



An Improved Synthetic Method of Phenazine-1-carboxylic Acid

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An improved synthetic method of a natural fungicide, phenazine-1-carboxylic acid, was reported. In brief, the process constitutes of (a) one-pot synthesis of 1-methylphenazine (**IV**) from pyrocatechol and 3-methyl-2-aminoaniline, (b) Wohl-Ziegler bromination of **IV**, (c) hydrolyzation of 1-bromomethylphenazine (**III**) in aqueous solution of $\text{Na}_2\text{CO}_3/\text{N,N}$ -dimethylformamide (1.1:1, v/v), (d) oxidation of 1-phenazinemethanol (**II**) by O_2 under the catalyzation of *N*-bromosuccinimide. This method provided an effective synthesis of phenazine-1-carboxylic acid in the overall yield of 66 %.

Keywords: Natural fungicide, Phenazine-1-carboxylic acid, One-pot, Oxidation.

INTRODUCTION

Substituted phenazine cores are important biologically active structures and are usually found in natural products, pesticides and antibiotics¹⁻⁷. Majority of the natural products phenazine derivatives are produced by diverse genera of bacteria⁸⁻¹³ and existing knowledge indicates that dozens of them originate from either phenazine-1,6-dicarboxylic acid (PDC) or phenazine-1-carboxylic acid (PCA, **I**) (Fig. 1)¹⁴⁻¹⁷. As a more than simple secondary metabolite produced by various pseudomonad strains, phenazine-1-carboxylic acid is also a natural excellent fungicide due to its effectiveness against various phytopathogens, low toxicity to humans and animals and environmental friendliness¹⁸⁻¹⁹.

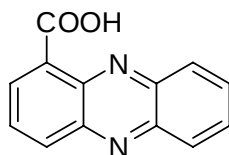


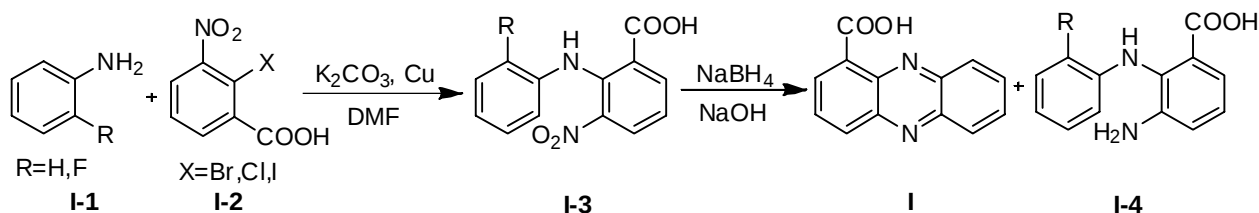
Fig. 1. Phenazine-1-carboxylic acid (PCA, **I**)

In 1989, phenazine-1-carboxylic acid was firstly found in *P. fluorescens* 2-79²⁰⁻²². In 2011, phenazine-1-carboxylic acid was registered as a new synthesized biologically fungicide named 'Shenqinmeisu' by the Ministry of Agriculture of China, which attracted wide attention from all around the world²². Now, phenazine-1-carboxylic acid was mainly isolated from *P. aeruginosa* strain M18 in the biosynthetic pathway where

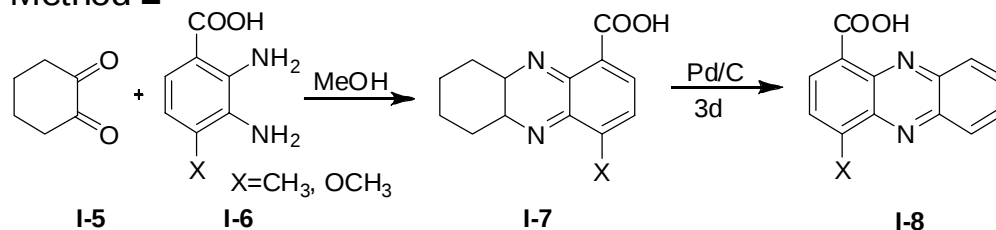
the ring of phenazine was catalyzed by enzymes encoded in the conserved 'phz operon' through symmetrical head-to-tail double condensation of two chorismic acid^{7,19-27}. For the biosynthetic method, wide-type strains were reported to produce only 200-300 mg/L of phenazine-1-carboxylic acid and even the new optimization strain M18MSU1 was found to give 4771.2 mg/L²². However, the disadvantages of the biological fermentation, such as low yield, the effluent and the offscum, restricted the large-scale production of phenazine-1-carboxylic acid.

