One-Pot Synthesis of Quinazolinone Derivatives from Nitro-Compounds with the Aid of Low-Valent Titanium

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The synthesis of a series of quinazolinone derivatives such as 2-thioxoquinazolinones, imidazo[1,2-*c*]quinazolin-5-amines, and benzimidazo[1,2-*c*]quinazolin-5-amines, starting from nitro-compounds has been described. This general approach features a easy way for access to the target quinazolinone derivatives. The key cyclization step embraces the formation of a thiourea intermediate, mediated by low-valent titanium, and the other important intermediate was also obtained. A variety of substrates can participate in the process with good yields, making this methodology suitable for library synthesis in drug discovery efforts.

The quinazolinone skeleton is a building block for the preparation of natural purine base,[1] alkaloids, many biologically active compounds and intermediates in organic synthesis.[2] Quinazolinone derivatives are interesting because of their diverse range of biological activities, such as anticancer, diuretic, anti-inflammatory, anticonvulsant, and antihypertensive activities.[3] The quinazoline moiety present in imidazoquinazolines is responsible for a wide range of biological activities ranging form anticonvulsants[4] and antibacterial to antidiabetic agents.[5]

As a consequence, much attention has been paid to the development of efficient methods for the preparation of quinazolinone derivatives. The most common approach involves amidation of 2-aminobenzonitrile,[6] 2-aminobenzoic acid,[7] and 2-aminobenzamide.[8] As an example, the reaction of 2-aminobenzonitriles with carbon dioxide in the presence of an excess amount of DBU or DBN produced 1*H*-quinazoline-2,4-diones.[9] However, these synthetic methods are considerably limited because of long reaction times, multiple steps, and unsatisfactory yields.[10] Recently, several methods have been developed for synthesizing this heterocyclic system. Li et al.[11] reported the synthesis of 2-thioxoquinazolinones; however in addition to requiring special equipment, their methodology is still limited by high temperature and unsatisfactory product yields. Alagarsamy et al.[2] reported the synthesis of 3-phenyl-2-substituted-3*H*-quinazolin-4-ones by reaction of the amino group of 2-hydrazino-3-phenyl-3*H*-quinazolin-4-one with different aldehydes and ketones, but the method needs multiple steps and the reaction time is very long. Sharma et al.[12] developed an efficient strategy for the preparation of a novel structural variant of imidazoquinazolines, but the use of DBU and multiple steps limited the method. We found that all the methods mentioned above used amino-compounds other than nitro-compounds as starting materials. Therefore, we became interested in developing a novel and convenient synthetic methods for the preparation of quinazolinone derivatives start with nitro-compounds.

In recent years, our interest has been focused on the synthesis of quinazolines using low-valent titanium reagent. We have previously reported the synthesis of quinazolinones,[12] quinazoline-2,4-diones,[13] imidazo[1,2-*c*]quinazolines,[14] and imidazo[1,2-*c*]quinazolinones[13] by the reaction of nitro-compounds with orthoformates, triphosgene, aldehydes, and ketones, respectively, induced by low-valent titanium reagent. As our earlier works goes, herein, we report a novel and convenient protocol for the synthesis of quinazolinone derivatives in one pot via the novel reductive cyclization of various isothiocyanates and nitro-compounds by low-valent titanium system.

Initially, we wanted to study the synthesis of 3-aryl-2-aminoquinazolin-4(3*H*)-one using *N*-(3-chloro-4-methylphenyl)-2-nitrobenzamide (**1a**) and (*p*-methyl)phenyl isothiocyanate (**2a**) as starting materials. To our surprise, 2-thioxo-3-*p*-tolyl-2,3-dihydroquinazolin-4(1*H*)-one (**4a**) was obtained as our final product (the scheme above Table 1), while the expected product **3a**, was not detected. So a one-pot protocol for the synthesis of 2-thioxoquinazolinones was found. The reaction conditions were optimized by testing several parameters, such as reaction temperature and the the ratio of substrate and low-valent titanium reagent. A summary of the optimization experiments is provided in Table 1. No product was obtained when the reaction was carried out at rt or 40 °C, respectively. Compound **4a** was obtained when the temperature was increased to 60 °C (entry 3, Table 1), which indicates that the reaction requires higher temperature, and the results showed that at refluxing temperature the reaction proceeded smoothly. When the ratio of substrate and low-valent titanium reagent was 1:1, no reaction took place; however, when the ratio was 1:2, no product **4a** was detected. Product **4a** was observed when the ratio was further increased. So we concluded that the best ratio for this reaction was 1:3.

