Proline potassium salt: a superior catalyst to synthesize 4-trifluoromethyl quinoline derivatives via Friedlander annulation

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ABSTRACT

Proline potassium salt was successfully firstly used to catalyze the Friedlander annulation toward the synthesis of 4-trifluoromethyl-substituted quinolines from the substituted 2-trifluoroacetyl anilines and variety carbonyl compounds under mild conditions in good to excellent yields. This catalyst provides several advantages, such as shorter reaction time, high regioselectivity, functional group tolerance, and broad substrate scope.

1. Introduction

Fluorine-containing quinoline derivatives, particularly trifluoromethyl quinoline derivatives, have received a great deal of interest in the medicinal, agricultural, and material sciences in recent years because of their special physical, chemical, and biological properties. To synthesize the trifluoromethyl quinoline derivatives, multiple steps synthesis or indirect synthetic protocol have been appealed due to the unavailability of starting materials and poor regioselectivity when traditional methods for the synthesis of quinoline compounds are employed. In our previous works, two new methods for the synthesis of 4-trifluoromethyl quinoline derivatives with high regioselectivity and yields were developed and the first proline-catalyzed synthesis of 2-substituted 4-trifluoromethyl quinoline derivatives was realized from the reaction of alkyl ketones and o-trifluoroacetyl anilines. However, the method using proline as catalyst was too much time consuming (>24 h) and many useful functionalized ketones, such as ethyl pyruvate and ethyl acetylacectate could not work in this condition, which greatly limited its popularity in applications (Scheme 1).

When exploring the reaction mechanism, we concluded that proline-catalyzed Friedlander annulation presumably experienced an aldol reaction followed by the acid-catalyzed cyclization sequence (Scheme 2) and the aldol reaction was the rate-determined step. Then we suppose that the hydrogen-bonded effect between the oxygen of trifluoroacetyl and the proton of carboxylic group (Fig. 1) is presumably the key factor during the annulation, according to the mechanism of the aldol reaction catalyzed by proline as before. With this background, we tried to replace proline with proline alkali salt as a catalyst to synthesize 4-trifluoromethyl quinoline derivatives via Friedlander annulation. And we found that proline potassium salt was a superior catalyst to...
synthesize 4-trifluoromethyl quinoline derivatives possessing many advantages, such as the reaction time could be greatly reduced and many useful functionalized ketones (aromatic ketones, ethyl pyruvate, ethyl acetylacetate, and so on) could also work under this condition in good to excellent yields. Significantly, the 3-substituted quinolone derivatives could be obtained, when using aldehydes as the reagents instead of ketones.

2. Results and discussion

We initiated our investigation with the reaction between 4-chloro-2-trifluoroacetyl aniline 1a and 2-pentanone 2a (Table 1, entry 1). Gratifyingly, the use of proline potassium salt (25 mol %) as catalyst in DMSO at rt yielded 3a in 98% yield and the reaction finished within 35 min, which was much shorter than that (48 h, 50 °C) when proline was employed as catalyst. For comparison, a range of catalyst loadings and other alkali salts were screened and outlined in Table 1. The result showed that lithium and sodium proline salts led to slightly lower yields (Table 1, Entries 2, 3). Reactions performed with lower catalyst loading gave lower yields and required much longer reaction time (Table 1, Entry 4, 5). While raising the catalyst loading did not result in any effect in yield or reaction time (Table 1, Entry 6, 7). To verify that whether just incorporation of potassium cation into reaction can produce such a result, the mixture of proline and potassium iodide in equal molar ratio served as the co-catalyst for this reaction (Table 1, entry 8). As expected, the reaction was completed after 12 h, which was similar to what the proline as the only catalyst did. The striking difference of the catalyst activity between proline and proline potassium salt is likely a result of difference in the substrate–catalyst interaction model. In addition to the coordination effect with the oxygen of the trifluoroacetyl group, the potassium cation may be an additional effect with the nitrogen of the amino group, which probably leads to a great energy decrease in the transition state.

Having established the optimized reaction conditions, we tested the methodology with an array of substituent of o-trifluoroacetyl anilines (Table 2). It was found that the electronic nature of the substituents did not play a key role in this annulation reaction. Substrates substituted with strong electron-withdrawing groups, such as NO2 (3f) and donating groups, such as MeO (3e), were well tolerated providing the desired quinoline derivatives in excellent yields. Notably, the tolerance of the nitro (3f), fluoro, chloro, and bromo groups (3a–c) offers the opportunity for further functionalization.

