Tetrahedron Letters 53 (2012) 3237–3241

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A highly regioselective Friedländer reaction mediated by lanthanum chloride

Ying Chen *, Jinkun Huang *, Tsang-Lin Hwang, T.J. Li, Sheng Cui, Johann Chan, Matthew Bio

Chemical Process Research & Development, Amgen Inc., One Amgen Center Dr., Thousand Oaks, CA 91320, USA

ARTICLE INFO

Article history:
Received 16 February 2012
Revised 4 April 2012
Accepted 5 April 2012
Available online 25 April 2012

Keywords:
Friedländer reaction
Regioselective
Quinolines

ABSTRACT

A highly efficient and regioselective Friedländer reaction of unsymmetrical 1,3-diketones with 2-aminoaryl aldehydes (ketones) is described. The methodology leads to the synthesis of a broad scope of substituted quinolines in high yield and excellent regioselectivity.

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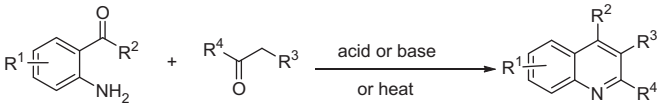
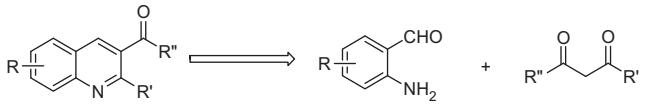
Quinoline and its derivatives are among the most important synthetic or natural heterocycles with interesting biological activities showing anti-malarial, anti-inflammatory, anti-bacterial, and anti-asthmatic properties.[1] As a result, the quinoline scaffolds have spurred the development of a great deal of synthetic methodologies. Among those variations, the Friedländer reaction[2] is one of the simplest, straightforward, and most widely used approaches.[3] This classical method condenses 1 equiv of 2-aminoaromatic carbonyl compound with 1 equiv of carbonyl species bearing a reactive methylene group to provide the quinoline product and formation of 2 equiv of water (Scheme 1). The reaction is typically carried out in the presence of an acid or base, or otherwise harsh conditions are required.

As part of our continuing efforts toward the development of efficient syntheses of quinolines,[4] we were interested in the regio-selective synthesis of 2-substituted-3-acylquinolines. However, practical and general approaches to this type of substituted quinolines are rare in the literature. Conceivably, the desired substituted quinoline could be synthesized from Friedländer condensation as shown in Scheme 2. Recently Lewis acids such as $ZnCl_2$, $FeCl_3$, $Sc(OTf)_3$, and $Nd(NO_3)_3{\cdot}6H_2O$ have been shown to be effective on Friedländer reaction for the substituted quinoline synthesis under mild conditions but without discussion of regioselectivity issues.[5] Although the attractive Friedländer reaction has the potential to form highly substituted quinolines, limited attention has been paid to specifically address the regio-selectivity issue of the resulting products.[6] In 2007, Masciadri and coworkers reported a gold-catalyzed Friedländer condensation of 2-aminoaryl ketone with 1,3-diones to form substituted quinolines.[7] However the reaction was not general and typically gave low to moderate yields even under forcing conditions. To overcome the problems with the current art such as harsh conditions, limited scope, and poor selectivity, herein, we report our development of a mild, efficient, and regio-selective synthesis of substituted quinolines via lanthanum chloride—mediated Friedländer reaction.

Synthesis of 3-(2-methylquinolinyl) phenyl ketone **3a** was our initial target. As shown in Scheme 3, the Friedländer annulation of 2-aminobenzaldehyde **1a** with 1-phenylbutane 1,3-dione **2a** may provide the most straightforward synthesis of **3a**. Under typical Friedländer conditions in a variety of solvents and under different temperatures, the best conditions (Table 1, entry 1) gave modest yield (43%) and low selectivity (**3a**/**4a** = 64:36) of the desired compound. We envisioned that Lewis acids, which have been shown effective in many carbonyl-related organic transformations, might lead to a different reaction profile in terms of reactivity and selectivity.[8] A broad scope of Lewis acids and conditions was



Scheme 1. General scheme of Friedländer reaction.



Scheme 2. Retrosynthetic analysis of 2-substituted-3-acylquinoline.