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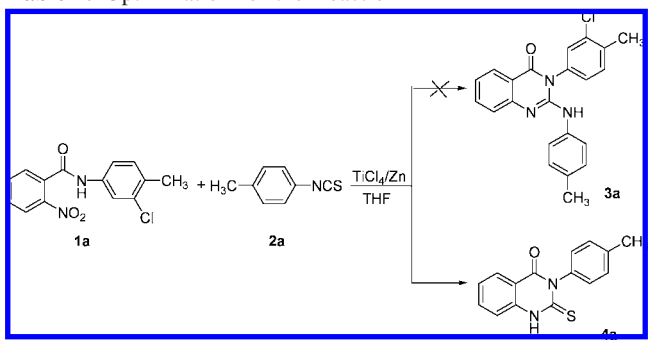
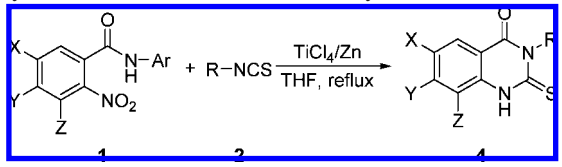
Table 1. Optimization for the Reaction



entry	ratio[a]	temp (°C)	yields[b] (%)
1	1:3	rt	0
2	1:3	40	0
3	1:3	60	67
4	1:3	reflux	79
5	1:1	reflux	NR
6	1:2	reflux	0
7	1:4	reflux	75
8	1:5	reflux	71

[a] Ratio of **1** and the low-valent titanium system ($TiCl_4$/Zn). [b] Isolated yields.

Table 2. Synthesis of Compound **4** from *N*-Aryl-*o*-nitrobenzamides **1** and Isothiocyanates **2**



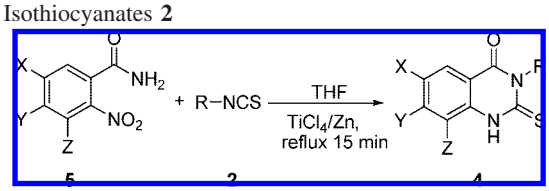
entry	X	Y	Z	Ar	R	products	yields (%)
1	H	H	H	3-Cl-4-$CH_3C_6H_3$	4-$CH_3C_6H_4$	**4a**	79
2	H	H	H	3-$CH_3C_6H_4$	*n*-butyl	**4b**	85
3	H	Cl	H	4-ClC_6H_4	C_6H_5	**4c**	71
4	H	Cl	H	3-ClC_6H_4	$C_6H_5CH_2$	**4d**	77
5	H	H	CH_3	3-Cl-4-FC_6H_3	C_6H_5	**4e**	67
6	H	H	H	3-Cl-4-$CH_3C_6H_3$	C_6H_5	**4f**	73

With the optimized conditions in hand, we then performed the reaction of a variety of *N*-aryl-*o*-nitrobenzamides **1** and isothiocyanates **2** via low-valent titanium reagent ($TiCl_4$/Zn). The results are summarized in Table 2.

Considering atom economy, we next began to study the reaction of *o*-nitrobenzamides **5** and isothiocyanates **2** under optimized conditions. The desired products **4** were obtained in good yields (Table 3).

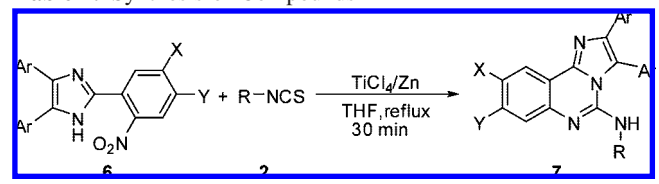
As shown in Table 3, we were pleased to find that the method was applicable to a broad substrate scope on both substituted *o*-nitrobenzamides and isothiocyanates. It can be seen that this protocol can be applied not only to the aryl isothiocyanates with electron-withdrawing groups (such as halide groups) or electron-donating groups (such as alkyl groups) but also to aliphatic isothiocyanates under the same conditions, which highlighted the wide scope of this reaction. The yields of aliphatic isothiocyanates were superior to those of aryl-substituted ones. Meanwhile it was found that good yields were also obtained when 3-methyl-substituted *o*-nitrobenzamide reacted with isothiocyanates. However, the reaction was impeded by severe steric hindrance. For example, no desired product was obtained when 2,6-di-*i*-Pr-isothiocyanate was used.

