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Iron(III) Chloride-Catalyzed Decarboxylative–Deaminative Functionalization of Phenylglycine: A Tandem Synthesis of Quinazolinones and Benzimidazoles

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Abstract: The first iron(III) chloride-catalyzed decarboxylative–deaminative functionalization of phenylglycine with *o*-substituted nitroarenes was achieved for the synthesis of 4(3*H*)-quinazolinones and benzimidazoles. The reaction of 2-nitrobenzonitrile/2-nitro-*N,N*-diphenylamine with phenylglycine at 120 °C in the presence of potassium carbonate as a base in toluene generated the products in 45–87% yields. Various functional groups like nitro, fluoride, chloride and trifluoromethyl were well tolerated under the present reaction conditions. In this tandem approach, involvement of transfer hydrogenation of the nitro functionality with *in situ* generated ammonia, imination, nitrile hydration to amide and oxidative cyclization sequences have been established. The process avoids the use of an external hydrogen source, costly catalysts as well as the isolation of amine and amide intermediates.

Keywords: benzimidazoles; iron catalysts; phenylglycine; quinazolinones; tandem synthesis

Introduction

Tandem reactions lower the cost of production of target molecules by minimizing energy consumption, waste, and purification of intermediates which increases the sustainability of the whole process. In the same way, tandem decarboxylation or deamination is a fundamental metabolic process involved in biochemistry and peptide cleavage. For example, in plants, the aromatic amino acid decarboxylase (AAAD) enzyme catalyzes either decarboxylation or decarboxylation–deamination on various aromatic amino acids.[1] In non-biological system, oxidative decarboxylation of α-amino acids can be induced at high temperature or achieved by the use of various oxidants to generate Strecker aldehydes.[2] In recent years, various biologically important molecules have been synthesized by decarboxylative functionalization of abundantly available amino acids by using various catalyst and oxidants[3–9] (Scheme 1).

Although the decarboxylative functionalization of amino acids is known, simultaneous decarboxylative–deaminative functionalization (DDF) is new to organic synthesis and offers an economic protocol to convert the widely available amino acids into biologically active pharmacophores. Designing a catalytic transformation that targets simultaneous C–N bond cleavage and carbon dioxide excision for the synthesis of bioactive pharmacophore reveals a great significance. In this context, the Kalutharage group and Xiang et al. reported C–C bond formation *via* decarboxylative and deaminative functionalization of amino acids.[9a,b] To the best of our knowledge, C–N bond formation *via* DDF is still unknown.

Quinazolinones are an important class of nitrogen heterocycles present in a large number of natural products and have a broad range of biological activities including anti-HIV, anticancer, antitubercular, anti-inflammatory, antimalarial, antitumor, anticonvulsant, fungicidal, and antimicrobial.[10] In view of their importance, a number of approaches has been

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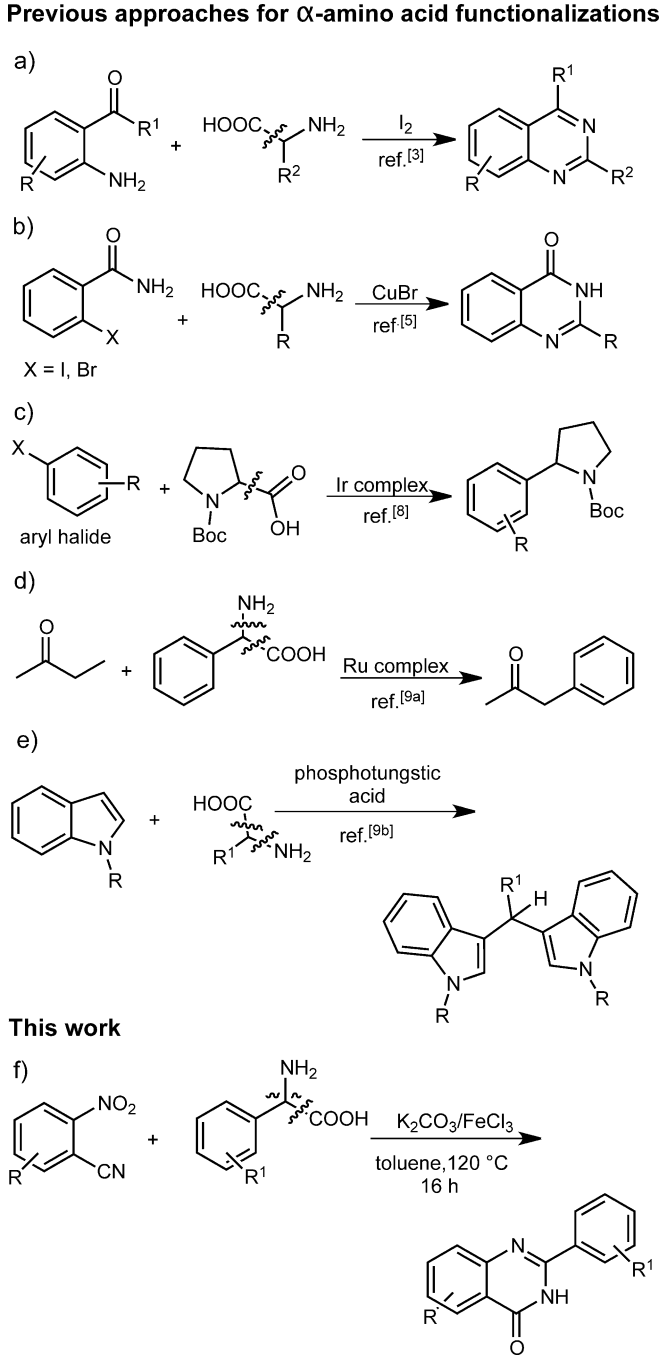

