A Novel Method for the Synthesis of 4(3*H*)-Quinazolinones

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Different metal perchlorates were screened to catalyze the three-component reaction of anthranilic acid, triethyl orthoformate and amines to afford quinazolin-4(3*H*)-ones in solvent-free conditions. $Ni(ClO_4)_2$ or $Zn(ClO_4)_2$ was demonstrated to be efficient to catalyze the reaction.

Keywords: Perchlorates; Quinazolin-4(3*H*)-ones; Amine; One-pot reaction.

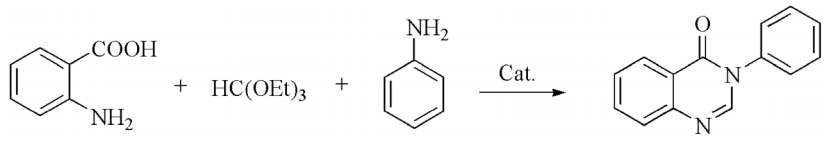
INTRODUCTION

4(3*H*)-Quinazolinones have emerged as an important class of nitrogenated heterocycles that have attracted significant synthetic interest because of their pharmacological and therapeutic properties such as antibacterial, antifungal, antimalarial, antihypertensive, anticonvulsant, anti-Parkinsonism, antihistaminic and local anaesthetic, analgesic, anti-inflammatory antiviral and anticancer activities.[1] A small number of quinazolinones have been reported as potent chemotherapeutic agents in the treatment of tuberculosis. For example, 3-aryl-6,8-dichloro-2*H*-1,3-benzoxazine-2,4-(3*H*)-diones, 3-arylquinazoline-2,4(1*H*,3*H*)-diones as antimycobacterial agents[2] and quinazolinone derivatives as antitubercular agents.[3] The antihyperlipidemic activities of these compounds were also investigated.[4] There are several methods for the synthesis of 4(3*H*)-quinazolinones.[5] However, most of these procedures have significant drawbacks such as long reaction time, low yields, harsh reaction conditions, difficult work-up and use of environmentally toxic reagents or media. In 2004, Das and his co-workers have demonstrated a green process for the synthesis of 4(3*H*)-quinazolinones, which is limited in that only phenyl groups are tolerated.[6] In 2005, Liu reported another procedure for the synthesis of these compounds through a two-step reaction in the presence of $(PhO)_3P$/anhydrous pyridine under microwave irradiation at 250 °C.[7] The second strategy seems to be more flexible but toxic reagents and harsh reaction conditions are required. More recently, Khosropour[8] and Narasimhulu[9] reported separately that $Bi(TFA)_3$-[nbp]$FeCl_4$ or $La(NO_3)_3 \cdot 6H_2O$ can promote to synthesis 4(3*H*)-quinazolinones. These catalysts also seem to be more flexible and a little expensive.

The demand for increasingly clean and efficient chemical synthesis is important for both economic and environmental points of view. One commonly used method is to perform reactions without use of harmful organic solvents and in solvent-free conditions. Herein, we want to present a high yield condensation of anthranilic acid, triethyl orthoformate and amines to synthesize 4(3*H*)-quinazolinones in solvent-free conditions.

First of all, we occasionally found that perchlorate, such as $Mn(ClO_4)_2$, can perform very well the condensation of anthranilic acid, triethyl orthoformate and amines to 4(3*H*)-quinazolinones in moderate yields. Screening of series of perchlorate catalysts for this reaction revealed that $Ni(ClO_4)_2$ and $Zn(ClO_4)_2$ are better than other perchlorates.

Scheme I



1 **2** **3a** **4a**

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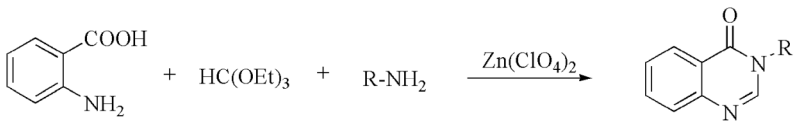
Scheme II



1 **2** **3** **4**

Table 1. One-pot reaction of anthranilic acid (**1**), triethyl orthoformate (**2**) and aniline (**3a**) catalyzed by various perchlorates under different reaction conditions[a] (Scheme I)

Entry	Catalyst	Amount of Catalyst (%)	Time (h)	Yield of **4a** (%)[b]
1	$Mn(ClO_4)_2$	5	3	43
2	$Co(ClO_4)_2$	5	3	80
3	$Cu(ClO_4)_2$	5	3	52
4	$Cd(ClO_4)_2$	5	3	44
5	$Ni(ClO_4)_2$	5	3	92
6	$Zn(ClO_4)_2$	5	3	92
7	$Ni(ClO_4)_2$	2.5	3	90
8	$Zn(ClO_4)_2$	2.5	3	94
9	$Ni(ClO_4)_2$	1	3	66
10	$Zn(ClO_4)_2$	1	3	58

[a] Refluxed at 70 °C for 3 h under solvent-free conditions.
[b] Isolated yield.

The results are summarized in Table 1.