* Corresponding authors.
E-mail addresses: Ying@amgen.com (Y. Chen), jhuang@amgen.com (J. Huang).

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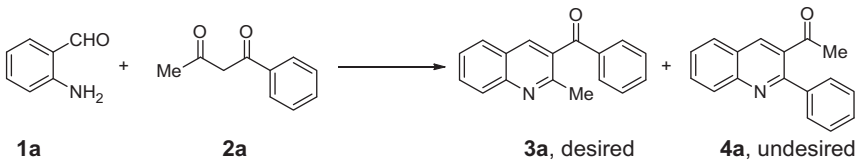
http://dx.doi.org/10.1016/j.tetlet.2012.04.038



Scheme 3. Model reaction.

Table 1
Lewis acid screening[a]

Entry	Lewis Acid	Yield[b] (**3a**, %)	Ratio **3a**/**4a**[c]
1	None	43	64/36
2	$Ca(OTf)_2$	63	78/22
3	$Sm(OTf)_3$	57	76/24
4	$Dy(OTf)_3$	44	72/28
5	$Ba(OTf)_2$	52	64/36
6	$Er(OTf)_3$	31	76/24
7	$La(OTf)_3$	52	73/27
8	$Yb(OTf)_3$	66	79/21
9	$DyCl_3$	44	81/19
10	$ZnCl_2$	61	83/17
11	$ErCl_3$	80	79/21
12	$CoCl_2$	30	89/11
13	$CeCl_3$	64	85/15
14	$LaCl_3$	60	86/14
15	$LaCl_3{\cdot}7H_2O$	85	86/14
16[d]	None	Trace	n/d

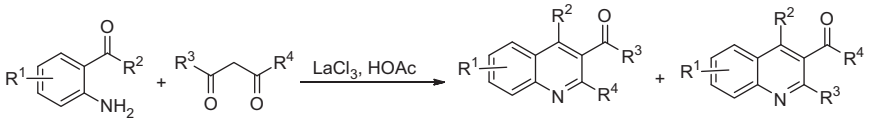
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), and additive (0.2 mmol) were mixed in 0.4 mL acetic acid and heated to 60 °C for 18 h. The resulting mixture was analyzed by HPLC.
[b] Yield was determined by HPLC with standard calibration of the pure sample.
[c] The ratio was determined by HPLC using both isomers as standard.
[d] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), and KOH (0.24 mmol) were mixed in 0.4 mL ethanol and heated to 60 °C for 26 h. The resulting mixture was analyzed by HPLC.

screened for the desired transformation. Based on the initial results, we further narrowed the screening to the more promising metal salts of the secondary group and lanthanum series in the periodic table. Our initial attempt with $Ca(OTf)_2$ improved the selectivity from 64/36–78/22, however the yield was not satisfactory (63%, Table 1, entry 2). To our delight, further screening indicated that lanthanum chloride was among the best to increase the reaction yield as well as the selectivity (Table 1, entry 14). It is well known that lanthanum salts enhance the reactivity and selectivity of many types of reactions, such as reduction, carbon–carbon bond formation, aldol condensation, cycloaddition, ring-opening, and polymerization.[9] To the best of our knowledge, a lanthanum salt mediated Friedländer has not been previously reported. In this case, the readily available, inexpensive, and non-hygroscopic $LaCl_3$ hydrate gave high selectivity and good yield of desired **3a** (Table 1, entry 15).[10] Other Lewis acids tested either gave less selectivity or much lower yield al beit higher selectivity in one case (Table 1, entry 12). Alternatively, the basic conditions[5a] essentially gave no product (Table 1, entry 16).