Scheme 1. Approaches for amino acid functionalizations.

developed for the synthesis of 4(3*H*)-quinazolinones.[11–13] These methods mainly rely on the condensation of *o*-aminobenzamide with aldehydes,[11e] alcohols,[13d] or carboxylic acids[11a] and their derivatives[11b,c] as coupling partners. Usually amines are prepared by the reduction of nitro compounds for which a stoichiometric amount of reagents is required. Therefore, designing a one-pot multistep synthetic route starting from less expensive nitroarenes will be an attractive approach in terms of economy and reducing the amount of waste generated.

In continuation of our previous efforts on the utilization of natural products as reagent/catalyst in organic synthesis,[14] we screened various amino acids and found that phenylglycine, although a non-natural amino acid, is a good coupling partner for C–N bond formation with various *o*-nitrobenzonitriles and *o*-nitro-*N,N*-diphenylamines. Herein, we disclose an $FeCl_3$-catalyzed decarboxylative–deaminative oxidative cyclization of phenylglycine with *o*-nitrobenzonitriles/*o*-nitro-*N,N*-diphenylamines in a toluene/K_2CO_3 system to afford various 2-aryl-4(3*H*)-quinazolinone/1,2-diphenylbenzimidazole derivatives.

Results and Discussion

The preliminary experiments were carried out with 2-nitrobenzonitrile (**1a**) and phenylglycine (**2a**) as a model substrates for the optimization of reaction conditions. After initial screening of different iron salts, bases, solvents and reaction temperature it was found that 10 mol% of $FeCl_3$ in toluene with two equivalents of K_2CO_3 at 120 °C after 16 hours afforded the desired product (**3a**) in 87% isolated yield (Table 1, entry 3). As expected, **3a** was not observed in the absence of $FeCl_3$ (Table 1, entry 10). With other iron salts a relatively lower yield of **3a** was observed (Table 1, entries 11–15). A very good yield of **3a** was observed with two equivalents of K_2CO_3, whereas three equivalents lowered the yield (Table 1, entries 3 and 4). In the absence of base, 12% of **3a** was observed (Table 1, entry 9) while other selected bases resulted in traces or lower yields (Table 1, entries 5–8). The use of other solvents like PEG-400, DMF, and DMSO gave lower yields of **3a** while in water the corresponding amide was observed as a major product (Table 1, entries 16–19).

With the optimized reaction conditions in hand, we examined the scope and limitations of the method for structurally diverse *o*-nitrobenzonitriles (**1**) and phenylglycines (**2**).