Table 3. Synthesis of Compounds **4** from *o*-Nitrobenzamides **5** and Isothiocyanates **2**



entry	X	Y	Z	R	products	yields (%)
1	H	H	H	4-$CH_3C_6H_4$	**4a**	78
2	H	H	H	*n*-butyl	**4b**	95
3	H	Cl	H	C_6H_5	**4c**	90
4	H	Cl	H	$C_6H_5CH_2$	**4d**	93
5	H	H	CH_3	C_6H_5	**4e**	82
6	H	H	H	C_6H_5	**4f**	82
7	H	H	H	4-ClC_6H_4	**4g**	94
8	H	Cl	H	4-$CH_3C_6H_4$	**4h**	73
9	H	Cl	H	3-$CH_3C_6H_4$	**4i**	73
10	H	Cl	H	*n*-butyl	**4j**	90
11	Cl	H	H	4-ClC_6H_4	**4k**	87
12	Cl	H	H	4-$CH_3C_6H_4$	**4l**	76
13	Cl	H	H	$C_6H_5CH_2$	**4m**	90
14	H	H	CH_3	$C_6H_5CH_2$	**4n**	95
15	H	H	CH_3	*n*-butyl	**4o**	89
16	H	H	H	$C_6H_5CH_2$	**4p**	92
17	H	H	H	2,6-di-*i*-PrC_6H_4	**4q**	0

Table 4. Synthesis of Compounds **7**



entry	Ar	X	Y	R	products	yields(%)
1	Ph	Cl	H	*p*-Tol	**7a**	85
2	Ph	Cl	H	Ph	**7b**	78
3	Ph	Cl	H	4-ClC_6H_4	**7c**	83
4	Ph	Cl	H	3-Tol	**7d**	87
5	Ph	Cl	H	$C_6H_5CH_2$	**7e**	85
6	Ph	H	H	Ph	**7f**	88
7	Ph	H	H	*p*-Tol	**7g**	90
8	Ph	H	H	4-ClC_6H_4	**7h**	85
9	4-BrC_6H_4	H	H	3-Tol	**7i**	86
10	4-BrC_6H_4	CH_3O	CH_3O	4-ClC_6H_4	**7j**	79
11	4-$CH_3OC_6H_4$	Cl	H	$C_6H_5CH_2$	**7k**	87
12	Ph	H	H	C_6H_5CO	**7l**	80
13	Ph	Cl	H	C_6H_5CO	**7m**	84
14	4-FC_6H_4	Cl	H	*n*-Butyl	**7n**	83

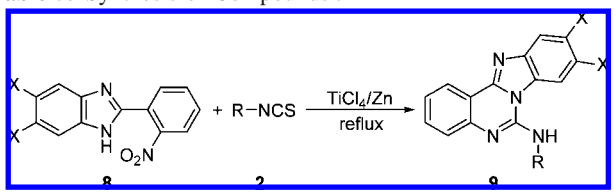
Encouraged by these results, we next focused our attention on the synthesis of imidazo[1,2-*c*]quinazolin-5-amines.

In order to demonstrate the efficiency and the applicability of the present method, we performed the reaction of a variety of 2-(2-nitrophenyl)-imidazoles **6** and isothiocyanates **2** under the optimized conditions. Table 4 summarizes our results on the cyclization of **6** and **2**.

Moreover, treatment of 2-(2-nitrophenyl)benzoimidazoles **8** and isothiocyanates **2** with $TiCl_4$/Zn in anhydrous THF under the same reaction afforded benzimidazo[1,2-*c*]quinazolin-5-amines **9** in moderate to good yields. The results are summarized in Table 5.

