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Facile Preparation of 4-(4-Nitrophenyl)morpholin-3-one via the Acid-catalyzed Selective Oxidation of 4-(4-Nitrophenyl)morpholine by Sodium Chlorite as the Sole Oxidant

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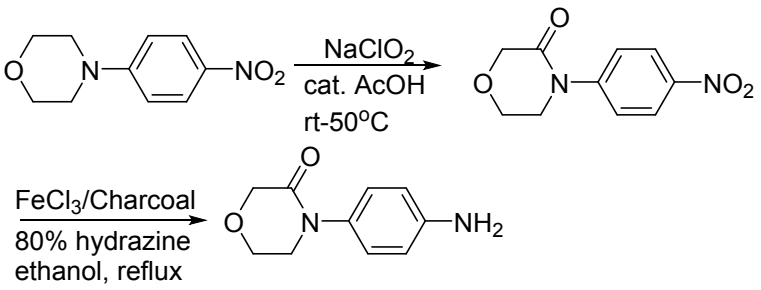
TOC graphic



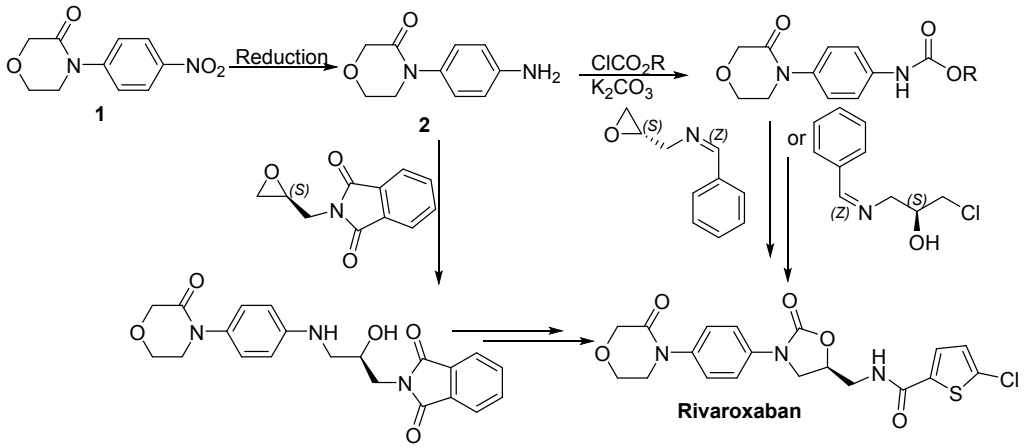
ABSTRACT: 4-(4-nitrophenyl)morpholin-3-one and 4-(4-aminophenyl) morpholin-3-one are the key intermediates for rivaroxaban synthesis. A facile and economic efficient process has been developed for the preparation of these intermediates. An excellent yield of 4-(4-nitrophenyl)morpholine is obtained by condensing 4-chloronitrobenzene and morpholine, and 4-(4-nitrophenyl)morpholine is oxidized using inexpensive sodium chlorite to achieve a good yield of the corresponding 4-(4-nitrophenyl)morpholin-3-one. Finally, the key intermediate of rivaroxaban, 4-(4-aminophenyl) morpholin-3-one, is achieved by the iron (III)-catalyzed reduction of the nitro group with aqueous hydrazine. No high-cost materials were used, and the process did not require column purification.

KEYWORDS: rivaroxaban; 4-(4-nitrophenyl)morpholin-3-one; oxidation; sodium chlorite.

