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Graphical Abstract

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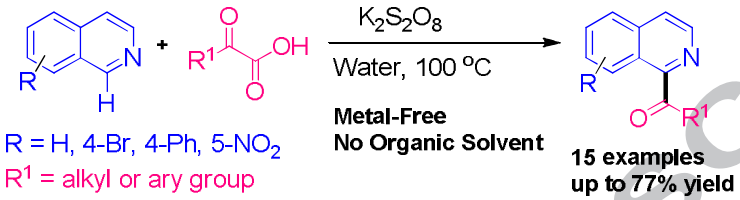

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Metal-Free Decarboxylative Acylation of Isoquinolines using α-Keto Acids in Water

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ABSTRACT

An efficient method for acylation of isoquinolines has been developed using α-ketoacids under metal- and additive-free conditions in water. The protocol involves C(sp^2)-H functionalization of isoquinolines providing an easy access to C1-benzoylated isoquinolines, which constitute the core structure of a number of biological active compounds and serve as key intermediate in the synthesis of many alkaloids.

C_1-Substituted *N*-heterocycles constitute the core structure of many biologically-active compounds and synthetic pharmaceuticals containing antitussive, antipsychotic, antispasmodic, anxiolytic, antibacterial, antifungal, and anticancer properties.[1] Among them, C_1-benzyl and benzoyl substituted isoquinolines are particularly important due to their bio-medical applications (Fig. 1), and also serve as intermediates in the synthesis of many alkaloids.

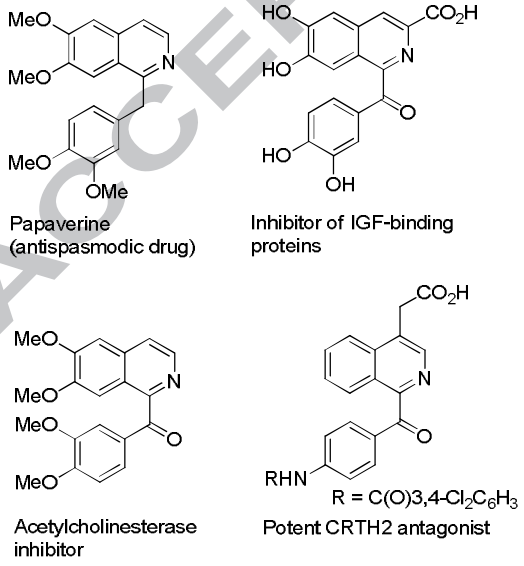

Fig. 1. Bio-active C_1-benzyl/benzoyl-isoquinolines

Direct C-H functionalization has emerged as a potentially useful tool for the synthesis of such vital molecules.[2] Many reports concerning the benzylation, benzoylation or acylation of *N*-heterocycles have appeared in the last few years.[3-8] Antonchick et al. have developed a nice protocol for the benzoylation of isoquinolines using aldehydes and $PhI(OCOCF_3)/TMSN_3$ in benzene.[3] Prabhu et al. employed $TBAB/K_2S_2O_8$ combination with aldehydes in dichloroethane for the acylation of isoquinolines and quinoxaline.[4] Afterwards, Patel et al. made use of methyl benzenes for benzoylation of such N-heterocycles using $AlCl_3$/TBHP via a Minisci-type reaction.[5] In the same year, Liu and co-workers carried out the benzylation and benzoylation of isoquinolines using methyl arenes in the presence of $Y(OTf)_3$/DTBP and MnO_2/TBHP/TFA blends respectively (Scheme 1).[6]

However, most of the previously reported methods for the acylation of isoquinolines and similar *N*-heterocycles require either the use of metals or oxidants with different additives or initiators. Thus, there is adequate scope to bring about the reaction using different reacting partners under mild and green conditions. As a part of our ongoing programme on developing greener approaches for C-H functionalization,[9,10] and considering the biological significance of C_1-benzoyl substituted *N*-heterocycles, it was thought worthwhile to explore the benzoylation of isoquinolines using keto acids as a reacting partner in an environmentally benign way.

In order to optimize the reaction conditions, a model reaction employing isoquinoline (**1a**) with phenylglyoxylic acid (**2a**) was initially carried out using $K_2S_2O_8$ as an oxidant and TFA as an additive in acetonitrile at room temperature for 12 hours, but without success to the desired benzoylated product **3a** (Table 1, entry 1).