Although the studies on chemical synthesis of phenazines had attracted wide interest²⁸⁻³³, only three methods to phenazine-1-carboxylic acid were reported. Method 1 disclosed a method to phenazine-1-carboxylic acid in two steps (**Scheme-I**)^{6,31-32}. Ullmann coupling of substituted anilines (**I-1**) and 2-halogeno-3-nitrobenzoic acid (**I-2**) yielded substituted *N*-phenyl-3-nitro-anthranilic acids (**I-3**). Then, reductive cyclization of **I-3** provided phenazine-1-carboxylic acid (**I**). Meanwhile, it was possible to isolate varying amounts of substituted *N*-phenyl-3-aminoanthranilic acid (**I-4**), which was the direct reduction product of the nitro group without ring formation. This was one important factor causing the low yield of method 1. Another noteworthy factor was that **I-2** could not be commercially available. Method 2 disclosed another method in only 26 % yield (**Scheme-I**)⁹. Condensation of cyclohexane-1,2-dione (**I-5**) with substituted 2,3-diaminobenzoic acids (**I-6**) furnished substituted 6,7,8,9-tetrahydro-1-carboxy-phenazine (**I-7**), which was dehydrogenated with Pd/C in 3d, gave substituted phenazine-1-carboxylic acid. The yield of method

