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Transition-Metal-Free Acylation of Quinolines and Isoquinolines with Arylmethanols via Oxidative Cross-Dehydrogenative Coupling Reactions

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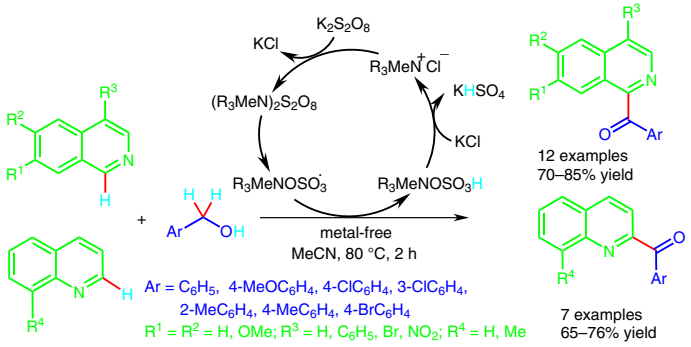

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Abstract An efficient acylation of quinolines and isoquinolines is described by use of arylmethanols as the acylating agents through a C–C bond formation via an oxidative cross-dehydrogenative coupling (CDC) strategy. This C-aroylation reaction was carried out by use of $K_2S_2O_8$ as oxidant and methyltrioctylammonium chloride (Aliquat 336) as a transfer agent in MeCN at 80 °C under transition-metal-free conditions.

Key words cross-dehydrogenative coupling reaction, C–C bond formation, metal-free coupling reaction, $K_2S_2O_8$, Aliquat 336, 2-aroyl quinolones, 1-aroyl isoquinolines

The exploration and development of ideal synthetic procedures to achieve C–C bond formation via functionalization of C–H bonds is an attractive and crucial challenge in the area of organic synthesis.[1] Recently, there has been a great interest in developing metal-free approaches as valuable complements and powerful strategies for the direct functionalization of C–H bonds to access C–C and C–heteroatom bonds.[2] In the meantime, formation of C–C bonds can be accessed by the cross-dehydrogenative coupling reaction (CDC) that has played a crucial role for functionalization of organic compounds. CDC reactions are effective, atom-economical, and rapid approaches for the synthesis of a variety of functionalized molecules, natural, and pharmaceutical products.[3]

Quinoline and isoquinoline derivatives are prevalent structural motifs found in pharmaceuticals, numerous natural products, and synthetic analogues.[4] Among them, 2-acylquinolines and 1-acylisoquinolines have been shown to possess a diverse range of biological properties such as antitumor,[5] CRTH2 antagonist (e.g. **I**, Figure 1),[6] anticancer (e.g. **II**, Figure 1),[4a] antimicrobial,[7] and CB_2-selective receptor activities (e.g. **III** and **IV**, Figure 1).[8]

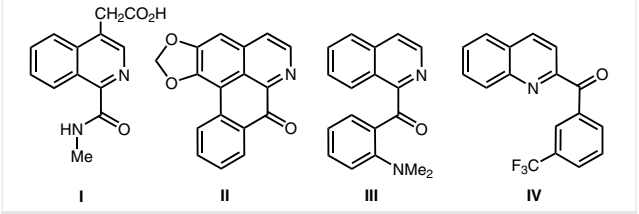
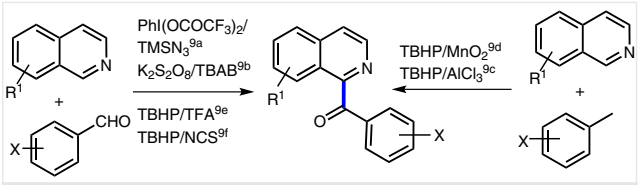


Figure 1 Some representative biologically active 1-acyl isoquinolines and 2-acyl quinolines

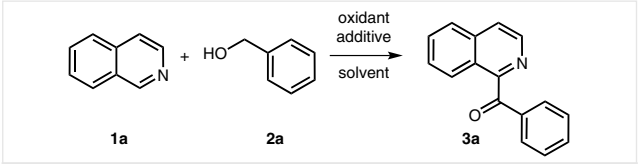
Commonly, 1-aroylisoquinoline and 2-aroylquinoline derivatives have been prepared from aldehydes or methylarenes by use of various oxidants under different conditions (Scheme 1). In 2013, Antonchick et al. developed an aroylation of these heterocycles with aldehydes by use of $PhI(OCOCF_3)_2$ and $TMSN_3$ under metal-free conditions.[9a] Prabhu and co-workers reported a similar acylation with aldehydes using a substoichiometric amount of TBAB and $K_2S_2O_8$.[9b] In 2015, Patel et al. developed an $AlCl_3$-catalyzed acylation by methylbenzenes in the presence of TBHP as oxidant.[9c] Acylation of isoquinoline derivatives was also carried out with TBHP/MnO_2 and TBHP/TFA systems by Liu and co-workers by use of methylbenzenes and benzaldehydes, respectively.[9d,e] Very recently Prabhu et al. have reported a metal-free acylation of heteroarenes by use of a TBHP/NCS system.[9f] Furthermore, several other reports have been presented in recent years regarding C–H functionalization of isoquinolines and quinolines.[10]