As illustrated in Table 2, various 2-nitrobenzonitriles, regardless of the presence of electron-donating and electron-withdrawing groups reacted smoothly to give the corresponding 4(3*H*)-quinazolinones in good to excellent yields. Electron-withdrawing groups like chloro, nitro, and trifluoromethyl were well tolerated and afforded the desired products (**3f–3n**, **3u–3x**) in 45–72% yields. The unsubstituted substrate **1a** and those with electron-donating groups like methyl and methoxy on **1** afforded the desired products (**3a–3e**, **3o–3t**) in 55–87% yields which is comparably higher than those substrates bearing electron-withdrawing groups. When **1a** was treated with other α-amino acids, such as phenylalanine, tryptophan and glycine

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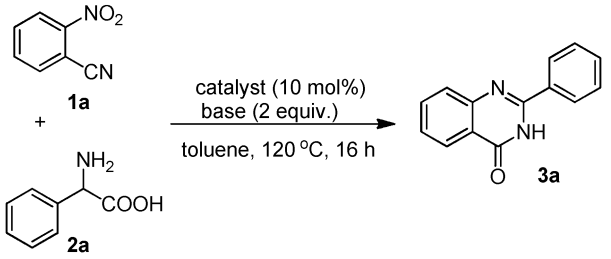
Table 1. Optimization of reaction conditions.[a]



Entry	Base	Solvent	Catalyst	Yield [%][b]
1	K_2CO_3	toluene	$FeCl_3$	15[c]
2	K_2CO_3	toluene	$FeCl_3$	35[d]
3	**K_2CO_3**	**toluene**	**$FeCl_3$**	**87**
4	K_2CO_3	toluene	$FeCl_3$	80[e]
5	Na_2CO_3	toluene	$FeCl_3$	trace
6	Cs_2CO_3	toluene	$FeCl_3$	10
7	$NaHCO_3$	toluene	$FeCl_3$	trace
8	K*t*OBu	toluene	$FeCl_3$	8
9	no base	toluene	$FeCl_3$	12
10	K_2CO_3	toluene	–	NR
11	K_2CO_3	toluene	$FeCl_2$	54
12	K_2CO_3	toluene	ferrocene	5
13	K_2CO_3	toluene	iron powder	10
14	K_2CO_3	toluene	$Fe(OAc)_2$	trace
15	K_2CO_3	toluene	$FeSO_4{\cdot}7H_2O$	8
16	K_2CO_3	PEG-400	$FeCl_3$	35
17	K_2CO_3	DMF	$FeCl_3$	10
18	K_2CO_3	DMSO	$FeCl_3$	12
19	K_2CO_3	H_2O	$FeCl_3$	0[f]

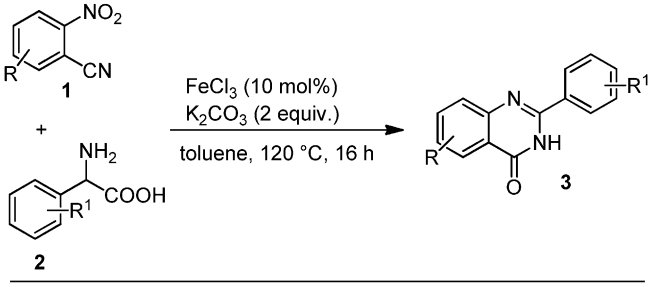
[a] All the reactions were carried out using **1a** (1 mmol), **2a** (1.5 mmol), catalyst (10 mol%), base (2 mmol), solvent (5 mL) at 120 °C for 16 h unless otherwise indicated.
[b] Isolated yields.
[c] 1 mmol of K_2CO_3 used.
[d] 1.5 mmol of K_2CO_3 used.
[e] 3 mmol of K_2CO_3 used.
[f] Corresponding amide was isolated as the major product.