INTRODUCTION

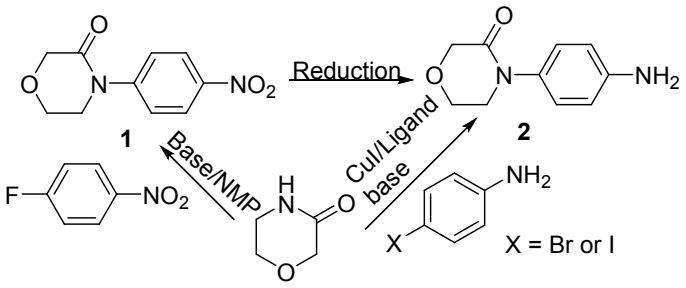
4-(4-nitrophenyl)morpholin-3-one (**1**) and 4-(4-aminophenyl) morpholin-3-one (**2**) are the key intermediates in the preparation of rivaroxaban (marketed as XARELTO), an oxazolidinone derivative anticoagulant, which displays remarkable therapeutic effects in the management of several diseases [1]. (**Scheme 1**)

Scheme 1. Synthetic routes of rivaroxaban



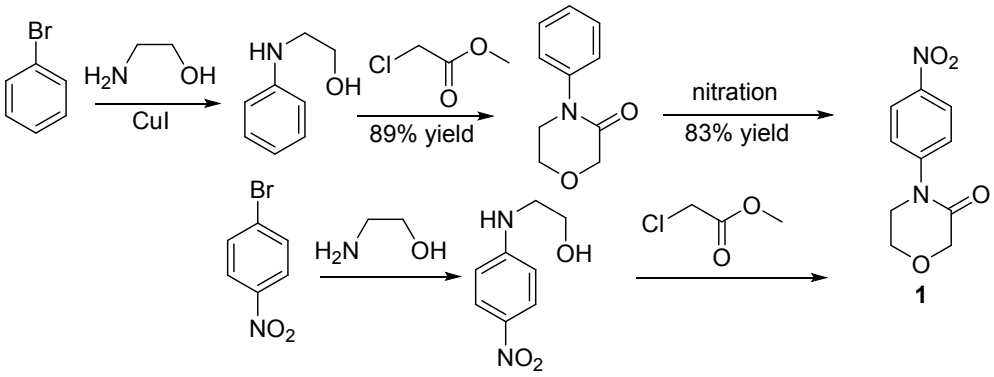
The intermediate **1** can be transformed to the corresponding **2** easily via nitro reduction reaction, and compound **2** is usually used as the starting material for the preparation of rivaroxaban[2]. Several methods for the synthesis of compound **1** have been reported. Bayer AG reported the condensation of 3-morpholinone with 1-fluoro-4-nitrobenzene in the presence of *t*-BuOK or NaH in NMP to give **1** with lower yield (17.4%) [3]. An alternative route was applied to achieve precursor **2** directly by coupling 3-morpholinone with 4-halogen-aniline (4-bromo aniline or 4-iodo aniline) with good yield [2a]. However, in both cases, 3-morpholinone is the key material, but it is difficult to obtain due to its low yield [4], thereby increasing the cost of the whole process. (**Scheme 2**)

Scheme 2. Synthetic routes of intermediates **1** and **2**.



Other routes to obtain intermediates **1** and **2** have also been reported. The coupling of bromobenzene with 2-amino ethanol yielded 2-phenylamino ethanol, which was condensed with methyl 2-chloro acetate, and subsequently nitrated to achieve **1**. Alternatively, compound **1** was also prepared by the condensation of 4-bromo nitrobenzene with 2-amino ethanol, followed by cyclization with methyl 2-chloro acetate. Both methods displayed low efficiency because of two reactive sites existing in both reactants, resulting in a complicated reaction system.[5] (**Scheme 3**)

