One-Pot Synthesis of Imidazo[1,2-*c*]quinazoline Derivatives from Nitro-Componds Reduced by Zinc

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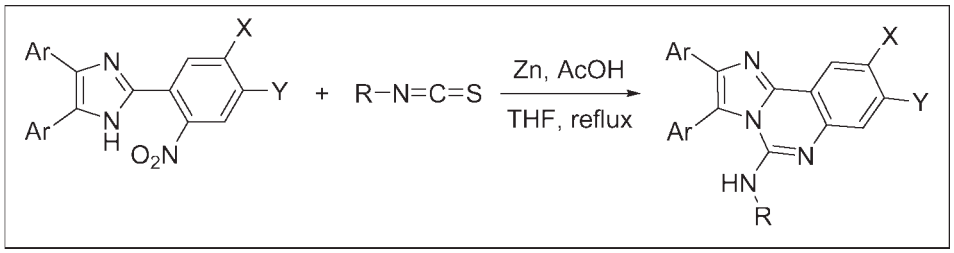

An efficient, convenient, one-pot synthesis of imidazo[1,2-*c*]quinazolines was accomplished in good yields via the novel reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazole with isothiocyanates mediated by zinc dust.

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INTRODUCTION

The quinazolinone skeleton is a building block for the preparation of natural purine base, alkaloids [1], many biologically active compounds, and intermediates in organic synthesis [2]. The quinazoline moiety present in imidazoquinazolines is responsible for a wide range of biological activities ranging form anticonvulsants and antibacterial to antidiabetic agents [3–9].

As a consequence, much attention has been paid to the development of efficient methods for the preparation of 5-amino derivatives of imidazo[1,2-*c*]quinazoline. The first method involved treatment of 6-mercaptobenzimidazoquinazoline with amines [10] and the second method involved an aza-wittig reaction of iminophosphoranes derived from 2-(*o*-azido)phenylbenzimidazole with isocyanates [11]. Recently, several methods have been developed for synthesizing this heterocyclic system. Sharma et al. [12] developed an efficient strategy for the preparation of imidazoquinazolines, but the use of DBU and multiple steps limited the method. We developed an efficient and one-pot synthesis of imidazoquinazolines from 2-(2-nitrophenyl)-1*H*-imidazole induced by low-valent titanium reagent [13], but this method required anhydrous system. As mentioned in our earlier works, herein, we reported a convenient protocol for the synthesis of imidazo[1,2-*c*]quinazolines in one-pot via the reductive cyclization of 2-(2-nitrophenyl)-1*H*-imidazole and isothiocyanates mediated by zinc dust.

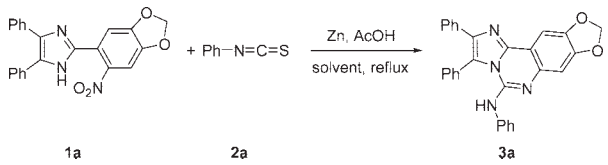
RESULTS AND DISCUSSION

On the basic of our previous experience, we selected 2-(2-nitro-4,5-methylenedioxyphenyl)-4,5-diphenyl-1*H*-imidazole (**1a**) and phenyl isothiocyanate (**2a**) as model substrates to optimize the experimental conditions for the proposed reductive cyclization reaction (Scheme 1). The results are summarized in Table 1.

The results obtained from these experiments indicated that the reaction solvents had a significant influence on the success of this reaction. No product was obtained when the solvent was H_2O or MeOH. When the solvent was AcOH, DMF, CH_3CN or $CHCl_3$, the yield of the product was 40–80%. When THF was used as solvent at refluxing temperature, the products **3a** was obtained in highest yield. To further evaluate the influence of the ratio of **1a**: Zn, this reaction was carried out with different ratio. When the ratio of substrate:Zn was 1:1, 45% yield of the product was obtained in 20 h, it can be seen that increasing the catalyst loading increase the yield. When the ratio of substrate:Zn was 1:5, the yield of the product decrease. From the results, it is obvious that the best ratio is 1:4.

