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The First Proline-Catalyzed Friedlander Annulation: Regioselective Synthesis of 2-Substituted Quinoline Derivatives

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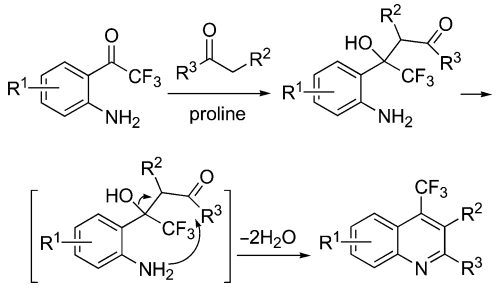
The first proline-catalyzed Friedlander annulation for the synthesis of 2-substituted 4-trifluoromethyl quinoline derivatives is described. Excellent regioselectivity as well as good yields were shown in a variety of cases, and a tandem aldol-cyclization pathway might be involved.

Introduction

The Friedlander synthesis,[1] which involves the formation of quinoline derivatives by condensation of aromatic *o*-aminoaldehydes or *o*-aminoketones with an aldehyde- or a ketone-containing methylene group alpha to the carbonyl moiety, was regarded as one of the most simple and straightforward methods for the synthesis of substituted quinolines. Depending on the catalyst employed, two different reaction pathways that include an aldol cyclization and a Schiff base cyclization sequence have been postulated.[2] Over the past years, several catalysts such as amines,[3] Brønsted acids,[4] Lewis acids[5] and molecular iodine[6] were developed for the Friedlander reaction. In addition, some metal complexes such as Ru,[7] Ir[8] and Rh[9] were found to be successful catalysts for the modified Friedlander reaction.[10] However, most of the methods suffered from harsh reaction conditions, poor yields or the use of expensive catalysts. In recent years, proline, the bifunctional and cheap catalyst, played an important role in the direct aldol reaction between an aldehyde and an unmodified ketone via an enamine intermediate.[11] By considering the postulated Friedlander annulation pathway, it is possible that the proline-catalyzed aldol reaction followed by a cyclization sequence would deliver substituted quinolines. To our surprise, it was found that research on proline-catalyzed Friedlander annulation has been mostly ignored so far.[12]

Fluorine-containing quinoline derivatives, particularly trifluoromethyl quinoline derivatives, have attracted considerable attention because of their unique physical, chemical and biological properties.[13] However, conventional methods for the synthesis of quinoline compounds starting from aniline, such as Skraup, Doebner–Miller and Combes, were inappropriate for the preparation of trifluoromethyl quinoline compounds owing to the unavailability of starting materials and poor regioselectivity.[14] An indirect synthetic protocol for these types of compounds via the quinolinone intermediate was also reported, although the overall yield was low.[15] Previously, our group disclosed the first Zn^{II}-catalyzed one-pot reaction of alkynes with *o*-trifluoroacetyl anilines toward the synthesis of 4-trifluoromethyl quinoline derivatives.[16] Herein, we report the first proline-catalyzed Friedlander annulation toward the synthesis of 4-trifluoromethyl quinoline derivatives. We envisioned that 4-trifluoromethyl quinoline derivatives could be synthesized by the proline-catalyzed aldol reaction followed by the acid-catalyzed cyclization sequence as outlined in Scheme 1.



Scheme 1. Proposed pathway for the synthesis of 4-trifluoromethyl quinolines.

Results and Discussion

Initially, acetone and *o*-trifluoroacetyl anilines were used as model substrates for the aldol reaction. For comparison, a variety of catalysts were tried, and the results are shown in Table 1. Surprisingly, in addition to proline, an inorganic

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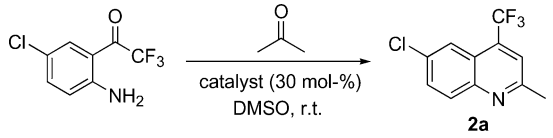
base such as NaOH as well as an organic base such as ammonia and piperidine led to the formation of 4-trifluoromethyl quinoline **2a** directly in one pot at room temperature in good yields (Entries 5, 6, 8). Interestingly, the amino acid alanine also gave a moderate yield for the product (Entry 4). In particular, when 30 mol-% proline was used as the catalyst, the desired quinoline was obtained in an almost quantitative yield, and the reaction time was significantly shorter (12 h, Entry 2). When the catalyst loading was decreased to 5 mol-%, a much longer reaction time was required (Entry 3). In addition, it was found that no other intermediate was isolated when proline was used as the catalyst, which prompted us to investigate the reaction pathway.