Encouraged by the successful results in the annulation of substituent of o-trifluoroacetyl anilines, we turned our attention to additional substrates bearing synthetically useful functionalized carbonyl compounds. In most cases, not only aliphatic ketones but also aromatic ketones exclusively led to give the desired products in good to excellent yields, as shown in Table 3. It is noteworthy that...
the reaction between 4-chloro-2-trifluoroacetyl aniline and acetone was complete within 3 min even without stirring at rt in 92% yield (4a). In contrast, aliphatic ketones with bulky substituents were tolerated with good yields obtained, despite the requirement of the longer reaction time (4b, 4c). For cyclic ketone substrates, such as cyclopentanone, the desired Friedlander annulation proceeded smoothly as well (4d). In addition, enone substrate, such as mesityl oxide, was readily converted to the corresponding product in good yield (4e). It is interesting that two acetone derivatives bearing different activated groups was transformed to the quinolines with opposite regioselectivity (4f, 4g). However, when other carbonyl compounds, such as ethyl pyruvate and ethyl acetylacetate were treated under the optimized conditions, no desired product was obtained. We speculated that self-condensation or other side reaction might lead to the failure in releasing catalyst. Finally, we were pleased to find that this reaction was successful by adding of three drops of acetic acid into the mixture, which can probably help to stimulate the decomposition of the imine intermediate, providing the corresponding products in mild yield (4h, 4i). The aromatic ketones bearing electron rich groups worked equally well to get the corresponding products in good yields with the requirement of higher temperature or longer reaction time (4k–m, 4p). Particularly remarkable was the participation of aldehydes in this reaction, providing the corresponding C3-substituted quinolines in good yield (4q, 4r).

3. Conclusion

In summary, we have developed a mild and efficient method for the synthesis of 4-trifluoromethyl-substituted quinolines derivatives utilizing proline potassium salt as a novel catalyst via Friedlander annulation in good to excellent yields. This catalyst provides several advantages, such as shorter reaction time, high regioselectivity, functional group tolerance, and broad substrate scope. Most importantly, the 3-substituted quinoline derivatives could be obtained, when using aldehydes as the reagents instead of ketones.

4. Experimental section

4.1. General methods and materials

Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. 1H and 13C NMR spectra were determined on Bruker AM-300, Bruker AM-400, using tetramethylsilane as internal reference. Data are presented as follows: chemical shift, multiplicity (s=singlet, br= broad singlet, d=dublet, d=doublet, t=triplet, m=multiplet), J= coupling constant in hertz (Hz). Silica gel 60H (200–300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography. All the reagents were purchased from Aldrich and used without further purification. Prolinate alki salt was synthesized according to published procedures.

4.2. Preparation of the prolinate alki salt

The alki metal hydroxide (10 mmol) was added rapidly to the solution of proline (L, o or D, o or DL) (1.15 g, 10 mmol) dissolving in a solution of proline (L, o or D, o or DL) (1.15 g, 10 mmol) dissolving in methanol at 0°C with stirring. After 30 min, the system was allowed stirring at rt for 2 h. Concentration of the solution under reduced pressure provided white solid, which was dried in vacuo for 10 h and used to catalyze the Friedlander annulation reaction without further purification.

4.3. General procedures and characterizations

To a solution of o-trifluorooacetyl aniline (1.0 mmol) and methyl ketone (7.0 mmol) in DMSO (4.0 mL) was added potassium prolinate (38.2 mg, 0.25 mmol) in one portion (for 4h, 4i, 4q, 4r in Table 3, three drops of acetic acid was added) and the resulted mixture was stirred at the temperature indicated in Tables 2 and 3. The reaction was monitored by TLC until the verification of the disappearance of the reagent. Then the reaction mixture was diluted with ethyl acetate (50 mL) and ether (10 mL) and washed with saturated brine three times (20 mL per times). The organic phase was dried over anhydrous sodium sulfate and the solvent was removed under the reduced pressure to give the crude product. Purification of the crude product by flash chromatography on silica gel afforded 4-trifluoromethyl quinoline derivatives.

4.3.1. 3a: 6-Chloro-2-propyl-4-(4-trifluoromethyl)quinoline. Following general procedure, the indicated compound was purified by flash column chromatography on silica as a white solid, yield 98%, mp: 39.0–39.9 °C. 1H NMR (300 MHz in d6-acetone): δ 1.02 (t, J=7.4 Hz, 3H), 1.81–1.97 (m, 2H), 3.02 (t, J=7.7 Hz, 2H), 7.76 (dd, J=8.9, 1.9 Hz, 1H), 7.81 (s, 1H), 7.99 (t, J=2.0 Hz, 1H), 8.06.
(d, J = 9.2 Hz, 2H). 13C NMR (100 MHz in d6-acetone): δ 12.4, 22.6, 40.6, 119.8 (q, J = 5.2 Hz), 121.7, 122.4 (q, J = 2.0 Hz), 123.6 (q, J = 274.7 Hz), 130.9, 132.0, 132.8 (q, J = 31.3 Hz), 133.2, 147.3, 163.2. IR (cm⁻¹): 686.46, 778.98, 743.32, 832.45, 1176.40, 1258.98, 1295.56, 1496.30, 1559.42, 1614.22, 2925.64, 2972.51, 3035.24, 3058.01. 19F NMR (282 MHz in d6-acetone): δ −62.60. EI-MS: 273 (M⁺). HR-MS(El): calcd for C13H12F3ClN: 273.0532; found: 273.0533.