From Table 1, we know that when reducing the amount of catalyst to 2.5%, the yields were slightly effected (entries 7 and 8). When the amount of catalyst was reduced to 1%, the yields were significantly reduced from good to moderate (entries 9 and 10). Then a wide range of structurally varied amines, including aromatic amines and aliphatic amines were examined in the presence of a catalytic amount (2.5% mol.) of $Zn(ClO_4)_2$ under solvent-free conditions (Scheme II). The results are summarized in Table 2.

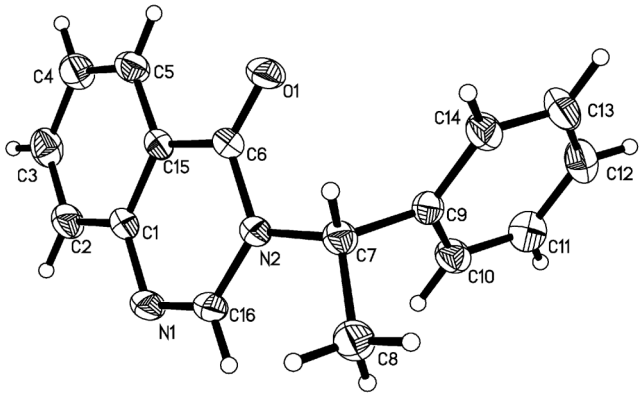


Fig. 1. X-ray crystal structure of **4k**.

From Table 2, we come to realize that either aromatic amines or aliphatic amines work very well in this reaction, **4f**, **4h and 4j** are unknown compounds whose structures are fully supported by ^1H, ^{13}C NMR, GC-MS, EA and IR spectroscopy. The other compounds are also confirmed by ^1H, ^{13}C NMR, EA and IR spectroscopy. The structure of **4k** was confirmed by a single crystal X-ray analysis (Fig. 1). Crystal data and structure refinement are given in Table 3.

We propose a methanism similar to that of Wang[5f] for the reaction. The first step in this reaction involves the zinc-catalyzed formation of imidic ester **5** by reaction of ortho ester with anthranilic acid; meanwhile the intermediate **5** was stabilized by zinc species. The imidic ester is very prone to react immediately with amine and to form an amidine intermediate 6 stabilized by zinc complex, which is the key rate-limiting step. Subsequently, the reaction proceeds via the amidine intermediate **6** by intramolecular attack of the nitrogen nucleophile at carbonyl carbon, which is activated by zinc salt to produce the corresponding

Scheme III

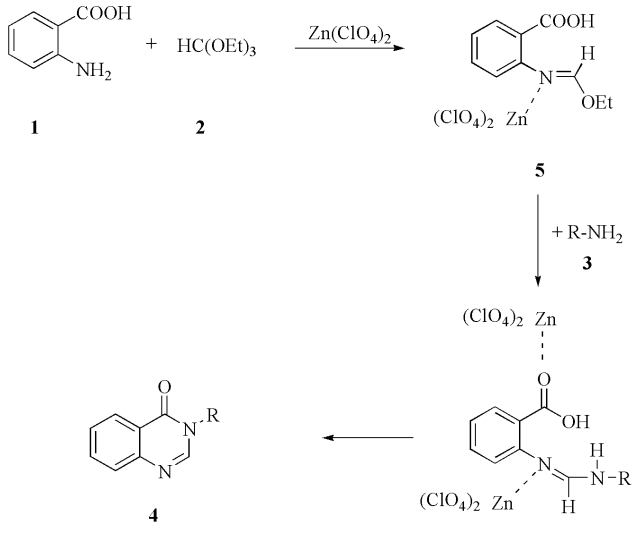
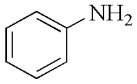
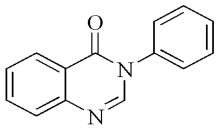
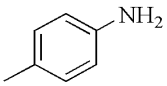
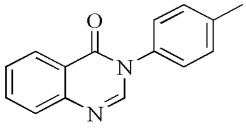
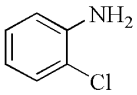
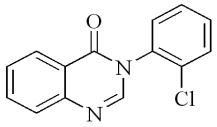
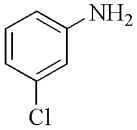
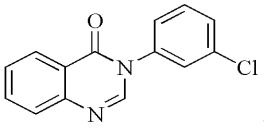
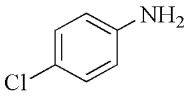
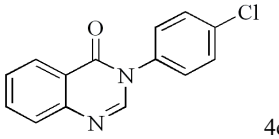
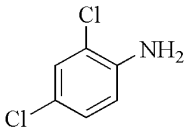
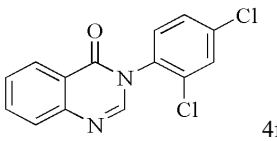
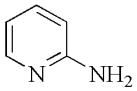
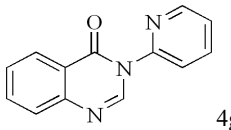
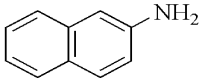
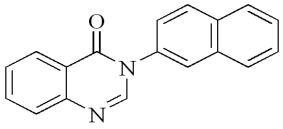
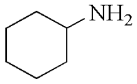
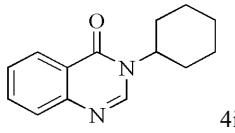
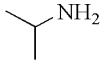
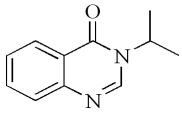
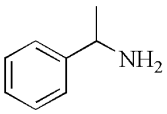
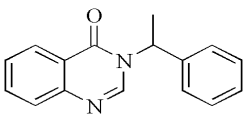
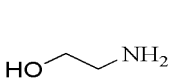
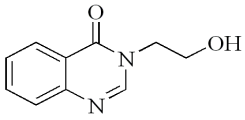
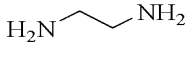
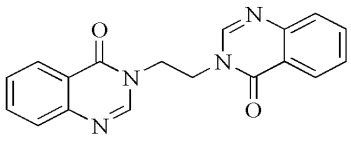


