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Gallium(III) triflate-catalyzed one-pot selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones

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Abstract

A series of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones have been synthesized in good to excellent yields and high selectivity by one-pot reaction using isatoic anhydride, ammonium acetate (or amines), and aldehydes in ethanol or in DMSO under mild conditions, respectively. The reaction was efficiently promoted by 1 mol % $Ga(OTf)_3$ and the catalyst could be recovered easily after the reactions and reused without evident loss of reactivity.

Keywords: Gallium(III) triflate; 2,3-Dihydroquinazolin-4(1*H*)-ones; Quinazolin-4(3*H*)-ones; One-pot; Selective synthesis

2,3-Dihydroquinazolin-4(1*H*)-ones are an important class of heterocycles with a wide range of pharmacological and biological activities.[1] A number of synthetic methods to prepare these compounds have been described in the past few years. The typical procedure for the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones involves the condensation reaction of anthranilamide with aldehyde or ketone using *p*-toluenesulfonic acids as a catalyst under vigorous conditions.[2] In 2002, our group reported a method to prepare 2,3-dihydroquinazolin-4(1*H*)-ones by reductive cyclization of *o*-nitrobenzamide or *o*-azido-benzamide with aldehydes and ketones using metallic samarium in the presence of iodine or SmI_2.[3] A recent report described the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones by the reductive desulfurization of 2-thioxo-3*H*-quinazolin-4-ones with nickel boride in dry methanol.[4] Shi reported the synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones by the novel reductive cyclization of *o*-nitrobenzamides and orthoformate, aldehydes, or ketones with the aid of a low-valent titanium reagent.[5] Recently, Kurth reported a one-pot conversion of 2-nitro-*N*-arylbenzamides to 2,3-dihydroquinazolin-4(1*H*)-ones using $SnCl_2$.[6] Salehi and co-workers reported a new one-pot synthesis of these compounds using *p*-toluenesulfonic acids,[7a] silica sulfuric acid,[7b] alum,[7c] and Montmorillonite K-10.[7d] Very recently, we reported a method for the preparation of 2,3-dihydroquinazolin-4(1*H*)-ones in ionic liquids without additional catalyst.[7e]

Quinazolin-4(3*H*)-ones are also important building blocks in the synthesis of natural and pharmacological compounds.[8] Various approaches toward the synthesis of quinazolin-4(3*H*)-ones derivatives have been explored during the past years. One of the most common approaches is the cyclization of anthranilamides with aldehyde in the presence of various promoting agents, such as $NaHSO_3$,[9] *p*-toluenesulfonic acids/DDQ,[10] I_2,[11] $CuCl_2$ (3.0 equiv),[12] and $FeCl_3$ (2.0 equiv).[13] Some other methods include cyclization reaction of 2-amino benzamides with substituted benzoyl chlorides in ionic liquid,[14] and cyclization of *o*-acylaminobenzamides,[15] 2-amino-benzonitrile,[16]

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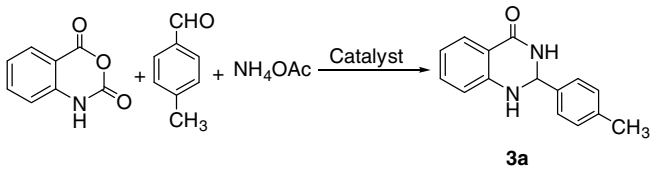
N-arylorthanilamides,[17] nitroenes,[18] and aza-Wittig reactions of α-azido-substituted aromatic imides.[19] Recently, Rao reported a one-pot three-component coupling of isatoic anhydride/anthranilic acid, orthoesters, and amines using Nafion-H as a heterogeneous catalyst under microwave irradiation conditions.[20]

However, methods for the selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones have not been explored before. Thus, developing versatile approaches to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones selectively still remains a highly desired goal in organic synthesis.

Recently, we have successfully applied metal triflates into several reactions.[21] As a result of our great interest in Lewis acid-catalyzed organic reactions, we herein report a practical method for the selective synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones by employing isatoic anhydride, ammonium acetate (amines), and aldehydes in one-pot.

Initially, we investigated various conditions in the model reaction (Table 1). Among all the solvents screened, such as dichloromethane, acetonitrile, water, THF, ethanol, and nitromethane, ethanol is the best. Without any catalyst, the yield was poor even for longer time. $Ga(OTf)_3$ proved to be a superior catalyst among all the catalysts screened in this transformation. It should be noted that 1 mol % of $Ga(OTf)_3$ was efficient enough to catalyze the reaction, and increasing the amount of catalyst did not improve the yield significantly (Table 1, entries 13–15). Finally, we achieved an optimized condition using 1 mol % of $Ga(OTf)_3$ as the catalyst in ethanol.