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 2-(2-nitrophenyl)-1*H*-imidazole as well as different isothiocyanates was examined (Scheme 2). The results are summarized in Table 2. As

Scheme 1



1a 2a 3a

shown in Table 2, for series of **3**, either the aromatic ring containing electron-withdrawing groups (such as halides) or electron-donating groups (such as alkyl group), reacted well to give the corresponding products **3** in good 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.

We propose the possible following mechanism to account for the reaction. At first step 2-(2-nitrophenyl)-1*H*-imidazole **1** was reduced by Zn/H^+ to 2-(2-aminophenyl)-1*H*-imidazole **4**, the addition reaction of reductive product **4** with isothiocyanates **2** to afford intermediate **5**, intermediate **5** was cyclized by the nucleophilic attack of nitrogen atoms on C=S group and gave the intermediate **6**. Finally the expected products **3** were afforded by losing of H_2S (Scheme 3).

The structures of product **3** were identified by IR, ^1H NMR, and HRMS. The structure of product **3a** was further confirmed by X-ray diffraction analysis (Fig. 1).

In conclusion, a series of imidazo[1,2-*c*]quinazolines were synthesized by the reaction of 2-(2-nitrophenyl)-1*H*-imidazoles and isothiocyanates induced by zinc dust. This protocol has advantages of accessible materials, handy manipulation (only one-pot), and isolation of products via simple recrystallization.

Table 1

Optimization for the reductive cyclization reaction.

Entry	Solvent	Ratio[a]	Reaction time (h)	Yield (%)
1	THF	1:2	20	45
2	THF	1:3	12	60
3	THF	1:4	1.5	86
4	THF	1:5	1.5	85
5	MeOH	1:4	12	0
6	H_2O	1:4	12	0
7	AcOH	1:4	2	50
8	CH_3CN	1:4	1.5	80
9	$CHCl_3$	1:4	2	42
10	DMF	1:4	1.5	73

[a] Ratio of **1a** and zinc dust.

EXPERIMENTAL

THF was untreated. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Varian FT-1000 spectrometer in KBr with absorptions in cm^{-1}. ^1H NMR was determined on a Varian Inova-400 MHz or a Varian NMR System 300 MHz spectrometer in DMSO-d_6 solution. *J* values are in Hz. Chemical shifts are expressed in ppm downfield from internal standard TMS. HRMS data were obtained using TOF–MS microma GCT-TOF instrument. X-ray diffraction was recorded on a Mercury Bruker Smart-1000 CCD diffractometer.

General procedure for the synthesis of 2-(2-nitrophenyl)-1*H*-imidazole 1. A solution of benzil (5 mmol) in AcOH was treated with 2-nitrobenzaldehyde (5 mmol) and NH_4OAc (40 mmol) [12]. The reaction mixture was refluxed for 4 h, then AcOH was evaporated, and the residue was treated with a 10% aqueous solution of $NaHCO_3$ (pH 8). The mixture was extracted with EtOAc (2 × 25 mL), washed with brine (25 mL), and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give a yellow solid.

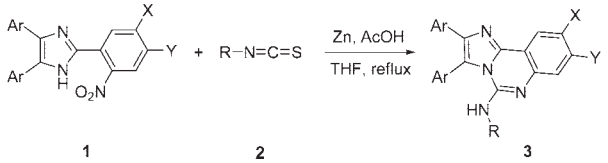
General procedure for the synthesis of imidazol[1,2-*c*]quinazolines 3. To a solution of 2-(2-nitrophenyl)-1*H*-imidazole (1 mmol) and isothiocyanates (1 mmol) in THF (15 mL), zinc dust (4 mmol) and AcOH (0.5 mL) was added. The reaction mixture was refluxed for 2 h. After this period, TLC analysis of the mixture showed the reaction to be completed. The reaction mixture was quenched with 5% HCl (15 mL) and extracted with $CHCl_3$ (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 acetone.

