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Research Article

PYRROLIDINE: AN EFFICIENT CATALYST FOR THE SYNTHESIS OF 2-ARYL-2, 3-DIHYDROQUINOLIN-4(*1H*)-ONE DERIVATIVES IN AQUEOUS ETHANOL MEDIA

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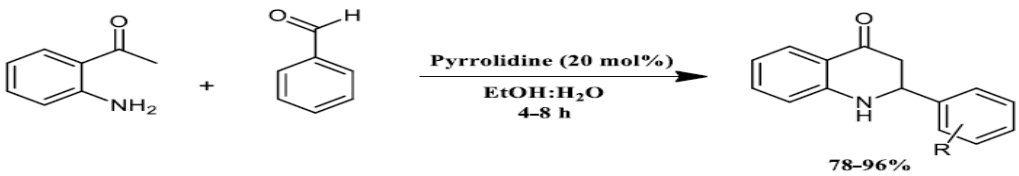
ABSTRACT
A facile, greener and direct synthetic method has been introduced for synthesis of 2-aryl-2,3-dihydroquinoli-4(*1H*)-ones from 2-aminoacetophenone and substituted benzaldehydes using pyrrolidine as an organobase catalyst under mild reaction condition. The merits of this method are short reaction time, operational simplicity, high yield and greener solvent media.

Keywords: Pyrrolidine, 2-aryl-2,3-dihydroquinoli-4(*1H*)-ones, 2-aminoacetophenone, Substituted benzaldehydes.

1. INTRODUCTION
2-Aryl-2,3-dihydroquinolin-4(1H)-one derivatives show variety of therapeutic properties such as anticancer, antibiotic, antitumor agent and further biological activities [1-3]. Bearing in mind valuable biological and therapeutic properties of 2-aryl-2,3-dihydroquinolin-4(1H)-one derivatives researchers developed several routes by using several catalysts like transition metals or metal triflates [4], bifunctional thiourea or ionic liquids [5]. Besides, the researchers have also synthesized from o-aminoacetophenone and aromatic aldehydes by using organocatalyst [6], also microwave irradiation with solid support [7].
Nevertheless, most of the above mentioned methods having disadvantages such as the need for strongly acidic condition [7], toxic solvents [4, 5], lengthy reaction time and significant quantity of catalyst [6]. Recently, with the objective of developing environmentally benign reaction conditions and media for organic reactions with excellent efficiency, it's found that the pyrrolidine and its derivatives are an efficient organocatalyst for some organic transformations [8]. In continuation of our research to find fruitful routes for synthesis of fused heterocyclic compounds [9], here we report the use of pyrrolodine for the synthesis of 2-aryl-2,3-dihydroquilino-4(*1H*)-one derivatives by the cyclization of 2-aminoacetophenone and substituted aromatic aldehydes in aqueous ethanol as shown in scheme 1.



Scheme 1: Pyrrolidine catalyzed synthesis of 2-aryl-2,3-dihydroquilino-4(1H)-ones

2. EXPERIMENTAL
All the chemicals were purchased from commercial suppliers and used without further purification. All solvents were treated according to the standard procedure. The progress of the reaction was monitored by TLC using silica gel 60 F_{254} pre-coated plates. ^{1}H and ^{13}C NMR were recorded on 400 MHz & 100 MHz respectively, in $CDCl_3$ using TMS as the internal

standard. Melting points were determined with a capillary apparatus and were not further corrected.

2.1. General procedure for synthesis of 2-aryl-2,3-dihydroquilino-4(*1H*)-ones

A mixture of 2-aminoacetophenone (1 mmol), benzaldehyde (1 mmol), ethanol: water (5 mL, 1:1) and pyrrolidine (20 mol%) was heated under stirring at 50°C. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was decomposed with 5 mL water and extracted with diethyl ether (3 × 10 mL), washed with brine solution (5 mL) and dried over anhydrous Na_2SO_4. Products were purified by silica gel column chromatography using hexane- diethyl acetate (10:1) as eluent. All the structures were confirmed by their analytical data and comparison with literature data.

2.2. Spectroscopic data for selected compounds

2.2.1. 2-phenyl-2,3-dihydroquilino-4(1H)-ones (Table 2, entry a) [5b, 6b, 10]

Mp: 154-156°C. IR (KBr): 3060, 3028, 1638, 1572, 1494, 1358, 1324, 1295, 1157, 1095, 974, 861 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.5, 1.2 Hz, 1 H), 7.42 (d, *J* = 7.4 Hz, 2 H), 7.40-7.36 (m, 2 H), 7.35-7.33 (m, 2 H), 6.76 (t, *J* = 7.4 Hz, 1 H), 6.68 (d, *J* = 8.5 Hz, 1 H), 4.70 (dd, *J* = 13.5, 3.6 Hz, 1 H), 4.65 (s, 1 H, NH), 2.82 (dd, *J* = 16.3, 14.4 Hz, 1 H), 2.70 (dd, *J* = 15.6, 3.6 Hz, 1H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 192.9, 152.4, 140, 136.1, 128.6, 128.3, 127.4, 126.5, 119.2, 117.2, 116.7, 59.1, 45.7. MS (EI): *m/z* = 223.10 [M^+].