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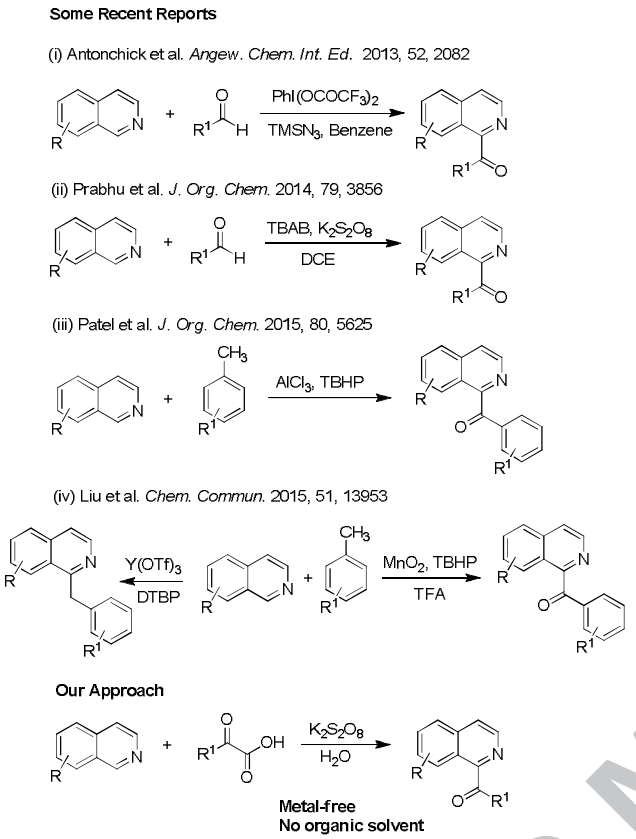
However, when the reaction temperature was raised to 100 °C under similar conditions, we were happy to note the formation of C_1-benzoyl isoquinoline (**3a**) in 56% yield (entry 2).

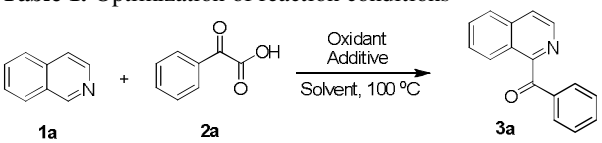


Scheme 1. Previous reports and our strategy

Interestingly, the functionalization of isoquinoline (**1a**) occurred regioselectively at C_1-position. When the solvent was changed to DMSO, a reasonable increase in the yield of the product **3a** was observed (68%, entry 3). To ascertain the role of the additive, the reaction was then carried out without the use of TFA, which eventually yielded the product **3a** in almost same yield (entry 4). Nevertheless, no reaction was observed in DMSO without using the oxidant and additive (entry 5). Also, only a trace of the product **3a** was formed when the reaction was carried out without using solvent (entry 7). When the reaction time was reduced from 12 h to 6 h, just a marginal decrease in the yield of the product was noticed (entry 6). Taking into cognizance the intrinsic green credentials of water as solvent, the reaction was subsequently carried out in water, which delightedly led to the formation of the product in considerably high yield (77%, entry 8). When $K_2S_2O_8$ was changed to TBHP or AIBN as oxidant, the desired product was not formed at all (entries 9 & 10). The use of I_2/TBHP and TBAI/TBHP combinations was also helpless, as the product yields remained much poor (entries 11-13). The application of an ionic liquid as catalyst in the reaction was also futile (entry 14).

After establishing the optimized conditions, the scope and versatility of the reaction was studied in detail using different isoquinolines and keto acids. The outcome is summarized in **Scheme 2**. Arylglyoxylic acids containing para substituents like methyl, chloro and methoxy underwent the reaction smoothly with isoquinoline affording the products **3d**, **3e** and **3f** in good yields. Amusingly the reaction of sterically hindered mesitylglyoxylic acid **2b** with isoquinoline gave rise to a fairly high yield (**3b**, 74%).