Scheme 1 Synthesis of 1-aroyl isoquinoline derivatives

However, to the best of our knowledge there is no report on the cross-dehydrogenative coupling of quinolines and isoquinolines with arylmethanols under transition-metal-free conditions. With this in mind, and in continuation of our attempts toward the synthesis of biologically active heterocycles,[11] herein we describe a new and efficient transition-metal-free approach for the oxidative acylation of quinolines and isoquinolines by use of arylmethanols as the acylating agents.

We started our study with a model reaction between isoquinoline (**1a**) and benzyl alcohol (**2a**) as the acylating agent (Scheme 2) for which the effects of different conditions on the efficiency of this oxidative cross-dehydrogenative coupling reaction including the molar ratio of the reactants, the type and amount of oxidant, type and amount of additive, suitable solvent, and reaction temperature would be optimized (Table 1).



Scheme 2 Acylation of isoquinoline with benzyl alcohol

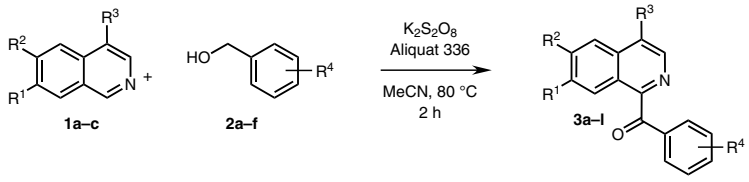
When the reaction was performed with a 1:2 molar ratio of **1a**/**2a** in MeCN as solvent in the presence of two equivalents of $K_2S_2O_8$ as oxidant and 15 mol% of Aliquat 336 as additive at ambient temperature or at 50 °C, the reaction was absolutely ineffective (Table 1, entries 1 and 2). However, when the temperature raised to 80 °C, the desired product **3a** was obtained in 70% yield (Table 1, entry 3). It was demonstrated that $K_2S_2O_8$ was the best oxidant in comparison to the others such as BPO, TBHP, H_2O_2, and DDQ that were tested during the optimization process. With BPO, **3a** was detected in 62% yield (Table 1, entry 4) but the reaction was ineffective with TBHP, H_2O_2, and DDQ (Table 1, entries 5–7). By using 2.5 equivalents of $K_2S_2O_8$, the yield improved to 75% (Table 1, entry 8). Increasing the amount of oxidant further led to a decrease in yield (Table 1, entry 9). The solvent system also notably affected the efficiency of this reaction. Solvents such as 1,2-dichloroethane, chlorobenzene, toluene, dioxane, DMSO–H_2O, and DMSO were examined, showing that MeCN was the best among all the tested solvents (Table 1, entries 8, 10–15). In 1,2-dichloroethane, chlorobenzene, toluene, and DMSO, the yield of the reaction decreased (Table 1, entries 10–12 and 15) and in 1,4-dioxane or DMSO–H_2O (1:1) no acylation product was observed (Table 1, entries 13 and 14). When carrying out the reaction using additives such as molecular iodine, KI, and CuI, no acylation product was observed (Table 1, entries 16–18). By increasing the amount of Aliquat 336 to 30 mol%, the yield of **3a** improved to 85% (Table 1, entry19). Carrying out the reaction with 1:1, 1:3, and 1:4 ratios of **1a**/**2a** led to **3a** in lower yields (Table 1, entries 20–22). Two further control experiments were performed in the absence

Table 1 Optimization of the Reaction Conditions for Metal-Free Dehydrogenative Cross-Coupling of Isoquinoline (**1a**) with Benzyl Alcohol (**2a**)[a]

