknowledgments

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11. *General experimental procedure for acylation reaction: representative one for acylation of bromobenzene with octanal* (Table 2, entry 2): a mixture of bromobenzene (157 mg, 1 mmol), octanal (154 mg, 1.2 mmol), $Pd(OAc)_2$ (9 mg, 4 mol %), tetrabutyl ammonium bromide (323 mg, 1 mmol), pyrrolidine (142 mg, 2 mmol), and 4 Å MS (1 g) in DMF (4 mL) was heated with stirring at 100 °C under argon for 8.5 h (TLC). The reaction mixture was extracted with Et_2O (4 × 15 mL). The extract was washed with water, brine, and then dried (Na_2SO_4). Evaporation of solvent left the crude product, which was purified by column chromatography over silica gel (60–120 mesh) (hexane/ether 97:3) to provide 1-phenyl-octan-1-one as a colorless liquid (169 mg, 83%). The spectroscopic data (IR, ^{1}H NMR, and ^{13}C NMR) of this compound are in good agreement with those reported earlier.[13] This procedure was followed for all the reactions listed in Table 2. Many of these products are known compounds and were easily identified by comparison of their spectroscopic data with those reported (see Table 2). The unknown compounds were properly characterized by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS data.
1-(4-Acetyl-phenyl)-butan-1-one (Table 2, entries 8 and 9): brown gummy liquid; IR (neat): 2961, 2931, 2875, 1684, 1605, 1456, 1265, 1215 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.99 (t, J = 7.4 Hz, 3H), 1.73–1.80 (m, 2H), 2.63 (s, 3H), 2.96 (t, J = 7.3 Hz, 2H), 8.01 (s, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 17.7, 26.9, 41.0, 128.3 (2C), 128.6 (2C), 140.1, 140.4, 197.7, 199.9; HRMS Calcd for $C_{12}H_{14}O_2$ ([M+Na]$^+$): 213.0892. Found: 213.0872.
1-(3-Fluoro-phenyl)-dodecan-1-one (Table 2, entry 11): yellow liquid; IR (neat): 2924, 2855, 1693, 1589, 1466, 1442, 1248, 1151, 896, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.87 (t, J = 6.3 Hz, 3H), 1.18–1.25 (m, 16H), 1.67–1.74 (m, 2H), 2.93 (t, J = 7.3 Hz, 2H), 7.20–7.26 (m, 1H), 7.39–7.43 (m, 1H), 7.62 (d, J = 9.4 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.8, 24.3, 28.8, 28.9, 29.0, 29.4, 29.6, 29.7, 32.0, 38.9, 114.9 (d, J = 28.8 Hz, 1C), 119.9 (d, J = 21.3 Hz, 1C), 123.9, 130.3, 139.2, 163.0 (d, J = 246.2 Hz, 1C), 199.3; HRMS Calcd for $C_{18}H_{27}FO$ [M+Na]$^+$: 301.1944. Found: 301.1941.
1-(3-Amino-phenyl)-dodecan-1-one (Table 2, entry 12): yellow liquid; IR (neat): 3462, 3370, 2953, 2924, 2853, 1678, 1624, 1602, 1456, 1323, 1288, 1190, 993 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.86 (t, J = 6.3 Hz, 3H), 1.22–1.30 (m, 16H), 1.67–1.71 (m, 2H), 2.86–2.93 (m, 2H), 3.86 (br s, 2H), 6.83–6.87 (m, 1H), 7.18–7.32 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.7, 24.5, 29.3, 29.4, 29.5, 29.6, 29.7, 31.4, 38.7, 114.1, 118.5, 119.6, 129.4, 138.2, 146.6, 200.9; HRMS Calcd for $C_{18}H_{29}NO$ ([M+Na]$^+$): 298.1709. Found: 298.1705.