The reaction was further optimized by examining the amount of $LaCl_3$,[11] solvents,[12] and reaction temperature.[13] The optimal reaction was performed in acetic acid in the presence of lanthanum chloride heptahydrate (1.0 equiv) at 60 °C for 3–5 h.[14]

With the optimal conditions in hand, we extended the reaction scope to a variety of unsymmetrical 1,3-diketones with different

Table 2
Scope of 2-aminobenzaldehyde (or ketone)



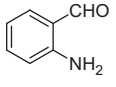
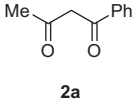
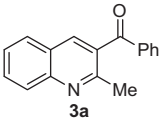
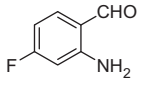
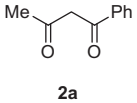
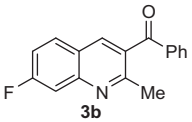
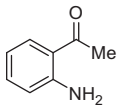
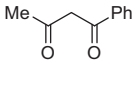
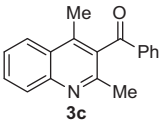
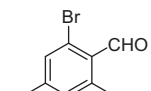
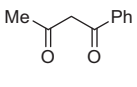
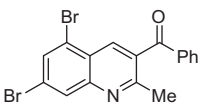
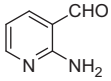
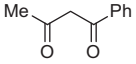
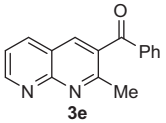
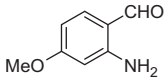
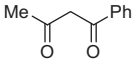
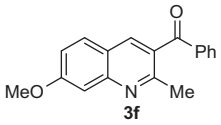
Entry	Aniline	1,3-Diketone	Major isomer	Yield[a] (%)	Selectivity major/minor[b]
1	 **1a**	 **2a**	 **3a**	72	86/14
2	 **1b**	 **2a**	 **3b**	70	86/14
3	 **1c**	 **2a**	 **3c**	68	91/9
4	 **1d**	 **2a**	 **3d**	62	93/7

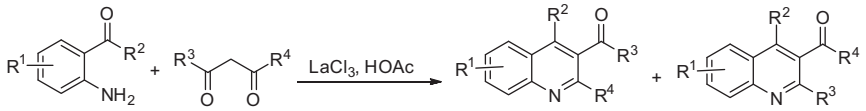
Table 2 (*continued*)

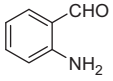
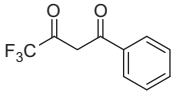
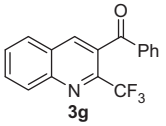
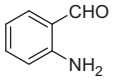
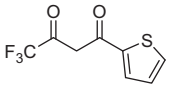
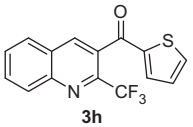
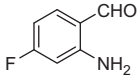
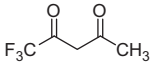
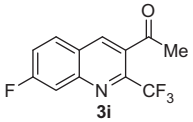
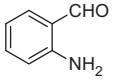
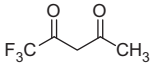
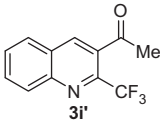
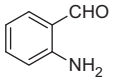
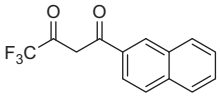
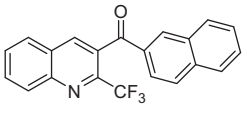
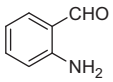
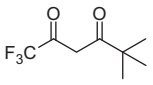
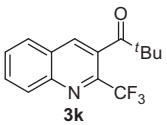
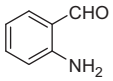
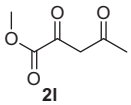
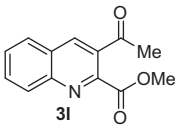
Entry	Aniline	1,3-Diketone	Major isomer	Yield[a] (%)	Selectivity major/minor[b]
5	 **1e**	 **2a**	 **3e**	90	94/6
6	 **1f**	 **2a**	 **3f**	69	100/0

[a] Yield of isolated major isomer.
[b] Ratio determined by NMR of the crude mixture after workup.

types of 2-aminobenzaldehydes (or ketone). As shown in Table 2, the reaction of 1-phenylbutane 1,3-dione with several substituted 2-aminobenzaldehydes (Table 2, entries 2 and 4) worked as well as the parent substrate (Table 2, entry 1). The ketone was found to be an excellent substrate in this condensation to give 2,3,4-substitued quinoline in appreciable yield (Table 2, entry 3). The 2-aminonicotinaldehyde showed superior selectivity (Table 2, entry 5) to give the corresponding azaquinoline in an excellent isolated yield of

Table 3
Electronic effect of 1,3-diketones



Entry	Aniline	1,3-Diketone	Major isomer	Yield[a] (%)	Selectivity major/minor[b]
1	 **1a**	 **2g**	 **3g**	81	100/0
2	 **1a**	 **2h**	 **3h**	83	100/0
3	 **1b**	 **2i**	 **3i**	80	89/11
3′	 **1a**	 **2i**	 **3i'**	77	90/10
4	 **1a**	 **2j**	 **3j**	85	100/0
5	 **1a**	 **2k**	 **3k**	78	100/0
6	 **1a**	 **2l**	 **3l**	85	96/4

[a] Yield of isolated major isomer.
[b] Ratio determined by NMR of the crude mixture after workup.