Table 2. One-pot synthesis of different quinazolin-4(3*H*)-ones catalyzed by $Zn(ClO_4)_2$ under solvent-free conditions[a] (Scheme II)

Entry	R	Product	Time (h)	Yield (%)[b]
1		 4a	3	94
2		 4b	2	95
3		 4c	3	92
4		 4d	3	93
5		 4e	2.5	91
6		 4f	3	86
7		 4g	3	84
8		 4h	3.5	87
9		 4i	1.5	94
10		 4j	2	88
11		 4k	2.5	90

12		 4l	2	95
13		 4m	1	98

[a] Refluxed at 70 °C for the time given under solvent-free conditions.
[b] Isolated yield.

Table 3. Crystal data and structure refinement

Formula	$C_{16}H_{14}N_2O$
Formula weight	250.29
Crystal size (mm)	0.30 × 0.30 × 0.20 mm
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	
a (Å)	5.8843(11)
b (Å)	9.3707(18)
c (Å)	11.762(2)
α (°)	92.312(2)
β (°)	97.266(2)
γ (°)	94.253(2)
V (Å^3)	640.8(2)
Z	2
D_c (g cm^{-1})	1.297
F (000)	264
T (K)	296(2)
μ (MoKα) (mm^{-1})	0.083
Limiting indices	$-7 \le h \le 6$, $-11 \le k \le 12$, $-15 \le l \le 15$
Completeness to theta = 27.63	97.4%
θ range (°)	1.8 to 27.6
Absortion crrection	None
Reflections collected/unique	5653/2900 [R(int) = 0.026]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2900/0/173
Final *R* indices [I > 2σ(I)]	R1 = 0.0461, wR2 = 0.1259
R indices (all data)	R1 = 0.0645, wR2 = 0.1424
GoF	1.024
Largest diff. peak and hole (e Å^{-3})	0.201 and -0.272

cyclized product **4** (Scheme III).

In summary, we have demonstrated an efficient procedure for the synthesis of 4(3*H*)-quinazolinones. The notable features of this procedure are mild reaction conditions, clear reaction profiles, improved yields for both anilines and primary amines, enhanced rates and simplicity in operation, which make it a useful and attractive process for the synthesis of 4(3*H*)-quinazolinones.

EXPERIMENTAL

Melting points were obtained on a hot-plate microscope apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectroscopies were recorded with a Bruker AV-600 spectrophotometer. IR spectra were obtained on a Nicolet FT-IR 740 spectrometer (KBr disc). Mass spectra were performed using FINIGAN Trace DSQ instrument. Elemental analysis was determined on Perkin Elmer 1102b Instrument. X-ray data were collected on a Bruker Smart APEX-2 diffractometer. The structures were refined by full-matrix least square method using SHELXL97. In the final step of refinement procedure, all nonhydrogen atoms were refined with anisotropic displacement parameters.

Typical procedure for the synthesis of 3-(pyridin-2-yl)-quinazolin-4(3*H*)-one (4g)

To a mixture of anthranilic acid (1 mmol), triethyl orthoformate (1.5 mmol) and pyridin-2-amine (1 mmol), $Zn(ClO_4)_2$ (0.025 mmol) was added. The reaction mixture was stirred at 70 °C for 3 h. After completion of the reaction (monitored by TLC), the mixture was washed with water (3 × 10 mL). The residue was chromatographed on silica gel to afford pure (**4g**): White needle; Mp: 131-132 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 8.64 (t, *J* = 7.3 Hz, 2H), 8.39 (s, 1H), 7.90-7.91 (m, 2H), 7.78-7.83 (m, 2H), 7.54-7.57 (m, 1H), 7.39-7.41 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 160.4, 149.6, 149.2, 147.5, 144.9, 138.1, 134.8, 127.7, 127.2, 123.6, 122.2, 121.5; IR (KBr): 3061, 1684, 1608, 1474, 1435, 1328, 1290, 1256, 915, 870, 771 cm^{-1}; Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.81; H, 3.92; N, 18.97.

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Supplementary data

Crystallographic data (CCDC-680038 for **4k**) has been deposited at the Cambridge Crystallographic Database Centre.

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