2.2.2. 2-(4-Chlorophenyl)-2,3-dihydroquinolin-4 (1H)-one (Table 2, entry b) [4a, 10, 11]

Mp: 166-168°C. IR (KBr): 3343, 3210, 2980, 1666, 1585, 1221, 1150, 750 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 7.8, 1.2 Hz, 1 H), 7.38-7.31 (m, 5 H), 6.78 (t, *J* = 7.2 Hz, 1 H), 6.71 (d, *J* = 7.8 Hz, 1 H), 4.69 (dd, *J* = 14.5, 4.2 Hz, 1 H), 4.54 (s, 1 H, NH), 2.79 (dd, *J* = 17.3, 14.5 Hz, 1 H), 2.71 (dd, *J* = 17.3, 4.2 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.5, 152.3, 138.4, 136.4, 134.1, 129.2, 127.8, 127.5, 119.2, 118.7, 115.9, 57.8, 46.3. MS (EI): *m/z* = 257.07 [M^+].

2.2.3. 2-(4-Methoxyphenyl)-2,3-dihydroquinolin-4 (1H)-one (Table 2, entry j) [3e, 4a, 12]

Mp: 146-148°C. IR (KBr): 3330, 3145, 2978, 2737, 1663, 1585, 1305, 1224, 1132cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.37-7.33 (m, 2 H), 7.31-7.28 (m, 1 H), 6.95-6.86 (m, 2 H), 6.81-6.74 (m, 1 H), 6.67 (d, *J* = 8.1 Hz, 1 H), 4.69 (dd, *J* = 13.5, 3.6 Hz, 1 H), 4.33 (s, 1 H, NH), 3.80 (s, 3 H), 2.89-2.70 (m, 2 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 193.3, 158.9, 152.1, 135.5, 133.2, 127.9, 127.7, 119.1, 118.4, 116.0, 114.1, 58.0, 55.5, 46.6. MS (EI): *m/z*= 253.10 [M^+].

2.2.4. 2-(4-Bromophenyl)-2,3-dihydroquinolin-4 (1H)-one (Table 2, entry k) [4a, 6b, 11]

Mp: 168-170°C. IR (KBr): 3324, 3053, 1654, 1492, 1325, 1110, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.85 (dd, *J* = 7.8, 1.5 Hz, 1 H), 7.53-7.48 (m, 2 H), 7.36-7.30 (m, 3 H), 6.81-6.76 (m, 1 H), 6.70 (d, *J* = 8.2 Hz, 1 H), 4.71 (dd, *J* = 17.4, 4.8 Hz, 1 H), 4.44 (s, 1 H, NH), 2.87-2.77 (m, 1 H), 2.77-2.70 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.7, 152.3, 141.3, 136.9, 132.3, 128.5, 127.8, 123.4, 119.2, 118.8, 117.1, 58.1, 47.1. MS (EI): *m/z* = 301.02 [M^+].

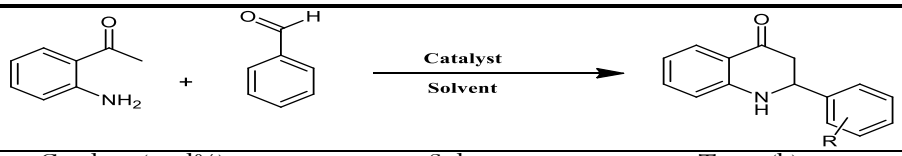
3. RESULT AND DISCUSSION

In order to find optimize reaction condition, we select the synthesis of 2-phenyl-2,3-dihydroquinolin-4(1H)-one from o-aminoacetophenone, substituted aromatic aldehydes and pyrrolidine as a model reaction. We also specify the parameters such as optimum concentration of the catalyst and solvents as summarized in table 1. Pyrrolidine (20 mol%) was found to be most suitable for reaction in aqueous ethanol (1:1) as compared to other solvents such PEG, 1,4-dioxane and DMF (Table 1, entry e).