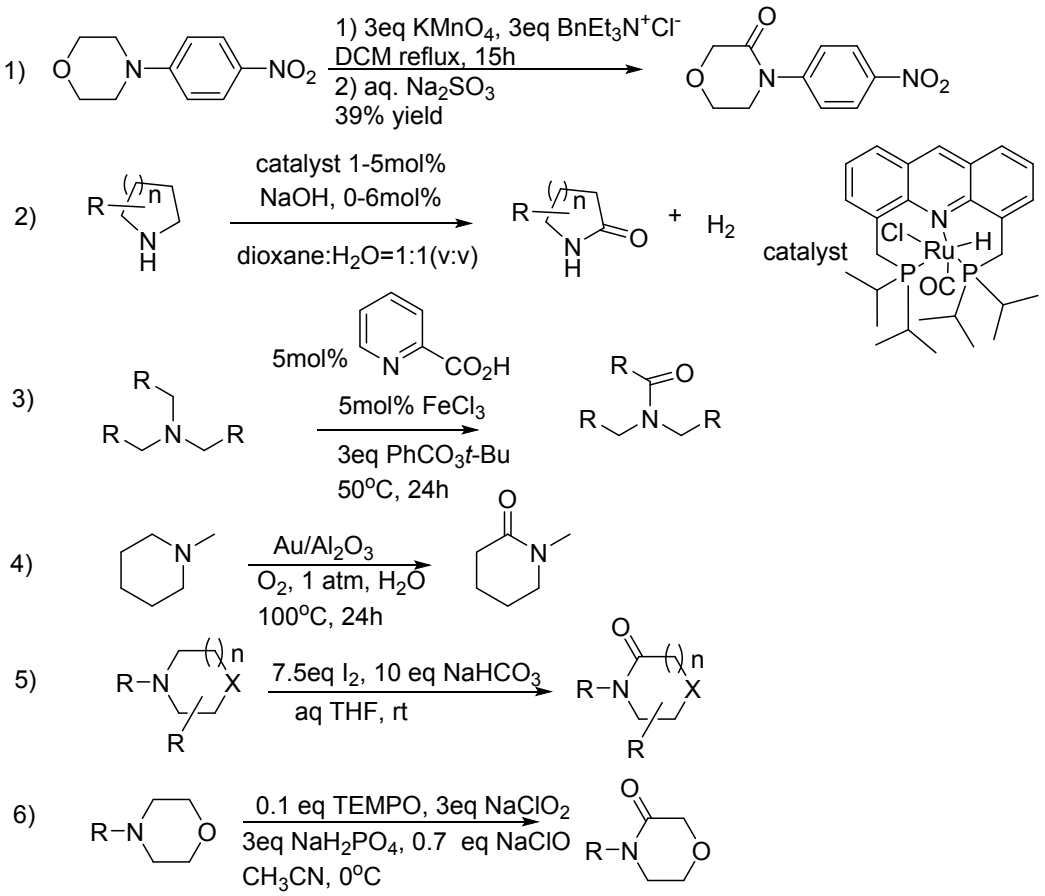
Scheme 3. Alternative synthetic routes of intermediate 1.



Several processes have been reported for the transformation of cyclic amines to corresponding lactams via the chemoselective and regioselective oxidation of C−H bonds directly adjacent to a cyclic amine. In 2009, a patent showed an oxidation protocol for preparing compound **1 (Scheme 4, equation 1)** [3]. In this case, large amounts of heavy metal oxidants, $KMnO_4$, were utilized;