1-(4-Hydroxy-phenyl)-octan-1-one (Table 2, entry 13): brown low melting solid; IR (neat): 3312, 3300, 2957, 2928, 2856, 1659, 1602, 1583, 1491, 1456, 1269, 1224, 1166 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.91–0.97 (m, 3H), 1.34–1.42 (m, 8H), 1.73–1.83 (m, 2H), 2.98 (t, J = 7.3 Hz, 2H), 6.34 (broad, 1H), 6.98 (d, J = 8.7 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.2, 22.7, 25.1, 29.3, 29.5, 31.8, 38.5, 115.8 (2C), 129.3, 130.9 (2C), 161.9, 200.9.
1-Naphthalen-1-yl-heptan-1-one (Table 2, entry 14): yellow liquid; IR (neat): 3049, 2955, 2928, 2857, 1682, 1593, 1509, 1464, 1234, 1172, 1087, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.90–0.94 (m, 3H), 1.33–1.42 (m, 6H), 1.75–1.83 (m, 2H), 3.06 (t, J = 7.3 Hz, 2H), 7.47–7.62 (m, 3H), 7.84–7.89 (m, 2H), 7.98 (d, J = 8.2 Hz, 1H), 8.56 (d, J = 8.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.5, 24.7, 29.0, 31.7, 42.3, 124.4, 125.8, 126.4, 127.1, 127.8, 128.4, 130.1, 132.3, 133.9, 136.5, 205.2.
1-Thiophen-2-yl-octan-1-one (Table 2, entry 15): yellow liquid; IR (neat): 2955, 2928, 2854, 1663, 1518, 1415, 1234 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.84–0.92 (m, 3H), 1.17–1.35 (m, 8H), 1.70–1.78 (m, 2H), 2.88 (t, J = 7.4 Hz, 2H), 7.09–7.12 (m, 1H), 7.59 (d, J = 4.92 Hz, 1H), 7.68 (d, J = 3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.9, 22.5, 24.7, 29.0, 29.2, 31.6, 39.4, 127.9, 131.6, 133.2, 144.4, 193.5.
1-(1H-Indol-4-yl)-hexan-1-one (Table 2, entry 17): brown gummy liquid; IR (neat): 3316, 2957, 2930, 2870, 2860, 1685, 1651, 1612, 1454, 1350, 1248, 1094, 758 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95–0.99 (m, 3H), 1.26–1.47 (m, 4H), 1.80–1.88 (m, 2H), 3.11 (t, J = 7.3 Hz, 2H), 6.71 (s, 1H), 7.33 (s, 1H), 7.47 (d, J = 8.6 Hz, 1H), 7.92 (d, J = 8.6 Hz, 1H), 8.40 (s, 1H), 9.22 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 22.6, 24.8, 31.8, 38.6, 104.1, 111.3, 122.0, 122.7, 126.0, 127.5, 129.6, 138.7, 201.6; HRMS Calcd for $C_{14}H_{17}NO$ ([M+Na]$^+$) 238.1208. Found: 238.1206.
1-Quinolin-3-yl-hexan-1-one (Table 2, entry 18): brown solid; mp: 62–64 °C; IR (KBr): 3057, 2947, 2931, 2850, 1688, 1682, 1620, 1572, 1454, 1176, 1126, 954 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.89–0.99 (m, 3H), 1.24–1.47 (m, 4H), 1.78–1.82 (m, 2H), 3.08 (t, J = 7.3 Hz, 2H), 7.61 (t, J = 7.5 Hz, 1H), 7.82 (t, J = 7.3 Hz, 1H), 7.93 (d, J = 8.2 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 8.69 (s, 1H), 9.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.0, 22.6, 23.9, 31.5, 38.9, 126.9, 127.6, 129.3, 129.4, 129.5, 131.9, 136.9, 149.2, 149.8, 199.3; HRMS Calcd for $C_{15}H_{17}NO$ ([M+H]$^+$): 228.1383. Found: 228.1384.
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