Entry	Oxidant (equiv)[b]	Additive (mol%)[b]	Solvent	Temp (°C)	Yield (%)
1	$K_2S_2O_8$ (2)	Aliquat 336 (15)	MeCN	r.t.	NR[c]
2	$K_2S_2O_8$ (2)	Aliquat 336 (15)	MeCN	50	NR
3	$K_2S_2O_8$ (2)	Aliquat 336 (15)	MeCN	80	70
4	BPO (2)	Aliquat 336 (15)	MeCN	80	62
5	TBHP[d] (2)	Aliquat 336 (15)	MeCN	80	NR
6	H_2O_2[e] (2)	Aliquat 336 (15)	MeCN	80	NR
7	DDQ (2)	Aliquat 336 (15)	MeCN	80	NR
8	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	MeCN	80	75
9	$K_2S_2O_8$ (3)	Aliquat 336 (15)	MeCN	80	70
10	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	DCE	80	65
11	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	PhCl	80	50
12	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	PhMe	80	50
13	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	1,4-dioxane	80	NR
14	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	DMSO–H_2O (1:1)	80	NR
15	$K_2S_2O_8$ (2.5)	Aliquat 336 (15)	DMSO	80	60
16	$K_2S_2O_8$ (2.5)	I_2 (15)	MeCN	80	NR
17	$K_2S_2O_8$ (2.5)	KI (15)	MeCN	80	NR
18	$K_2S_2O_8$ (2.5)	CuI (15)	MeCN	80	NR
19	$K_2S_2O_8$ (2.5)	Aliquat 336 (30)	MeCN	80	85
20[f]	$K_2S_2O_8$ (2.5)	Aliquat 336 (30)	MeCN	80	55
21[g]	$K_2S_2O_8$ (2.5)	Aliquat 336 (30)	MeCN	80	70
22[h]	$K_2S_2O_8$ (2.5)	Aliquat 336 (30)	MeCN	80	70
23	–	Aliquat 336 (30)	MeCN	80	NR
24	$K_2S_2O_8$ (2.5)	–	MeCN	80	NR
25	$K_2S_2O_8$ (2.5)	Aliquat 336 (30)	MeCN	100	80

[a] Reaction conditions: isoquinoline (**1a**, 1 mmol), benzyl alcohol (**2a**, 2 mmol; except for entries 20–22), solvent (3 mL), 2 h.
[b] In respect to **1a**.
[c] NR = no reaction.
[d] 70 wt% *t*-BuOOH in H_2O.
[e] 30 wt% H_2O_2 in H_2O.
[f] 1:1 ratio of **1a**/**2a**.
[g] 1:3 ratio of **1a**/**2a**.
[h] 1:4 ratio of **1a**/**2a**.

Table 2 Cross-Dehydrogenative Coupling of Arylmethanols with Isoquinolines[a]



Entry	R^1	R^2	R^3	R^4	3	Yield (%)[b]	Observed mp (°C)	Reported mp (°C)
1	H	H	H	H	**3a**	85	74–75	75–7714
2	H	H	H	4-MeO	**3b**	78	78–79	748
3	H	H	H	4-Cl	**3c**	80	86–88	1038
4	H	H	H	2-Me	**3d**	75	72–74	oil9c
5	H	H	H	3-Cl	**3e**	72	100–102	104–10513
6	H	H	H	4-Br	**3f**	80	74–76	70–729c
7	OMe	OMe	H	H	**3g**	74	136–138	131–13312
8	OMe	OMe	H	4-MeO	**3h**	70	150–152	145–1489b
9	H	H	C_6H_5	H	**3i**	75	132–134	–9d
10	H	H	C_6H_5	4-MeO	**3j**	72	142–145	1459b
11	H	H	Br	H	**3k**	70	133–135	129–1309c
12	H	H	NO_2	H	**3l**	72	104–106	106–1089c

[a] Reaction conditions: isoquinoline **1** (0.5 mmol), arylmethanol **2** (1 mmol), $K_2S_2O_8$ (2.5 mmol), Aliquat 336 (30 mol%).
[b] Isolated yields (in respect to **1**).

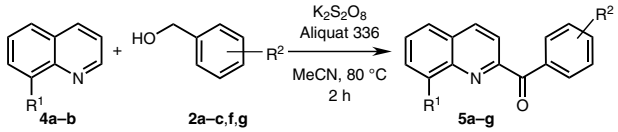
of oxidant or additive, which revealed the requirement of the presence of both oxidant and additive for promotion of this reaction (Table 1, entries 23 and 24). Moreover, carrying out the reaction in a higher temperature led to a decrease in the observed yield of the reaction (Table 1, entry 25).

Thus, a 1:2 molar ratio of **1a**/**2a**, MeCN as solvent, 2.5 equivalents of $K_2S_2O_8$ as oxidant, 30 mol% of Aliquat 336 as additive, and a reaction temperature of 80 °C were selected as the optimized conditions for this oxidative cross-dehydrogenative coupling reaction (Table 1, entry 19).

