Synthesis of Quinazolines and Imidazo[1,2-*c*]quinazolines with the Aid of a Low-Valent Titanium Reagent

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Received 20 February 2004

Abstract: A short and facile synthesis of a series of quinazolines and imidazo[1,2-c]quinazolines was accomplished in good yields via the novel reductive cyclization of 2-nitrobenzyl amines or 2-(2-nitrophenyl)imidazoles with ortho-ester, aldehydes or ketones promoted by $TiCl_4$/Zn system. The structures were established by spectroscopic data and confirmed by X-ray analysis.

Key words: low-valent titanium, quinazoline, imidazo[1,2-*c*]quinazoline, 2-nitrobenzyl amine, 2-(2-nitrophenyl)imidazole

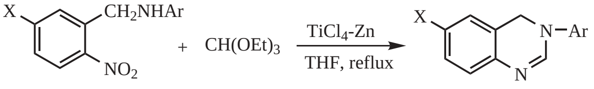
In recent years, the low-valent reagent system has been extensively used in organic synthesis. It has exceeding efficiency in the reductive coupling of carbonyl compounds[1] and in a variety of other functional groups.[2–5] Recently, we have reported the low-valent titanium-induced intermolecular reductive coupling reaction of carboxylic derivatives with aromatic ketones,[6] the intramolecular reductive coupling reaction of 4,4-dicyano-1,3-diaryl-1-butanone[7] and the cyclodimerization of α,β-unsaturated ketones.[8]

Quinazoline derivatives have attracted a great deal of interest, mainly concerning their synthesis, reactions and biological properties, as this structural motif appears in a large number of pharmaceutical agents and natural products.[9,10]

Our interest in recent years has been focused on the use of the low-valent reagent in synthesis. We have previously reported the synthesis of bioactive molecules such as: indoles,[11] 2-aminoquinolines[12] and 2-arylquinolines[13] with the aid of this reagent.

Here we wish to describe a method induced by the $TiCl_4$/Zn system for the preparation of quinazolines and imidazo[1,2-c]quinazolines using 2-nitrobenzyl amines and 2-(2-nitrophenyl)imidazoles as the starting materials.

When 2-nitrobenzyl amines **1** and triethyl orthoformate (**2**) were treated with low-valent titanium prepared from titanium tetrachloride and zinc powder in anhydrous THF, the reductive cyclization products 3-arylquinazolines **3** were obtained in good yields (Scheme 1). The results are summarized in Table 1.



1 **2** **3**

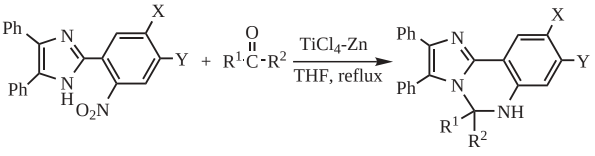
Scheme 1

Table 1 The Synthesis of 3-Arylquinazolines Promoted by $TiCl_4$/Zn

Entry	X	Ar	Yield (%)[a]
3a	H	4-ClC_6H_4	73
3b	Cl	C_6H_5	71
3c	Cl	4-$CH_3C_6H_4$	83
3d	Cl	4-BrC_6H_4	82
3e	H	4-BrC_6H_4	84
3f	H	3-Cl-4-FC_6H_3	79
3g	Cl	4-ClC_6H_4	79
3h	Cl	3-Cl-4-FC_6H_3	91

[a] The ratio of low-valent titanium reagent, **1** and **2** is 4:1:2, in THF, reflux for 5 h.[14]

Moreover, treatment of 2-(2-nitrophenyl)imidazoles **4** and ortho-ester **5** with $TiCl_4$/Zn in anhydrous THF under the same reaction conditions afforded imidazo[1,2-*c*]quinazolines **6** in moderate yields (Scheme 2). Table 2 summarizes our results.