(8,9-Methylenedioxy-2,3-diphenylimidazo[1,2-c]quinazolin-5-yl)phenylamine (3a). This compound was obtained as solid with mp 215–217°C; IR (KBr) ν: 3393, 3059, 2902, 1623, 1598, 1557, 1533, 1466, 1377, 1340, 1271, 1217, 1148, 1036, 941, 864, 824, 750, 706 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 6.19 (s, 2H, OCH_2O), 6.78 (s, 1H, NH), 7.00 (t, J = 8.0 Hz, 1H, ArH), 7.15 (s, 1H, ArH), 7.18 (s, 2H, ArH), 7.25–7.31 (m, 5H, ArH), 7.54 (d, J = 7.6 Hz, 2H, ArH), 7.68–7.72 (m, 2H, ArH), 7.76–7.82 (m, 4H, ArH).

HRMS [Found: *m/z* 456.1578 (M^+), Cacld for $C_{29}H_{20}N_4O_2$: M, 456.1586].

(2,3-Diphenylimidazo[1,2-c]quinazolin-5-yl)phenylamine (3b). This compound was obtained as solid with mp 195–197°C (ref. 12, 200–201°C); IR (KBr) ν: 3340, 1625, 1567, 1597, 1537, 1497, 1477, 1444, 1371, 1331, 1232, 1110, 1027, 927, 765, 703 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 6.89 (s, 1H, NH), 7.02–7.06 (m, 1H, ArH), 7.21–7.23 (m, 2H, ArH), 7.27–7.33 (m, 5H, ArH), 7.47–7.51 (m, 1H, ArH), 7.56–7.58 (m, 2H, ArH), 7.65–7.85 (m, 7H, ArH), 8.43–8.45 (m, 1H, ArH).

Scheme 2



1 2 3

Table 2

Synthesis of imidazo[1,2-*c*]quinazolines.

Entry	Ar	X	Y	R	Time (h)	Yield (%)[a]
3a	C_6H_5	OCH_2O		C_6H_5	1.5	86
3b	C_6H_5	H	H	C_6H_5	2.5	80
3c	4-$CH_3C_6H_4$	H	H	C_6H_5	3	92
3d	4-$CH_3OC_6H_4$	Cl	H	4-$CH_3C_6H_4$	2.5	75
3e	C_6H_5	H	H	4-$CH_3C_6H_4$	1.5	83
3f	C_6H_5	H	H	4-ClC_6H_4	3	65
3g	C_6H_5	Cl	H	C_6H_5	4	63
3h	4-$CH_3C_6H_4$	Cl	H	C_6H_5	3	81
3i	4-$CH_3OC_6H_4$	H	H	3-$CH_3C_6H_4$	1.5	85
3j	C_6H_5	H	H	3-$CH_3C_6H_4$	1.5	72

[a] Isolated yield.

HRMS [Found: *m/z* 412.1688 (M^+), Cacld for $C_{28}H_{20}N_4$: M, 412.1688].

{2,3-Bis(4-methylphenyl)imidazo[1,2-c]quinazolin-5-yl}phenylamine (3c). This compound was obtained as solid with mp 241–243°C; IR (KBr) ν: 3387, 3031, 2915, 2857, 1623, 1599, 1565, 1534, 4550, 1498, 1474, 1461, 1353, 1338, 1282, 1185, 1111, 924, 896, 823, 763, 707, 689, 671 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.27 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.95 (s, 1H, NH), 7.02–7.05 (m, 1H, ArH), 7.11 (d, J = 8.0 Hz, 2H, ArH),7.21–7.24 (m, 2H, ArH), 7.29–7.33 (m, 2H, ArH), 7.45–7.49 (m, 3H, ArH), 7.53 (d, J = 7.2 Hz, 2H, ArH), 7.62–7.71 (m, 4H, ArH), 8.41–8.43 (m, 1H, ArH).

HRMS [Found: *m/z* 440.2008 (M^+), Cacld for $C_{30}H_{24}N_4$: M, 440.2001].