Table 1. Optimization of reaction conditions



1a **2a** **3a**

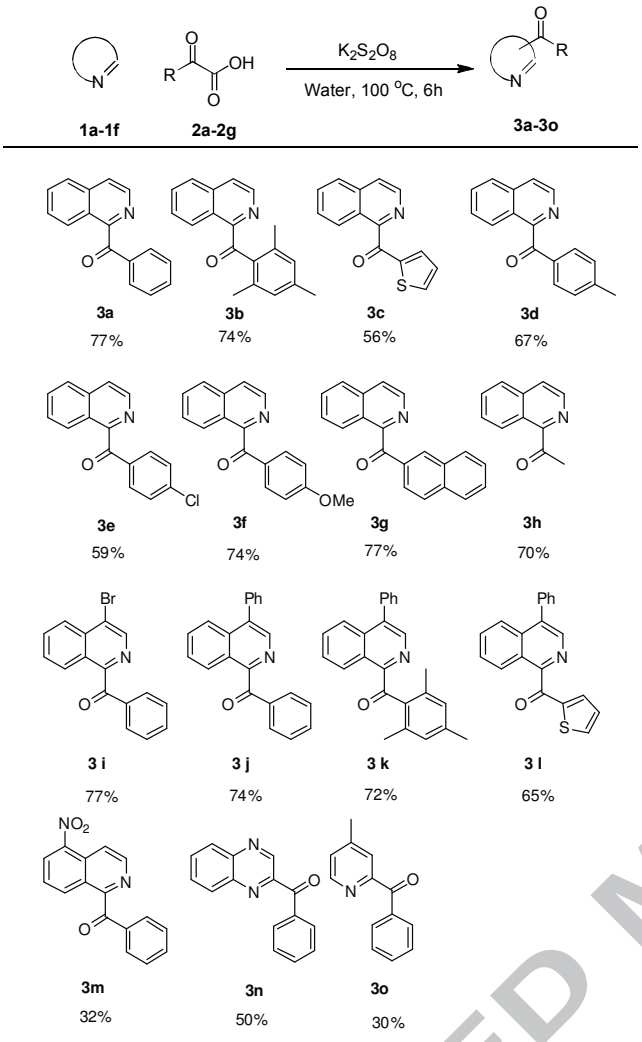
Entry	Oxidant	Additive	Solvent	*t* [h]	Yield [%][a]
1	$K_2S_2O_8$ (3 eq.)	TFA	CH_3CN	12	N. R.[b]
2	$K_2S_2O_8$ (3 eq.)	TFA	CH_3CN	12	56
3	$K_2S_2O_8$ (3 eq.)	TFA	DMSO	12	68
4	**$K_2S_2O_8$ (3 eq.)**		**DMSO**	**12**	**70**
5			DMSO	12	N. R.
6	$K_2S_2O_8$ (3 eq.)		DMSO	6	68
7	$K_2S_2O_8$ (3 eq.)			6	trace
8	**$K_2S_2O_8$ (3 eq.)**		**H_2O**	**6**	**77**
					56[c]
					74[d]
9	TBHP (3 eq.)		H_2O	6	N. R.
10	AIBN (3 eq.)		H_2O	6	N. R.
11	I_2/TBHP		H_2O	6	38
12	I_2/TBHP		DMSO	12	35
13	TBAI/TBHP		H_2O	12	30
14	$BMIM(BF)_4$		H_2O	6	N. R.

Reaction Conditions: **1a** (0.5 mmol), **2a** (1.25 mmol), oxidant (1.5 mmol), solvent (2 mL), 100 °C.
[a]Yields refer to isolated product.
[b]Reaction at room temperature.
[c]Reaction at 80 °C.
[d]Reaction at 120 °C.

When use was made of a heteroaromatic keto acid **2c**, somewhat lower product yield was observed (**3c**, 56%). Reaction of 2-(naphthalene-2-yl)-2-oxoacetic acid (**2g**) under similar conditions was also quite successful (**3g**, 77%). To check the behaviour of aliphatic keto acid under standard conditions, the reaction of pyruvic acid **2h** with **1a** was also undertaken, which afforded the product **3h** in 70% yield. Our next move was to study the scope of isoquinolines and other *N*-heterocycles, which reacted smoothly under the optimized reaction conditions. 4-Bromoisoquinoline (**1b**) gave rise to the product **3i** in 77% yield. Likewise, 4-phenyl isoquinoline (**1c**) reacted smoothly with different keto acids providing fairly high yield of the products **3j** (74%), **3k** (72%) and **3l** (65%). Nitro group of the 5-nitroisoquinoline (**1d**) was well tolerated during the course of the reaction, although with a relatively lower product yield (**3m**, 32%). When the reaction was extended to quinoxaline (**1e**), it provided mono acylated product **3n** in 50% yield; whereas 4-picoline (**1f**) gave rise to the mono acylated product **3o** in 30% yield. In order to study the behaviour of 1-substituted isoquinolines, the reaction of a mono acylated compound **3h** was carried out in the presence of pyruvic acid **2h** under the optimized conditions, but no further acylation was observed in this case.