With the optimized conditions in hand, we explored the generality of this dehydrogenative cross-coupling reaction. It was found that benzyl alcohol (**2a**), 4-methoxybenzyl alcohol (**2b**), 4-chlorobenzyl alcohol (**2c**), 2-methylbenzyl alcohol (**2d**), 3-chlorobenzyl alcohol (**2e**), and 4-bromobenzyl alcohol (**2f**) all smoothly reacted with electron-neutral isoquinoline (**1a**) and afforded the corresponding 1-aroylisoquinolines in 72–85% yields (Table 2, entries 1–6). The reaction of the electron-rich 6,7-dimethoxyisoquinoline (**1b**) gave substituted isoquinoline derivatives **3g** and **3h** in 74% and 70% yields, respectively (Table 2, entries 7 and 8). The presence of phenyl, Br, and NO_2 substituents on the C4 position of the isoquinoline was also tolerated, and the corresponding products were formed in good yields (Table 2, entries 9–12).[14]

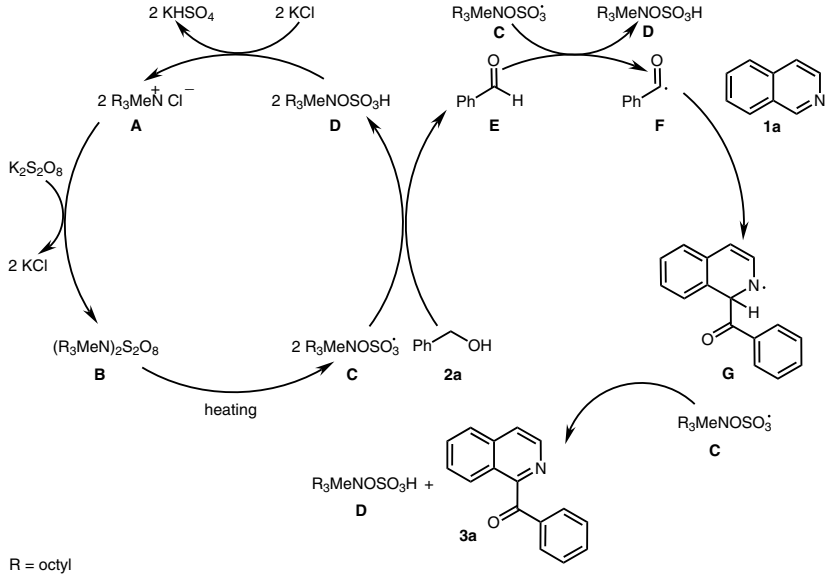
Quinolines also coupled effectively with arylmethanols **2a**–**c**,**f**,**g** (4-methylbenzyl alcohol) under the same optimized conditions. The reactions went to completion within two hours, and the corresponding 2-aroylquinolines **5a**–**g** were obtained in 65–76% yields (Table 3).[14]

Table 3 Cross-Dehydrogenative Coupling of Arylmethanols with Quinolines[a]



Entry	R^1	R^2	5	Yield (%)[b]	Observed mp (°C)	Reported mp (°C)
1	H	H	**5a**	76	99–100	96–98[9c]
2	H	4-MeO	**5b**	70	82–85	65–68[9c]
3	H	4-Cl	**5c**	70	128–129	105–107[9c]
4	H	4-Br	**5d**	72	109–110	111–113[9c]
5	H	4-Me	**5e**	73	65–66	63–65[9b]
6	Me	H	**5f**	68	65–67	63–64[9c]
7	Me	4-Cl	**5g**	65	84–86	79–81[9c]

[a] Reaction conditions: quinoline **4** (0.5 mmol), arylmethanol **2** (1 mmol), $K_2S_2O_8$ (2.5 mmol), Aliquat 336 (30 mol%).
[b] Isolated yields (in respect to **4**).

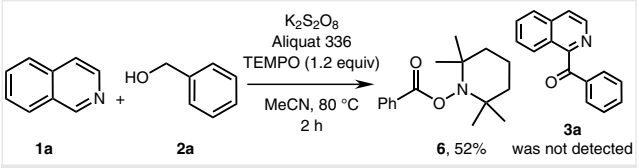


Scheme 3 Tentative mechanism for the CDC reaction for acylation of isoquinoline **1** with arymethanols **2** mediated by $K_2S_2O_8$/Aliquat 336