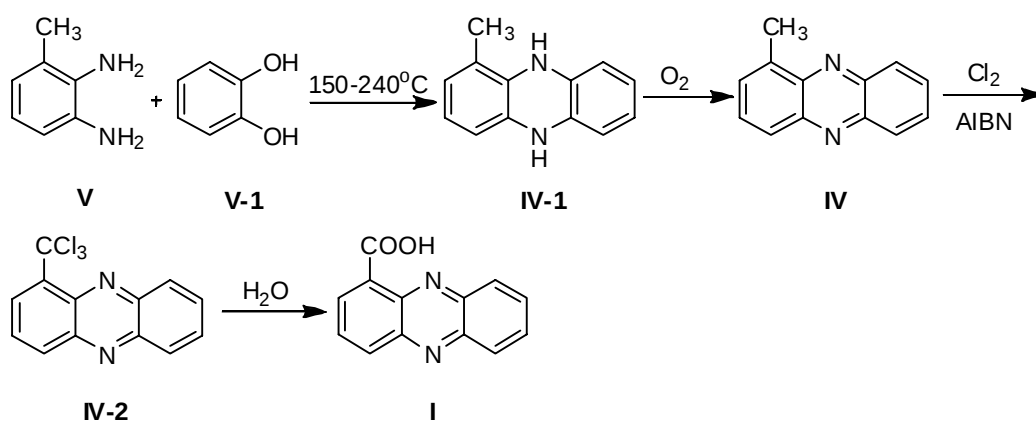
Method 1



Method 2



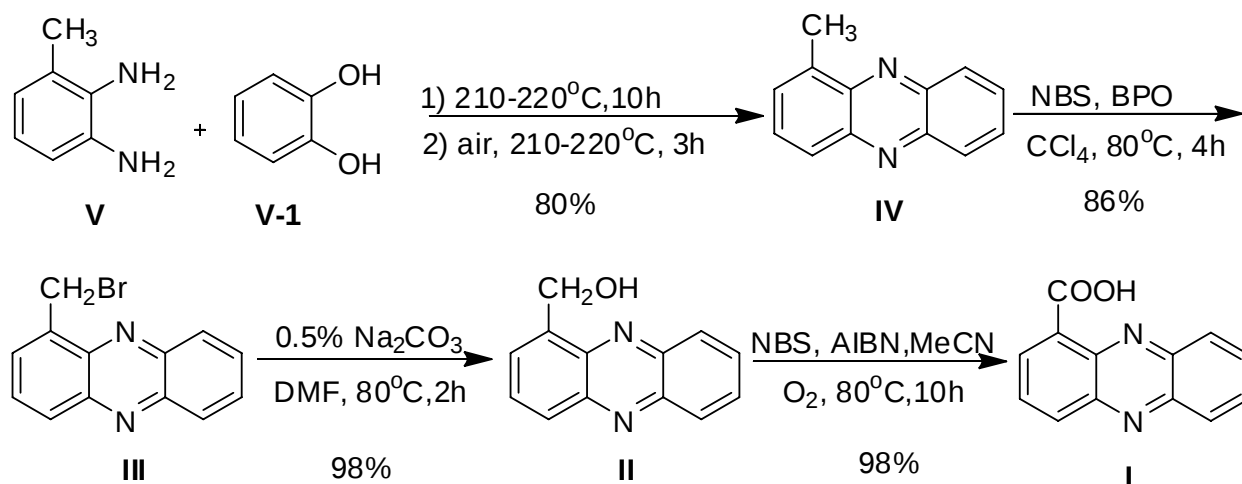
Method 3



Scheme-I: Reported synthetic methods of phenazine-1-carboxylic acid

2 was lower and the route needed long reaction time. These drawbacks of these two routes made them unsuitable for the synthesis of phenazine-1-carboxylic acid. Recently, our group reported the method 3, which comprised condensation, oxidation, chlorination and hydrolyzation starting from 3-methylbenzene-1,2-diamine (V) and pyrocatechol (V-1)³³ (Scheme-I).

Based on the previous work, an improved synthetic method of phenazine-1-carboxylic acid was developed. The route starting from V and V-1, includes condensation in one-pot, bromination with N-bromosuccinimide (NBS), hydrolyzation in 0.5 % Na_2CO_3 aqueous solution/*N,N*-dimethylformamide (1.1:1, v/v) and oxidation with O_2 , employing readily available and non-metallic reagents showed in Scheme-II. For



Scheme-II: Synthetic route of phenazine-1-carboxylic acid

further application in scale synthesis of phenazine-1-carboxylic acid, the overall yield was up to 66 % by optimizing each step.

EXPERIMENTAL

Unless otherwise specified, all reagents was procured from commercial sources and used without further purification. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer. Mass spectra were recorded on a mass spectrometry (MS) spectrometer VG12-250 MS. Melting points (m.p.) were taken on an X-4 microscope electro thermal apparatus. Reactions were monitored by reverse phase HPLC on a Varian 1200 chromatograph equipped with a Symmetry Shield RP column (C_{18} , 150 mm $\times$ 4.6 mm). Content by HPLC refers to chromatographic area percentage. The column temperature was at 25 $^{\circ}\text{C}$ and the flow rate of mobile phase ($\text{CH}_3\text{OH}/\text{H}_2\text{O} = 7/3$, v/v) was to 1.0 mL/min.

Synthesis of 1-methylphenazine (IV): To a round bottom flask was charged compound **V** (22.4 g, 0.18 mol) and **V-1** (29.7 g, 0.27 mol). The reaction mixture was heated at 210–220 $^{\circ}\text{C}$ for 10 h under N_2 . Then the mixture was heated for another 3 h under air. After cooling to room temperature, it was diluted with EtOAc and washed with 40 % NaOH aqueous solution (100 mL), water (50 mL $\times$ 2). The organic layer was then dried with Na_2SO_4 and the solvent was removed under reduced pressure. Yellow powder was obtained, yield 80 %. m.p. 106–109 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ : 2.92 (s, 3H), 7.62–7.64 (m, 1H), 7.69–7.73 (m, 1H), 7.78–7.85 (m, 2H), 8.07 (dd, $J_1 = 8.8$, $J_2 = 1.6$, 1H), 8.20–8.25 (m, 1H), 8.26–8.29 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 143.6, 143.2, 143.1, 142.7, 137.9, 130.4, 130.2, 130.1, 129.9, 129.5, 129.4, 127.5, 17.7; ESI-MS m/z : 195.0 (100 %).