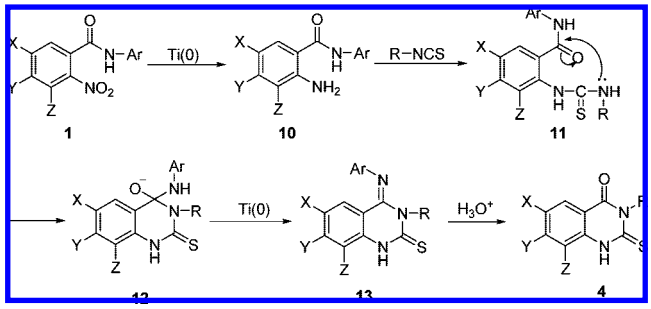
As shown in Table 4, it can be seen that either aryl isothiocyanates or alphatic ones were well tolerated. Aryl isothiocyanates containing electron-donating and electron-withdrawing substituents were reacted under the optimized conditions, and the corresponding products were obtained in good yields. No remarkable electronic effects on the

Table 5. Synthesis of Compounds **9**



entry	X	R	products	yields (%)
1	H	C_6H_5	**9a**	74
2	H	*p*-Tol	**9b**	79
3	H	$C_6H_5CH_2$	**9c**	68
4	H	C_6H_5CO	**9d**	71
5	CH_3	C_6H_5CO	**9e**	65

Scheme 1



reaction was observed. The effects of substituted 2-(2-nitrophenyl)imidazoles were also investigated and no obvious effects from the electronic or nature of the aromatic ring substrates were found. Compared with 2-(2-nitrophenyl)imidazoles, 2-(2-nitrophenyl)benzoimidazoles showed similar reactivity trends, however, it was found that the yields of 2-(2-nitrophenyl)benzoimidazoles were a little lower than that of 2-(2-nitrophenyl)imidazoles. Meanwhile, it was also found that good yields were also obtained when benzoyl isothiocyanates reacted with 2-(2-nitrophenyl)imidazoles or 2-(2-nitrophenyl)benzoimidazoles (entries 12−13, Table 4, and entries 4−5, Table 5).

Because the nitro compounds are easy to reduce to amines by low-valent titanium reagent,[15] we think this reaction may proceed through the intermediate amine **10**. As shown in Scheme 1, the nitro compound was reduced by low-valent titanium to generate amine **10**, which was then reacted with isothiocyanates to give intermediate carbamide **11**. Then **12** was obtained by addition, and **12** was then reacted via low-valent titanium to give intermediate **13**. Finally, the expected products **4** were produced by hydrolysis.

To prove this point, we chose **1f** and **2f** as starting materials. To our surprise, intermediate **13f** was obtained (in 76% yield) (see Supporting Information) (Scheme 2). The structure of **13f** was identified by IR and ^{1}H NMR and further confirmed by X-ray diffraction analysis (Figure 1).

Meanwhile it was found that the reaction temperature and the equivalents of low-valent reagent plays an important role in the synthesis. When the reaction temperature is rt or 40 °C, only the intermediates **11** were obtained. Moreover, the use of 2 equiv of $TiCl_4$/Zn at reflux also gave **11**. The intermediate **11a** was isolated and identified by spectral data. When compound **11a** was reacted further with low-valent titanium reagent ($TiCl_4$/Zn), the final product **4a** was obtained (Scheme 3).

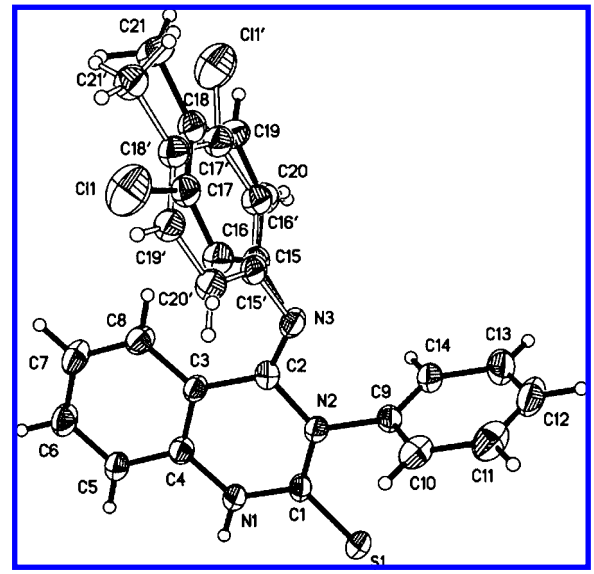


Figure 1. Molecular structure of **13f**.