A plausible mechanism for the formation of 1-aroyl isoquinolines is depicted in Scheme 3. The reaction sequence is assumed to begin with the reaction between methyltrioctylammonium chloride (**A**, Aliquat 336) as the transfer agent and potassium persulfate ($K_2S_2O_8$) to generate methyltrioctylammonium persulfate (**B**) that, on heating, would convert into methyltrioctylammonium sulfate radical (**C**). Sulfate radical **C** may react with benzyl alcohol (**2a**) through a radical hydrogen-abstraction process and formation of benzaldehyde (**E**) together with methyltrioctylammonium hydrogensulfate (**D**). Next, the sulfate radical **C** reacts with benzaldehyde (**E**) to give acyl radical **F**, followed by radical attack of **F** on isoquinoline (**1a**) to form the corresponding α-acyl amine radical **G**. Finally, hydrogen abstraction and rearomatization of **G** by sulfate radical **C** give the desired product **3a** as well as **D**. Methyltrioctylammonium hydrogensulfate (**D**) reacts with KCl to regenerate methyltrioctylammonium chloride (**A**).

To validate the proposed mechanism of this CDC, reaction between isoquinoline (**1a**) and benzyl alcohol (**2a**) under the optimized reaction conditions was carried out in the presence of the radical trap TEMPO. In this reaction, 2,2,6,6-tetramethylpiperidino benzoate (**6**) was isolated in 52% yield, and the desired acylated product **3a** was not detected (Scheme 4). This observation strengthens the proposal that radical intermediates are present in the CDC reaction.

In conclusion, we have developed a new and efficient dehydrogenative cross-coupling reaction for acylation of isoquinolines and quinolines. The reactions were carried out in the presence of $K_2S_2O_8$ as oxidant and methyltrioctylammonium chloride (Aliquat 336) as transfer agent. The use of arylmethanols as the acylating agents, metal-free and mild reaction conditions, high yields of the products, and short reaction times are the salient advantages of this method. To the best of our knowledge this is the first report of the acylation of isoquinolines and quinolines using arylmethanols.



Scheme 4 Control experiment supporting the proposed mechanism

Acknowledgement

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1562135.

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(14) **General Procedure for the Preparation of Compounds 3 and 5, Exemplified with 3a**

In a 10 mL sealable tube, benzyl alcohol (**2a**, 0.216 g, 2 mmol), Aliquat 336 (0.121 g, 0.3 mmol), and $K_2S_2O_8$ (0.675 g, 2.5 mmol) were added to a solution of isoquinoline (**1a**, 0.129 g, 1.0 mmol) in MeCN (3 mL). The resultant mixture was heated at 80 °C for 2 h. After completion of the reaction, as indicated by TLC, the reaction mixture was cooled to ambient temperature and treated with sat. aq $NaHCO_3$ (10 mL). The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and the solvent was evaporated under vacuum. The residue was purified by column chromatography using *n*-hexane–EtOAc (8:1) as eluent to afford **3a**.

(Isoquinolin-1-yl)(phenyl)methanone (3a)

Yield: 0.198 g (85%); white solid; mp 74–75 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.47 (dd, *J* = 7.7, 7.4 Hz, 2 H, 2 × CH), 7.60–7.63 (m, 2 H, 2 × CH), 7.75 (t, *J* = 7.5 Hz, 1 H, CH), 7.81 (d, *J* = 5.9 Hz, 1 H, CH), 7.94 (d, *J* = 8.6 Hz, 1 H, CH), 7.96 (d, *J* = 7.7 Hz, 2 H, 2 × CH), 8.20 (d, *J* = 8.6 Hz, 1 H, CH), 8.54 (d, *J* = 5.9 Hz, 1 H, CH). ^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 123.1, 125.8, 126.1, 127.3, 127.9, 128.3, 130.9, 131.2, 133.5, 136.4, 136.6, 141.7, 155.5, 194.1.

(4-Chlorophenyl)(quinolin-2-yl)methanone (5c)

Yield 0.187 g (70%); white solid; mp 128–129 °C. ^{1}H NMR (300.1 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 7.62 (t, *J* = 8.0 Hz, 1 H, CH), 7.75 (t, *J* = 7.2 Hz, 1 H, CH), 7.88 (d, *J* = 7.5 Hz, 1 H, CH), 8.12 (d, *J* = 8.7 Hz, 1 H, CH), 8.19 (d, *J* = 7.9 Hz, 1 H, CH), 8.24 (d, *J* = 8.5 Hz, 2 H, 2 × CH), 8.35 (d, *J* = 8.7 Hz, 1 H, CH). ^{13}C NMR (75.1 MHz, $CDCl_3$): δ = 119.9, 127.5, 128.5, 128.9, 129.1, 130.3, 130.6, 133.3, 134.6, 137.0, 140.1, 147.2, 154.3, 193.1.