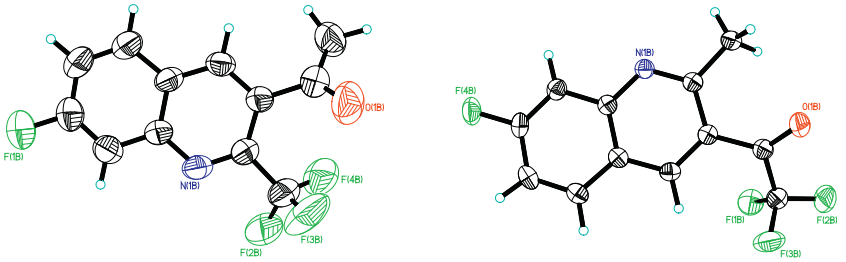
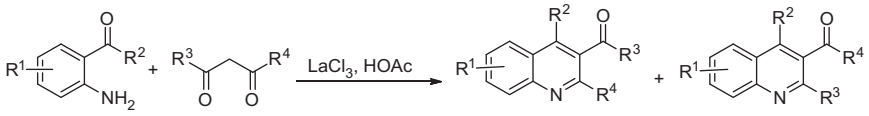
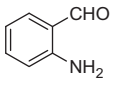
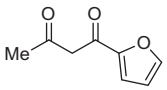
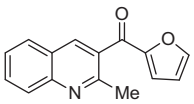
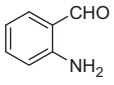
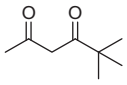
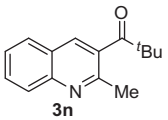
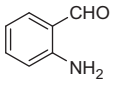
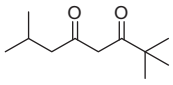
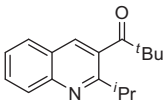
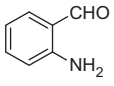
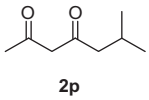
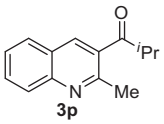


Figure 1. The X-ray structure of **3i** and **4i**.

Table 4
Steric effect of 1,3-diketones



Entry	Aldehyde	1,3-Diketone	Major isomer	Yield[a] (%)	Selectivity major/minor[b]
1	 **1a**	 **2m**	 **3m**	85	96/4
2	 **1a**	 **2n**	 **3n**	81	100/0
3	 **1a**	 **2o**	 **3o**	72	80/20
4	 **1a**	 **2p**	 **3p**	85	93/7

[a] Yield of isolated major isomer.
[b] Ratio determined by NMR of the crude mixture after workup.

the product. Electron-rich aminoaldehyde provided exclusively one isomer (Table 2, entry 6). The major products consistently showed the same substitution pattern as their parent compound in all cases.

Next, we turned our attention to the scope of unsymmetrical 1,3-diketones. Due to steric and electronic differences of the two ending substitution groups on 1,3-diketones, the product outcome would be difficult to predict. To differentiate the two carbonyl groups electronically, 1,3-diketone with an electron withdrawing group such as trifluoromethyl (CF_3) at one side was tested (Table 3). It is shown that the resulting major products share the same feature with the CF_3 directly attached to the quinoline ring (Table 3, entries 1–5).[15] It is clear that the electronic difference dominates the outcome of the selectivity as most of the reactions exclusively give one product (Table 3, entries 1, 2, 4, and 5). Even for the sterically similar CF_3 versus CH_3, the regioisomeric ratio is still as high as 89:11[16] and 90:10 (Table 3, entries 3 and 3′). Furthermore, in the case of entry 3, both of the regioisomers were isolated and structurally confirmed by NMR and X-ray diffraction analyses (Fig. 1, **3i,** and **4i**).