4 **7** **8**

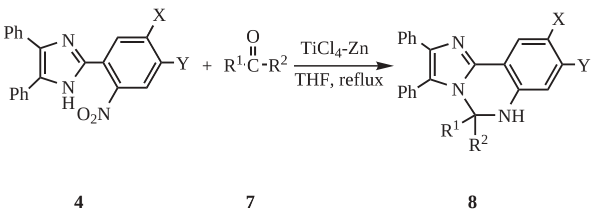
Scheme 2

SYNLETT 2004, No. 6, pp 1098–1100
Advanced online publication: 25.03.2004
DOI: 10.1055/s-2004-822893; Art ID: U0504ST

Table 2 The Synthesis of Imidazo[1,2-*c*]quinazolines Promoted by $TiCl_4$/Zn

Entry	X	Y	R	Yield (%)[a]
6a	H	H	H	68
6b	Cl	H	H	74
6c	CH_3O	CH_3O	H	62
6d	H	H	CH_3	67
6e	Cl	H	CH_3	65
6f	CH_3O	CH_3O	CH_3	61

[a] The ratio of low-valent titanium reagent, 4 and 5 is 5:1:2, in THF, r.t. for 6 h [15]



Scheme 3

However, treatment of 2-(2-nitrophenyl)imidazoles **4** and acetone or aromatic aldehydes **7** with $TiCl_4$/Zn in anhydrous THF under the same reaction conditions, the cross-coupling products 1,2-dihydroimidazo[1,2-*c*]quinazolines **8** were obtained in moderated yields (Scheme 3).

Table 3 summarizes our results. All reactions could be carried out under mild conditions. However, 2-(2-nitrophenyl)imidazoles failed to react with butanone, 3-pentanone, cyclohexanone, acetophenone under the same conditions.

The structures **3**, **6** and **8** were confirmed by IR, ^1H NMR and elemental analysis.[16] The structures of **6a** and **8b** were further confirmed by X-ray analysis (Figure 1 and Figure 2) [17].

In summary, a series of 3-arylquinazolines, imidazo[1,2-*c*]quinazolines and 1,2-dihydroimidazo [1,2-*c*]quinazolines were synthesized via reductive cyclization of 2-nitrobenzyl amines or 2-(2-nitrophenyl)imidazoles with *ortho*-ester, aldehydes or ketones induced by the $TiCl_4$/Zn system. The advantages of our method are the easily accessible starting materials, convenient manipulation and moderate to high yields.

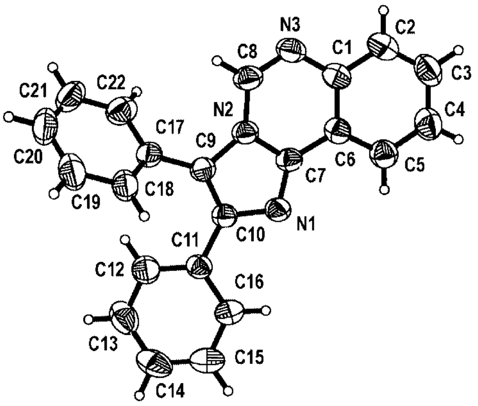


Figure 1 ORTEP diagram of **6a**

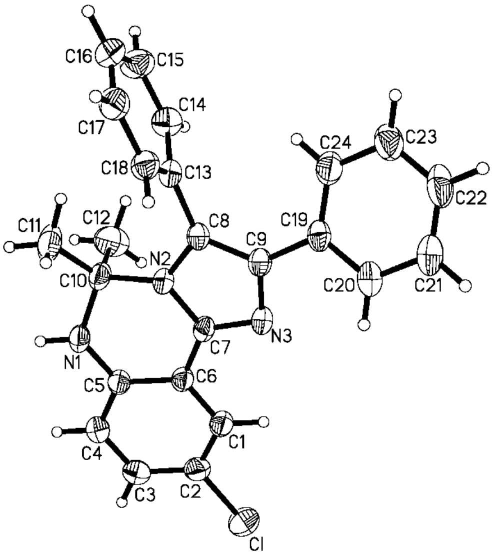


Figure 2 ORTEP diagram of **8b**

Table 3 The Synthesis of 1,2-Dihydroimidazo[1,2-*c*]quinazolines Promoted by $TiCl_4$/Zn

Entry	X	Y	R^1	R^2	Yield (%)[a]
8a	H	H	CH_3	CH_3	71
8b	Cl	H	CH_3	CH_3	74
8c	OCH_2O		CH_3	CH_3	62
8d	H	H	H	4-$CH_3C_6H_4$	65
8e	H	H	H	4-ClC_6H_4	65
8f	Cl	H	H	4-$CH_3C_6H_4$	77
8g	Cl	H	H	3,4-$(CH_3O)_2C_6H_3$	78
8h	H	H	H	3,4-$(CH_3O)_2C_6H_3$	68
8i	CH_3O	CH_3O	H	4-$CH_3C_6H_4$	76
8j	CH_3O	CH_3O	H	4-$CH_3OC_6H_4$	64

[a] The ratio of low-valent titanium reagent, **4** and **7** is 3.3:1:1, in THF, r.t. for 5 h

Acknowledgment

We are grateful to the Natural Science Foundation of Jiangsu Education Committee (03KJB150136) for financial support.