Synthesis of 1-(bromomethyl)phenazine (III): Compound **IV** (10 g, 51.5 mmol), NBS (13.7 g, 77.2 mmol) and benzoyl peroxide (1.41 g, 8.8 mmol) were dissolved in CCl_4 (150 mL) in a two necked flask equipped with an efficient reflux condenser. The mixture was stirred for 4 h at reflux. After completion of the reaction, the mixture poured into water (100 mL) and extracted with dichloromethane (DCM) (50 mL $\times$ 3). The obtained DCM was dried with anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by flash chromatography on silica gel with ethyl acetate-petroleum ether (1:15, v/v) to give the intermediate **III** (12.1 g, 86.3 %) as yellow solid. m.p. 163–165 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ : 5.35 (s, 2H), 7.77–7.81 (m, 1H), 7.85–7.88 (m, 2H), 7.96 (d, $J = 6.7$, 1H), 8.21–8.25 (m, 2H), 8.30–8.34 (m, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 143.6, 143.4, 142.9, 141.2, 136.8, 131.0, 130.9, 130.6, 130.5, 130.2, 130.1, 129.5, 28.4; ESI-MS m/z : 272.9 (100 %) and 274.9 (97 %).

1-(Dibromomethyl)phenazine (**III-1**) as yellow solid. m.p. 158–161 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.87–7.95 (m, 3H), 8.22–8.31 (m, 3H), 8.34 (s, 1H), 8.49–8.51 (dd, $J_1 = 7.1$, $J_2 = 0.94$, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 143.8, 142.7, 142.4, 140.0, 138.1, 131.4, 131.2, 131.1, 131.0, 130.2, 130.0, 129.5, 35.8; ESI-MS m/z : 352.9 (100 %), 350.8 (50 %) and 354.9 (50 %).

Synthesis of 1-phenazinemethanol (II): Compound **III** (10 g, 36.6 mmol) was dissolved in the mixture of DMF (80 mL) and 0.5 % Na_2CO_3 aqueous solution (88 mL) in a three

necked flask equipped with an efficient reflux condenser. The mixture was heated at 80 $^{\circ}\text{C}$ for 2 h under stirring. Then, the mixture was cooled and poured into water (100 mL) and extracted with EtOAc (50 mL $\times$ 3). The obtained EtOAc extract was washed with 0.2 N HCl (30 mL $\times$ 2) and finally washed with saturated NaCl solution. After drying with anhydrous Na_2SO_4 , the organic layer was concentrated in vacuum to get the crude product. The residue was purified by recrystallization to obtain **II** (7.6 g, 98.4 %) as yellow solid. m.p. 132–134 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ : 4.50 (t, $J = 6.4$, 1H), 5.33 (d, $J = 6.3$, 2H), 7.72–7.78 (m, 2H), 7.84 (t, $J = 4.1$, 2H), 8.14–8.24 (m, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 143.7, 142.4, 141.9, 138.8, 138.7, 130.7, 130.6, 130.3, 129.6, 129.5, 129.2, 128.2, 63.9; ESI-MS m/z : 211.1 (100 %).

Synthesis of phenazine-1-carboxylic acid (I): To one three necked flask was added compound **II** (12.0 g, 57.1 mmol) and anhydrous MeCN (100 mL). Then azobisisobutyronitrile (1.0 g, 5.7 mmol) and NBS (5.1 g, 22.8 mmol) were added into the mixture under O_2 atmosphere with stirring. The reaction mixture was heated at 80 $^{\circ}\text{C}$ for 10 h. The solution was chilled and poured into water, then was extracted with EtOAc (50 mL $\times$ 3). After dried with anhydrous Na_2SO_4 , the organic layer was concentrated in vacuum to get the crude product. The residue was purified by recrystallization to obtain the target compound **I** (12.6 g, 98.2 %) as yellow powder. m.p. 240–242 $^{\circ}\text{C}$; ^1H NMR (CDCl_3 , 400 MHz) δ : 7.88–7.98 (m, 2H), 8.18–8.26 (m, 2H), 8.44 (t, $J = 4.3$, 2H), 8.89 (d, $J = 7.2$, 1H), 15.5 (s, 1H); ^{13}C NMR (CDCl_3 , 100 MHz) δ : 164.9, 143.0, 142.3, 139.9, 138.7, 136.4, 134.1, 132.2, 130.7, 129.2, 129.0, 126.9, 123.8; ESI-MS m/z : 225.0 (100 %).

