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Zirconyl Nitrate as an Efficient Catalyst for Facile Synthesis of 2-Aryl-2,3-dihydroquinolin-4(1*H*)-one Derivatives in Aqueous Medium

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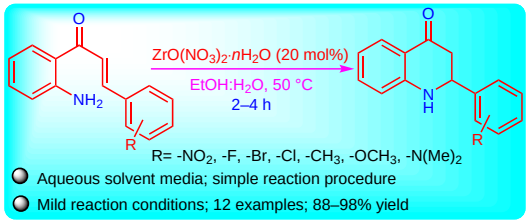

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Abstract A simple, green, and efficient method is introduced for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones under mild reaction conditions with improved yields by intramolecular cyclization of *o*-aminochalcones with zirconyl nitrate [$Zn(O)(NO_3)_2{\cdot}nH_2O$] as a water-tolerant Lewis-acid catalyst.

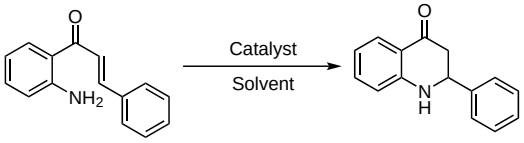
Key words zirconyl nitrate, dihydroquinolinones, aminochalcones, cyclization, Lewis acids

2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones exhibit a variety of pharmaceutical properties, such as anticancer, antibiotic, and antitumor activities.[1–3] Several routes have been reported for their synthesis from *o*-aminochalcones by using catalysts such as transition metals or metal triflates,[4] thiourea, or ionic liquids.[5] In addition, 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones have also been synthesized by reaction between *o*-aminoacetophenone and aromatic aldehydes in the presence of an organocatalyst,[6] under microwave irradiation, or on a solid support.[7]

However, most of these methods have drawbacks such as the need for strongly acidic or basic reagents[7] or the use of toxic solvents,[4,5] long reaction times, or large quantities of catalyst.[6] In the context of developing environmentally benign reaction conditions and media for organic transformations, zirconyl nitrate [$Zn(O)(NO_3)_2{\cdot}nH_2O$] and its salts have been found to be effective, water-tolerant, reusable Lewis acids.[8] We have been engaged in finding productive routes for the synthesis of fused heterocyclic compounds.[9] In this work, we report for the first time the use of zirconyl nitrate in the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones by the intramolecular cyclization of *o*-aminochalcones in aqueous ethanol.

To find the best experimental conditions, we targeted the synthesis of 2-phenyl-2,3-dihydroquinolin-4(1*H*)-one from (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one. We also optimized such parameters as the concentration of the catalyst and the solvents, as summarized in Table 1. Zirconyl nitrate (20 mol%) was found to be best suited catalyst

Table 1 Optimization of Reaction Conditions for the Synthesis of 2-Phenyl-2,3-dihydroquinolin-4(1*H*)-one[a]

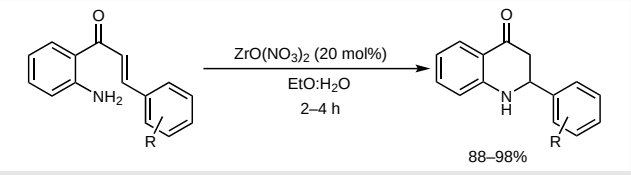


Entry	Catalyst (mol%)	Solvent	Time (h)	Yield[b] (%)
1	$SbCl_3$(20 mol%)	CH_3CN	3	60
2	ZnO (20 mol%)	CH_3CN	5	52
3	ZnO (20 mol%)	EtOH	4	58
4	$ZrO(NO_3)_2{\cdot}nH_2O$ (10 mol%)	CH_3CN	3	70
5	$ZrO(NO_3)_2{\cdot}nH_2O$ (10 mol%)	EtOH	3	79
6	$ZrO(NO_3)_2{\cdot}nH_2O$ (20 mol%)	EtOH	3	96
7	$ZrO(NO_3)_2{\cdot}nH_2O$ (20 mol%)	1:1 EtOH–H_2O	3	98
8	$ZrO(NO_3)_2{\cdot}nH_2O$ (20 mol%)	1,4-dioxane	4	80
9	$ZrO(NO_3)_2{\cdot}nH_2O$ (20 mol%)	toluene	4	78

