Synthesis of Imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and Benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones with the Aid of Low-Valent Titanium Reagent

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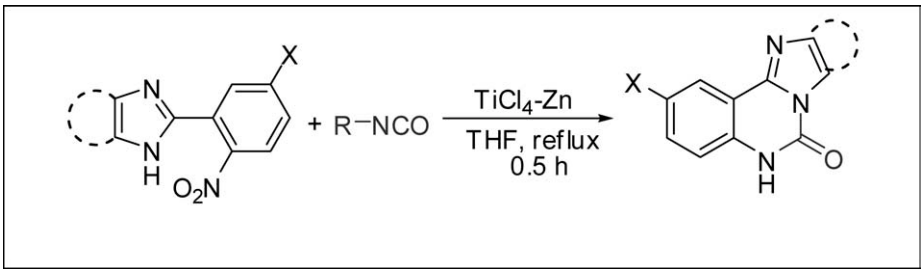

A short and facile synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones was accomplished in good yields *via* the novel reductive cyclization of 2-(2-nitrophenyl)-imidazoles or 2-(2-nitrophenyl)benzoimidazoles with isocyanates promoted by low-valent titanium reagent.

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INTRODUCTION

Low-valent titanium reagents have an exceedingly high ability to promote reductive coupling of carbonyl compounds, and are attracting increasing interest in organic synthesis [1]. Many other functional groups can also be coupled [2]. Recently, we have reported the low-valent titanium induced intermolecular reductive coupling reaction of carboxylic derivatives with aromatic ketones [3], the intramolecular reductive coupling reaction of 4,4-dicyano-1,3-diaryl-1-butanone [4], the cyclodimerization of α,β-unsaturated ketones [5], and the intramolecular reductive coupling reaction of ketomalononitriles [6].

A literature survey reavealed that quinazolinones show antihypertonic, antirheumatic, antiana-phylactic, antiasthmatic, tranquilizing, neuro-stimulating, and benzodiazepine binding activity [7,8]. For example, 3-substituted quinazolinones, such as SGB-1534 (**1**) [9] and ketanserin (**2**) have been found to have antihypertensive activities mediated *via* α-adrenoceptor and serotonic receptor anatgonism, respectively. Addition of a (2-methoxyphenyl)piperazine side chain at the 2- or 3-position of the angular tricyclic 2,3-dihydroimidazo[1,2-*c*]quinazoline ring system of SGB-1534 resulted in the formation of potent antihypertensive agents such as 2-[[4-(2-methoxyphenyl)-piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**3**) and 3-[[4-(2-methoxyphenyl)piperazin-1-yl]methyl]-2,3-dihydroimidazo[1,2-*c*]-quinazolin-5(6*H*)-one (**4**) that selectively antagonized the α_1-adrenoceptor [10]. (Fig. 1).

The synthesis of quinazolinones is well studied, and recent development in combinatorial chemistry made the preparation of large number of quinazolinones in a short time possible. Sequential cyclizations of 2-isothio- cyanatobenzonitrile and 2-isocyanatobenzonitrile with α-aminoketones resulted 6*H*-imidazo[1,2-*c*]quinazolinones with high yields [11]. A series of 2-[(substituted- phenylpiperazin-1-yl)methyl]- and 2-[(substitutedphenyl-piperidin-1-yl)methyl]-2,3-dihydroimidzao[1,2-*c*]quinazolin-5(6*H*)-ones were synthesized by bromo-cyclization with NBS in THF at room temperature [10,12]. But many of these still suffer from drawbacks such as drastic conditions, unsatisfactory yields, long-reaction time, high temperature, complex manipulation, and inaccessible starting materials.

Therefore, the development of more efficient methods for the preparation of this kind of compounds is still an active ongoing research area, and there is scope for further improvement toward milder reaction conditions and improved yields. In recent years, our interest has been focused on the synthesis of quinazolines uing low-valent titanium reagent. We have previously reported the synthesis of quinazolines [13], quinazoline-2,4-diones [14], imidazo[1,2-*c*]quinazolines [15], 2-thioxoquinazolinones, imidazo[1,2-*c*]quinazolin-5-amines, and benzimidazo[1,2-*c*] quinazolin-5-amines [16] by the reaction of nitro-