To look into the insights of the mechanism, a typical reaction of **1a** with **2a** was carried out in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO, 1 equiv), which completely suppressed the formation of **3a**, thereby revealing the involvement of a radical pathway. Based on this observation, isolation of products and existing knowledge,[11] a plausible mechanism is outlined in **Fig. 2**.

In conclusion, an efficient method for acylation of isoquinolines has been developed using α-ketoacids without using metal and additive in water. The generality of the reaction is demonstrated by using different keto acids and isoquinolines; and is extendable to some other N-heterocycles. The methodology is endowed with an easy isolation of products and avoids the formation of oxidation by-products.



Reaction Conditions: *N*-Heterocycle **1** (0.5 mmol), keto acid **2** (1.25 mmol), $K_2S_2O_8$ (1.5 mmol), H_2O (2 mL), 100 °C, 6h. Yields refer to isolated products after column chromatography.

Scheme 2. Scope of the reaction

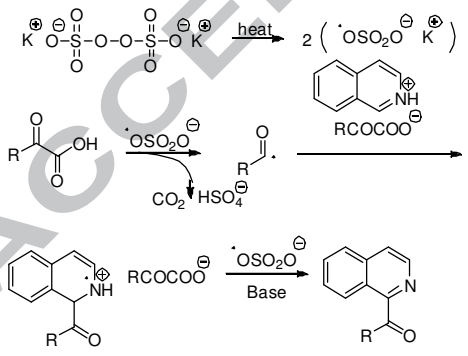


Fig. 2. Plausible reaction mechanism

Characterization data of new compounds:

Isoquinolin-1-yl(mesityl)methanone (3b). Thick yellow gum, IR (KBr) 3055, 2920, 2854, 1670, 1609, 1242, 913, 821, 756 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.03 (m, 1 H), 8.53 (d, *J* = 5.5 Hz, 1 H), 7.88 (m, 1 H), 7.74 (m, 3 H), 6.89 (s, 2 H), 2.31 (s, 3 H), 2.12 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 154.1, 141.7, 138.9, 138.4, 137.0, 134.9, 130.3, 129.1, 128.5, 127.1, 126.4, 126.1, 124.1, 21.2, 19.7. HRMS: Calcd for $C_{19}H_{17}NO$ (M^+ + H) 276.1310; Found 276.1402.

Isoquinolin-1-yl(thiophen-2yl)methanone (3c). Brown viscous oil; IR (KBr) 3058, 2926, 2854, 1642, 1410, 1384, 1352, 1248, 776 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 8.54 (d, *J* = 5.5 Hz, 1 H), 8.47 (d, J = 8.5 Hz, 1 H), 7.82 (m, 2 H), 7.74 (d, *J* = 6 Hz, 1 H), 7.66 (m, 2 H), 7.57 (m, 1 H), 7.07 (t, *J* = 5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) 186.1, 154.6, 142.6, 140.8, 136.9, 136.6, 136.1, 130.7, 128.6, 128.1, 127.1, 126.4, 126.2, 123.5. HRMS: Calcd for $C_{14}H_9NOS$ (M^+ + H) 240.0405; Found 240.0465.

Mesityl(4-phenylisoquinolin-1-yl)methanone (3k). Thick yellow gum; IR (KBr) 2919, 1678, 1611, 1239, 846, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) 9.05 (d, *J* = 8.5 Hz, 1 H), 8.42 (s, 1 H), 7.91 (d, *J* = 8 Hz, 1 H), 7.66 (m, 2 H), 7.43 (m, 5 H), 6.83 (s, 2 H), 2.24 (s, 3 H), 2.09 (s, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$) 202.4, 153.4, 141.8, 139.1, 138.6, 136.9, 136.8, 135.5, 135.0, 130.6, 130.2, 129.1, 128.8, 128.7, 128.5, 126.8, 126.2, 125.6, 21.4, 20.0. HRMS: Calcd for $C_{25}H_{21}NO$ (M^+ + H) 352.1623; Found 352.1723.

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Highlights:

- Our methodology is free from the use of metals and additives.
- Use of water as an environmentally benign medium.
- Our protocol avoids the formation of oxidation by-products and is endowed with an easy isolation of products.