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An Improved Synthetic Method of Phenazine-1-carboxylic Acid

Q.Y. ZHAN, X.L. ZHU, H. HUANG, Q. LIU and H.J. ZHU*

Department of Applied Chemistry, College of Sciences, Nanjing Tech University, Nanjing 211816, P.R. China

*Corresponding author: Fax: +86 25 83172358; Tel: +86 25 58139480; E-mail: zhuhj@njtech.edu.cn

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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-methyphenazine (**IV**) from pyrocatechol and 3-methyl-2-aminoaniline, (b) Wohl-Ziegler bromination of **IV**, (c) hydrolyzation of 1-bromomethylphenazine (**III**) in aqueous solution of Na_2CO_3/*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 antibiotics[1-7]. Majority of the natural products phenazine derivatives are produced by diverse genera of bacteria[8-13] 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 friendliness[18-19].

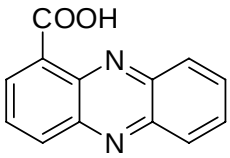
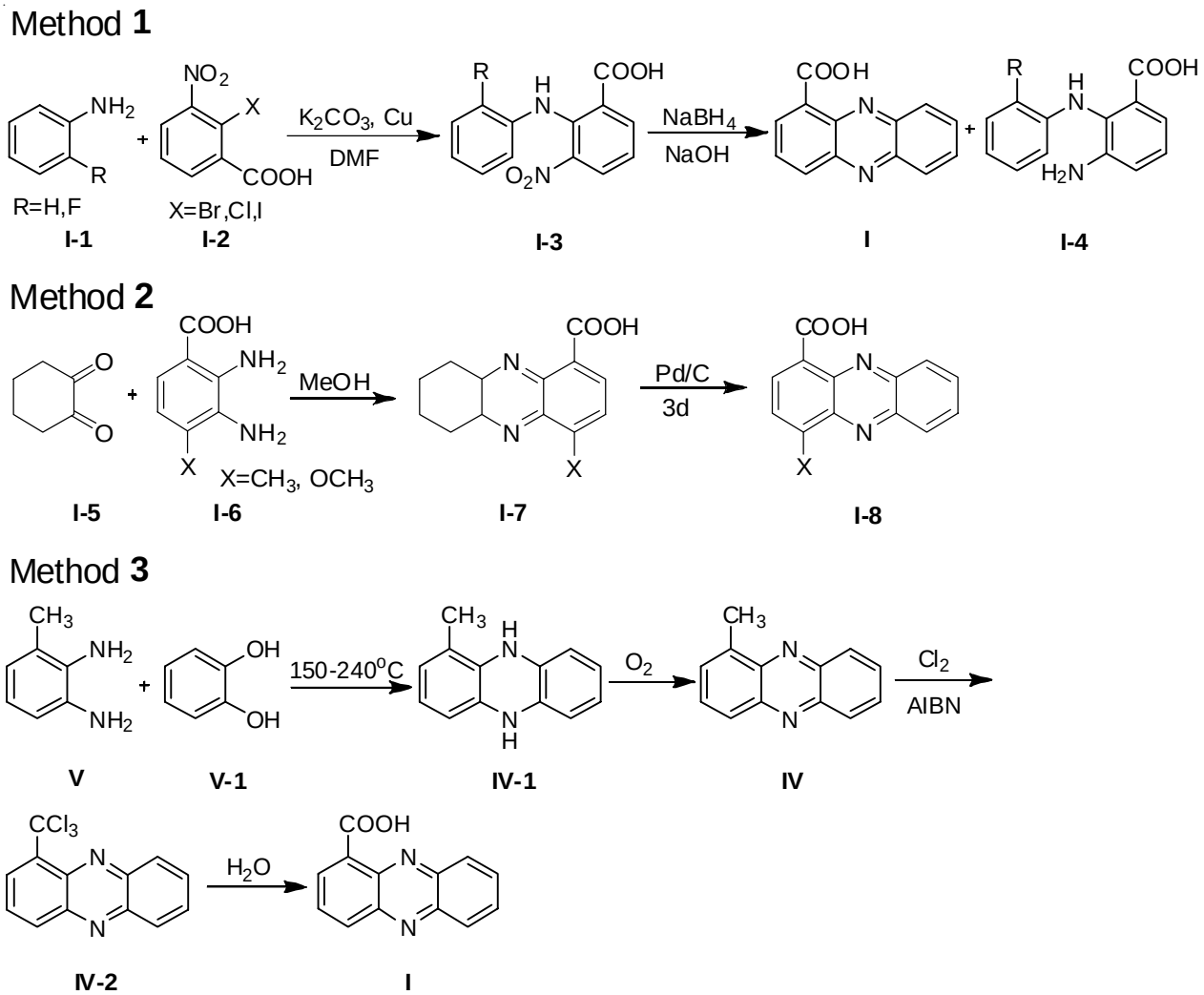


Fig. 1. Phenazine-1-carboxylic acid (PCA, **I**)

In 1989, phenazine-1-carboxylic acid was firstly found in *P. fluorescens* 2-79[20-22]. 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 world[22]. 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/L[22]. 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.