RESULTS AND DISCUSSION

Synthesis of 1-methylphenazine (IV): The synthesis of **IV** via condensation of **V** and **V-1** at 230 $^{\circ}\text{C}$ for 24–50 h to give the intermediate 1-methyl-5,10-dihydrophenazine (**IV-1**) and its subsequent conversion under O_2 in 2–7 h had been reported³³. In this paper, one-pot method was found to be carried out instead of two-steps method, which was advantageous with respect to reaction time and purification. Therefore, the intermediate **IV** was obtained in one-pot by condensation of **V** and **V-1** at 210–220 $^{\circ}\text{C}$ for only 10 h and then oxidation with air at 210–220 $^{\circ}\text{C}$ for 3 h in 80 % yield.

Synthesis of 1-bromomethylphenazine (III): As per the reported process, **III** was obtained in 57 % yield under Wohl-Ziegler bromination condition³⁴. Therefore, the study was started by the reported process and got the required compound **III** in low yield contaminated with the byproduct 1-(dibromomethyl)phenazine (**III-1**). **III-1** was identified by ^1H NMR, ^{13}C NMR and isolated. In order to enhance the yield of **III** and minimize the level of **III-1**, the equivalent of NBS and benzoyl peroxide (BPO) was investigated and the results were summarized in Table-1. In the initial trial, the reactions were carried out in different equivalent of NBS in 0.16 equivalent of benzoyl peroxide (entries 1–4). The optimum quantity of NBS was found to be 1.5 equivalent in which **III** was present in 84.6 % with a better yield (determined by HPLC) along with 5.3 % of **III-1** (entry 3). Due to the incomplete reaction of **IV** in 10.1 %, the equivalent of benzoyl peroxide was further screened using

TABLE-1
EFFECTS OF REACTION CONDITIONS^a ON THE YIELD OF **III**

Entry	<i>n</i> (IV): <i>n</i> (NBS): <i>n</i> (BPO)	Content by HPLC ^b			Yield (%) ^c
		IV (%)	III (%)	III-1 (%)	
1	1.00:1.00:0.16	76.2	23.7	0	20.5
2	1.00:1.30:0.16	36.7	60.3	2.9	56.6
3	1.00:1.50:0.16	10.1	84.6	5.3	81.3
4	1.00:1.60:0.16	2.1	82.2	15.7	79.2
5	1.00:1.50:0.12	65.6	32.3	2.1	26.8
6 ^d	1.00:1.50:0.17	5.4	88.8	5.5	86.3
7	1.00:1.50:0.18	3.2	73.8	22.9	70.9

^aReaction conditions: the compound **IV**, NBS and benzoyl peroxide (BPO) were in CCl₄ at reflux; ^bHPLC; ^cIsolated yield; ^dStarting material (4 %) was recovered.

1.5 equivalent of NBS (entries 3, 5-7). Increasing the amount of benzoyl peroxide from 0.12 to 0.17 equivalent improved the yield of **III** from 26.8 to 86.3 % and then the yield decreased to 70.9 % which the equivalent was to 0.18. The optimized conditions showed that 0.17 equivalent of benzoyl peroxide and 1.5 equivalent of NBS achieved the good result of **III** (88.8 %) with only 5.5 % of **III-1** and 4 % of **IV** was isolated and recovered.

