Mendeleev Communications

Mendeleev Commun., 2025, **35**, 530–532

One-pot synthesis of acetyl(iso)quinolines/pyridines employing the sodium-promoted Claisen condensation of the corresponding carboxylates

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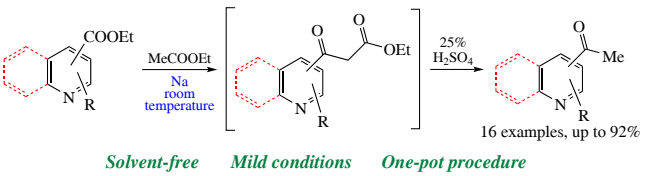
DOI: 10.71267/mencom.7748

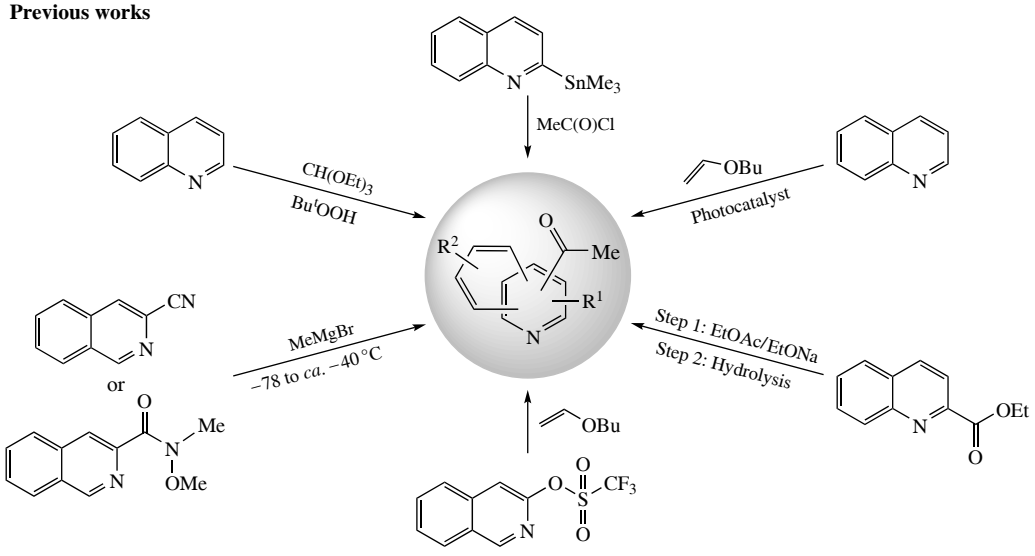
A convenient one-pot synthesis of acetylated quinolines/isoquinolines/pyridines involves the sodium-promoted Claisen condensation of the corresponding ethyl hetarenecarboxylates with ethyl acetate as the reactant and the solvent. The thus formed intermediate ethyl 3-hetaryl-3-oxopropanoates can be decarboxylated in the same reactor by refluxing with 25% H_2SO_4 to afford the title products in good to excellent yields.



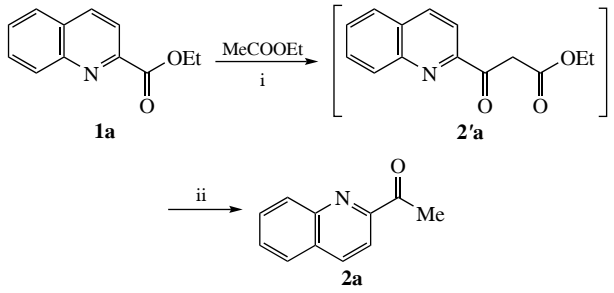
Keywords: acetylquinolines, acetylisoquinolines, acetylpyridines, acetylation, Claisen condensation, one-pot synthesis, solvent-free process.

Acetylquinoline and acetylisoquinoline scaffolds are frequently utilized in pharmaceutical molecules.[1–3] Introducing an acetyl group to the (iso)quinoline ring can result in various pharmacological activities, such as antibacterial,[4,5] anti-inflammatory,[6,7] and neuroregulatory effects.[8] In particular, it can significantly impact tumor cell growth and proliferation in certain cases, thereby highlighting its potential as a promising antitumor agent.[9–12]