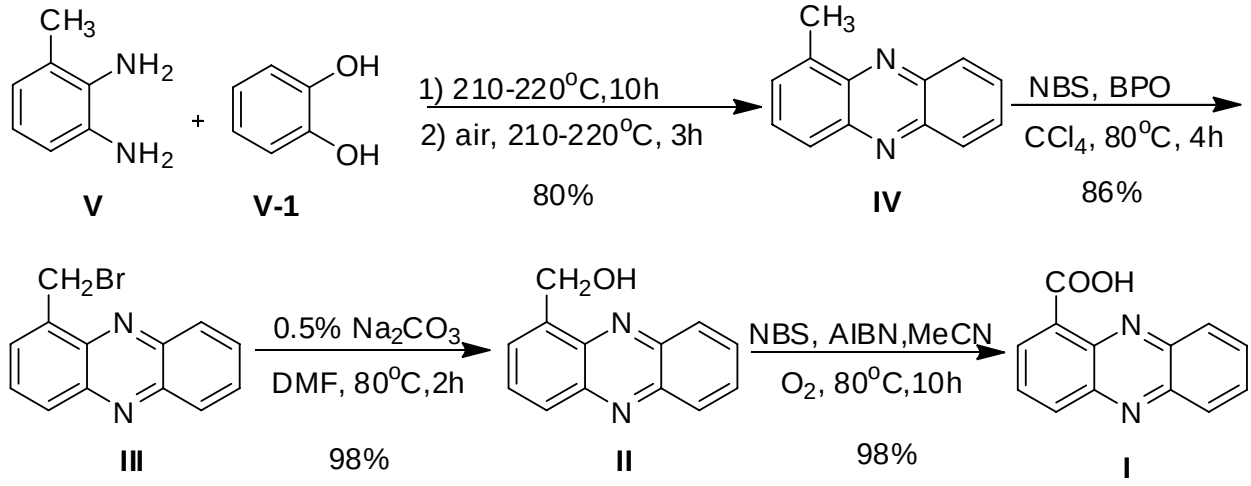
Although the studies on chemical synthesis of phenazines had attracted wide interest[28-33], only three methods to phenazine-1-carboxylic acid were reported. Method 1 disclosed a method to phenazine-1-carboxylic acid in two steps (**Scheme-I**)[6,31-32]. Ullmann coupling of substituted anilines (**I-1**) 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



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. ^{1}H 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 × 4.6 mm). Content by HPLC refers to chromatographic area percentage. The column temperature was at 25 °C and the flow rate of mobile phase (CH_3OH/H_2O = 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 °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 × 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 °C; ^{1}H 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 dichloromehtane (DCM) (50 mL × 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 °C; ^{1}H 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 °C; ^{1}H 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 °C for 2 h under stirring. Then, the mixture was cooled and poured into water (100 mL) and extracted with EtOAc (50 mL × 3). The obtained EtOAc extract was washed with 0.2 N HCl (30 mL × 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 °C; ^{1}H 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 °C for 10 h. The solution was chilled and poured into water, then was extracted with EtOAc (50 mL × 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 °C; ^{1}H 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-methyphenazine (IV): The synthesis of **IV** *via* condensation of **V** and **V-1** at 230 °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 reported[33]. 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 °C for only 10 h and then oxidation with air at 210-220 °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 condition[34]. 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 ^{1}H 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	*n*(IV):*n*(NBS):*n*(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

[a]Reaction conditions: the compound **IV**, NBS and benzoyl peroxide (BPO) were in CCl_4 at reflux; [b]HPLC; [c]Isolated yield; [d]Starting 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 % Na_2CO_3 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 % Na_2CO_3 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 Na_2CO_3 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 (K_2CO_3, $NaHCO_3$, $KHCO_3$, NaOH and KOH) were screened (entries 15-19), but only K_2CO_3 gave good yield in 92.8 %. Taking all these into account, **II** was achieved in 98.4 % yield in the mixture of 0.5 % Na_2CO_3 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 (CrO_3, $KMnO_4$, RuO_4, $RuCl_3/H_5IO_6$, *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 O_2 as oxidant and catalyzing by irradiation in the presence of bromo sources, or a base, were developed[37-43]. In this paper, a new method was developed to achieve the target product in the presence of NBS and azobisisobutyronitrile (AIBN) under O_2