{9-Chloro-2,3-bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5-yl}-p-tolylamine (3d). This compound was obtained as solid with mp 199–200°C; IR (KBr) ν: 3370, 1624, 1610, 1579, 1559, 1533, 1516, 1490, 1473, 1377, 1335, 1289, 1252, 1177, 1073, 1036, 833, 668 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.25 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 6.89 (d, J = 8.4 Hz, 2H, ArH), 6.97 (s, 1H, NH), 7.11–7.16 (m, 4H, ArH), 7.26–7.28 (m, 2H, ArH), 7.49–7.52 (m, 2H, ArH), 7.62–7.65 (m, 2H, ArH), 7.72–7.75 (m, 2H, ArH), 8.32 (s, 1H, ArH).

HRMS [Found: *m/z* 520.1665 (M^+), Cacld for $C_{31}H_{25}{}^{35}ClN_4O_2$: M, 520.1666].

(2,3-Diphenylimidazo[1,2-c]quinazolin-5-yl)-p-tolylamine (3e). This compound was obtained as solid with mp 196–198°C (ref. 13, 192–194°C); IR (KBr) ν: 3400, 3055, 2921, 1630, 1599, 1564, 1543, 1509, 1472, 1378, 1351, 1334, 1240, 1227, 1109, 1026, 924, 831, 814, 778, 760, 712 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.24 (s, 3H, CH_3), 6.78 (s, 1H, NH), 7.01 (s, 4H, ArH), 7.26–7.33 (m, 3H, ArH), 7.46–7.48 (m, 1H, ArH), 7.56–7.58 (m, 2H, ArH), 7.64 (d, J = 4.0 Hz, 2H, ArH), 7.70–7.84 (m, 5H, ArH), 8.42–8.44 (m, 1H, ArH).

HRMS [Found: *m/z* 426.1846 (M^+), Cacld for $C_{29}H_{22}N_4$: M, 426.1844].

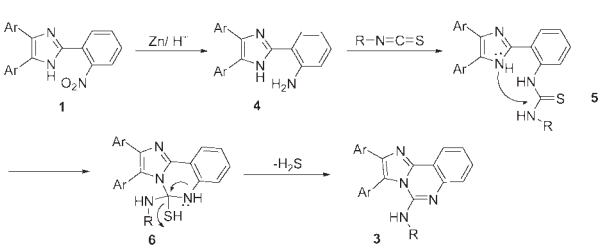
4-Chlorophenyl(2,3-diphenylimidazo[1,2-c]quinazolin-5-yl)amine (3f). This compound was obtained as solid with mp 212–214°C (ref. 13, 208–210°C); IR (KBr) ν: 3400, 3054, 1625, 1596, 1566, 1536, 1490, 1472, 1444, 1404, 1332, 1293, 1088, 830, 802, 757, 709 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 6.92 (s, 1H, NH), 7.21–7.23 (m, 2H, ArH), 7.26–7.52 (m, 5H, ArH), 7.47–7.51 (m, 1H, ArH), 7.56 (d, J = 7.6 Hz, 2H, ArH), 7.66–7.82 (m, 7H, ArH), 8.44 (d, J = 8.0 Hz, 1H, ArH).

HRMS [Found: *m/z* 446.1296 (M^+), Cacld for $C_{28}H_{19}{}^{35}ClN_4$: M, 446.1298].

(9-Chloro-2,3-diphenylimidazo[1,2-c]quinazolin-5-yl)phenylamine (3g). This compound was obtained as solid with mp 190–191°C (ref. 13, 182–184°C); IR (KBr) ν: 3387, 3058, 1627, 1598, 1559, 1532, 1497, 1472, 1446, 1378, 1336, 1234, 1071, 1027, 925, 877, 818, 774, 755, 714, 689 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 6.89 (s, 1H, NH), 7.04 (t, J = 7.6 Hz, 1H, ArH), 7.19 (d, J = 8.4 Hz, 2H, ArH), 7.27–7.31 (m, 5H, ArH), 7.55–7.57 (m, 2H, ArH), 7.61–7.74 (m, 4H, ArH), 7.78 (d, J = 7.2 Hz, 1H, ArH), 7.84 (d, J = 7.2 Hz, 2H, ArH), 8.34 (d, J = 2.4 Hz, 1H, ArH).

HRMS [Found: *m/z* 446.1296 (M^+), Cacld for $C_{28}H_{19}{}^{35}ClN_4$: M, 446.1298].