After finding the standard optimization condition, we synthesized the number of 2-aryl-2,3-dihydroquilino-4(1H)-ones in moderate to excellent yield and 20 mol% pyrrolidine in aqueous ethanol was found suitable for all transformations, results are summarized in table 2. Upon increasing concentration of pyrrolidine over 20 mol%, no significant effect was observed on rate of reaction and yield of product (table 1, entry f), while on decreasing the concentration of pyrrolidine, less than 10 mol% yield was dropped. We also examined the electronic effect of substituents on benzaldehyde and found that electron withdrawing group on benzaldehyde gives better yield as compared to electron donating group. Hence, we can say that the rate of reaction is mostly reliant on electronic nature of substituent present on benzaldehyde. Aqueous-ethanol as a green solvent media is used in this present work, it makes clear that, our ecofriendly approach for synthesis of 2-

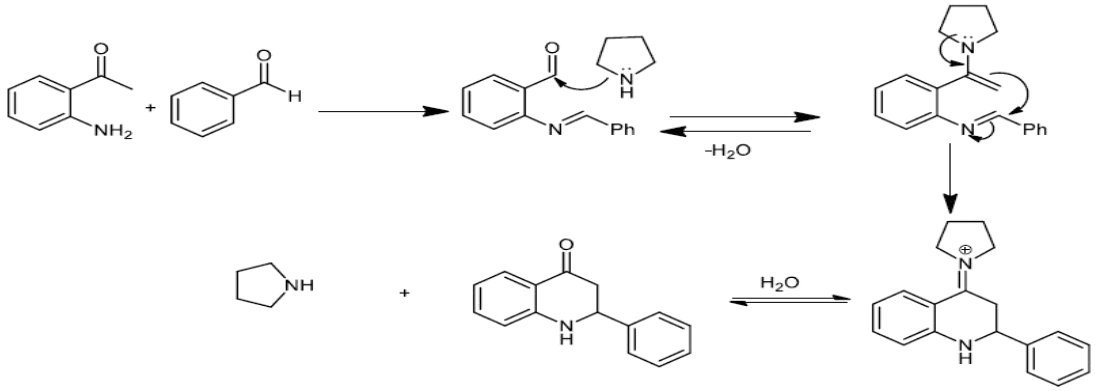
aryl-2,3-dihydroquilino-4(1H)-ones will be an effective step in current progress of aqueous based synthesis over toxic organic mediated approaches and catalyst as well. The structures of products were confirmed from their spectral data and comparison with available literature data. On the basis of results and experimental condition, the formation of 2-phenyl-2,3-dihydroquilino -4(1H)-one by cyclization of 2-aminoacetophenone and benzaldehyde can be revealed by the mechanism in scheme 2.

Table 1: Optimization of reaction conditions for the synthesis of 2-phenyl-2,3-dihydroquinolin-4(1H)-one[a]



Entry	Catalyst (mol%)	Solvents	Time (h)	Yield (%)[b]
a	No catalyst	EtOH	8	28
b	L-proline (30 mol%)	CH_3OH	48	85[6b]
c	Pyrrolidine (10 mol%)	EtOH	8	78
d	Pyrrolidine (20 mol%)	EtOH	6	85
e	**Pyrrolidine (20 mol%)**	**EtOH:H_2O**	**5**	**95**
f	Pyrrolidine (30 mol%)	EtOH:H_2O	5	96
g	Pyrrolidine (20 mol%)	PEG	8	70
h	Pyrrolidine (20 mol%)	1,4-Dioxane	6	65
i	Pyrrolidine (20 mol%)	DMF	6	70

[a]Reaction condition: 2-aminoacetophenone (1 mmol); benzaldehyde (1 mmol); ethanol: water (5mL, 1:1), stirring at 50°C, [b]Isolated yield



Scheme 2: Possible mechanism for the formation of 2-phenyl-2,3-dihydroquilino-4(1H)-one

Table 2: Synthesis of 2-aryl-2,3-dihydroquilino-4(1H)-ones[a]

Entry	R-	Time (h)	Yield[b] (%)
a	Ph-	5	95
b	4-ClC_6H_4	6	88
c	2-ClC_6H_4	6	90
d	4-MeC_6H_4	7	88
e	4-$NO_2C_6H_4$	4	92
f	2,4-$(NO_2)_2C_6H_3$	4	96
g	2-MeC_6H_4	8	90
h	3-$NO_2C_6H_4$	5	82
i	4-$N(Me)_2C_6H_4$	6	78
j	4-$MeOC_6H_4$	8	80
k	4-BrC_6H_4	5	84
l	4-FC_6H_4	5	88

[a]Reaction condition: 2-aminoacetophenone (1 mmol); benzaldehyde (1 mmol), pyrrolidine (20 mol%); EtOH: H2O (1:1); stirring at 50°C, [b]Isolated yield

4. CONCLUSION

In conclusion, an efficient and greener methodology has been developed for the preparation of 2-aryl-2,3-dihydroquilino-4(1H)-ones by using pyrrodine as a water tolerant base. The main benefits of our scheme are excellent yield of product, mild reaction condition, easy to work-up and most important no use of any hazardous metal catalyst and solvents.

5. ACKNOWLEDGEMENT

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