When trifluoromethyl group is replaced by carboxylic methyl ester, another electron withdrawing group, the regioselectivity reached 96/4 and the same selectivity trend holds true that the electronic withdrawing group (ester) is attached to the quinoline ring (Table 3, entry 6).

As electronic effect of the unsymmetrical 1,3-diketones was established in terms of regioselectivity, the steric effect was also examined. When the sterically unsymmetrical 1,3-diketones were used, in all the cases examined, the less hindered group tends to stay on the aromatic quinoline ring as the major products (Table 4). The larger the steric difference the better the regioselectivity is shown as comparing entry 2 (Me to *t*-butyl) versus entry 4 (*i*-Pr to *t*-Bu). When less steric difference is present, the selectivity declines (Table 4, entry 4).

Two different pathways are proposed for Friedländer reaction as generally recognized mechanisms. The first step is either an intermolecular Schiff base formation[17] or aldol condensation.[18] Both intermediates can then go through a ring-closing process to form the quinoline products. The origin of the regioselectivities of the current lanthanum chloride mediated Friedländer condensation

is not well understood. One rationale is that lanthanum chloride facilitated the Schiff base formation as the first step,[19] and the resulting Schiff base(s) dictate the outcome of the regioselectivity. Although the exact role of lanthanum chloride is not clear, this proposal explains both the electronic and steric effects of the 1,3-diketones on the selectivities: the nucleophilic amine favors to attack either the electron-poor or the sterically less hindered carbonyl group of the 1,3-diketone to form the corresponding enaminone as the major intermediate.[20]

In conclusion, we have developed a regioselective and efficient protocol for substituted quinolines based on the lanthanum chloride mediated Friedländer reaction. The Friedländer reaction between an unsymmetrical 1,3-diketone with the corresponding 2-carbonyl aniline gives high regioselective quinoline in moderate to excellent yields.[21] The protocol presented here is effective for a broad range of both substituted 2-carbonyl aniline and 1,3-diketones.

Acknowledgment

We thank Ms. Maosheng Chen (HPLC), Mr. Mike Ronk (HRMS), and Dr. Richard Staples (X-ray) for their analytical support.

References and notes

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11. Substoichiometric amount of $LaCl_3$ is effective to give comparable selectivity but leads to a slower reaction rate and a lower yield.
12. Other solvents tested such as THF, toluene, and acetonitrile were less effective as acetic acid.
13. The reaction can be run at room temperature but a longer reaction time is required.
14. *A typical experimental procedure.* To a reaction vial loaded with substituted 1,3-diketone (0.24 mmol), amino benzaldehyde, (0.2 mmol) and lanthanum chloride heptahydrate was added acetic acid (3.5 mL). The resulting suspension was heated to 60 °C for 3–5 h. The reaction progress was monitored by LC–MS. At the completion, the reaction mixture was allowed to cool to room temperature. Ethyl acetate (5 mL) was added and the resulting mixture was washed with water (5 mL) and 1 N NaOH (5 mL), the organic layer was dried on $MgSO_4$ and concentrated to give a crude product. The major quinoline product was isolated by column chromatography.
15. Interestingly, the selectivity observed is opposite to that reported for the gold-catalyzed Friedländer reaction results wherein the CF_3 was found exclusively on the carbonyl group in a slightly different setting (Ref. 6).
16. When no $LaCl_3$ was used, the reaction gave an overall yield of 52% (**3h**/**4h** = 54/46). The typical KOH/EtOH conditions gave only a trace amount of product as in the case of. Table 1, entry 16.
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19. Lanthanum chloride catalyzed enaminone formation was recently reported which may indirectly support this rationale: Lenin, R.; Raju, M. *ARKIVOC* **2007**, *viii*, 204.
20. Preliminary ^1H and ^{19}F NMR studies showed the imine formation when aniline and 1-trifluromethylbutane 1,3-dione was mixed with $LaCl_3{\cdot}7H_2O$ in CD_3CO_2D, although the ratio of the isomeric imines could not be determined. However, the ultimate mechanism is yet to be probed in more details.
21. The current protocol of Friedländer reaction was optimized and scaled up to synthesize a building block for our internal program.