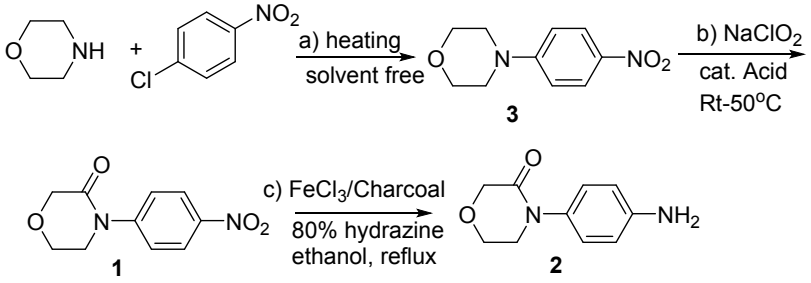
however, this protocol is not environment friendly and is thus unfit for industry use. In 2014, Milstein et al. showed that cyclic amines can be transformed to lactams via ruthenium-catalyzed dehydrogenation **(Scheme 4, equation 2)**; however, completing this transformation involves harsh reaction conditions and an air sensitive and precious metal catalyst [6]. Ferric chloride-catalyzed oxidation cyclic amines offered a lower cost process for obtaining lactams, **(Scheme 4, equation 3)** but the substrate scope is currently limited due to the use of a strong peroxide oxidant [7]. The heterogeneous gold nanoparticle supported on alumina is a mild and chemoselective route for amide and lactam formation **(Scheme 4, equation 4)** [8]; however, the catalyst loading is too large, and gold catalyst costs high, and the catalyst preparation is tedious. From an environmental perspective, the transient metal-free process is promising. In 2017, Talbot et al. developed a metal-free, chemoselective, and regioselective lactam formation method using molecular iodine as oxidant to oxidize cyclic amine **(Scheme 4, equation 5)** [9]. However, this process uses a large amount of iodine and sodium bicarbonate, which produces too much waste. In 2018, Sartillo-Piscil et al. reported TEMPO-catalyzed oxidation of piperazines and morpholines under transition-metal-free conditions **(Scheme 4, equation 6)**[10]. This protocol uses low-cost and environmentally friendly oxidants, including sodium chlorite and sodium hypochlorite. Herein, we applied this catalytic reaction system to transform 4-(4-nitrophenyl)morpholine to 4-(4-nitrophenyl)morpholin-3-one **1**.

Scheme 4. Processes for the transformation of amines to their corresponding amides via chemoselective and regioselective oxidation



However, use of a TEMPO-catalyzed oxidation system in industrial processes has obvious disadvantages, as it involves a high-cost TEMPO catalyst and produces high amounts of waste salts. Furthermore, the complex reaction system would cause reaction control problems. The mixture of sodium chlorite and bleach appears unstable, which may lead to spray incidents [11]. As such, we describe here a novel acid-catalyzed oxidation of 4-(4-nitrophenyl) morpholine to **1** under mild conditions, by using the low-cost and environmentally friendly sodium chlorite as the sole oxidant. (**Scheme 5**)

Scheme 5. Oxidation route for the preparation of intermediate **1** and **2**.



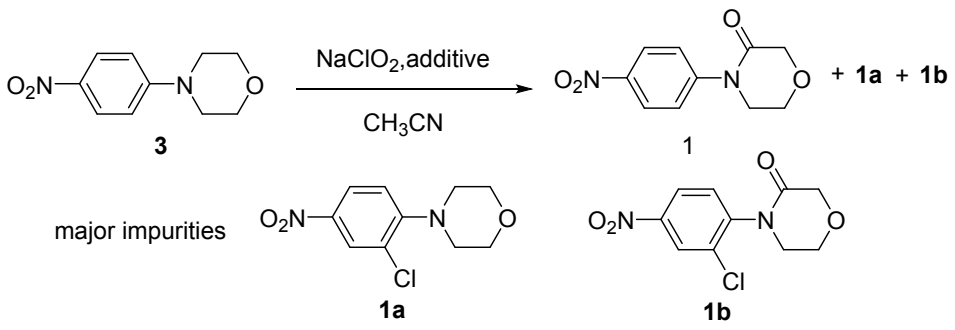
Reaction conditions: a, morpholine (1mol), 4-chloro nitrobenzene (0.2mol), Na_2CO_3 (0.12mol), 100°C, 4.5h; b, $NaClO_2$ (300mol%), acetic acid (30% mol) c, $FeCl_3$/Charcoal(15 mol%), aq. hydrazine (500mol%), reflux.