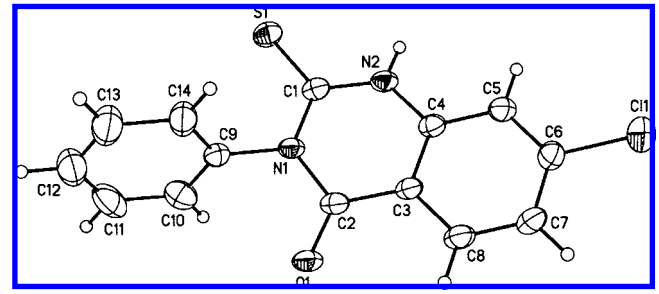
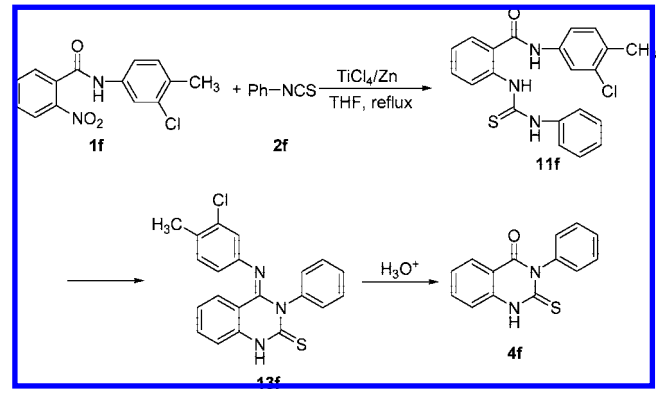
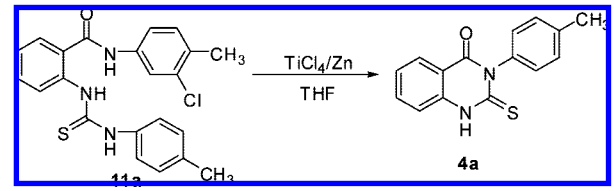


Figure 2. Molecular structure of **4c**.

Scheme 2



Scheme 3



All the products were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS spectra. The structures of **4c** and **7i** were further confirmed by X-ray diffraction analysis. The molecular structures of the products **4c** and **7i** are shown in Figures 2 and 3, respectively.

In conclusion, a series of 2-thioxoquinazolinones, imidazo[1,2-*c*]quinazolin-5-amines and benzimidazo[1,2-*c*]-

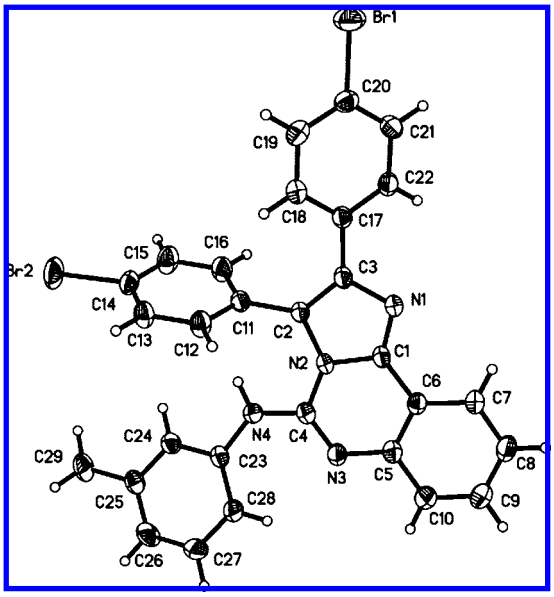


Figure 3. Molecular structure of **7i**.

quinazolin-5-amines were synthesized by the reaction of nitro-compounds and isothiocyanates induced by low-valent titanium reagent ($TiCl_4$/Zn). A variety of substrates can participate in the process with good yields. Our protocol is characterized by (i) faster reaction times and generally good to excellent yields, (ii) accessible materials and handy manipulation (only one pot), and (iii) isolation of products via simple recrystallization to give higher purities.

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Supporting Information Available. Detailed descriptions of experimental procedures and spectroscopic and analytical data are available for compounds **4**, **7**, **9**, **11a**, and **13f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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