[a] Reaction condition: (*E*)-1-(2-aminophenyl)-3-phenylprop-2-en-1-one (1 mmol), solvent (4 mL), stirring, 50 °C.
[b] Isolated yield.

for the reaction and 1:1 aqueous ethanol (Table 1, entry 7) was the best solvent, as compared with CH_3CN, 1,4-dioxane, or toluene (entries 2, 8, and 9).

By using the optimized conditions of 20 mol% of zirconyl nitrate in 1:1 aqueous ethanol at 50 °C, we went on to prepare a number of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones from various substituted 2-aminochalcones (Scheme 2). The yields and reaction times are summarized in Table 2. In these transformations, we confirmed that 20 mol% of zirconyl nitrate is the optimum concentration. Increasing the concentration of the catalyst (>20 mol%) did not affect the rate of reaction or the yield of the product. We also studied the effect of substituents on the progress of reaction, and we found that electron-donating substituents facilitate the reaction compared with electron-withdrawing substituents.



Scheme 1 Zirconyl nitrate-catalyzed synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones

Table 2 Synthesis of 2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones[a]

Entry	R	Time (h)	Yield[b] (%)
1	Ph	3	98
2	4-Cl	4	97
3	2-Cl	3	96
4	4-CH_3	3	98
5	4-NO_2	4	88
6	2,4-$(NO_2)_2$	4	86
7	2-CH_3	2.5	99
8	3-NO_2	3	93
9	4-$N(CH_3)_2$	3	95
10	4-OCH_3	2.5	99
11	4-Br	3	96
l2	4-F	3	94

[a] Reaction condition: 2-aminochalcone (1 mmol), $ZrO(NO_3)_2{\cdot}nH_2O$ (46 mg, 20 mol%), 1:1 EtOH– H_2O (4 mL), stirring, 50 °C.
[b] Isolated yield.

We have also confirmed the structures of the synthesized products from their spectroscopic (IR and ^1H and ^{13}C NMR) and mass spectrometric data, and by comparison with data available in the literature.

In conclusion, a simple, efficient, and greener one-pot method has been developed for the synthesis of 2-aryl-2,3-dihydroquinolin-4(1*H*)-ones by using zirconyl nitrate as a water-tolerant Lewis acid catalyst.[10] Compared with previously reported methods, this method proceeds under mild reaction conditions.

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(10) **2-Aryl-2,3-dihydroquinolin-4(1*H*)-ones; General Procedure**

A mixture of the appropriate 2-aminochalcone (1 mmol), EtOH (2 mL), H_2O (2 mL), and $ZrO(NO_3)_2{\cdot}nH_2O$ (46 mg, 20 mol%) was heated with stirring at 50 °C while the progress of the reaction was monitored by TLC. The reaction was then quenched with H_2O (5 mL), and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine (5 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography [silica gel, hexane–EtOAc (10:1)].

2-Phenyl-2,3-dihydroquinolin-4(1*H*)-one (Table 2, Entry 1)[5b,6b,11]

Off-white solid; yield: 218 mg (98%); mp 153–155 °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, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 192.9, 152.4, 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-(4-Chlorophenyl)-2,3-dihydroquinolin-4(1*H*)-one (Table 2 Entry 2)[4a,11,12]

Red solid; yield: 249 mg (97%); mp 168–170 °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-(4-Methoxyphenyl)-2,3-dihydroquinolin-4(1*H*)-one (Table 2, Entry 10)[3e,4a,13]

Brown solid; yield: 250 mg (99%); mp 145–147 °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-(4-Bromophenyl)-2,3-dihydroquinolin-4(1*H*)-one (Table 2, Entry 11)[4a,6b,12]

Brown solid; yield: 290 mg (96%); mp 167–169 °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^+].

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