Table 1
Condensation of isatoic anhydride, *p*-methylbenzaldehyde, and ammonium acetate under various different reaction conditions[a]



3a

Entry	Solvent	Catalyst (mol %)	Yield[b] (%)
1	EtOH	$Cu(OTf)_2$ (10)	68
2	EtOH	$Zn(OTf)_2$ (10)	74
3	EtOH	$Mg(OTf)_2$ (10)	43
4	EtOH	$Sr(OTf)_2$ (10)	73
5	EtOH	$Sc(OTf)_3$ (10)	86
6	EtOH	$Y(OTf)_3$ (10)	80
7	EtOH	$Bi(OTf)_3$ (10)	78
8	EtOH	$La(OTf)_3$ (10)	79
9	EtOH	$Sm(OTf)_3$ (10)	80
10	EtOH	$Eu(OTf)_3$ (10)	81
11	EtOH	$Er(OTf)_3$ (10)	77
12	EtOH	$Yb(OTf)_3$ (10)	78
13	EtOH	$Ga(OTf)_3$ (10)	88
14	EtOH	$Ga(OTf)_3$ (5)	88
15[c]	EtOH	$Ga(OTf)_3$ (1)	87, 85, 84
16	EtOH	$Ga(OTf)_3$ (0.5)	81
17	CH_2Cl_2	$Ga(OTf)_3$ (1)	33
18	CH_3CN	$Ga(OTf)_3$ (1)	50
19	H_2O	$Ga(OTf)_3$ (1)	42
20	THF	$Ga(OTf)_3$ (1)	48
21	CH_3NO_2	$Ga(OTf)_3$ (1)	61
22[d]	EtOH	None	15

[a] Reaction conditions: isatoic anhydride (5.5 mmol), ammonium acetate (6.0 mmol), *p*-methylbenzaldehyde (5 mmol), catalyst (0.5–10 mol %), 70 °C, 45 min.
[b] Isolated total yield.
[c] Catalyst was reused three times.
[d] 70 °C for 4 h.

Next, we studied the scope of this reaction (Table 2). As expected, this reaction proceeded smoothly and the desired products were obtained in good to excellent yields. A series of aldehydes with either electron-donating or electron-withdrawing groups attaching to aromatic ring were investigated. The substitution groups on the aromatic ring had no obvious effect on the yield. We also examined reaction of aromatic heterocyclic aldehydes with anthranilamide, and the desired products of **3m**,**n** were obtained in high yields (Table 2, entries 13 and 14). Similarly, **3o**–**s** in good yields were obtained from 5-chloro isatoic anhydride, aldehydes, and ammonium acetate (Table 2, entries 15–19).

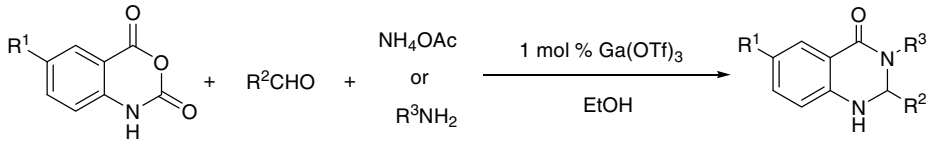
On the other hand, we investigated the synthesis of 2,3-disubstituted 2,3-dihydroquinazolin-4(1*H*)-ones from isatoic anhydride, amines, and aldehydes under the optimized reaction condition (Table 2, entries 20–25). The disubstituted products of **3t**–**y** were obtained in high yields. Meanwhile, we confirmed the structure of **3v** by X-ray single crystal diffraction analysis (Fig. 1).[22]

Interestingly, a trace of **3a** could be transformed to 2-*p*-tolylquinazolin-4(3*H*)-one **4a** when **3a** was dissolved in DMSO for about 12 h. According to the literature,[23] DMSO could act as a mild oxidant that oxidize **3a** into **4a**. The unexpected results prompted us to focus on the synthesis of quinazolin-4(3*H*)-ones **4** using isatoic anhydride, aldehyde, and ammonium acetate in the presence of $Ga(OTf)_3$.

