Tetrahedron 67 (2011) 7090–7095

Contents lists available at ScienceDirect

Tetrahedron

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

A novel Friedlander-type synthesis of 3-aryl quinolines from 3-oxo-2,3-diaryl-propionaldehydes

Wanrong Luo [a], Qiuchao Mu [a], Wenwei Qiu [b], Ting Liu [a], Fan Yang [a], Xiaofeng Liu [c,*], Jie Tang [a,*]

[a] Institute of Drug Design and Development, East China Normal University, Shanghai 200062, China
[b] Department of Chemistry, East China Normal University, Shanghai 200062, China
[c] Reata Pharmaceuticals, Inc. 2801 Gateway Drive, Suite 150, Irving, TX 75063, USA

ARTICLE INFO

Article history:
Received 10 April 2011
Received in revised form 27 June 2011
Accepted 1 July 2011
Available online 6 July 2011

Keywords:
Novel Friedländer-type reaction
3-Aryl quinolines
Enaminone
3-oxo-2,3-diaryl-propionaldehydes

ABSTRACT

3-Aryl quinolines are readily synthesized by a novel Friedländer-type reaction with 3-oxo-2,3-diaryl-propionaldehydes and 2-amino arylaldehydes. A preliminary mechanism of this novel one pot, two-step synthesis has been explored with the proofs of isolation of the enaminone intermediate and the eliminated benzoic acid in this reaction.

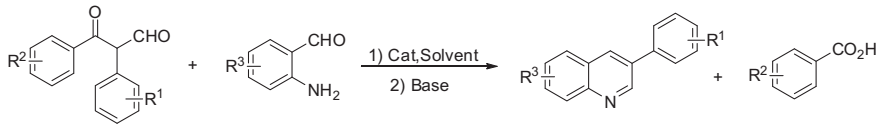
1. Introduction

Many quinoline containing compounds exhibit a wide variety of pharmacological and biological activities,[1] such as antiasthmatic,[2] anti-inflammatory,[3] anti-HIV-1[4] and tyrosine kinase inhibiting properties.[5] Therefore, exploration of efficient synthetic methods to construct quinoline framework has continually drawn great attentions for many decades. As a result, many quinoline syntheses, such as Combes, Skraup, Döbner–Von Miller, Conrad–Limpach, Pfitzinger, Friedländer and Povarov reactions, etc. have been developed.[6] However, many of these classic synthetic approaches suffer from limited source of precursors, harsh reaction conditions, low yields or selectivity. Hence, variant or modified approaches of these classic quinoline syntheses continue to emerge with significant improvements in terms of the synthetic feasibility. For instance, some modified Friedländer syntheses have been recently described, either catalyzed with organometal catalysts, such as ruthenium,[7] or without expensive transition metal catalysts.[8] By using these methods, 2-substituted or 2,3-substituted quinolines could be successfully synthesized in good yields.

In our recent work for preparation of biological active heterocycles, we expected to synthesize a series of 3-aryl substituted quinolines by the Friedländer approach. However, the less accessibility of aryl acetaldehydes combined with the instability of *o*-amino arylaldehydes under the reaction conditions indicated less feasible syntheses with unsatisfactory yields. These disadvantages urged us to seek a new, mild condition variation of the Friedländer synthesis with readily available precursors to achieve our target compounds. It is known that less reactive α-methylenecarbonyl counterparts (e.g., aryl acetaldehydes) usually require more drastic reaction conditions, therefore increase the self-condensation tendency of *o*-amino arylaldehydes and thus result in low yields. In light of this mechanism understanding, we envisaged that replacing the hydrogen with an electron-withdrawing group on the α-methylene position of aryl acetaldehydes could activate these reactants, thus milder reaction conditions could be employed to diminish the yield deterioration caused by *o*-amino arylaldehydes self-condensation. Importantly, this introduced auxiliary electron-withdrawing group should be readily eliminated under the same reaction conditions after fulfilling its mission. Herein, we describe a new Friedländer-type approach to synthesize 3-aryl quinolines starting from 3-oxo-2,3-diaryl-propionaldehydes, which could be obtained efficiently from chalcone epoxides.[9] The auxiliary acyl (substituted benzoyl) groups eliminate during the reactions to give the same products while the normal aryl acetaldehydes are used as precursors (Scheme 1). To the best of our knowledge, this novel modification of the Friedländer-type quinoline synthesis is the first report of its type.

* Corresponding authors. Tel.: +86 21 62232764; fax: +86 21 62232100; e-mail addresses: xiaofeng.liu@reatapharma.com (X. Liu), jtang@chem.ecnu.edu.cn (J. Tang).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.07.004



Scheme 1. Synthesis of 3-aryl quinolines.