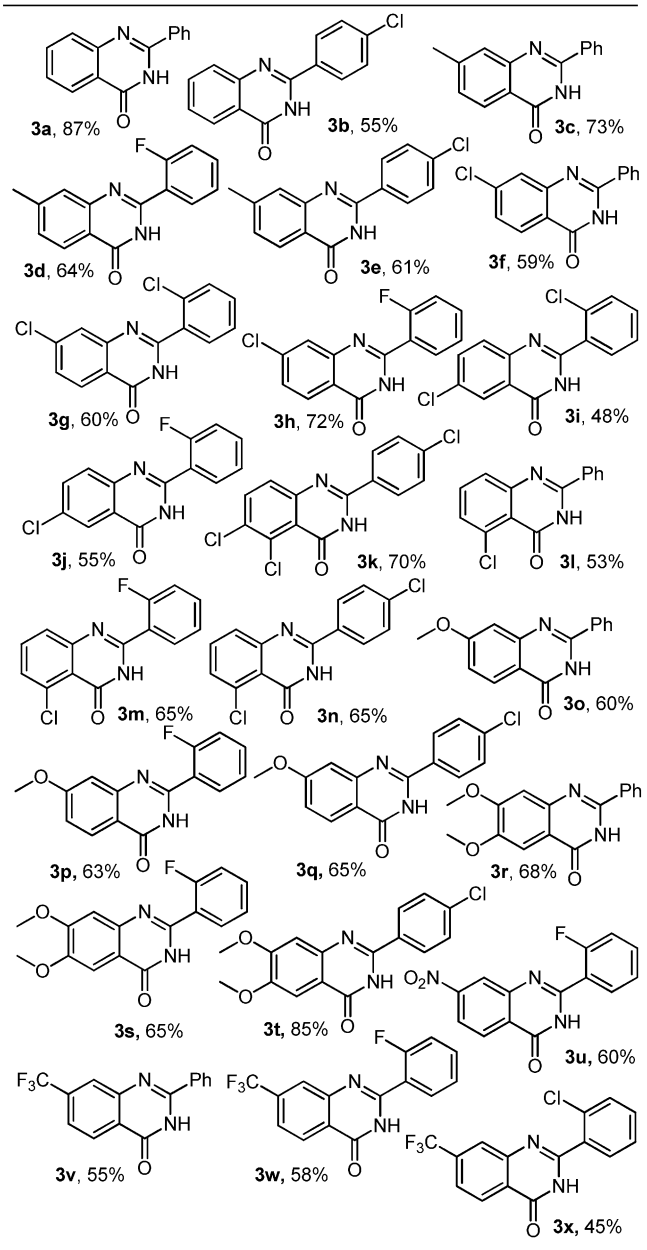
under the standard reaction conditions, the corresponding Strecker aldehyde was formed and no further reaction was observed.

The scope of the optimized method was further extended towards the synthesis of 1,2-diphenylbenzimidazoles (Table 3, **5a–5d**), where *o*-nitrobenzonitrile was replaced with 2-nitro-*N,N*-diphenylamine (**4**). Previously, for the synthesis of benzimidazoles various methods have been developed starting either from 1,2-phenylenediamine, or 2-nitroaniline *via* condensation with various carboxylic acids,[15] alcohols,[16] and aldehydes.[17] Including this, Buchwald[18] and Ma et al.[19] also reported a benzimidazole synthesis *via* condensation of 2-haloacetanilide with various anilines. The present method represents a new and direct approach for the synthesis of benzimidazoles.

The mechanism of the product formation was established by different control experiments.

Table 2. Decarboxylative–deaminative coupling of phenylglycines with 2-nitrobenzonitriles.[a]





[a] All the reactions were carried out using **1** (1 mmol), **2** (1.5 mmol), K_2CO_3 (2 mmol) and $FeCl_3$ (10 mol%) in toluene (5 mL) at 120 °C for 16 h. All the yields indicated after purification are averages of two runs.