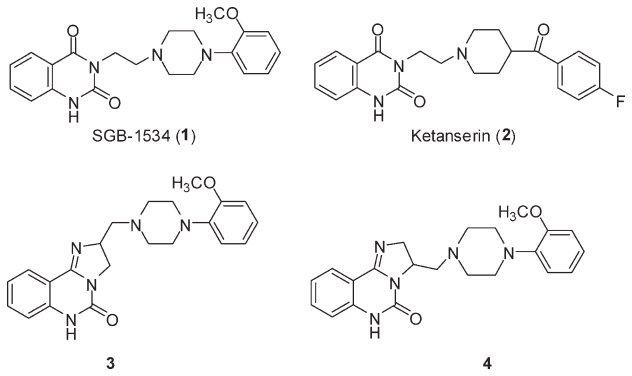


Figure 1. SGB-1534 (**1**), Ketanserin (**2**).

compounds with orthoformates, triphosgene, aldehydes, ketones, and isothiocyanates, respectively, induced by low-valent titanium reagent.

As our earlier works goes, herein, we wish to describe a method induced by low-valent titanium reagent for the preparation of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-one using 2-(2-nitrophenyl)imidazole, 2-(2-nitrophenyl)benzoimidazole and isocyanates as starting materials.

RESULTS AND DISCUSSION

On the basis of our previous experience, we selected 2-(2-nitrophenyl)-4,5-diphenyl-1*H*-imidazoles **1a** and the 1-isocyanato-4-methylbenzene **2a** as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

As shown in Table 1, we briefly examined the effect of different temperatures and low-valent titanium systems. The results obtained from these experiments indicated that the reaction temperatures had a significant influence on the success of this reaction. To our delight at refluxed the reaction proceeded smoothly in high yield (entry 3). To further evaluate the influence of low-valent titanium system, this reaction was carried out with different low-valent titanium reagents. From the results it is obvious that the best system is $TiCl_4$/Zn.

Having established an optimal condition for the protocol, we performed a more detailed examination of the substrates. Thus, the behavior of a variety of substrates, which include different isocyanates as well as different

Table 1

Optimization for the reductive cyclization reaction.

Entry	Temperature (°C)	$TiCl_4$/M	Isolated yield (%)
1	r.t.	$TiCl_4$/Zn	42
2	40	$TiCl_4$/Zn	55
3	reflux	$TiCl_4$/Zn	89
4	reflux	$TiCl_4$/Fe	34
5	reflux	$TiCl_4$/Mg	48

2-(2-nitrophenyl)imidazoles or 2-(2-nitrophenyl) benzoimidazoles was examined.

First of all, we performed the reaction of a variety of 2-(2-nitrophenyl)imidazoles **1** and isocyanates **2** via $TiCl_4$/Zn system in anhydrous THF (Scheme 2, Table 2).

Furthermore, treatment of 2-(2-nitrophenyl)benzoimidazoles **4** and isocyanates **2** with $TiCl_4$/Zn in anhydrous THF under the same reaction conditions, the reductive cyclization products benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones **5** were obtained in good yields (Scheme 3). The results are summarized in Table 3.

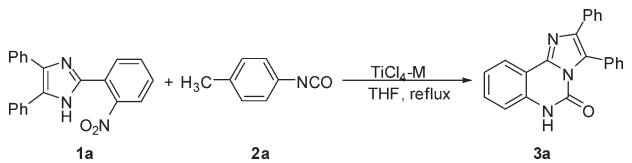
As shown in Table 1 and Table 2, for series of **1** and **2**, either the aromatic ring containing weak electron-withdrawing groups (such as halides) or electron-donating groups (such as alkyl group), reacted well to give the corresponding products **3** in high yields under the same reaction conditions. So we concluded that no obvious effects from the electronic or nature of the aromatic ring substrates were observed in the above reactions.

Because the nitro compounds are easy to be reduced to amines by low-valent titanium reagent [17], we think this reaction may proceed through the intermediate amine **6**. As shown in Scheme 4, the nitro compound was reduced by low-valent titanium to generate amine **6**, which was then reacted with isocyanates to give intermediate **7**. Finally, the expected products **3** were produced by addition and elimination.

All the products were characterized by ^{1}H-NMR and IR.

In conclusion, a series of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones and benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones were synthesized induced by low-valent titanium reagent ($TiCl_4$/Zn). The process was carried out only

Scheme 1



Scheme 2

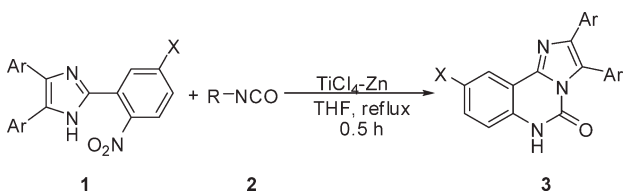


Table 2

The synthesis of imidazo[1,2-*c*]quinazolin-5(6*H*)-ones **3**.