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

Entry	Solvent	Base	Concentration of base (wt %)	Time (h)	Yield (%)[e]
1	–	Na_2CO_3	0.5	10.0	20.8
2	EDC[b]	Na_2CO_3	0.5	15.0	32.8
3	Toluene[b]	Na_2CO_3	0.5	20.0	47.4
4	EtOH	Na_2CO_3	0.5	30.0	59.4
5	THF	Na_2CO_3	0.5	4.0	80.2
6	1,4-Dioxane	Na_2CO_3	0.5	4.5	96.7
7	DMF	Na_2CO_3	0.5	2.0	98.4
8[c]	DMF	Na_2CO_3	0.5	4.5	97.5
9[d]	DMF	Na_2CO_3	0.5	0.5	80.3
10	DMF	Na_2CO_3	0.1	9.0	95.2
11	DMF	Na_2CO_3	0.8	1.5	89.4
12	DMF	Na_2CO_3	1.0	2.5	82.5
13	DMF	Na_2CO_3	5.0	1.0	78.1
14	DMF	Na_2CO_3	10.0	3.5	69.6
15	DMF	K_2CO_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

[a]Reaction conditions: the compound **III** was in solvents/base aqueous solution mixture (1:1.1, v/v) at 80 °C; [b]Added Bu_4NBr as phase transfer catalyst; [c]The reaction was at 60 °C; [d]The reaction was at 100 °C; [e]Isolated yield

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

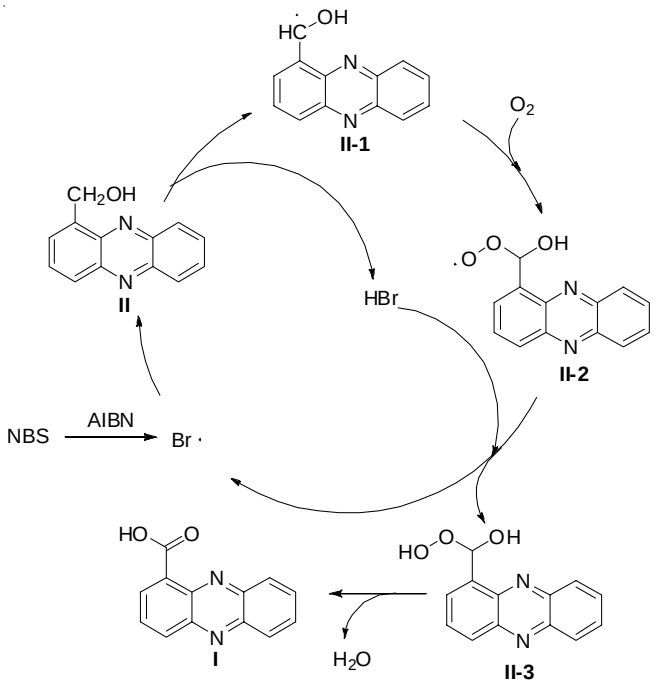
Entry	Bromo sources	*n*(II):*n*(AIBN):*n*(NBS/Br_2)	Content by HPLC[b]		Yield (%)[c]
			I (%)	**II** (%)	
1	NBS	1:0.1:0.1	14.3	76.7	9.6
2	NBS	1:0.1:0.2	36.5	63.5	29.4
3	NBS	1:0.1:0.3	65.9	19.8	58.7
4	NBS	1:0.1:0.4	100.0	0	98.2
5	NBS	1:0.1:0.4	–	–	0[d]
6	–	1:0.1:0.0	–	–	0
7	Br_2	1:1.0:0.4	–	–	Trace
8	Br_2	1:1.0:0.4	–	–	0[d]

[a]Reaction conditions: the compound **II**, azobisisobutyronitrile (AIBN) and NBS/Br_2 were under O_2 atmosphere in anhydrous MeCN at 80 °C; [b]HPLC; [c]Isolated yield; [d]The reaction was carried out under N_2.

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

Different equivalent of NBS in 0.1 equivalent of azobisisobutyro-nitrile 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 N_2 atmosphere or in the absence of bromo sources showed the necessity of both NBS and molecular oxygen (entries 5-6). Furthermore, Br_2 was examined instead of NBS in O_2 or N_2 and gave bad performances (entry 7-8), which demonstrated that O_2 was the oxidant and NBS/Br_2 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 O_2 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 aviable 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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