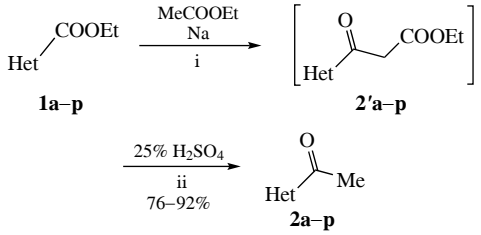
In recent years, the methods for the acetylation of (iso)-quinolines were documented as follows (Scheme 1). (i) Trimethylstannylquinolines were reacted with acetyl chloride according to the Friedel–Crafts acylation technique.[13] (ii) Iron-catalyzed reaction of quinoline with triethyl orthoformate was performed in the presence of *tert*-butyl hydroperoxide.[14] (iii) 3-Cyanoiso-quinoline or *N*-methoxy-*N*-methylisoquinoline-3-carboxamide were reacted with the Grignard reagents.[15,16] (iv) Isoquinolin-3-yl triflate was subjected to palladium-catalyzed C–C cross-coupling reactions.[17,18] (v) Ethyl quinoline-3-carboxylate was involved in the reaction with dry ethyl acetate in the presence of sodium ethoxide *via* the high-temperature Claisen condensation to afford ethyl 3-quinolinyl-3-oxo-propanoate,[19] which was then hydrolyzed to yield the target product. (vi) Quinolines were reacted with vinyl ethers on treatment with $Na_2S_2O_8$ and 3.0 equiv. of trifluoroacetic acid.[20]



Scheme 1



Scheme 2 *Reagents and conditions (for optimization, see Table 1)*: i, base, solvent, temperature T, reaction time t_1 = 4–5 h; ii, acid or base (aq.), reflux, reaction time t_2 = 3–5 h, then 30% NaOH.



a Het = quinolin-2-yl
b Het = quinolin-3-yl
c Het = quinolin-4-yl
d Het = quinolin-5-yl
e Het = quinolin-6-yl
f Het = quinolin-7-yl
g Het = quinolin-8-yl
h Het = 2-methylquinolin-6-yl
i Het = isoquinolin-1-yl
j Het = isoquinolin-3-yl
k Het = isoquinolin-4-yl
l Het = pyridin-2-yl
m Het = pyridin-3-yl
n Het = pyridin-4-yl
o Het = 2-chloropyridin-4-yl
p Het = 2-cyanopyridin-4-yl

Scheme 3 *Reagents and optimized conditions*: i, **1a**–**p** (5.0 mmol), EtOAc (2.0 equiv.), Na metal (1.2 equiv.), under air, room temperature, 4 h; ii, 25% H_2SO_4, reflux, 3 h. For product **2a**, 50 mmol scale yield was 92%.

These literary sources often suffer from the need for highly scarce substrates and expensive catalysts, serious pollution, difficult separation, hash conditions, and long-time response. Among them, the protocol starting with ethyl quinoline-3-carboxylate showed superior potency compared to the others owing to its cost-effectiveness and streamlined operation. However, when reproducing it we encountered the following drawbacks: sodium ethoxide usually necessitates fresh preparation, the condensation reaction mandates toluene and benzene as inert solvents, in addition to a lengthy reaction cycle involving multiple steps. Herein, we report an improved protocol for the synthesis of acetylated quinolines and some related derivatives by the Claisen condensation and hydrolysis/decarboxylation performed in a 'one-pot' manner (Schemes 2 and 3).[†] Although the cases when sodium metal was utilized in the Claisen ester condensation are not unknown, to this day the preparation of acetylquinolines in this way remains unreported.

Table 1 Optimization of the Claisen condensation and hydrolysis steps in the preparation of 2-acetylquinoline **2a** from ethyl quinoline-2-carboxylate **1a**.[a]

Entry	Base	Solvent	T/°C	t_1/h	Acid/base	Yield of **2a** (%)[b]
1	EtONa	Toluene	110	5	30% HCl	49
2	Bu^{t}OK	Toluene	110	5	30% HCl	33
3	NaH	Toluene	40	5	30% HCl	52
4	Na	Toluene	110	5	30% HCl	67
5	IMNa	Toluene	110	5	30% HCl	40
6	Na	Toluene	110	5	30% HCl	75[c]
7	Na	THF	40	5	30% HCl	35
8	Na	1,4-Dioxane	80	5	30% HCl	54
9	Na	EtOAc	80	5	30% HCl	82 (83)[d]
10	Na	EtOAc	25	5	30% HCl	82[e]
11	Na	EtOAc	25	4	30% HCl	89[f]
12	Na	EtOAc	25	4	5% NaOH	77
13	Na	EtOAc	25	4	15% HCl	84
14	Na	EtOAc	25	4	50% H_2SO_4	78
15	Na	EtOAc	25	4	25% H_2SO_4	92 (92[g])

[a] *Conditions for the condensation*: **1a** (1.0 mmol), ethyl acetate (1.0 equiv. for entries 1–8, 2.0 equiv. for entries 10–15), base (1.0 equiv.), solvent (5 ml for entries 1–9), argon, t_1 = 4–5 h. *Conditions for the hydrolysis*: **2′a** (1.0 mmol), acid/base (3 ml), reflux, t_2 = 5 h. [b] Isolated yields. [c] With 1.2 equiv. of Na. [d] With 5 ml of EtOAc; case with 2.0 equiv. of EtOAc is in parentheses. [e] At room temperature, under air. [f] Condensation (4 h) and hydrolysis were performed in a one-pot manner. [g] Hydrolysis for 3 h.