3.4. 3d: 8-Bromo-6-chloro-2-propyl-4-(trifluoromethyl)quinoline.
Following general procedure, the indicated compound was purified by flash column chromatography on silica as light yellow oil, yield 99%. 1H NMR (300 MHz in d6-acetone): δ 1.03 (t, J = 7.6 Hz, 3H), 1.87−2.01 (m, 2H), 3.08 (t, J = 7.5 Hz, 2H), 7.93 (s, 1H), 8.97 (s, 1H). 13C NMR (100 MHz in d6-acetone): δ 13.2, 21.7, 40.3, 120.9 (q, J = 5.0 Hz), 122.2 (q, J = 2.2 Hz), 124.3 (q, J = 274.9 Hz), 126.7, 132.7, 133.3 (q, J = 31.1 Hz), 133.9, 144.1, 164.1. IR (cm⁻¹): 683.1, 698.4, 773.8, 864.5, 907.9, 1058.9, 1139.5, 1263.6, 1369.9, 1465.5, 1551.7, 1599.2, 1615.5, 2874.0, 2932.3, 2963.4, 3100.1. 19F NMR (282 MHz in d6-acetone): δ −62.24. EI-MS: 352 (M⁺). HR-MS(El): calcd for C18H12BrF3N: 350.9637; found: 350.9642.

3.4. 3c: 5,6-Difluoro-2-propyl-4-(trifluoromethyl)quinoline.
Following general procedure, the indicated compound was purified by flash column chromatography on silica as a white solid, yield 92%, mp: 42.0−43.3°C. 1H NMR (300 MHz in d6-acetone): δ 0.98 (t, J = 7.4 Hz, 3H), 1.79−1.93 (m, 2H), 3.02 (t, J = 7.5 Hz, 2H), 7.87 (q, J = 9.2 Hz, 1H), 7.95 (s, 1H), 8.00 (q, J = 4.6 Hz, 1H). 13C NMR (100 MHz in d6-acetone): δ 13.1, 21.8, 40.2, 112.35 (d, J = 10.7 Hz), 120.2 (d, J = 21.4 Hz), 120.9 (q, J = 6.6 Hz, 123.1), 127.22 (d, J = 7.4 Hz, 11.4), 130.6 (d, J = 34.3, 6.5 Hz), 142.4 (dd, J = 257.5, 15.4 Hz), 145.8, 148.3 (dd, J = 24.7, 13.7 Hz, 162.8. IR (cm⁻¹): 645.93, 682.80, 739.72, 833.22, 1065.07, 1488.24, 1615.81, 1639.44, 2883.11, 2942.10, 2970.38, 3083.28. 19F NMR (282 MHz in d6-acetone): δ −62.60 (d, J = 39.5 Hz, 3F). −138.99 (m, 1F), −140.45 (m, 1F). EI-MS: 275 (M⁺). HR-MS(El): calcd for C13H10BrClF3N: 350.9637; found: 350.9642.

3.4. 3b: 2-Propyl-6-(trifluoromethoxy)-4-(trifluoromethyl)quinoline.
Following general procedure, the indicated compound was purified by flash column chromatography on silica as a white solid, yield 92%, mp: 47.0−48.3°C. 1H NMR (300 MHz in d6-acetone): δ 1.45 (d, J = 6.8 Hz, 6H), 3.50−3.73 (m, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.06−8.13 (m, 2H), 8.48 (dd, J = 8.8, 11.1 Hz, 1H). 13C NMR (100 MHz in d6-acetone): δ 71.2 (2C), 35.8 (t, J = 19.7 Hz, 1H), 118.7 (q, J = 5.4 Hz, 121.9, 122.4 (q, J = 2.0 Hz), 123.4 (q, J = 274.4 Hz). 131.1, 131.2, 133.7 (q, J = 32.4 Hz), 134.6, 146.0, 167.6. IR (cm⁻¹): 665.01, 692.69, 715.20, 838.65, 1090.43, 1123.07, 1254.52, 1496.43, 1560.61, 1619.14, 2963.50, 2989.57, 3072.20, 3411.63, 3470.55. 19F NMR (282 MHz in d6-acetone): δ −62.69. EI-MS: 275 (M⁺). HR-MS(El): calcd for C13H12F3N: 273.0219; found: 273.0227.