Scheme 3



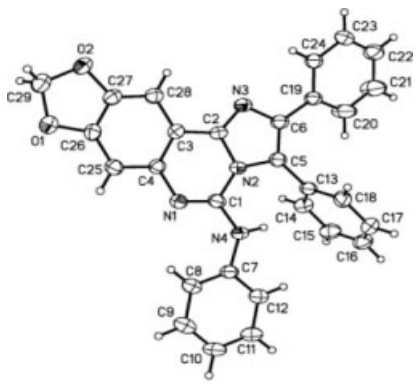


Figure 1. X-ray structure of **3a**.

{9-Chloro-2,3-bis(4-methylphenyl)imidazo[1,2-c]quinazolin-5-yl}phenylamine (3h). This compound was obtained as solid with mp 226–227°C. IR (KBr) ν: 3387, 2916, 2857, 1626, 1597, 1559, 1530, 1497, 1472, 1450, 1374, 1342, 1246, 1185, 1072, 1016, 929, 819, 755, 691 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.28 (s, 3H, CH_3), 2.53 (s, 3H, CH_3), 6.97 (s, 1H, NH), 7.03–7.08 (m, 1H, ArH), 7.12 (d, J = 8.0 Hz, 2H, ArH), 7.21–7.23 (m, 2H, ArH), 7.31 (t, J = 8.0 Hz, 2H, ArH), 7.46 (d, J = 8.4 Hz, 2H, ArH), 7.54 (d, J = 7.6 Hz, 2H, ArH), 7.63–7.72 (m, 4H, ArH), 8.35 (d, J = 2.4 Hz, 1H, ArH).

HRMS [Found: *m/z* 474.1609 (M^+), Cacld for $C_{30}H_{23}{}^{35}ClN_4$: M, 474.1611].

{2,3-Bis(4-methoxyphenyl)imidazo[1,2-c]quinazolin-5-yl}-m-tolylamine (3i). This compound was obtained as solid with mp 202–204°C. IR (KBr) ν: 3383, 3064, 2962, 2934, 2834, 1623, 1612, 1567, 1535, 1515, 1493, 1475, 1461, 1411, 1375, 1333, 1286, 1248, 1174, 1109, 1024, 839, 806, 784, 762, 742, 673 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): 2.26 (s, 3H, CH_3), 3.74 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 6.85–6.87 (m, 2H, ArH), 6.89 (s, 1H, NH), 6.96 (s, 2H, ArH), 7.15–7.21 (m, 2H, ArH), 7.28 (d, J = 8.4 Hz, 2H, ArH), 7.43–7.47 (m, 1H, ArH), 7.52 (d, J = 8.4 Hz, 2H, ArH), 7.60–7.67 (m, 2H, ArH), 7.74 (d, J = 8.4 Hz, 2H, ArH), 8.41 (d, J = 3.6 Hz, 1H, ArH).

HRMS [Found: *m/z* 486.2038 (M^+), Cacld for $C_{31}H_{26}N_4O_2$: M, 486.2056].

(2,3-Diphenylimidazo[1,2-c]quinazolin-5-yl)-m-tolylamine (3j). This compound was obtained as solid with mp 168–170°C. IR (KBr) ν: 3399, 3050, 2917, 1624, 1588, 1566, 1533, 1473, 1441, 1374, 1331, 1264, 1194, 1109, 776, 761, 716, 705 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): 2.23 (s, 3H, CH_3), 6.80–6.84 (m, 2H, NH + ArH), 6.98–7.00 (m, 2H, ArH), 7.14 (t, J = 7.8 Hz, 1H, ArH), 7.24–7.30 (m, 3H, ArH), 7.42–7.48 (m, 1H, ArH), 7.53–7.56 (m, 2H, ArH), 7.59–7.66 (m, 2H, ArH), 7.69–7.82 (m, 5H, ArH), 8.40 (d, J = 7.5 Hz, 1H, ArH).

HRMS [Found: *m/z* 426.1844 (M^+), Cacld for $C_{29}H_{22}N_4$: M, 426.1844].

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