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(14) The general procedure is represented as follow: $TiCl_4$ (2.2 mL, 20 mmol) was added dropwise using a syringe to a stirred suspention of zinc dust (2.6 g, 40 mmol) in freshly distilled anhyd THF (20 mL) at r.t. under anhyd nitrogen 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-nitrobenzyl amine **1** (5 mmol) and triethyl orthoformate (**2**) (10 mmol) in anhyd THF (10 mL) was added carefully at r.t. When the reaction was completed (at refluxing for 5 h under N_2), most of the solvent was removed in vacuo. The residue was poured into 10% HCl (100 mL), and extracted with $CHCl_3$ (3 × 50 mL). The combined organic layers were washed with water (3 × 50 mL), dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude product to give the pure product **3**.

(15) The general procedure is represented as follow: A solution of 2-(2-nitrophenyl) imindazole **4** (2 mmol) and *ortho*-ester **5 (**4mmol) in anhyd THF (10 mL) was added carefully at r.t. to a suspension of low-valent titanium reagent (10 mmol) prepared as mentioned above. When the reaction was completed (at r.t. under N_2), the reaction mixture was poured into 10% HCl, and extracted with $CHCl_3$. The combined organic layers were washed with water, dried (Na_2SO_4), and the solvent was removed in vacuo to give the crude product. The crude product was purified by column chromatography on silica gel (200–300 mesh) using petroleum ether (bp 60–90 °C)–acetone (5:1) as eluent.

(16) Typical physical data for representative compounds: Compound **3a**: mp 140–141 °C. IR (KBr): 3067, 1600, 1565, 1550, 1470, 1290, 1230, 1160, 920, 800, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 4.92 (s, 2 H, C^4-H), 7.01 (d, J = 6.4 Hz, 1 H, C^5-H), 7.10 (d, J = 8.8 Hz, 2 H, $C^{2'}$-H, $C^{6'}$-H), 7.15 (d, J = 7.6 Hz, 1 H, C^8-H), 7.21–7.29 (m, 2 H, C^6-H, C^7-H), 7.40 (d, J = 8.8 Hz, 2 H, $C^{3'}$-H, $C^{5'}$-H), 7.56 (s, 1 H, C^2-H). Anal. Calcd for $C_{14}H_{11}ClN_2$: C, 69.29; H, 4.57; N, 11.54. Found: C, 69.53; H, 4.26; N, 11.72%. Compound **6a**: mp 193–195 °C. IR (KBr): 3058, 1603, 1473, 1379, 1353, 1310, 1262, 1235, 894, 778, 746, 704, 693 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): 7.30–7.41 (m, 3 H, ArH), 7.53–7.59 (m, 5 H, ArH), 7.70–7.74 (m, 4 H, ArH), 7.86 (d, J = 8.0 Hz, 1 H, ArH), 7.97 (d, J = 7.6 Hz, 1 H, ArH), 8.72 (s, 1 H, ArH). Anal. Calcd for $C_{22}H_{15}N_3$: C, 82.22; H, 4.70; N, 13.08. Found: C, 82.41; H, 4.46; N, 13.16. Compound **8a**: mp 240–241 °C. IR (KBr): 3240, 3012, 2979, 1614, 1512, 1479, 1444, 1367, 1275, 1211, 1161, 1072, 964, 916, 791, 773, 752, 698 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 1.36 (s. 6 H, 2 × CH_3), 6.52 (s, 1 H, NH), 6.79 (d, J = 8.8 Hz, 1 H, ArH), 6.83 (d, J = 7.2 Hz, 1 H, ArH), 7.08–7.19 (m, 4 H, ArH), 7.36 (d, J = 7.2 Hz, 2 H, ArH), 7.51–7.54 (m, 5 H, ArH), 7.84 (d, J = 7.2 Hz, 1 H, ArH). Anal. Calcd for $C_{24}H_{21}ClN_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.25; H, 5.89; N, 12.10.

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