3.4. 3a: 6-Chloro-2-isopropyl-4-(trifluoromethyl)quinoline.
Following general procedure, the indicated compound was purified by flash column chromatography on silica as colorless oil, yield 85%. 1H NMR (300 MHz in d6-acetone): δ 1.45 (d, J = 6.8 Hz, 6H), 3.50−3.73 (m, 1H), 7.96 (d, J = 9.0 Hz, 1H), 8.06−8.13 (m, 2H), 8.48 (dd, J = 8.8, 11.1 Hz, 1H). 13C NMR (100 MHz in d6-acetone): δ 11.3 (2C), 165.1, 169.3, 176.0, 179.8. 19F NMR (282 MHz in d6-acetone): δ −66.88. EI-MS: 271 (M⁺). HR-MS(El): calcd for C13H12F3N: 271.0376; found: 271.0372.
Following general procedure, the indicated compound was purified by flash column chromatography on silica as a white solid, yield 95%, mp: 152.5–155.0 °C. 1H NMR (300 MHz in d$_6$-acetone): δ 7.26–7.30 (m, 1H), 7.86 (d, δ = 4.9 Hz, 1H), 7.94 (dd, δ = 9.2, 1.8 Hz, 1H), 7.98 (t, δ = 2.2 Hz, 1H), 8.16 (d, δ = 8.9 Hz, 1H), 8.28 (d, δ = 3.6 Hz, 1H), 8.54 (s, 1H). 13C NMR (100 MHz in DMSO): δ 113.5, 113.6, 116.6 (d, δ = 5.3 Hz), 121.7, 122.6, 123.5 (q, δ = 275.6 Hz), 123.2, 123.5, 133.4, 133.3 (q, δ = 311 Hz), 146.8, 147.2, 147.8, 152.1. IR (cm$^{-1}$): 664.48, 692.39, 746.65, 1081.28, 1263.73, 1495.82, 1448.45, 1553.20, 1616.83, 3072.20, 3117.36, 3158.18. 19F NMR (282 MHz in d$_6$-acetone): δ −62.66. HR-MS (EI): calcd for C$_{14}$H$_2$ClF$_5$NO: 297.0168; found: 297.0170.

4.3.19. 4m: 6-Chloro-2-((thiophen-2-yl)-4-(trifluoromethyl)quinoline. Following general procedure, the indicated compound was purified by flash column chromatography on silica as a white sheet-like crystal, yield 90%, mp: 158.6–160.3 °C. 1H NMR (300 MHz in d$_6$-acetone): δ 8.02–8.08 (m, 2H), 8.10 (d, δ = 3.4 Hz, 1H), 8.16 (d, δ = 3.1 Hz, 1H), 8.30 (d, δ = 8.7 Hz, 1H), 8.60 (s, 1H). 13C NMR (100 MHz in DMSO): δ 116.5 (q, δ = 5.8 Hz), 122.8 (d, δ = 5.3 Hz), 123.3 (q, δ = 274.9 Hz), 123.3, 125.5, 127.6, 132.7, 133.7 (q, δ = 32.0 Hz), 134.8, 145.4, 146.9, 151.3, 166.9. IR (cm$^{-1}$): 663.73, 735.12, 856.08, 1063.65, 1254.79, 1492.63, 1557.03, 1607.86, 3035.56, 3063.89, 3084.81. 19F NMR (282 MHz in d$_6$-acetone): δ −62.99. HR-MS (EI): calcd for C$_{14}$H$_2$ClF$_5$NO: 313.9892; found: 313.9898.

4.3.21. 4o: 6-Chloro-2-((pyridin-4-yl)-4-(trifluoromethyl)quinoline. Following general procedure, the indicated compound was purified by flash column chromatography on silica as white powder, yield 82%, mp: 206.2–207.5 °C. 1H NMR (300 MHz in d$_6$-acetone): δ 7.85 (dd, δ = 9.1, 2.1 Hz, 1H), 8.00 (s, 1H), 8.21 (d, δ = 9.0 Hz, 1H), 8.31 (d, δ = 9.3 Hz, 2H), 8.49–8.58 (m, 3H). 13C NMR (100 MHz in d$_6$-DMSO): δ 118.5 (d, δ = 5.1 Hz), 122.5, 123.6 (q, δ = 7.5 Hz), 124.5 (2C), 129.4 (2C), 132.5, 133.8 (d, δ = 33.2 Hz), 134.7, 143.2, 147.1, 149.1, 154.8. IR (cm$^{-1}$): 669.03, 721.60, 839.89, 1055.53, 1269.77, 1490.34, 1541.44, 1607.18, 3083.45, 3440.84. 19F NMR (282 MHz in d$_6$-acetone): δ −62.59. HR-MS (EI): calcd for C$_{14}$H$_2$ClF$_5$NO: 352.0226; found: 352.0225.
References and notes