Compd.	Ar	X	R	Yield/%[a]
3a	Ph	H	4-$CH_3C_6H_4$	89
3b	Ph	Cl	4-$CH_3C_6H_4$	85
3c	4-$CH_3C_6H_4$	Cl	4-$CH_3C_6H_4$	88
3d	4-$CH_3OC_6H_4$	Cl	4-ClC_6H_4	92
3e	4-BrC_6H_4	H	4-ClC_6H_4	83

[a] Isolated yield.

one step to generate diversity on the imidazo[1,2-c]quinazolines. The yields are higher and the reaction times are shorter than the protocol we reported earlier [14]. The short reaction times (0.5 h) and simple reaction conditions make this protocol attractive.

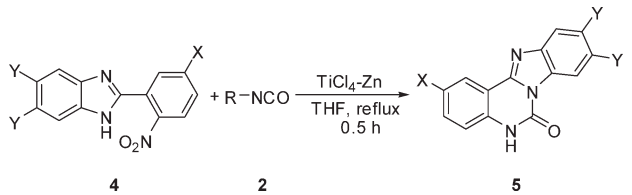
EXPERIMENTAL

THF was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under N_2 atmosphere. Melting points are uncorrected. IR spectra were recorded on Tensor 27 spectrometer in KBr with absorptions in cm^{-1}. ^{1}H-NMR spectra were determined on NMRststem-300 MHz or UNITY INOVA 400 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS.

General procedure for the synthesis of 3 and 5 is represented as follows. $TiCl_4$ (0.3 mL, 3 mmol) was added dropwise using a syringe to a stirred suspension of zinc powder (0.384 g, 6 mmol) in freshly distilled anhydrous THF (10 mL) at r.t. under a dry N_2 atmosphere. After completion of the addition, the mixture was refluxed for 2 h. The suspension of the low-valent titanium reagent formed was cooled to r.t. and a solution of 2-(2-niteophenyl)imidazole or 2-(2-nitrophenyl) benzoimidazole (1 mmol) and isocycanates (1 mmol) in THF (5 mL) was added dropwise. The reaction mixture was then refluxed for 30 min under N_2. After this period, the TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $ClCH_2CH_2Cl$ (3 × 20 mL). The combined extracts were washed with water (3 × 20 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by recrystallization from 95% ethanol.

2,3-Diphenylimidazo[1,2-c]quinazolin-5(6H)-one (3a): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3160, 1706, 1596, 1553, 1480, 1443, 1378, 1335, 803, 779, 749, 702 cm^{-1}.

Scheme 3



4 2 5

Table 3

The synthesis of benzimidazo[1,2-*c*]quinazolin-6(5*H*)-ones **5**.

Compd.	X	Y	R	Yield/%[a]
5a	H	H	4-ClC_6H_4	90
5b	H	Cl	4-ClC_6H_4	81
5c	H	CH_3	4-$CH_3C_6H_4$	87
5d	Cl	H	4-$CH_3C_6H_4$	89

[a] Isolated yield.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.23–7.29 (m, 3H, ArH), 7.33–7.37 (m, 2H, ArH), 7.43–7.47 (m, 7H, ArH), 7.55–7.59 (m, 1H, ArH), 8.26 (d, J = 8.0 Hz, 1H, ArH), 11.75 (s, 1H, NH).

9-Chloro-2,3-diphenylimidazo[1,2-c]quinazolin-5(6H)-one (3b): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3160, 1706, 1596, 1553, 1480, 1443, 1378, 1335, 803, 779, 749, 702 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.23–7.25 (m, 3H, ArH), 7.34–7.36 (m, 1H, ArH), 7.43–7.45 (m, 7H, ArH), 7.92–7.94 (m, 1H, ArH), 8.16–8.17 (m, 1H, ArH), 11.84 (s, 1H, NH).

9-Chloro-2,3-di(4-methylphenyl)imidazo[1,2-c]quinazolin-5(6H)-one (3c): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3220, 1706, 1598, 1551, 1480, 1443, 1370, 1334, 1280, 1234, 1073, 813, 797, 749, 760 cm^{-1}.

^{1}H-NMR (300 MHz, DMSO-d_6) δ: 2.24 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 7.05 (d, J = 7.8 Hz, 2H, ArH), 7.19–7.35 (m, 7H, ArH), 7.55–7.59 (m, 1H, ArH), 8.15 (d, J = 2.1 Hz, 1H, ArH), 11.79 (s, 1H, NH).