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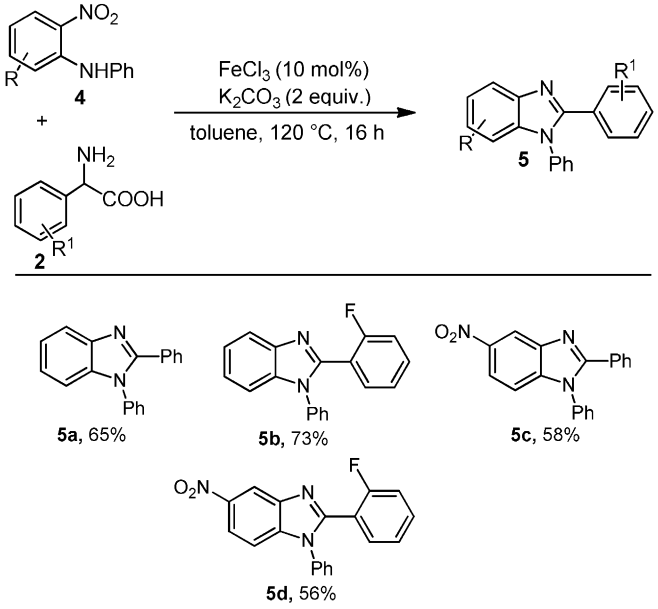
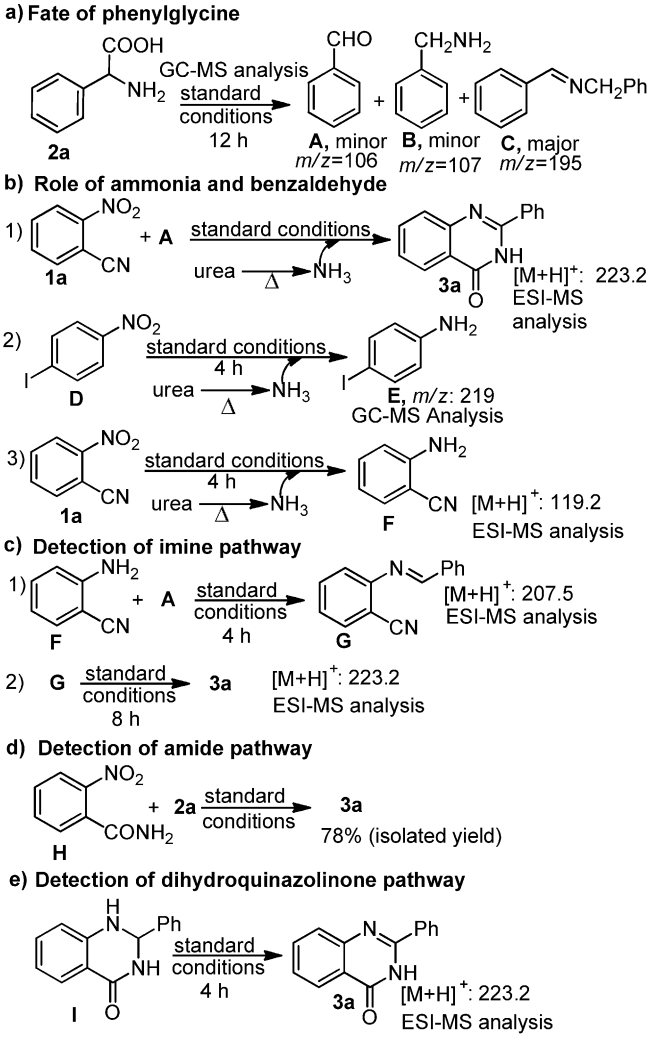
Table 3. Decarboxylative–deaminative coupling of phenylglycine with 2-nitro-*N,N*-diphenylamine.[a]



[a] All the reactions were carried out using **4** (1 mmol), **2** (1.5 mmol), K_2CO_3 (2 mmol) and $FeCl_3$ (10 mol%) in toluene (5 mL) at 120 °C for 16 h.



Scheme 2. Mechanistic studies.

(Scheme 2). First to establish the fate of phenylglycine (**2a**), it was heated in the absence of 2-nitrobenzonitrile (**1a**) under the optimized reaction conditions. GC-MS analysis of the reaction mixture after 12 h showed the formation of benzaldehyde (**A**, $m/z=$ 106), benzylamine (**B**, $m/z=107$) and Schiff base of (**A**+**B**), i.e, *N*-benzylidenebenzylamine (**C**, $m/z=195$) which supported the iron(III)-induced oxidative decarboxylation of amino acids (Scheme 2a). The formation of benzaldehyde ($\delta_H=9.75$ for CHO) was further confirmed by ^{1}H NMR analysis of phenylglycine under standard reaction conditions in the absence of **1a** in deuterated benzene at different time intervals (see the Supporting Information).

Further, we assumed that ammonia generated *in situ* by the degradation of phenylglycine reduces the nitro functionality of **1a** to furnish 2-aminobenzonitrile (**F**), since during the optimization of reaction conditions **F** was also observed as a minor product. In order to confirm the involvement of ammonia as a reducing agent, it (generated by heating urea) was passed through the reaction mixture of **1a** and benzaldehyde (**A**) which resulted in the formation of product **3a** [Scheme 2b (1)], while no product was observed in the absence of ammonia under the same reaction conditions. It was further supported by the successful reduction of 4-iodonitrobenzene to the corresponding aniline in the presence of ammonia [Scheme 2b (2)].