RESULTS AND DISCUSSION

4-(4-Nitrophenyl)morpholine (**3**) is prepared via the condensation of 4-chloro nitrobenzene with morpholine under neat conditions. Other 4-halogen nitrobenzene, such as 4-bromo-nitrobenzene, 4-fluoro-nitrobenzene and 4-iodo-nitrobenzene are suitable for preparing 4-(4-nitrophenyl)morpholine [12]. In the next step, we explored the oxidation of 4-(4-nitrophenyl) morpholine (**Table 1**). When the oxidation reaction was performed according to the reference reaction condition[10], 98% of the substrate (**3**) was consumed. Aside from the generated target product 4-(4-nitrophenyl) morpholine-3-one, two side products (**1a** and **1b**) were detected, suggesting that side chlorination reaction also occurred (**Table 1**, entry 1). Further increasing the reaction temperature (from 0°C to room temperature) expedited this oxidation reaction dramatically with almost the same regioselectivity (**Table 1**, entry 2). Given that TEMPO is an expensive catalyst, which would be destroyed in reaction conditions to form impurities, we

performed the reaction without TEMPO. Almost the same result was achieved (**Table 1**, entry 3). Further experiment shows that both TEMPO and sodium hypochlorite could cause chloride (**1a**) formation and resulted in better selectivity without using TEMPO and sodium hypochlorite as additives (**Table 1**, entries 4 and 5). The buffer NaH_2PO_4 is the key species for this reaction, because it acts as acid to adjust the reaction system's pH. No reaction was observed when only NaClO or TEMPO was used, as well as without any additives. (**Table 1**, entries 6, 7 and 8)

Table 1. Critical parameters of the oxidation reaction



Entry	Additive (mol)			Temp. (°C)	T (h)	Conv.(%) [b]	Molar ratio[b] 1:1a:1b
	NaH_2PO_4	NaClO	TEMPO				
1	3 equiv.	0.7 equiv.	0.1 equiv.	0-r.t	18h	>98	86:7:6
2	3 equiv.	0.7 equiv.	0.1 equiv.	25	9h	>98	88:7:4
3	3 equiv.	0.7 equiv.	0	25	10.5h	>98	86:8:5
4	3 equiv.	0	0.1 equiv.	25	10h	>98	90:4:5
5	3 equiv.	0	0	25	3h	>99	94:3:2
6	0	0.7 equiv.	0	25	3h	0	nr
7	0	0	0.1 equiv.	25	3h	0	nr
8	0	0	0	25	3h	0	nr

[a] Reaction conditions: unless specified, a mixture of **2** (5 mmol), $NaClO_2$(15 mmol) in water(6 mL), in CH_3CN (15 mL) was stirred . [b] Conversions and yields based on HPLC (area normalization).

NaH_2PO_4, Na_2HPO_4 and Na_3PO_4 usually act as buffers in most reactions. NaH_2PO_4 was replaced with Na_2HPO_4 and Na_3PO_4 in this oxidation reaction, but no reaction is occurred (**Table 2,** entries 1 and 2), This result may be attributed to the difference in pH of the reaction system: Na_2HPO_4, 10.26, Na_3PO_4, 12.6, and NaH_2PO_4 , 4.12-4.24. Thus, we believed that the acidic condition is critical for this reaction. Furthermore, excessive amounts of NaH_2PO_4 in this reaction would lead to large amount of solid waste. Thus, several acid additives were screened for this cyclic amine oxidation reaction. This reaction was completed in 45 min with low selectivity by using 1.5 equiv. of acetic acid (**Table 2,** entry 3). Decreasing the amount of acetic acid can increase selectivity (**Table 2,** entries 4 and 5), and 0.3 equiv. acetic acid resulted in the best conversion and selectivity in 4 h (**Table 2,** entry 6). HPLC indicated that the reaction with 0.2 equiv. of acetic acid was only completed after 4 h, suggesting that the reaction was slow overall. **Table 2,** entry 7). Other acids, such as formic acid and phosphoric acid could also promote this reaction to consume all starting materials (**Table 2,** entries 8 and 9), but oxidation reaction with formic acid as an additive showed poor selectivity. The high reaction temperature would accelerate the reaction rate, and the reaction could be completed in 2h at 50 °C in the presence of 0.3 equiv. of acetic acid (pH 5.23 to 7.42) with good inversion rate and selectivity (**Table 2,** entry 10).