9-Chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5(6H)-one (3d): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3210, 1703, 1614, 1594, 1554, 1520, 1491, 1366, 1330, 1287, 1246, 1171, 1037, 828, 750, 740 cm^{-1}.

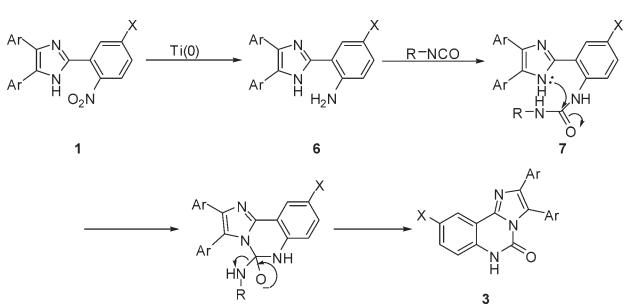
^{1}H-NMR (400 MHz, DMSO-d_6) δ: 3.73 (s, 3H, CH_3O), 3.33 (s, 3H, CH_3O), 6.85 (d, J = 8.8 Hz, 2H, ArH), 6.99 (d, J = 8.4 Hz, 2H, ArH), 7.34–7.36 (m, 3H, ArH), 7.42 (d, J = 8.8 Hz, 2H, ArH), 7.58 (d, J = 8.8 Hz, 1H, ArH), 8.16 (s, 1H, ArH), 11.79 (s, 1H, NH).

2,3-Bis(4-bromophenyl)imidazo[1,2-c]quinazolin-5(6H)-one (3e): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3227, 3172, 3073, 1709, 1594, 1572, 1550, 1492, 1478, 1392, 1072, 959, 744, 727, 694 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.33–7.41 (m, 6H, ArH), 7.49–7.51 (m, 2H, ArH), 7.53–7.57 (m, 1H, ArH), 7.61–7.63 (m, 2H, ArH), 8.22 (d, J = 8.0 Hz, 1H, ArH), 11.79 (s, 1H, NH).

Bezimidazo[1,2-c]quinazolin-6(5H)-one (5a): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3150, 3077, 2916,

Scheme 4



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2849, 1722, 1614, 1592, 1541, 1479, 1450, 1427, 1382, 1330, 1292, 1226, 1148, 928, 756, 699 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.34–7.50 (m, 4H, ArH), 7.62–7.66 (m, 1H, ArH), 7.84 (d, J = 7.6 Hz, 1H, ArH), 8.29 (d, J = 7.6 Hz, 1H, ArH), 8.35 (d, J = 8.0 Hz, 1H, ArH), 11.95 (s, 1H, NH).

9,10-Dichlorobenzimidazo[1,2-c]quinazolin-6(5H)-one (5b): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3156, 3089, 2928, 1713, 1626, 1614, 1547, 1510, 1480, 1415, 1392, 1324, 1300, 1267, 1232, 1209, 1160, 1099, 877, 867, 779, 748, 713, 688 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.35–7.39 (m, 2H, ArH), 7.66–7.69 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.25 (d, J = 8.0 Hz, 1H, ArH), 8.42 (s, 1H, ArH), 12.12 (s, 1H, NH).

9,10-Dimethylbenzimidazo[1,2-c]quinazolin-6(5H)-one (5c): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3156, 3066, 2975, 2913, 2842, 1720, 1624, 1596, 1551, 1511, 1479, 1455, 1380, 1344, 1291, 1230, 1159, 994, 914, 878, 744, 665 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 2.38 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.33–7.38 (m, 2H, ArH), 7.61–7.64 (m, 2H, ArH), 8.12 (s, 1H, ArH), 8.27 (d, J = 8.0 Hz, 1H, ArH), 11.91 (s, 1H, NH).

2-Chlorobenzimidazo[1,2-c]quinazolin-6(5H)-one (5d): white solid, m.p. >300°C (Lit [14] >300°C). IR (KBr) ν: 3204, 3037, 2922, 1712, 1611, 1551, 1476, 1436, 1385, 1328, 1238, 1167, 1146, 1110, 1081, 1059, 1008, 939, 911, 881, 825, 758, 714, 687 cm^{-1}.

^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.35–7.37 (m, 1H, ArH), 7.41–7.49 (m, 2H, ArH), 7.63–7.66 (m, 1H, ArH), 7.82–7.84 (m, 1H, ArH), 8.17–8.18 (m, 1H, ArH), 8.30–8.32 (m, 1H, ArH), 12.04 (s, 1H, NH).

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