The formation of imine (**G**), the expected key intermediate for product formation, was confirmed by the reaction of **F** with **A** [Scheme 2c (1)]. Heating of separately prepared imine (**G**) under the standard reaction conditions afforded the expected product **3a**, hence confirming the involvement of the imine pathway [Scheme 2c (2)]. The nitrile hydration to amide is a base-promoted process, hence we assumed that **G** was converted into its corresponding amide by $FeCl_3$/K_2CO_3 (however, prior to imine formation, hydration of 2-aminobenzonitrile to 2-aminobenzamide may also be possible) followed by oxidative cyclization to form quinazolinone. Earlier Wu et al. reported the oxidative synthesis of quinazolinones from 2-aminobenzamide and benzaldehyde.[13d] To confirm the involvement of the amide pathway, the reaction of 2-nitrobenzamide (**H**) with phenylglycine (**2a**) was carrried out under the standard conditions and **3a** was isolated as a major product in 78% yield (Scheme 2d).

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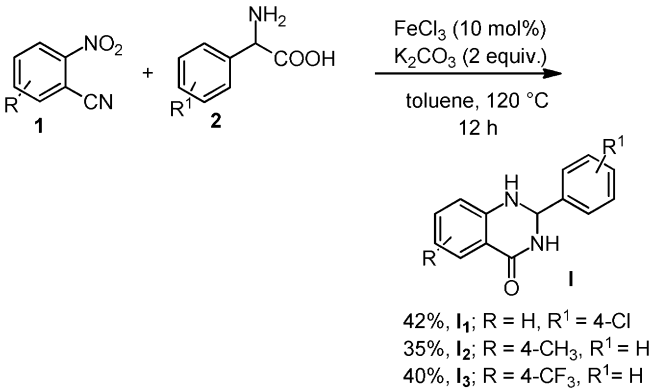
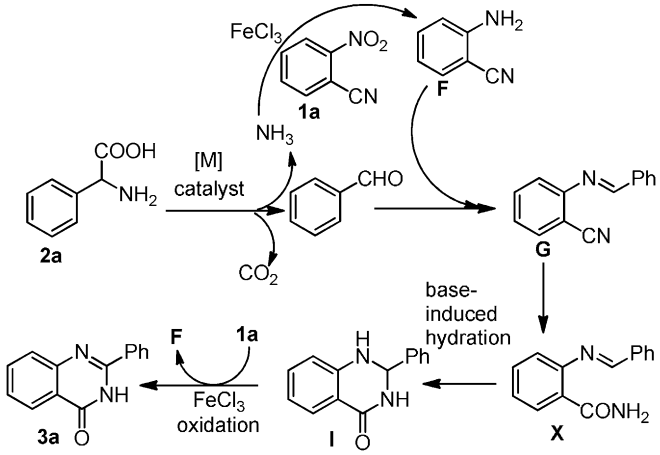


Scheme 3. Isolation of 2,3-dihydroquinazolin-4(1*H*)-one intermediates.



Scheme 4. Probable mechanism for 4(3*H*)-quinazolinone synthesis.

The respective 2,3-dihydroquinazolin-4(1*H*)-one intermediates (**I**) were also isolated after 12 h from the reaction mixture (Scheme 3). The isolated intermediate **I** was oxidized under the standard reaction conditions [Scheme 2 (e)] to afford the desired product **3a** after 4 h which supported the involvement of dihydroquinazolinone in the proposed mechanistic cycle (Scheme 4).

Therefore, in accordance with additional experiments and literature findings, a probable mechanism has been outlined for this $FeCl_3$-catalyzed decarboxylative–deaminative oxidative coupling of phenylglycine with *o*-substituted nitroarenes (Scheme 4). Initially phenylglycine (**2a**) after decarboxylation and deamination is converted into benzaldehyde. The ammonia evolved from **2a** reduces the nitro group of **1a** in the presence of $FeCl_3$ into **F**. The intermediate **F** condenses with benzaldehyde to form imine **G**. The imine (**G**) after base-induced controlled hydration is converted to **X**, which after cyclization is converted into 2,3-dihydroquinazolin-4(1*H*)-one (**I**). The intermediate **I** may help in the conversion of **1a** to **F** *via* transfer hydrogenation as established earlier,[20] and itself is converted into the desired product (**3a**).