We optimized the reaction conditions for the synthesis of acetylquinolines using toluene as the solvent. Initially, ethyl quinoline-2-carboxylate **1a** and ethyl acetate were selected as model substrates to optimize the condensation reaction conditions (see Scheme 2). A variety of bases, including sodium ethoxide,[21] potassium *tert*-butoxide,[22] sodium hydride,[23] sodium metal,[24] and sodium imidazolide,[25] were screened as promoters. Gas chromatography was employed to monitor the conversion of the starting material **1a** to the condensation product **2′a**, and the results revealed that sodium metal served as the most efficient reagent (Table 1, entries 1–5). The final hydrolysis/decarboxylation was performed routinely in the same reactor by reflux with 30% HCl followed by neutralization with NaOH thus leading to 2-acetylquinoline **2a**. Increasing the amount of sodium to 1.2 equiv. gave an improved yield (entry 6). Further investigation on the solvent effect revealed that among THF, 1,4-dioxane,[26] or ethyl acetate the latter was the most suitable solvent (entries 7–9). Reducing the amount of ethyl acetate to just 2.0 equiv. brought the procedure close to solvent-free conditions providing the 83% yield of **2a** (see entry 9). Notably, reacting at room temperature gave the desired product **2a** with a comparable yield (entry 10). Reducing the reaction time to 4 h provided even better yield (89%) of ketone **2a** (entry 11).

With the optimized condensation conditions established, we re-investigated the hydrolysis/decarboxylation step. Typically, acetylarenes are obtained *via* the 'ketone splitting' of aryl analogs of acetoacetates under dilute alkaline conditions. However, in this case, we found that acid hydrolysis could also effectively produce the desired ketone with a higher yield. Most probably, the basic quinoline moiety underwent protonation and the thus formed quinolinium salt was readily transferred into the aqueous phase, which was crucial for the efficient hydrolysis of the ester part. After conducting a comprehensive acid concentration screening, it was determined that a 25% dilute sulfuric acid solution exhibited the highest efficiency as a hydrolysis reagent (see Table 1, entries 12–15). Lastly, it was revealed that the hydrolysis step could be shortened to 3 h (see entry 15).

[†] *General procedure for the synthesis of* **2**. To a 25 ml flask equipped with a mechanical agitator and condenser, compound **1** (5.0 mmol) and dry ethyl acetate (0.89 g, 10.0 mmol) were added. Sliced sodium metal (0.14 g, 6.0 mmol) was carefully introduced into the flask. A noticeable rise in temperature was observed, after which the reaction mixture was allowed to cool naturally to room temperature, and this was stirred for 4 h. Once the reaction was complete (TLC control), absolute ethanol (0.1 ml) was added, and stirring was continued for additional 10 min. Subsequently, 25% sulfuric acid (3 ml) was added to the reaction flask, and the mixture was heated to reflux for 3 h. After cooling, the volatiles were evaporated under reduced pressure. The residue was treated with water (1 ml), and the pH was adjusted to 8–9 using a 30% sodium hydroxide solution. The aqueous layer was extracted with ethyl acetate (3 × 2 ml), and the combined organic phases were dried over anhydrous sodium sulfate. After the solvent removal under reduced pressure, the crude residue was purified by column chromatography to afford the desired product **2**.

Based on the optimized condensation and hydrolysis conditions, a novel protocol for a number of hetarycarboxylates was developed (see Scheme 3). Acetylated quinoline derivatives **2a**–**h** were synthesized *via* the sodium-promoted Claisen condensation under mild, solvent-free conditions, followed by a hydrolysis reaction, enabling a one-pot synthesis. To further expand this protocol toward isoquinolines, three derivatives **2i**–**k** were synthesized under optimized conditions achieving good yields ranging from 76 to 88%. Additionally, ethyl pyridinecarboxylates **1l**–**n** were transformed into the corresponding acetylpyridines **2l**–**n** in yields of 82–92%. Importantly, chlorine and cyano substituents in substrates **1o**,**p** tolerated the procedure conditions, and ketones **2o**,**p** were obtained with good (79–80%) yields.

To assess the potential of this process in industrial production, we carried out a 50 mmol scale reaction using ethyl quinoline-2-carboxylate **1a**. Under the optimized conditions, the desired product **2a** was obtained in 92% yield after crystallization of the crude material from 95% ethanol.

In summary, we have developed a sodium-mediated Claisen condensation followed by a hydrolysis method for the preparation of acetylated (iso)quinolines and pyridines, utilizing ethyl (iso)-quinolinecarboxylates or ethyl pyridinecarboxylates as the starting materials. In this one-pot procedure, room temperature and solvent-free conditions at the first step are advantageous. Ongoing work in our laboratory focuses on further functionalization of (iso)quinolines.

This project was financially supported by the Research Fund of Changzhou Vocational Institute of Engineering.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.71267/mencom.7748.

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Received: 17th February 2025; Com. 25/7748