Finally, the amount of oxidant was screened (**Table 3**). Two equiv. of sodium chlorite was enough to consume all substrates; however, both reaction rates and selectivity were low (4h, 83%) (Table 3, entry 1). Increasing the amount of oxidant could enhance selectivity (**Table 3**,

entry 2), and more than 3 equiv. of sodium chlorite resulted in the best selectivity (**Table 3**, entries 3 and 4).

Table 2. Screening additive acids in amine oxidation reactions

Entry	Additive(mol)	T (h)	Conv.(%)[b]	Molar ratio [b] 1:1a:1b
1	Na_2HPO_4(3 equiv.)	overnight	0	nr
2	Na_3PO_4(3 equiv.)	overnight	0	nr
3	CH_3CO_2H(1.5 equiv.)	0.75h	>99	82:12:6
4	CH_3CO_2H(1 equiv.)	1h	>99	87:9:4
5	CH_3CO_2H (0.5 equiv.)	3h	>99	91:6:3
6	CH_3CO_2H(0.3 equiv.)	4h	>99	94:3:2
7	CH_3CO_2H (0.2 equiv.)	7h	>99	90:5:3
8	HCO_2H(0.3 equiv.)	5h	96	89:3:3
9	H_3PO_4 (0.2 equiv.)	2h	>99	96:3: 1
10	CH_3CO_2H(0.3 equiv.) [a,]	2h	>99	96:2:2

[a] All reactions were performed at 50°C; [b] determined by area normalization on HPLC

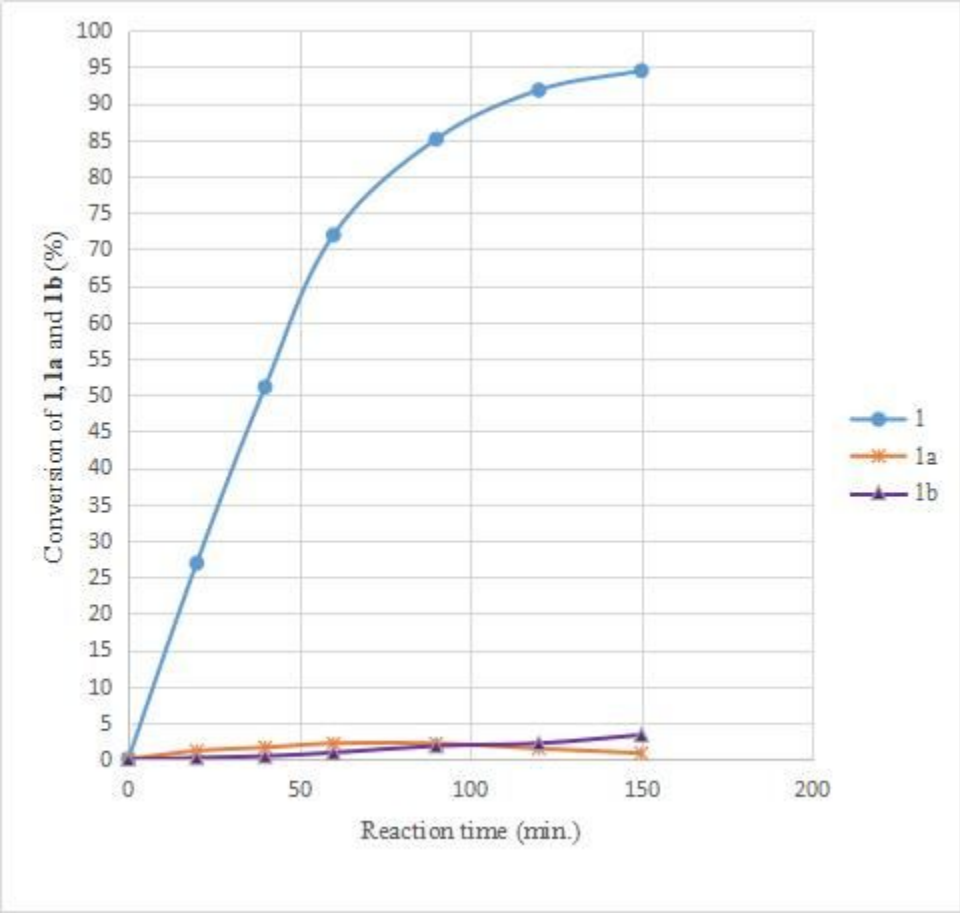
Table 3. Screening the amount of sodium chlorite