Initially, we investigated the reaction of isatoic anhydride, *p*-methylbenzaldehyde, and ammonium acetate in DMSO in the presence of $Ga(OTf)_3$. As expected, **4a** was obtained in good yield. The structure of **4a** was confirmed by IR, ^1H, ^{13}C NMR, and EI-MS spectral analysis as 2-*p*-tolylquinazolin-4(3*H*)-one. The structure of **3a** was determined by EI-MS analysis (*m*/*z* 238, M^+) as $C_{15}H_{14}N_2O$, which matches the expected 2-*p*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one. Compared with **3a**, the ^1H NMR of **4a** showed two additional proton signals disappearing and another proton signal shifting from 8.26 ppm to 12.44 ppm (N^3–H), which was similar to the previously reported value.[1b,12] In the ^{13}C NMR spectrum of compound **4a**, the peak of carbon signal also shifted from 66.5 ppm to 152.2 ppm (C-2). All spectral data confirmed our assignment of **4a** as 2-*p*-tolylquinazolin-4(1*H*)-one.

Then, various aldehydes with either electron-donating or electron-withdrawing groups on aromatic ring were investigated in DMSO in the presence of a catalytic amount of $Ga(OTf)_3$, and the results are listed in Table

Table 2
One-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones catalyzed by $Ga(OTf)_3$[a]



1 **3**

Entry	R^1	R^2	NH_4OAc or R^3NH_2	Time (min)	Product	Yield[b] (%)	Mp (°C)
1	H	*p*-$(CH_3)C_6H_4$	NH_4OAc	50	**3a**	86	233–234[5a]
2	H	C_6H_5	NH_4OAc	55	**3b**	87	218–219[5a]
3	H	*p*-$(OCH_3)C_6H_4$	NH_4OAc	35	**3c**	86	192–193[1b]
4	H	2,4-$(OCH_3)_2C_6H_3$	NH_4OAc	45	**3d**	90	186–187[7e]
5	H	*p*-$(N(CH_3)_2)C_6H_4$	NH_4OAc	35	**3e**	88	228–229[7e]
6	H	*p*-$(OH)C_6H_4$	NH_4OAc	50	**3f**	86	278–280
7	H	*m*-$(F)C_6H_4$	NH_4OAc	50	**3g**	85	266–267
8	H	*p*-$(Cl)C_6H_4$	NH_4OAc	35	**3h**	89	205–206[5a]
9	H	*p*-$(F)C_6H_4$	NH_4OAc	50	**3i**	83	199–200[7e]
10	H	*o*-$(NO_2)C_6H_4$	NH_4OAc	70	**3j**	71	193–194[7e]
11	H	*m*-$(NO_2)C_6H_4$	NH_4OAc	60	**3k**	78	216–217[7e]
12	H	*p*-$(NO_2)C_6H_4$	NH_4OAc	60	**3l**	73	213–214[7e]
13	H	2-Furyl	NH_4OAc	40	**3m**	91	167–168
14	H	2- Pyridyl	NH_4OAc	50	**3n**	88	187–188
15	Cl	C_6H_5	NH_4OAc	55	**3o**	80	249–250[3a]
16	Cl	*p*-$(CH_3)C_6H_4$	NH_4OAc	50	**3p**	86	250–251
17	Cl	*p*-$(OCH_3)C_6H_4$	NH_4OAc	40	**3q**	83	220–221
18	Cl	*p*-$(F)C_6H_4$	NH_4OAc	55	**3r**	83	248–249
19	Cl	*p*-$(NO_2)C_6H_4$	NH_4OAc	50	**3s**	80	220–221
20	H	C_6H_5	$^sBuNH_2$	55	**3t**	83	175–176
21	H	*p*-$(OH)C_6H_4$	$EtNH_2$	50	**3u**	87	183–184[7c]
22	H	*p*-$(Cl)C_6H_4$	$^nBuNH_2$	50	**3v**	89	150–151
23	H	*p*-$(NO_2)C_6H_4$	$^nPr\ NH_2$	50	**3w**	87	125–126[7c]
24	H	C_6H_5	$C_6H_5NH_2$	60	**3x**	79	214–215[7b]
25	H	*p*-$(Cl)C_6H_4$	$C_6H_5NH_2$	60	**3y**	82	219–220[7b]

[a] For general experimental procedure, see Ref. 25.
[b] Isolated total yield.

