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L-Proline-catalyzed one-pot synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones☆

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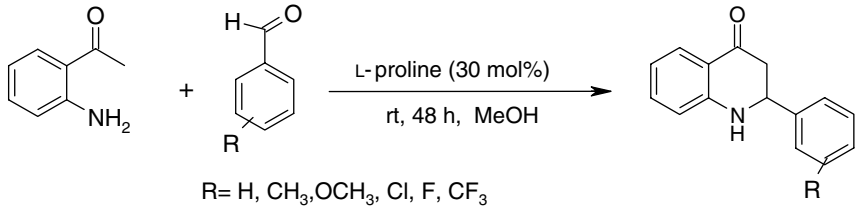
Abstract—L-Proline is utilized as an organocatalyst for the synthesis of substituted 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones, in good yields. The efficiency of the catalyst was proved with a variety of substrates ranging from electron-deficient to electron-rich aryl aldehydes.

2-Substituted dihydroquinolinones have important medicinal properties as New Chemical Entities and also serve as building blocks for creating further diversity in SAR studies in various therapeutic areas.[1] Generally, their synthesis is carried out using acid- or base-catalyzed isomerization of substituted 2-aminochalcones, mainly using corrosive reagents such as orthophosphoric acid, acetic acid or strong alkalis.[2] A recent trend has been to synthesize aza-analogs of natural oxygen heterocycles and screen for biological properties. A representative analog is aza-epothilone,[3] which showed better in vitro activity and also was easily accessible by synthesis.

Flavanones are oxygen heterocycles (benzo pyranones), which are abundant in nature. The synthesis of aza-flavanones/2-aryl-2,3-dihydroquinolin-4(1*H*)-ones has been achieved successfully from 2-amino-chalcones by intramolecular cyclization. Recently, we demonstrated that 2-hydroxyacetophenones and aryl aldehydes undergo a smooth one-pot condensation cyclization in the presence of L-proline as organocatalyst[4] to furnish flavanones in high yields.[5] Herein we describe a general strategy for the synthesis of aza-analogs of flavanones starting from *o*-aminoacetophenone (Scheme 1).[6]

The *o*-aminoacetophenone and benzaldehyde in equimolar quantities were stirred together in the presence of L-proline (30 mol %) and methanol (5 mL, Table 1, entry 1). Work-up furnished 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one in 85% yield. A plausible mechanism is shown in Scheme 2.

Following this result we showed that 4-methoxybenzaldehyde (entry 2) and *o*-aminoacetophenone, under identical reaction conditions gave 2-(4-methoxy-phenyl)-2,3-dihydroquinolin-4(1*H*)-one in 90% yield.



Scheme 1.

Keywords: L-Proline; 2-Aryl-2,3-dihdroquinolin-4(1*H*)-ones; *o*-Amino acetophenone.
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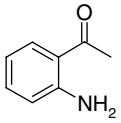
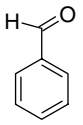
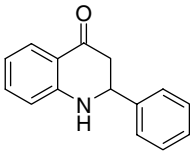
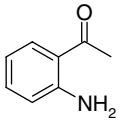
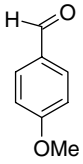
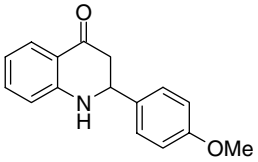
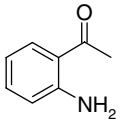
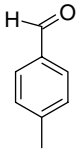
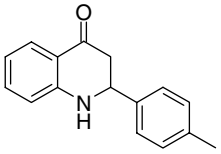
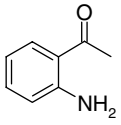
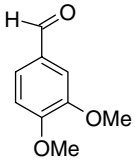
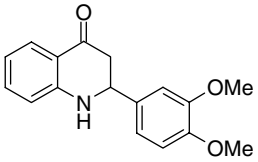
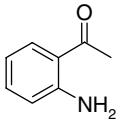
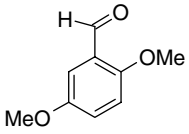
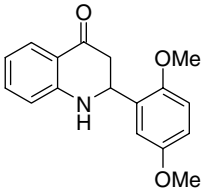
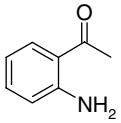
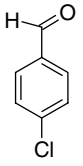
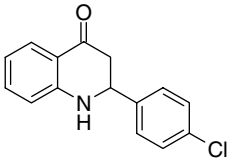
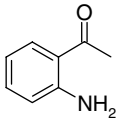
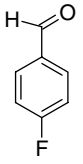
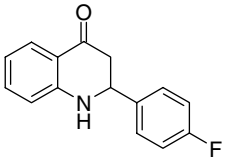
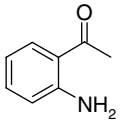
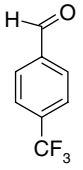
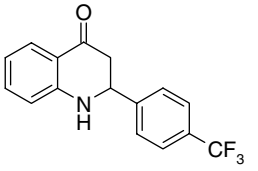
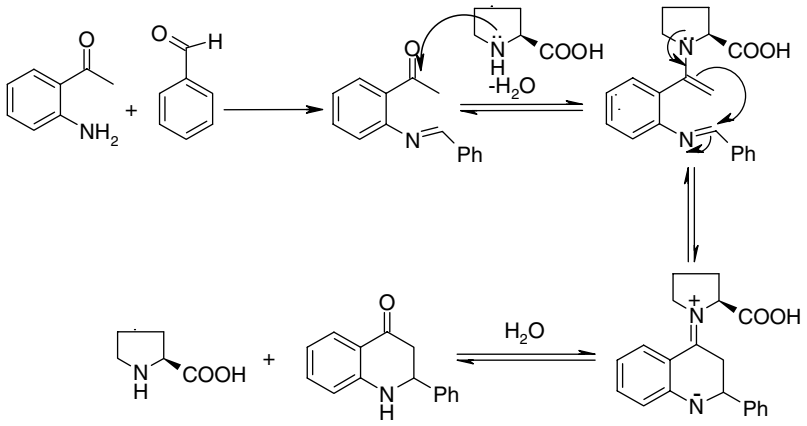
Table 1. L-Proline-catalyzed synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones[a]