2. Results and discussion

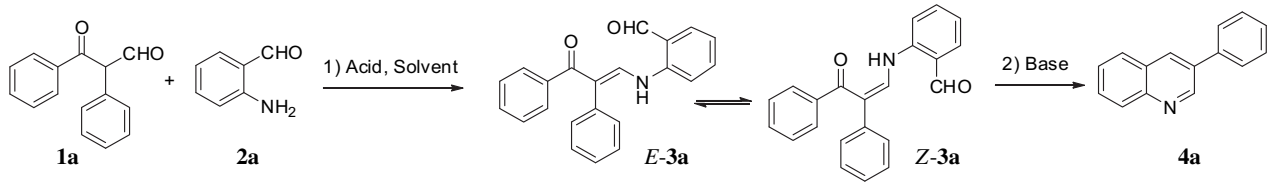
We started our investigation by subjecting our model substrates, 3-oxo-2,3-diphenylpropionaldehyde (**1a**) and *o*-amino benzylaldehyde (**2a**) to base-catalyzed Friedlander reaction conditions. Unfortunately, the reaction failed with messy results, and the self-condensation of **2a** was observed. Then, we turned our attention to the regular acid-catalyzed Friedländer conditions. Disappointingly, no quinoline product was obtained while either a Lewis acid $BF_3 \cdot Et_2O$ or a Brønsted acid TfOH was used as the catalyst (Table 1, entries 1 and 2). Instead, an enaminone intermediate **3a** (a mixture of *E*-, *Z*-isomers; *E*/*Z*=~7:3) was isolated and identified. However, while a base KO^{t}Bu was directly added to the reaction mixture containing the enaminone intermediate **3a**, the quinoline **4a** was formed rapidly in good yield in both cases (74% and 77%; Table 1, entries 3 and 4). Encouraged by these exciting results, we further explored the effects of various reaction parameters, such as acid catalysts (Table 1, entries 3–7), acid catalyst loading (Table 1, entries 4, 8 and 9), solvents (Table 1, entries 8 and 10–15), reaction temperature (Table 1, entries 8, 16 and 17) and bases (Table 1, entries 8 and 18–22). Under the optimized reaction (Table 1, entry 8), the quinoline **4a** was obtained in high yield (82%). Compared to the modest yields (31–53%)[10] achieved in classic Friedländer syntheses for the same product, this new protocol significantly improves the synthetic feasibility of 3-phenylquinoline **4a**.

Since one of the reactants, 3-oxo-2,3-diphenylpropionaldehyde (**1a**), is not a typical substrate for the classic Friedländer reaction, we speculated that an unusual reaction pathway could exist. Therefore, we are especially interested in understanding the mechanism of this novel Friedländer-type reaction and collecting the evidences to support our hypothesis. Thus, we subjected the isolated enaminone intermediate **3a** to the basic reaction condition. After work-up and purification, 3-phenylquinoline **4a** was obtained in 94% yield. In addition, benzoic acid **5** was also isolated as another product of the same reaction in 88% yield (Scheme 2).

The generality of this novel modification of the Friedländer synthesis has been investigated and the results are shown in Table 2. A series of condensation partners bearing substituents with various electronic (both electronic rich and deficient) properties at different (*ortho*-, *meta*- and *para*-) positions on the aromatic rings were subjected to this optimized reaction system and all afforded the 3-aryl quinolines **4** in good to high yields (Table 2).

In general, the variation of electronic properties of R^1 groups only has slight influence on yields although electron-donating substituents help to achieve relatively better yields than electron-withdrawing substituents do (Table 2, entries 1–7), and the methyl group, instead of phenyl group, substituted substrate 3-oxo-2-methyl-3-phenylpropionaldehyde also gave moderate yield (Table 2, entry 16). An exception was observed that thienyl group as R^1 caused a significant decreasing in yield (Table 2, entries 13),

Table 1
Optimization of reaction conditions for a novel Friedländer-type synthesis of 3-phenylquinolines[a]



Entry	Acid (mol %)	Solvent	Base	*T* (°C)	Yield[b] (%)
1	$BF_3 \cdot Et_2O$ (10)	C_6H_5Cl	—	100	—
2	TfOH (10)	C_6H_5Cl	—	100	—
3	$BF_3 \cdot Et_2O$ (10)	C_6H_5Cl	KO^{t}Bu	100	74
4	TfOH (10)	C_6H_5Cl	KO^{t}Bu	100	77
5	$FeCl_3$ (10)	C_6H_5Cl	KO^{t}Bu	100	66
6	TsOH (10)	C_6H_5Cl	KO^{t}Bu	100	60
7	TFA (10)	C_6H_5Cl	KO^{t}Bu	100	72
8	TfOH (5)	C_6H_5Cl	KO^{t}Bu	100	82
9	TfOH (2)	C_6H_5Cl	KO^{t}Bu	100	68
10	TfOH (5)	EtOH	KO^{t}Bu	Reflux	26
11	TfOH (5)	DCE	KO^{t}Bu	Reflux	65
12	TfOH (5)	CH_3CN	KO^{t}Bu	Reflux	60
13	TfOH (5)	Toluene	KO^{t}Bu	100	76
14	TfOH (5)	Dioxane	KO^{t}Bu	100	63
15	TfOH (5)	DMF	KO^{t}Bu	100	62
16	TfOH (5)	C_6H_5Cl	KO^{t}Bu	80	78
17	TfOH (5)	C_6H_5Cl	KO^{t}Bu	120	54
18	TfOH (5)	C_6H_5Cl	KOH	100	77
19	TfOH (5)	C_6H_5Cl	Li_2CO_3	100	Trace
20	TfOH (5)	C_6H_5Cl	Cs_2CO_3	100	75
21	TfOH (5)	C_6H_5Cl	TEA	100	Trace
22	TfOH (5)	C_6H_5Cl	DBU	100	78

[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.375 mmol), solvent (1.5 mL); then base (0.5 mmol).
[b] Isolated yield.