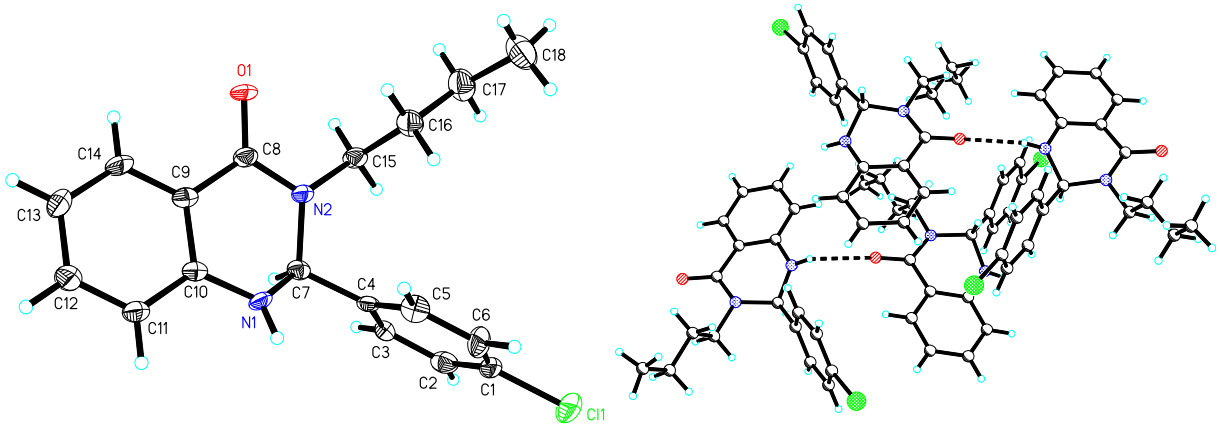
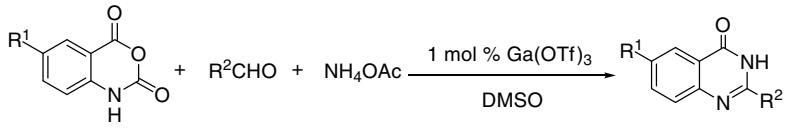


Fig. 1. X-ray molecular structure and intermolecular hydrogen bond of **3v**.

3, which exhibited a $Ga(OTf)_3$-catalyzed cyclization and a subsequent oxidation.

A tentative mechanism for the formation of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones was proposed (Scheme 1). The first step may involve the condensation of isatoic anhydride **1** with ammonia, and then anthranilamide **5** could be produced with the liberation of carbon dioxide. Next step, intermediate **6** could be obtained by addition of **5** with aldehydes promoted by $Ga(OTf)_3$. The part of amide in intermediate **6** could be converted into tautomer in the presence of $Ga(OTf)_3$. Meanwhile, the part of imine in intermediate **6** could be

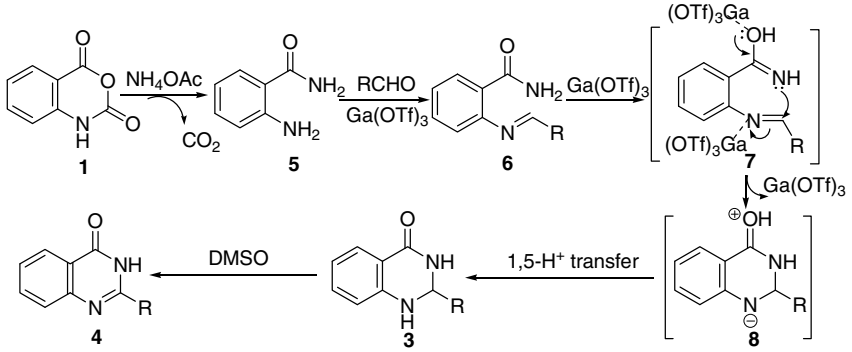
Table 3
One-pot synthesis of quinazolin-4(3*H*)-ones catalyzed by $Ga(OTf)_3$[a]



1 4

Entry	R^1	R^2	Product	Time (min)	Yield[b] (%)	Mp (°C)
1	H	*p*-$(CH_3)C_6H_4$	**4a**	50	84	240–241[14]
2	H	C_6H_5	**4b**	55	83	237–238[13]
3	H	*p*-$(OCH_3)C_6H_4$	**4c**	55	82	245–246[11]
4	H	2,4-$(OCH_3)_2C_6H_3$	**4d**	50	89	206–207
5	H	3,4-$(CH_2O_2)C_6H_3$	**4e**	55	84	278–279[13]
6	H	*p*-$(N(CH_3)_2)C_6H_4$	**4f**	55	87	239–240[13]
7	H	*p*-$(OH)C_6H_4$	**4g**	50	92	>300[13]
8	H	*m*-$(F)C_6H_4$	**4h**	55	84	267
9	H	*m*-$(Cl)C_6H_4$	**4i**	55	86	297–298
10	H	*p*-$(Cl)C_6H_4$	**4j**	55	89	>300[13]
11	H	*p*-$(Br)C_6H_4$	**4k**	60	86	296–297[13]
12	H	*m*-$(NO_2)C_6H_4$	**4l**	70	82	>300[13]
13	H	*p*-$(NO_2)C_6H_4$	**4m**	65	81	>300[13]
14	H	2-Furyl	**4n**	55	80	221–222[13]
15	Cl	C_6H_5	**4o**	60	80	212–213[14]
16	Cl	*p*-$(Cl)C_6H_4$	**4p**	60	79	>300[14]

[a] For general experimental procedure, see Ref. 26.
[b] Isolated total yield.