Table 1.Catalysts studied in the Friedlander annulation with acetone and *o*-trifluoroacetyl anilines as substrates.

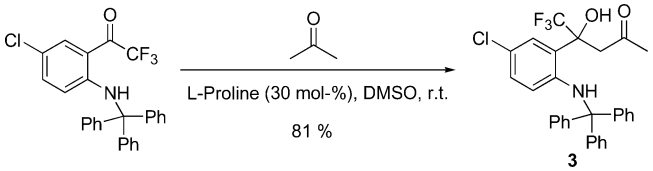


2a

Entry	Catalyst	*t* [h]	Yield [%][a]
1	none	48	no reaction
2	proline	12	98[b]
3	proline[c]	36	96
4	alanine	48	66
5[d]	NaOH	24	85
6[e]	$NH_3·H_2O$	24	89
7	NEt_3	72	<5
8	piperidine	48	72

[a] Yield was determined by ^{19}F NMR spectroscopy. [b] Isolated yield. [c] 5 mol-% Proline was used. [d] 20% Aqueous solution was used. [e] 28% Aqueous solution was used.

^{19}F NMR and ^1H NMR spectroscopy were used to monitor the reaction. However, neither the Schiff base intermediate nor the aldol adduct, with the exception of the substrate and product, was detected. The result indicates that the generated intermediate was highly reactive and underwent automatic dehydration and cyclization to provide the final quinoline product. Therefore, in order to trap the intermediate by slowing down the tandem reaction, bulky triphenylmethyl (Tr) protected *o*-trifluoroacetyl aniline was employed as the substrate. The aldol adduct **3** was isolated in 81% yield, which suggests that this reaction possibly follows the aldol-cyclization pathway when proline is used as the catalyst (Scheme 2).

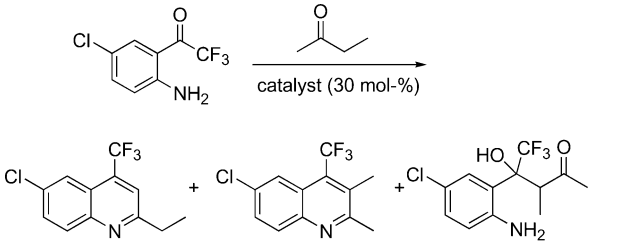


3

Scheme 2. Reaction with the *N*-protected *o*-trifluoroacetyl aniline afforded the aldol adduct.

When the unsymmetrical methyl ketone such as methyl ethyl ketone was investigated, excellent regioselectivity[17] was obtained when using proline as the catalyst (Table 2, Entry 1). The methyl residue reacted in preference to the much bulkier methylene moiety, and the 2-ethyl 4-trifluoromethyl quinoline product was formed exclusively in good yield. When a base such as NaOH was used as the catalyst, 4-trifluoromethyl quinoline products were obtained as a mixture of isomers because of the poor regioselectivity of the aldol reactions (Entry 2).

Table 2. Regioselectivty investigations with methyl ethyl ketone as the substrate.



2f **4** **5**

Entry	Catalyst	Solvent	*T* [°C]	*t* [h]	Conversion [%][a]	**2f/4/5**[a]
1	proline	DMSO	50	48	100	100:0:0
2[b]	NaOH	DMSO/H_2O	r.t.	4	100	38:52:10
3	$FeCl_3·6H_2O$	EtOH	50	48	0	–
4	CF_3COOH[c]	–	70	5	97	64:36:0

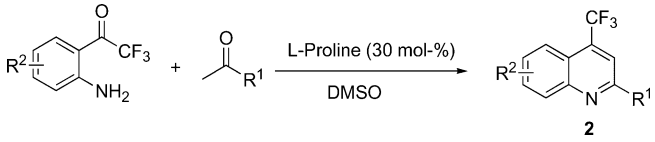
[a] Determined by ^{19}F NMR and ^1H NMR spectroscopy. [b] 20% Aqueous solution was used. [c] Neat CF_3COOH was used.

Other typical Friedlander annulation catalysts, such as the Lewis acid $FeCl_3·6H_2O$,[18] could not catalyze such a reaction at all (Entry 3). When the Brønsted acid CF_3COOH was used as the catalyst,[19] poor regioselectivity was still obtained (Entry 4).