Entry	Amount of sodium chlorite (mol)	Time	Molar ratio [b] 1:1a:1b
1	2 equiv.	4.0h	83:14:3
2	2.5 equiv.	3.0h	90:8:2
3	3 equiv.	2.0h	96:2:2
4	4 equiv.	1.5h	97:2:1

[a] Reaction conditions: unless specified, a mixture of 2 (5 mmol) and CH_3CO_2H (1.5 mmol) was dissolved in CH_3CN (10mL) and stirred at 50°C; then, $NaClO_2$ in water (3.5mL) was added dropwise; [b] determined by area normalization on HPLC

With the optimized reaction condition (3 equiv. of sodium chlorite, and 0.3 equiv. of acetic acid in acetonitrile), the oxidation reaction profile was established by using the HPLC yield (**1**/**1a**/**1b**). As shown in **Figure 1**, the oxidation reaction rate is dramatically faster than the chlorination reaction rate. The reaction was completed in 2.5 h, and the total amounts of **1a** and **1b** were not obviously increased.

Figure 1 HPLC yield (1/1a/1b) with reaction time

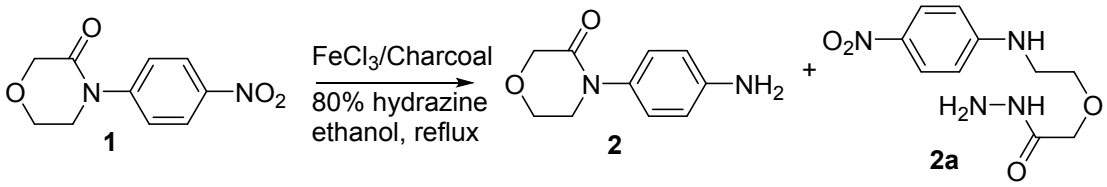


Furthermore, **1a** can be prepared by chlorinating **3** with sodium hypochlorite in acidic conditions with good yield. When **1a** is loaded in this oxidation reaction system, it can be oxidized smoothly to corresponding **1b** with 86% yield (HPLC purity, 98%). The control experimental shows that **1** cannot be chlorinated to **1b** with sodium hypochlorite in acidic conditions.

With the easily prepared intermediate **1**, the reduction of the nitro group in **1** was also investigated (**Scheme 5**). The known method uses Pd on charcoal to catalyze hydrogenation. However, a large amount of catalyst (5-20 weight%, 5% palladium on charcoal) is needed, thereby increasing the higher production cost [13]. We used iron(III)-charcoal catalyzed reduction of nitro group with aqueous hydrazine as reductant; however, one pot reaction resulted in the

morpholin-3-one ring opening compound **2a** as the main product. In the iron(III)-hydrazine reduction system, the real active species is diimide, which is formed via in situ oxidation of hydrazine by iron (III). Then, hydrazine was added dropwise to the reaction, and the side product was dramatically decreased.

Scheme 5 $FeCl_3$ catalyzed aqueous hydrazine reduction of intermediate 1 to 2.



We have developed a facile and convenient process of preparing 4-(4-nitrophenyl) morpholin-3-one, which can be further reduced to its corresponding 4-(4-aminophenyl) morpholin-3-one. Our process involves low-cost and easily available materials. Furthermore, working up the reaction in the whole process is quite convenient, and column chromatography is not needed. The product can be obtained via a simple slurry and filtration, and is suitable for industrial applications.

