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Laichun Luo, Zongbao Zhou, Jiayi Zhu, Xue Lu, Hong Wang

PII: S0040-4039(16)31270-9
DOI: http://dx.doi.org/10.1016/j.tetlet.2016.09.087
Reference: TETL 48157

To appear in: *Tetrahedron Letters*

Received Date: 4 August 2016
Revised Date: 25 September 2016
Accepted Date: 27 September 2016

Please cite this article as: Luo, L., Zhou, Z., Zhu, J., Lu, X., Wang, H., $ZnCl_2$-promoted Friedländer-type synthesis of 4-substituted 3-aroyl quinolines from o-aminoaryl ketones and enaminones, *Tetrahedron Letters* (2016), doi: http://dx.doi.org/10.1016/j.tetlet.2016.09.087

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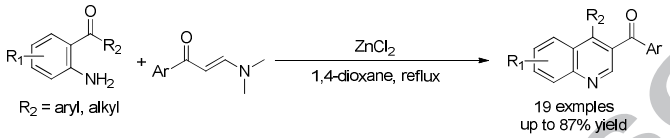

Tetrahedron Letters
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College of Pharmacy, Hubei University of Chinese Medicine, Wuhan 430065, China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Quinoline
o-Aminoaryl ketone
Enaminone
$ZnCl_2$
Friedländer reaction

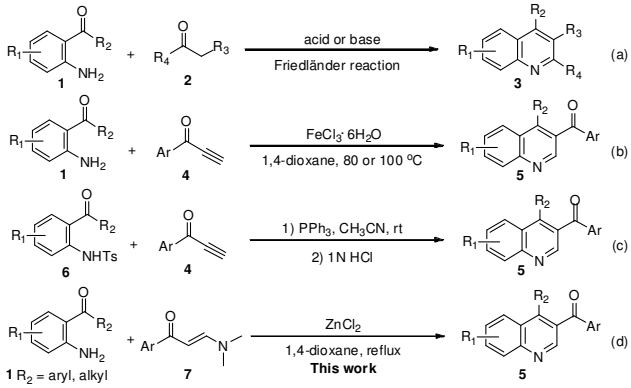
ABSTRACT

A practical synthesis of 4-substituted 3-aroyl quinolines via Friedländer-type reaction from readily available o-aminoaryl ketones and enaminones was developed. In the presence of $ZnCl_2$, the reaction proceeded smoothly affording the desired products with various functional groups in moderated to good yields.

1. Introduction

Quinoline scaffold is prevalent in various natural and synthetic products, including several important clinically used drugs and pharmaceutical candidates.[1–6] Due to their important applications, a variety of synthetic methods have been developed to construct quinolines over the past decades.[6–12] Among them, the classic Friedländer synthesis represents one of the most widely used methods, which involves the reaction of o-aminoaryl aldehyde/ketone **1** with a carbonyl compound **2** containing a reactive α-methylene group (Scheme 1a).[12] Recently, modified Friedländer reactions and related cascade reactions of **1** with various other substrates, such as alkynes,[13–16] alkenes,[17] alkenyl iodides,[18] alcohols,[19] α-enolic dithioesters,[20] α-oxoketene dithioacetals,[21] and 3-amino acrylontrile,[22] were intensively explored, which provided efficient approaches to qulinolines with structural diversity.

However, to the best of our knowledge, there is no report on the direct reaction of o-aminoaryl ketones **1** with enaminone **7**,[23] a versatile and readily obtainable reagent for heterocyclic synthesis.[23–30] We envisioned that a Friedländer-type reaction would occur, affording 4-substituted 3-aroyl quinoline **5**. Although compound **5** was successfully achieved via an iron-catalyzed cascade Michael addition–cyclization of **1** (R_2 = CH_3, Ph) with ynone **4** by Li et al. previously (Scheme 1b),[16] this protocol had some drawbacks, such as the requirement of 2 equiv of substrates **1**, long reaction times, and moderate yields. In 2012, Khong and Kwon reported a mild one-pot PPh_3-catalyzed synthesis of quinolines from o-tosylamidophenones **6** (R_2 = CH_3, Ph) and substrates **4** (Scheme 1c).[31] However, tosylation was required to prepare substrates **6** from corresponding o-aminoaryl ketones **1** beforehand. Besides, compound **5** was also synthesized from substituted quinolines through 1,4-addition/oxidation,[32] Palladium-catalyzed 1,2-addition/oxidation,[33] or Suzuki coupling.[34] Despite the presence of these established methods, practical, direct and more efficient synthetic route to 4-substituted 3-aroyl quinolines from simple and readily available starting material is still in demand.



Scheme 1. Synthesis of substituted quinolines.

As part of our continuing interest in the synthesis of fused-pyridines,[35] herein we reported a $ZnCl_2$ promoted Friedländer-type synthesis of 4-substituted 3-aroyl quinolines **5** from o-aminoaryl ketones **1** (R_2= aryl, alkyl) and enaminons **7** (Scheme 1d).

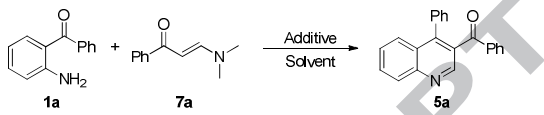
* Corresponding author. Tel.: +86-027-68890101; fax: +86-027-68890113; e-mail: laichunluo@163.com

2. Results and discussion

Initially, we chose 2-aminobenzophenone **1a** and enaminone **7a** as the model substrates to optimize the reaction conditions (Table 1). Attempts with common acidic (1.0 equiv of concentrated sulfuric acid in ethanol) or basic conditions (1.0 equiv of KOH in ethanol) under reflux failed to yield the quinoline product **5a** (Table 1, entries 1 and 2). Then $ZnCl_2$ was employed as an additive enlightened by our previous study.[35,36] In the presence of 1.0 equiv of $ZnCl_2$, the reaction of **1a** with **7a** in ethanol under reflux for 4 h gave the desired product **5a** in 24% yield (Table 1, entry 3). A solvent screen revealed that 1,4-dioxane was the optimal solvent (Table 1, entries 3–8), affording **5a** in 43% yield (Table 1, entry 8). Other Lewis acids, such as $FeCl_3.6H_2O$, CuCl, $ZnSO_4$, and $Zn(OAc)_2$, proved less effective (Table 1, entries 9–12). However, $Zn(OTf)_2$ was found more effective than $ZnCl_2$. In the presence of 1.0 equiv of $Zn(OTf)_2$, the reaction gave product **5a** in 78% yield (Table 1, entry 13). Unfortunately, the reaction did not work well with 0.5 equiv of $Zn(OTf)_2$ (Table 1, entry 14). Beacuse $ZnCl_2$ was more readily available and economically attractive, and it had a much lower molecular weight, it was still chose as optimal additive for this reaction instead of $Zn(OTf)_2$. When the amount of $ZnCl_2$ was increased, the yield was enhanced remarkably and the reaction time was also reduced (Table 1, entries 8, 15 and 16). And the best result was achieved in 81% yield with 3.0 equiv of $ZnCl_2$ (Table 1, entry 16).

With the optimal condition in hand, the reaction scope was subsequently explored (Table 2). A variety of enaminones **7b–h** bearing both electron-donating and electron-withdrawing groups reacted with **1a** smoothly, affording products **5b–k** in 62–87% yields (Table 2, entries 2–8). Enaminone with a naphthalen-1-yl (**7i**), naphthalen-2-yl (**7j**) or thiophen-2-yl (**7k**) substituent also furnished the corresponding products in moderate yields (Table 2, entries 9–11), although a longer reaction time was required for **7i** presumably due to the steric hindrance (Table 2, entries 9). Then the substrate scope of o-aminoaryl ketones **1** was examined. A series of substituted 2-aminobenzophenones **1b–f** were subjected to the reaction, and the corresponding products **5l–p** were obtained in 42–81% yields (Table 2, entries 12–16). Among them, substrate **1c** containing a strong electron-withdrawing nitro group appeared less reactive, but still afforded product **5m** in 42% yield after prolonged reaction time (Table 2, entry 13). Besides, 2- aminophenones bearing methyl (**1h**), sterically bulky isopropyl (**1i**) or cyclohexyl (**1j**) groups were successfully converted to 4-alkyl quinolines **5q-s** in 66–73% yields under the optimized conditions (Table 2, entries 17–19).

Table 1.
Optimization of reaction conditions[a]

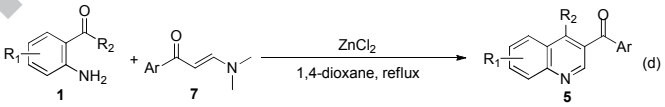


1a 7a 5a

Entry	Additive (equiv)	Solvent	Time (h)	Yield[b] (%)
1	H_2SO_4 (1.0)	C_2H_5OH	4	trace
2	KOH (1.0)	C_2H_5OH	4	0
3	$ZnCl_2$ (1.0)	C_2H_5OH	4	24
4	$ZnCl_2$ (1.0)	DMF	4	0[c]
5	$ZnCl_2$ (1.0)	DMSO	4	0[c]
6	$ZnCl_2$ (1.0)	CH_3CN	4	32
7	$ZnCl_2$ (1.0)	THF	4	27
8	$ZnCl_2$ (1.0)	1,4-dioxane	4	43
9	$FeCl_3·6H_2O$ (1.0)	1,4-dioxane	4	25
10	CuCl (1.0)	1,4-dioxane	4	18
11	$ZnSO_4$ (1.0)	1,4-dioxane	4	trace
12	$Zn(OAc)_2$ (1.0)	1,4-dioxane	4	0
13	$Zn(OTf)_2$ (1.0)	1,4-dioxane	4	78
14	$Zn(OTf)_2$ (0.5)	1,4-dioxane	4	35
15	$ZnCl_2$ (2.0)	1,4-dioxane	3	73
16	$ZnCl_2$ (3.0)	1,4-dioxane	2	81

[a] Reaction conditions: **1a** (5.0 mmol), **7a** (5.0 mmol), and an additive in refluxing solvent (5.0 mL).
[b] Isolated yields.
[c] Reaction occurred at 110 °C.

Table 2.
Synthesis of 4-substituted 3-aroyl quinolines **5** from o-aminoaryl ketones **1** and enaminones 7[a]



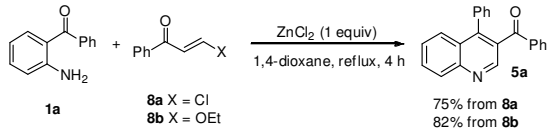
1 7 5

Entry	Substrate **1**	Substrate **2**	Time (h)	Product	Yield[b] (%)
1	**1a** R_1 = H, R_2 = Ph	**7a** Ar = Ph	2	**5a**	81
2	**1a**	**7b** Ar = 4-F-Ph	2	**5b**	75
3	**1a**	**7c** Ar = 4-Cl-Ph	2	**5c**	72
4	**1a**	**7d** Ar = 4-Br-Ph	2	**5d**	65
5	**1a**	**7e** Ar = 4-Me-Ph	2	**5e**	87
6	**1a**	**7f** Ar = 4-MeO-Ph	2	**5f**	82
7	**1a**	**7g** Ar = 4-NO_2-Ph	2	**5g**	62
8	**1a**	**7h** Ar = 3-Cl-Ph	2	**5h**	75
9	**1a**	**7i** Ar = naphthalen-1-yl	5	**5i**	60
10	**1a**	**7j** Ar = naphthalen-2-yl	3	**5j**	67
11	**1a**	**7k** Ar = thiophen-2-yl	2	**5k**	75

12	**1b** R_1 = 5-Cl, R_2 = Ph	**7a**	3	**5l**	63
13	**1c** R_1 = 5-NO_2, R_2 = Ph	**7a**	5	**5m**	42
14	**1d** R_1 = H, R_2 = 4-F-Ph	**7a**	2	**5n**	75
15	**1e** R_1 = H, R_2 = 4-Me-Ph	**7a**	2	**5o**	81
16	**1f** R_1 = H, R_2 = 4-MeO-Ph	**7a**	2	**5p**	80
17	**1g** R_1 = H, R_2 = Me	**7a**	3	**5q**	66
18	**1h** R_1 = H, R_2 = $CH(CH_3)_2$	**7a**	3	**5r**	73
19	**1i** R_1 = H, R_2 = Cyclohexyl	**7a**	3	**5s**	71

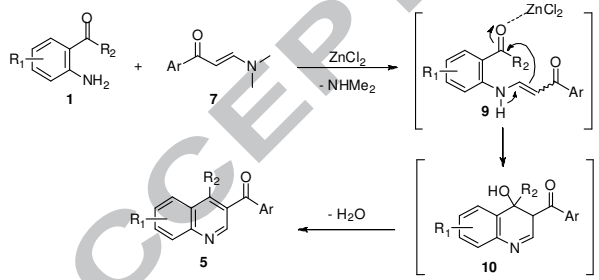
[a] Reaction conditions: **1** (5.0 mmol), **7** (5.0 mmol), and $ZnCl_2$ (15 mmol) in 1,4-dioxane (5.0 mL), reflux.
[b] Isolated yields.

Furthermore, the substrate scope was extended to enaminone analogues **8** bearing a chloro or ethoxy group.[37,38] In the presence of 1.0 equiv of $ZnCl_2$, the reaction of **1a** with **8a** or **8b** gave the expected product **5a** in 75% and 82%, respectively (Scheme 2). By contrast, more amount of $ZnCl_2$ was required for enaminone substrate **7a** to achieve a good yield of **5a** (Table 1, entries 15 and 16), which was probably due to the affinity of dimethylamine byproduct for $ZnCl_2$.[39]



Scheme 2. Synthesis of **5a** from enaminone analogues **8**.

According to the results and previous literatures, a plausible Friedländer-type mechanism for the reaction was proposed (Scheme 3). Initially, condensation of o-aminoaryl ketone **1** with enaminone **7** afforded the enamine intermediate **9** via a Michael addition/elimination process,[24,25] in which $ZnCl_2$ could serve a catalyst[40,41] and a Lewis acid to bind the dimethylamine byproduct. Subsequently, enamine **9** underwent a $ZnCl_2$-catalyzed intramolecular aldol reaction to give intermediate **10**.[21,35] Finally, the quinoline product **7** was formed by elimination of a water molecule. Secondary amine, quinoline and water could decrease the efficiency of $ZnCl_2$,[39] which could account for the fact that an excess amount of $ZnCl_2$ was beneficial for this reaction.



Scheme 3. Plausible reaction mechanism.

In summary, we have developed a $ZnCl_2$ promoted Friedländer-type reaction of o-aminoaryl ketones with enaminones. This cascade protocol provides an efficient and straightforward access to 4-substituted 3-aroyl quinolines in moderate to good yields from easily available starting materials, which may find practical applications in the synthesis and discovery of bioactive quinoline derivatives.

Acknowledgments

This work was supported by Doctoral Starting up Foundation of Hubei University of Chinese Medicine and Qingmiao Plan Project of Hubei University of Chinese Medicine.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/

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Highlights

1. Friedländer-type reaction of o-aminoaryl ketones with enaminones.
2. An efficient and straightforward approach to 4-substituted 3-aroyl quinolines.
3. Using $ZnCl_2$ as a cheap and effective additive.
4. Readily available starting materials, and short reaction times.