Synthesis of 1-phenazinemethanol (II): The hydrolyzation of **III** to produce **II** was carried out under the catalyst of a base in different reaction conditions in our process showed in Table-2. First, the initial study was conducted on 0.5 % Na₂CO₃ aqueous solution and the yield was only 20.8 % (entry 1). Considering to the poor soluble of **III** in water, two different reaction system in the mixtures of 0.5 % Na₂CO₃ aqueous solution-nonpolar solvent [1,2-dichloroethane and toluene] were also investigated and gave poor yield, even tetrabutylammonium bromide (TBAB) was added (entries 2-3). Reactions in polar solvents (EtOH, THF, DMF and 1,4-dioxane) were further tried for improving the yield (entries 4-7). The reaction proceeded successfully and the corresponding product **II** was obtained in 98.4 % yield in DMF (entry 7). Meanwhile, the investigations on the effect of the temperature in DMF

revealed that the yield of **II** was slightly influenced from 60 to 100 °C, but the reaction time could be obvious shorten from 4.5 to 0.5 h (entries 7-9). In addition, different concentrations of Na₂CO₃ aqueous solution were studied in DMF. Increasing of the concentration from 0.1 to 10 (wt %), the yield ranged from 98.4 to 69.6 % (entries 7, 10-14). Furthermore, some other bases (K₂CO₃, NaHCO₃, KHCO₃, NaOH and KOH) were screened (entries 15-19), but only K₂CO₃ gave good yield in 92.8 %. Taking all these into account, **II** was achieved in 98.4 % yield in the mixture of 0.5 % Na₂CO₃ aqueous solution and DMF at 80 °C for 2 h.

Synthesis of phenazine-1-carboxylic acid (I): Most of the reported methods for oxidation of primary alcohols to carboxylic acids were under metal catalysis, including high-valent metal salts (CrO₃, KMnO₄, RuO₄, RuCl₃/H₅IO₆, *etc.*)³⁵, or transition metal (Pd, Ru, W, Re, Cu, *etc.*)³⁶. However, these oxidative methods exhibited some limitations, such as stringent reaction conditions, high cost, high reagent load, or toxicity of the metal. Recently, several green methods, using O₂ as oxidant and catalyzing by irradiation in the presence of bromo sources, or a base, were developed³⁷⁻⁴³. In this paper, a new method was developed to achieve the target product in the presence of NBS and azobisisobutyronitrile (AIBN) under O₂

TABLE-2
EFFECTS OF REACTION CONDITIONS^a ON THE YIELD OF THE COMPOUND **II**

Entry	Solvent	Base	Concentration of base (wt %)	Time (h)	Yield (%) ^c
1	—	Na ₂ CO ₃	0.5	10.0	20.8
2	EDC ^b	Na ₂ CO ₃	0.5	15.0	32.8
3	Toluene ^b	Na ₂ CO ₃	0.5	20.0	47.4
4	EtOH	Na ₂ CO ₃	0.5	30.0	59.4
5	THF	Na ₂ CO ₃	0.5	4.0	80.2
6	1,4-Dioxane	Na ₂ CO ₃	0.5	4.5	96.7
7	DMF	Na ₂ CO ₃	0.5	2.0	98.4
8 ^c	DMF	Na ₂ CO ₃	0.5	4.5	97.5
9 ^d	DMF	Na ₂ CO ₃	0.5	0.5	80.3
10	DMF	Na ₂ CO ₃	0.1	9.0	95.2
11	DMF	Na ₂ CO ₃	0.8	1.5	89.4
12	DMF	Na ₂ CO ₃	1.0	2.5	82.5
13	DMF	Na ₂ CO ₃	5.0	1.0	78.1
14	DMF	Na ₂ CO ₃	10.0	3.5	69.6
15	DMF	K ₂ CO ₃	0.5	3.0	92.8
16	DMF	NaHCO ₃	0.5	4.0	83.2
17	DMF	KHCO ₃	0.5	4.5	80.0
18	DMF	NaOH	0.5	8.0	72.5
19	DMF	KOH	0.5	10.0	69.4

^aReaction conditions: the compound **III** was in solvents/base aqueous solution mixture (1:1.1, v/v) at 80 °C; ^bAdded Bu₄NBr as phase transfer catalyst; ^cThe reaction was at 60 °C; ^dThe reaction was at 100 °C; ^eIsolated yield