Scheme 1. A tentative mechanism for the formation of 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones.

activated by $Ga(OTf)_3$. Thus, intermediate **7** could be converted to intermediate **8** by intramolecule nucleophile attack of the nitrogen on imine carbon. Subsequently, 2,3-dihydroquinazolin-4(1*H*)-ones **3** could be formed by a 1,5- proton transfer. Finally, we obtained product **4** using DMSO as a solvent. Furthermore, when anthranilamide was replaced with 2-(methylamino)-benzamide, no desired product was obtained under the same conditions. We also investigated the condensation of anthranilamide **5** with aldehydes using $Ga(OTf)_3$. The corresponding products were obtained in good to excellent yields.[24] Moreover, **3a** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and **4a** was produced in good yield accordingly.

In summary, a new catalytic protocol to synthesize 2,3-dihydroquinazolin-4(1*H*)-ones and quinazolin-4(3*H*)-ones derivatives has been developed. The present protocol enjoys simple work-up, short reaction time, easy recovery and reuse of metal triflates as well as mild reaction conditions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.127.

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23. DMSO was supposed to act as a mild oxidant, see: (a) Schipper, E.; Cinnamon, M.; Rascher, L.; Chiang, Y. H.; Oroshnik, W. *Tetrahedron Lett.* **1968**, *9*, 6201; (b) Tsuji, T. *Tetrahedron Lett.* **1966**, *7*, 2413; (c) Deligeorgiev, T. C. *Dyes Pigments* **1990**, *12*, 243.
24. See Supplementary data.
25. General procedure for the one-pot synthesis of 2,3-dihydroquinazolin-4(1*H*)-ones: $Ga(OTf)_3$ (0.05 mmol, 1 mol %) was added to a solution of isatoic anhydrides **1** (5.5 mmol), ammonium acetate or amines (6.0 mmol), and aldehydes **2** (5 mmol) in ethanol (5 mL). The mixture was stirred at 70 °C for the specified period of time as indicated in Table 2. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was then allowed to cool to room temperature and water (10 mL) was added. The corresponding solid product **3** was obtained through simple filtering, and recrystallized from ethanol. Selected characterization data for the products: Compound **3a**: White solid; IR (KBr): 3440 (NH), 1670 (C=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.62 (d, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.17–7.25 (m, 3H), 7.07 (s, 1H), 6.75 (d, $J = 8.0$ Hz, 1H), 6.66 (t, $J = 7.6$ Hz, 1H), 5.72 (s, 1H), 2.28 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 163.7, 148.0, 138.7, 137.8, 133.3, 128.9, 127.4, 126.9, 117.1, 115.0, 114.5, 66.5, 20.8. MS (EI, 70 eV): m/z (%) 238 (M^+, 47), 237 ($[M-1]^+$, 92), 147 (100), 120 (48).
26. General procedure for the one-pot synthesis of quina-zolin-4(3*H*)-ones: To a solution of isatoic anhydrides **1** (5.5 mmol), ammonium acetate (6.0 mmol), and aldehydes **2** (5 mmol) in DMSO (5 mL), $Ga(OTf)_3$ (0.05 mmol, 1 mol %) were added. The mixture solution was stirred at 85 °C for an appropriate time as indicated in Table 3. The progress of the reaction was monitored by TLC. After completion, the system was cooled to room temperature and water (10 mL) was added. The solid product **4** was obtained through simple filtering, and recrystallized from ethanol. Selected characterization data for the products: Compound **4a**: White solid; IR (KBr): 3309 (NH), 1662 (C=O) cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ 12.44 (s, 1H), 8.15 (d, $J = 7.6$ Hz, 1H), 8.11 (d, $J = 8.0$ Hz, 2H), 7.83 (t, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.51 (t, $J = 8.0$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 162.2, 152.2, 148.8, 141.4, 134.5, 129.9, 129.1, 127.6, 127.3, 126.3, 125.8, 120.8, 20.9. MS (EI, 70 eV): m/z (%) 236 (M^+, 80), 147 (22), 119 (100).