Entry	Aminoacetophenone	Aldehyde	Product	Yield[b] (%)
1				85[c]
2				90
3				89
4				93[c]
5				91
6				80
7				82
8				79

[a] All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data.
[b] Isolated yields after column chromatography.
[c] The optical purity of products was found to be less than 10% ee and was not checked for other products.

Similar yields were obtained with various other aldehydes viz., *p*-tolualdehyde (entry 3), 3,4-dimethoxybenzaldehyde (entry 4), 2,5-dimethoxybenzaldehyde (entry 5),[7] 4-chlorobenzaldehyde (entry 6), 4-fluorobenzaldehyde (entry 7),[7] and 4-trifluoromethylbenzaldehyde (entry 8).

We wondered whether the organocatalyst could induce any chirality at the 2-position. Thus 2-phenyl-2,3 dihydroquinolin-4(1*H*)-one was synthesized as a racemate using a literature[1d] procedure, which showed a clear 1:1 mixture on chiral HPLC. However, the product made using L-proline as catalyst (entry 1) showed a mixture of two enantiomers (58:41). Even though the enantioselectivity was low, this method provides an opportunity for further improvements by either tailoring the substrates or the catalysts. Work toward this objective is currently underway.



Scheme 2.

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6. *Typical experimental procedure*: L-Proline (0.44 mmol) was stirred in 5 mL of methanol for 10 min, 2-aminoacetophenone (1.4 mmol) and aldehyde (1.4 mmol) were then added and the mixture was stirred for 48 h. The mixture was treated with 5 mL of saturated ammonium chloride solution and extracted with dichloromethane (3×10 mL). The combined organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography (hexane/ethyl acetate 2:1) to give 2-aryl-2,3-dihydroquinolin-4(1*H*)-one.
7. *Spectral data for selected compounds*: Table 1, entry 5: IR (KBr): ν 3363 (–NH), 1663 (C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.81 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.31–7.23 (m, 1H), 7.04 (d, $J = 2.6$ Hz, 1H), 6.78–6.64 (m, 4H), 5.12 (dd, $J = 11.4$, 4.8 Hz, 1H), 4.48 (br s, 1H, –NH), 3.81 (s, 3H), 3.75 (s, 3H), 2.83–2.66 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.5, 153.6, 151.8, 150.5, 135.0, 129.9, 127.2, 118.7, 117.8, 115.9, 112.9 112.7, 111.4, 55.6, 55.5, 51.2, 43.6; ESIMS: m/z 284 $(M+1)^+$, 306 $(M+Na)^+$; HRMS (EI): m/z calcd for $C_{17}H_{17}NO_3Na$ 306.3116 $(M+Na)^+$, found 306.3109. Table 1, entry 7: IR (KBr): ν 3299 (–NH), 1654 (–C=O) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.82 (dd, $J = 8.0$, 1.8 Hz, 1H), 7.47–7.37 (m, 2H), 7.34–7.25 (m,1H), 7.11–7.00 (m, 2H), 6.82–6.64 (m, 2H), 4.71 (dd, $J = 12.5$, 4.8 Hz, 1H), 4.41 (br s, –NH, 1H), 2.81–2.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 164.0, 161.0 151.5, 136.0, 135.4, 128.3 (2C), 127.5, 118.9, 115.9 (2C), 115.6,57.7, 46.4; ESIMS: m/z 242 $(M+1)^+$, HRMS (EI): m/z calcd for $C_{15}H_{13}FNO$ 242.2682 $(M+H)^+$, found 242.2678.