TABLE-3
 EFFECTS OF REACTION CONDITIONS^a ON THE YIELD OF THE COMPOUND **I**

Entry	Bromo sources	<i>n</i> (II): <i>n</i> (AIBN): <i>n</i> (NBS/Br ₂)	Content by HPLC ^b		Yield (%) ^c
			I (%)	II (%)	
1	NBS	1:0.1:0.1	14.3	76.7	9.6
2	NBS	1:0.1:0.2	36.5	63.5	29.4
3	NBS	1:0.1:0.3	65.9	19.8	58.7
4	NBS	1:0.1:0.4	100.0	0	98.2
5	NBS	1:0.1:0.4	—	—	0 ^d
6	—	1:0.1:0.0	—	—	0
7	Br ₂	1:1.0:0.4	—	—	Trace
8	Br ₂	1:1.0:0.4	—	—	0 ^d

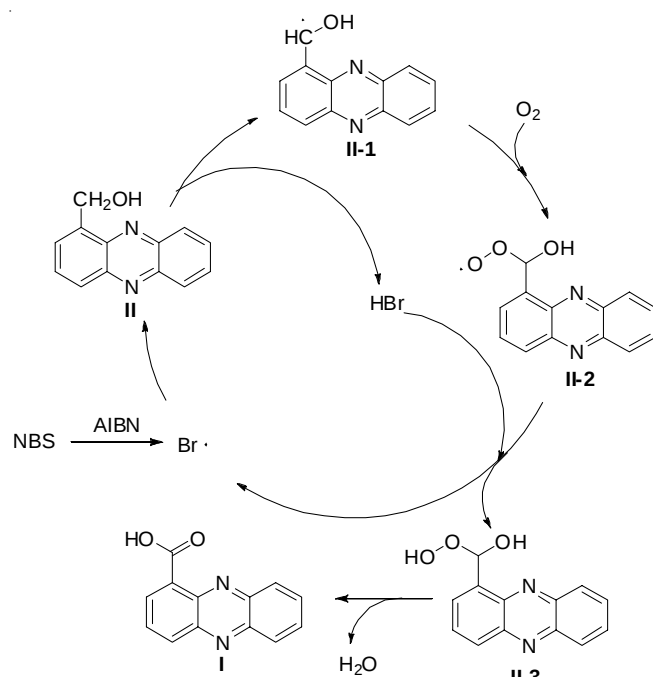
^aReaction conditions: the compound **II**, azobisisobutyronitrile (AIBN) and NBS/Br₂ were under O₂ atmosphere in anhydrous MeCN at 80 °C;

^bHPLC; ^cIsolated yield; ^dThe reaction was carried out under N₂.

atmosphere, which was an efficient, green and non-metal process.

Different equivalent of NBS in 0.1 equivalent of azobisisobutyronitrile was studied and the results were summarized in Table-3. The yield of **I** was improved by increasing the equivalent of NBS from 0.1 to 0.4 and **I** was obtained in 98 % yield with the addition of 0.4 equivalent NBS (entries 1-4). No reaction occurred when conducting the reaction in N₂ atmosphere or in the absence of bromo sources showed the necessity of both NBS and molecular oxygen (entries 5-6). Furthermore, Br₂ was examined instead of NBS in O₂ or N₂ and gave bad performances (entry 7-8), which demonstrated that O₂ was the oxidant and NBS/Br₂ provided the bromo radical in the reaction.

Based on these results, a possible mechanism was proposed as shown in **Scheme-III**. Firstly, the radical species **II-1** was generated by abstraction of one hydrogen radical with a bromo radical, formed under the initiation of azobisisobutyronitrile from NBS. Then, **II-1** trapped O₂ to afford **II-2**, which subsequently transformed to **I** via hydroperoxide **II-3**.



Scheme-III: Possible mechanism for the oxidation reaction from **II** to **I**

Conclusion

In summary, an improved synthetic method to phenazine-1-carboxylic acid was successfully developed in 66 % yield with the employment of commercially available reagents. The method involved condensation, bromination, hydrolyzation and oxidation. The intermediate **IV** was obtained in one-pot which is advantageous in workup and reaction time. An improved protocol was also established for the formation of **I** by treatment with molecular oxygen in the presence of NBS, in mild, green and metals-free reaction condition.

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