On the basis of the above results, a variety of unsymmetrical methyl ketones and substituted *o*-trifluoroacetyl anilines with different electronic proprieties were investigated for the catalytic activity of proline. As shown in Table 3, the desired 2-substutited 4-trifluoromethyl quinolines were exclusively obtained in excellent yields.

The electronic properties of the substituted *o*-trifluoroacetyl anilines substrates did not dramatically affect the yield (Entries 1–5). In addition to the linear alkyl methyl ketones, bulky unsymmetrical methyl ketones, such as cyclopropyl methyl ketone, also gave satisfactory yields at elevated temperatures (50 °C) with excellent regioselectivity (Entries 6–11). In particular, for cyclic ketone substrates, such as cyclohexanone, the desired Friedlander annulation proceeded smoothly as well (Scheme 3). Other functionalized ketones, such as ethyl pyruvate and ethyl acetylacetate, were also tried, but only a low conversion (≈5%) was obtained, which needs to be optimized in the future.

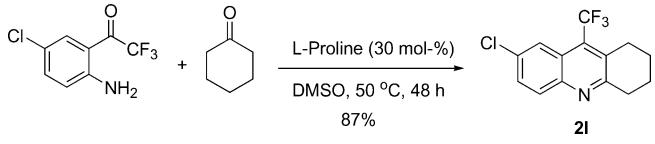
Table 3. Proline catalyzed Friedlander annulation for the synthesis of 4-trifluoromethyl quinoline derivatives.[a]



2

Entry	R^1	R^2	Product	*t* [h]	*T* [°C]	Yield [%][b]
1	Me	*p*-Cl	**2a**	24	r.t.	98
2	Me	*p*-OMe	**2b**	24	r.t.	94
3	Me	*o*-OMe	**2c**	24	r.t.	95
4	Me	*p*-CF_3	**2d**	48	r.t.	93
5	Me	H	**2e**	24	r.t.	95
6	Et	*p*-Cl	**2f**	48	50	93
7	Pr	*p*-Cl	**2g**	48	50	93
8	*i*Bu	*p*-Cl	**2h**	72	50	92
9	*c*-C_3H_5	*p*-Cl	**2i**	48	50	85
10	*n*Hex	*p*-Cl	**2j**	48	50	90
11	Ph	*p*-Cl	**2k**	48	50	91

[a] All reactions were performed on a 0.5-mmol scale. [b] Isolated yield.



2l

Scheme 3. Reaction with the cyclic ketone under the catalytic action of proline.

Conclusions

We have demonstrated the highly regioselective synthesis of 2-substituted 4-trifluoromethyl quinoline derivatives by unprecedented proline-catalyzed Friedlander annulation. This method probably involves a tandem aldol-cyclization reaction, which gives way to a novel, mild, efficient and cheap route for a wide range of 2-substituted 4-trifluoromethyl quinolines.

Experimental Section

General Procedure for Preparation of 2a–l and 3: A mixture of proline (L, or D or DL) (17 mg, 0.15 mmol), *o*-trifluoroacetyl aniline (0.5 mmol) and methyl ketone (3.5 mmol) in DMSO (2 mL) was stirred at the temperature indicated in Table 3. After the reaction was complete, H_2O (6 mL) was added and the reaction mixture was extracted with ethyl acetate. The combined organic phases were washed with brine and dried with anhydrous Na_2SO_4. Concentration under reduced pressure provided the crude product, which was purified by flash chromatography on silica gel (hexane/ethyl acetate, 20:1) to afford 4-trifluoromethyl quinoline derivatives.

6-Chloro-2-methyl-4-(trifluoromethyl)quinoline (2a): Yield: 98%; white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05–8.10 (m, 2 H), 7.70 (dd, *J* = 9.0, 2.4 Hz, 1 H), 7.63 (s, 1 H), 2.77 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.6, 146.8, 133.4, 133.2, 130.9, 123.0, 122.7, 121.7, 121.7, 119.6, 25.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = –62.2 ppm. MS (EI): *m*/*z* (%) = 245 (100) [M^+]. IR (KBr): $\tilde{\nu}$ = 3067, 1959, 1615, 1495, 1382, 1349 cm^{-1}. HRMS (EI): calcd. for $C_{11}H_8ClF_3N^+$ 246.0302; found 246.0292.

Supporting Information (see footnote on the first page of this article): Characterization data and ^{1}H NMR and ^{13}C NMR spectra for **2a**–**2l** and **3**.

Acknowledgments

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