Conclusions

In conclusion, we have developed a direct and efficient method for the synthesis of 4(3*H*)-quinazolinones/benzimidazoles *via* functionalization of phenylglycine using *o*-nitrobenzonitriles/*o*-nitro-*N,N*-diphenylamine as easily available substrates with cheap and non-toxic $FeCl_3$ in a tandem manner. The beauty of the method lies in the reduction of the nitro functionality with *in situ* generated ammonia which then couples with benzaldehyde followed by oxidative cyclization. The developed method involves a series of chemical transformations controlled in a one-pot operation thus minimizing the waste, energy and cost. This method offers a simple and direct synthesis of various biologically active pharmacophores/natural products having quinazolinone and benzimidazole frameworks.

Experimental Section

General Information

All reagents, high grade solvents and materials were used as received from commercial sources unless otherwise stated. Toluene was distilled from sodium and benzophenone. Column chromatography was carried out over 60–120 mesh silica gel (Merck India). TLC silica gel 60 F254 plates were purchased from Merck India Ltd. Nitro compounds, amino acids and NMR solvents were purchased from Sigma Aldrich and Spectrochem. $FeCl_3$ anhydrous (98%) was purchased from Loba chemie India. ^{1}H NMR and ^{13}C NMR experiments were performed on Bruker Avance 300 and 600 MHz spectrometers. NMR spectra were recorded in $CDCl_3$, CD_3OD, CD_3SOCD_3 and C_6D_6. Chemical shifts are reported in parts per million (ppm) downfield from an internal standard. Splitting patterns are given as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; brs, broad singlet; dd, double doublet; dp, doublet of triplet. All coupling constants are given in Hertz (Hz). GC-MS analysis was carried out using DB-5 MS capillary column, (30 m × 0.25 mm i.d., 0.25 μm) on a Shimadzu (QP 2010) series Gas Chromatograph-Mass Spectrometer (Tokyo, Japan) coupled with AOC-20i auto-sampler. The initial temperature of column was 70 °C held for 4 min and was programmed upto 230 °C at 4 °C min^{-1}, then held for 15 min at 230 °C; the sample injection volume was 2 μL in GC grade dichloromethane. Helium was used as carrier gas at a flow rate of 1.1 mL min^{-1} in split mode (1: 50). Mass spectra were recorded on a QTOF-Micro from Waters Micromass.

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General Procedure for the Synthesis of Quinazolinones

In a 12-mL test tube, the 2-nitrobenzonitrile (1 mmol), phenylglycine (1.5 mmol), K_2CO_3 (2 mmol), and anhydrous $FeCl_3$ (10 mol%) were dissolved in toluene (5 mL) and stirred at 120 °C for 16 h in an oil bath. After completion of the reaction, the reaction tube was cooled to room temperature and the reaction mixture was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with saturated brine and distilled water (3×5 mL each), dried over Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified using column chromatography (silica gel 60–120 mesh, *n*-hexane/ethyl acetate). Purified products were characterized by NMR, ESI-MS, and GC-MS techniques.

General Procedure for the Synthesis of Benzimidazoles

In a 12-mL tube, 2-nitro-*N*,*N*-diphenylamine (1 mmol), phenylglycine (1.5 mmol), K_2CO_3 (2 mmol), anhydrous $FeCl_3$ (10 mol%) were dissolved in toluene (5 mL) and stirred at 120 °C for 16 h in an oil bath. After completion of reaction, the reaction tube was cooled to room temperature and the reaction mixture was extracted with ethyl acetate (3×5 mL). The combined organic layer was washed with saturated brine and distilled water (3×5 mL each), dried over Na_2SO_4 and the solvent was evaporated under vacuum. Products were purified using column chromatography (silica gel 60–120 mesh, *n*-hexane/ethyl acetate). Purified products were characterized by NMR, ESI-MS, and GC-MS techniques.

Procedure for the Synthesis of 2-[(Benzylidene)-amino]benzonitrile (G)

Benzaldehyde (1 mmol), 2-aminobenzonitrile (1.5 mmol), and sodium metabisulfite (catalytic) was mixed and irradiated under multimode microwave (900 W) for 10 min. After completion of the reaction, the reaction mixture was cooled to room temperature and extracted with ethyl acetate. The ethyl acetate layer was washed with saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The product was purified using column chromatography (silica gel 60–120 mesh, *n*-hexane/ethyl acetate). The purified product was characterized by NMR and ESI-MS techniques.

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