EXPERIMENTAL SECTION

General Procedures. Reverse-phase HPLC was performed on an agilent 1260 series HPLC instrument using the following methods. Zorbax sb-c18 RP (150mm × 4.6mm, 3.5μ), Conditions: flow rate 1 ml/min; 30°C; mobile phase: (A) water, (B) acetonitrile; (C) methanol; gradient: 0–4 min, 65-10% A, 25-80% B, 10% C; 4-7min. , 10% A, 80% B, 10% C; 7-14min. , 10-65% A, 80-25% B, 10% C; 14-16min., 65% A, 25% B, 10% C; 230 nm UV detector; Retention times are uncorrected; Molar ratios are determined by area normalization.

4-Nitrophenyl morpholine (**3**). A mixture of *p*-nitrochlorobenzene (31.5g, 0.2mol), morpholine (87g, 1mol) and sodium carbonate (12.7g, 0.12mol) in a 500ml round bottom flask was stirred at 100 ℃ for 4.5h, TLC and HPLC detection showed that *p*-nitrochlorobenzene was almost consumed. Then most of the unreacted morpholine was recovered by vacuum distillation. After that, 200mL water was added to this residue, and stirred for a few moments. All solid products were collected by filtration, rinsed with 50mL water and dried under vacuum to afford 4-nitrophenyl morpholine (**3**). Yellow solid (isolated yield: 99%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22-8.13 (m, 2H), 6.93-6.84 (m, 2H), 3.95-3.86 (m, 4H), 3.44-3.36 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.77, 139.25, 125.87, 112.90, 66.28, 47.32. MS (ES-API）$[M+1]^+$= 209

4-(4-Nitrophenyl)morpholin-3-one (**1**): a solution of 4-nitrophenyl morpholine (20.8 g, 0.1 mol), acetic acid (1.8 g, 0.03 mol) in acetonitrile (200 ml) was added into a 1000 ml three port round bottom flask, and it was heated at 50℃. Then a solution of sodium chlorite (more than 80%, 33.8 g, 0.3mol) in 65 ml water was added dropwise in 20 min. The reaction system gradually turned to brown red, then light yellow. TLC and HPLC showed that the reaction was completed in 2.5 h. The reaction was quenched with aqueous saturated sodium sulfite, and the organic layer was separated. Removal of most of volatile left slurries, and the solid was collected by filtration rinsed with small amount water and dried, it could be used in the next step without further purification. **1**, Light yellow solid (isolated yield: 91%, purity 99%, HPLC);^{1}H NMR (400 MHz,$CDCl_3$) δ 8.28 (d, J = 8.8Hz, 2H), 7.61 (d, J = 8.8Hz, 2H), 4.40 (s, 2H), 4.08 (t, J = 4.8Hz, 2H), 3.85 (t, J = 4.8Hz, 2H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 166.79, 146.73, 145.40, 124.69, 124.54, 68.64 , 63.94, 48.87; MS (ES-API）$[M+1]^+$ = 223. Side products **1a** and **1b** were isolated from mother liquid, and purified on a silica gel (petroleum ether/ ethyl acetate as eluent). **4-(2-chloro-4-nitrophenyl)morpholine (1a):**Yellow solid (isolated 120 mg, yield: 0.5%)

; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 2.8 Hz, 1H), 8.11 (dd, J = 9.2, 2.8 Hz, 1H), 7.05 (d, J = 9.2 Hz, 1H), 3.89 (t, J = 4.8 Hz, 4H), 3.21 (t, J = 4.8 Hz, 4H); ^{13}C NMR (101 MHz,$CDCl_3$) δ 154.50, 142.43, 127.67 , 126.70, 123.45, 119.26, 66.71, 50.99; MS (ES-API） $[M+1]^+$ = 243; **4-(2-chloro-4-nitrophenyl)morpholine-3-one(1b):** