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p-Toluenesulfonic Acid Promoted Annulation of 2-Alkynylanilines with Activated Ketones: Efficient Synthesis of 4-Alkyl-2,3-Disubstituted Quinolines

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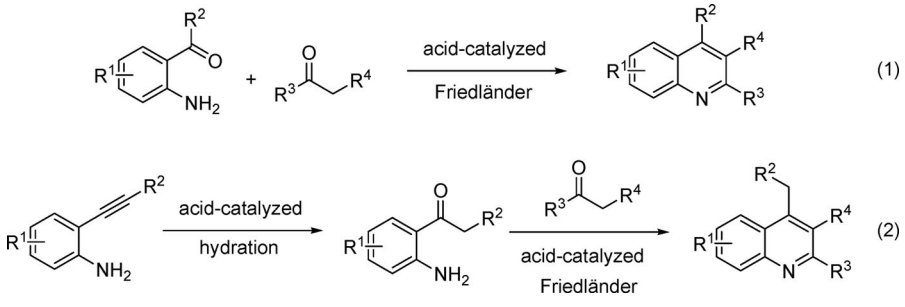
Reactions between readily available 2-alkynylanilines and activated ketones such as β-keto esters promoted by *p*-toluenesulfonic acid afford 4-alkyl-2,3-disubstituted quinolines in good to excellent yields. The generality of substituents at the other end of the triple bond of 2-alkynylanilines makes the method a valuable approach to diversified 4-alkylquinolines, which are difficult to obtain by classical methods such as the Friedländer reaction. Quinoline dimers can be prepared efficiently with alkyl or aryl linkers at C-4.

Introduction

As a very important class of heterocyclic compounds, quinolines, are known to display a wide range of pharmacological activities, such as antimalarial,[1] antibacterial,[2] anti-inflammatory,[3] antituberculosis,[4] anti-HIV,[5] and anticancer.[6] The quinoline scaffold is also present in many biologically active natural products, particularly in alkaloids.[7] Consequently, a large number of methodologies have been developed for the syntheses of functionalized quinolines, such as Skraup, Doebner–von Miller, Friedländer, and Combes syntheses.[8] However, many of these methods suffer from the need of high temperatures, prolonged reaction times, and drastic reaction conditions, and unsatisfactory yields are commonly obtained. To overcome the aforementioned drawbacks, more efficient methods such as modified Friedländer strategies,[9] hetero-Diels–Alder reaction of imines,[10] and transition-metal-catalyzed reactions[11] have been developed. Although, there are numerous methods available for the syntheses of multisubstituted quinolines, it is still a challenge to introduce a variety of alkyl groups at C-4 of the quinoline skeleton in a simple and straightforward manner.

Although the Friedländer reaction and its modifications are extensively studied and widely used for the syntheses of functionalized quinolines,[8,9] the availability of 2-aminophenylketones is limited to 2′-aminoacetophenones or 2-aminophenylarylketones in most cases (Scheme 1, Equation 1). As a result, the products are limited to 4-methyl- or 4-arylquinolines. Catalytic hydration of 2-alkynylanilines to the corresponding 2-substituted-2′-aminoacetophenones regioselectively is known to occur in high yields owing to the strong electron-donating ability of the *ortho*-amino group (Scheme 1, Equation 2).[12] Because the reaction conditions for the hydration of alkynes and the Friedländer reaction



Scheme 1. Friedländer and indirect Friedländer synthesis of multisubstituted quinolines.

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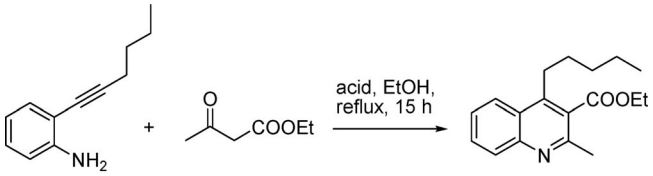
are similar (Brønsted acids or Lewis acids in polar solvents), it is viable to design a one-pot, indirect Friedländer reaction for the synthesis of a variety of 4-alkylquinolines starting from 2-alkynylanilines, which are easily accessible through Sonogashira couplings.[13]

Results and Discussion

To test the idea and search for optimized conditions, the initial attempt was carried out with 2-(1-hexynyl)aniline (**1a**) and ethyl acetoacetate (**2a**) as substrates in refluxing anhydrous ethanol in the presence of concentrated sulfuric acid (0.5 equiv.; Table 1, Entry 6).[14] Gratifyingly, desired product **3aa** was obtained in 57% isolated yield. The result encouraged us to screen different Brønsted acids for their effectiveness in this one-pot quinoline synthesis (Table 1, Entries 1–5). *p*-Toluenesulfonic acid (PTSA) monohydrate was the acid of choice and afforded the product in excellent yield (87%). Both catalytic (Table 1, Entry 7) and an excess amount of PTSA (Table 1, Entries 8–10) proved to be less effective. Altering the ratio of **2a**/**1a** suggested that the initial ratio of 1.5 was the best (Table 1, Entries 4, 11, 12). The reaction was much more sluggish in 95% ethanol than in anhydrous ethanol with otherwise identical conditions (result not shown).

Table 1. Acid-promoted annulation of 2-(1-hexynyl)aniline (**1a**) with ethyl acetoacetate (**2a**) in ethanol under various conditions.[a]



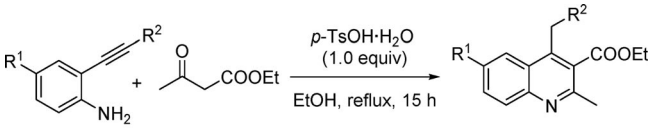
1a **2a** **3aa**

Entry	Acid (equiv.)	Ratio **2a**/**1a**	% Yield of **3aa**[b]
1	TMSCl (1.0)	1.5	38
2	conc. HCl (1.0)	1.5	33
3	TFA (1.0)	1.5	13
4	PTSA (1.0)[c]	1.5	87
5	CF_3SO_3H (1.0)	1.5	43
6	conc. H_2SO_4 (0.5)	1.5	57
7	PTSA (0.5)[c]	1.5	71
8	PTSA (1.2)[c]	1.5	82
9	PTSA (1.5)[c]	1.5	74
10	PTSA (2.0)[c]	1.5	74
11	PTSA (1.0)[c]	1.0	66
12	PTSA (1.0)[c]	2.0	80

[a] Conditions: Heating a solution of 2-(1-hexynyl)aniline (**1a**; 0.5 mmol) and ethyl acetoacetate (**2a**) in anhydrous ethanol (5 mL) with acids for 15 h. [b] Isolated yield. [c] *p*-Toluenesulfonic acid monohydrate was used.

With the optimized conditions identified, the scope of 2-alkynylanilines **1** was first examined with the activated ketone ethyl acetoacetate (**2a**; Table 2). In general, alkyl substituents R^2 (Table 2, Entries 1–5) give better yields than aryl ones (Table 2, Entries 11–17). This result agrees with the outcome of PTSA-catalyzed hydration of arylalkynes,[15] which suggests that the reaction may proceed via a hydration intermediate (Scheme 1, Equation 2). Both methyl and chloride substitutions on the aromatic ring (R^1) have negative effects on the yields, especially when R^2 is a phenyl group (Table 2, Entries 7–10). A wide range of electron-poor and electron-rich aromatics can tolerate the reaction (Table 2, Entries 11–17), albeit the yield for the strong electron-donating group OMe is low (59%; Table 2, Entry 12). Functionalities such as bromide and carboxylic ester make further modifications possible on the aromatic ring (Table 2, Entries 13 and 17). It is noteworthy that in all cases when R^2 = TMS, the silyl group is alcoholyzed to proton (R^2 = H) in the final products (Table 2, Entries 1, 7, and 9).

Table 2. *p*-Toluenesulfonic acid promoted annulation of 2-alkynylanilines **1** with ethyl acetoacetate (**2a**) in ethanol.[a]



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

Entry	2-Alkynylanilines **1**	Product **3**	% Yield[b]
1	**1b**: R^1 = H, R^2 = TMS	**3ba**[c]	97
2	**1c**: R^1 = H, R^2 = *t*Bu	**3ca**	89
3	**1d**: R^1 = H, R^2 = cyclohexyl	**3da**	83
4	**1e**: R^1 = H, R^2 = cyclopropyl	**3ea**	80
5	**1f**: R^1 = H, R^2 = Bn	**3fa**	71
6	**1g**: R^1 = H, R^2 = Ph	**3ga**	88
7	**1h**: R^1 = Me, R^2 = TMS	**3ha**[c]	88
8	**1i**: R^1 = Me, R^2 = Ph	**3ia**	60
9	**1j**: R^1 = Cl, R^2 = TMS	**3ja**[c]	94
10	**1k**: R^1 = Cl, R^2 = Ph	**3ka**	55[d]
11	**1l**: R^1 = H, R^2 = *p*-tolyl	**3la**	73
12	**1m**: R^1 = H, R^2 = 4-$MeOC_6H_4$	**3ma**	59
13	**1n**: R^1 = H, R^2 = 4-BrC_6H_4	**3na**	79
14	**1o**: R^1 = H, R^2 = 4-ClC_6H_4	**3oa**	76
15	**1p**: R^1 = H, R^2 = 3-ClC_6H_4	**3pa**	63
16	**1q**: R^1 = H, R^2 = 2-ClC_6H_4	**3qa**	80
17	**1r**: R^1 = H, R^2 = 4-$EtOOCC_6H_4$	**3ra**	72

[a] Conditions: Heating a solution of 2-alkynylanilines **1** (0.5 mmol) and ethyl acetoacetate (**2a**; 0.75 mmol) in anhydrous ethanol (5 mL) with *p*-toluenesulfonic acid monohydrate (1.0 equiv.) in anhydrous ethanol to reflux for 15 h. [b] Isolated yield. [c] R^2 = H. [d] Another 1.0 equiv. of PTSA was added after 15 h, and the mixture was stirred for another 5 h.

The scope of substrates was further explored by focusing on activated ketones, and the results are summarized in Table 3. Compatible yields were obtained when ethyl benzoylacetate (**2b**) and ethyl butyrylacetate (**2d**) were used, which introduced diversity at C-2 of the quinolines with aryl and long-chain alkyl groups (Table 3, Entries 1–4, 7). A wide range of activating groups other than carboxylic ester such as amides (Table 3, Entries 9–11), *p*-toluenesulfonyl (Table 3, Entry 8), ketone (Table 3, Entries 5 and 6), and cyanide (Table 3, Entry 12) all worked well. Consequently, the diversity at C-3 of the quinolines was largely expanded. Unfortunately, unactivated ketones such as acetophenone failed to give the desired product under the optimized conditions.

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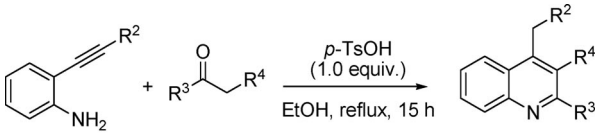
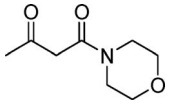
Table 3. *p*-Toluenesulfonic acid promoted annulation of 2-alkynylanilines **1** with activated ketones **2** in ethanol.[a].

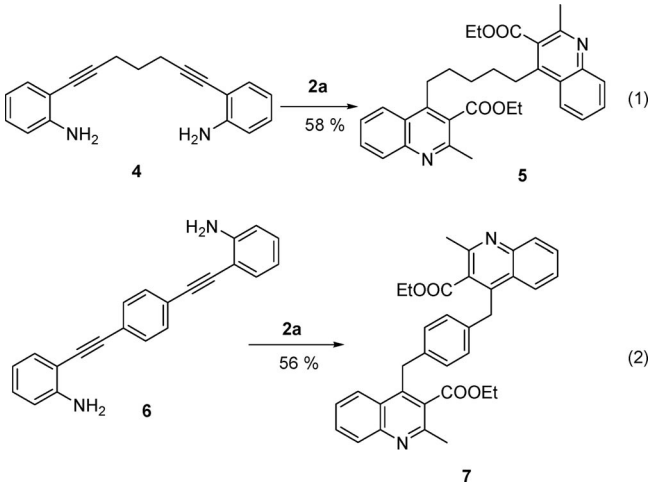


1 2 3

Entry	Anilines **1**	Ketones **2**		Product **3**[c]	% Yield[b]
1	**1a**	**2b**:	R^3 = Ph, R^4 = CO_2Et	**3ab**	91
2	**1b**	**2b**		**3bb**	99
3	**1g**	**2b**		**3gb**	73
4	**1n**	**2b**		**3nb**	66
5	**1a**	**2c**:	R^3 = Me, R^4 = CH_3CO	**3ac**	77
6	**1b**	**2c**		**3bc**	99
7	**1b**	**2d**:	R^3 = *n*Pr, R^4 = CO_2Et	**3bd**	94
8	**1b**	**2e**:	R^3 = Me, R^4 = *p*-Ts	**3be**	70
9	**1b**	**2f**:	R^3 = Me, R^4 = $CONH_2$	**3bf**	91
10	**1b**	**2g**:	R^3 = Me, R^4 = CONHPh	**3bg**	98
11	**1b**	**2h**:		**3bh**	87
12	**1b**	**2i**:	R^3 = Ph, R^4 = CN	**3bi**	92

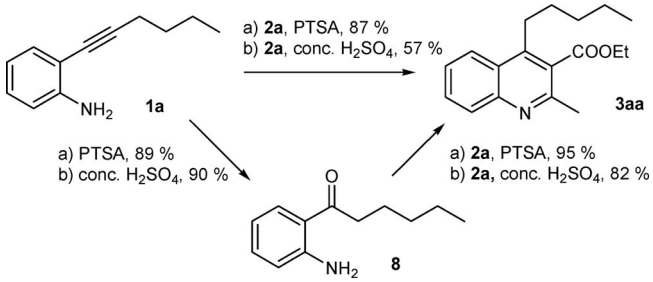
[a] Conditions: Heating a solution of 2-alkynylanilines **1** (0.5 mmol) and activated ketones **2** (0.75 mmol) in anhydrous ethanol (5 mL) with *p*-toluenesulfonic acid monohydrate (1.0 equiv.) in anhydrous ethanol to reflux for 15 h. [b] Isolated yield. [c] R^2 = H in the case where **1b** was used.

The current strategy can be applied to the synthesis of quinoline dimers linked at C-4 as shown in Scheme 2. Symmetric substrates **4** and **5** can be accessed easily by double Sonogashira couplings of 1,6-heptadiyne and 1,4-diethynylbenzene with 2.5 equivalents of 2-iodoaniline, respectively.[16] Under the standard reaction conditions, desired quinoline dimer **5** with a linear alkyl chain linkage was obtained in good yield. A similar yield was achieved for **7** with a 1,4-benzylic linker. This unprecedented dimeric quinoline synthesis will inspire us to prepare more derivatives and to explore their potential biological activities and other properties.



Scheme 2. Synthesis of dimeric quinolines with alkyl or aryl linkages at C-4.

To determine the mechanism of this one-pot quinoline synthesis, the results of a stepwise hydration of **1a** and the subsequent Friedländer reaction of the corresponding hydration product **8** promoted by PTSA and H_2SO_4 were compared side by side (Scheme 3). Both acids promoted the hydration of **1a** with almost equal effectiveness. Although PTSA was more effective than H_2SO_4 (95% vs. 82%) in the Friedländer reaction of **8** and **2a**, their difference in the one-pot reaction was much more significant (87% vs. 57%). The presence of **2a** in the one-pot procedure must play an important role, leading the reaction to different pathways with the use of different acids.



Scheme 3. Hydration of 2-(1-hexynyl)aniline (**1a**) and Friedländer reaction of 1-(2-aminophenyl)hexane-1-one (**8**) promoted by PTSA and H_2SO_4.

We propose the reaction pathways and rationalize the influence of the two acids on the yields as depicted in Scheme 4. In the presence of PTSA, **1a** is hydrated to **8** first (path a1), and then enamine **B** is formed with ethyl acetoacetate (**2a**; path a2) before cyclization and dehydration to furnish the final product. In the case of H_2SO_4

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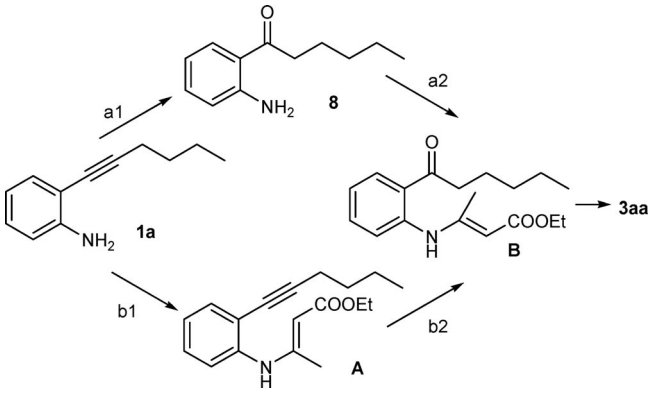
as catalyst, however, competitive formation of enamine intermediate **A** is preferred to some extent (path b1). The reduced electron density on nitrogen of intermediate **A** makes its further hydration less effective and less regioselective (path b2), which accounts for a much lower overall yield.



Scheme 4. Competitive pathways of the one-pot, indirect Friedländer quinoline synthesis.

Conclusions

In summary, we have demonstrated a convenient and single-step procedure for the conversion of readily available 2-alkynylanilines and activated ketones into the corresponding 4-alkylquinolines. The tolerance of a wide range of functionalities on both substrates gives complementary access to the Friedländer reaction, resulting in the formation of a variety of 4-alkylquinolines. Dimeric quinolines with potential biological interest can also be synthesized efficiently from symmetric 2-alkynylanilines.

Supporting Information (see footnote on the first page of this article): Experimental details and copies of the ^{1}H and ^{13}C NMR spectra of all new compounds.

Acknowledgments

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[16] See the Supporting Information for details.

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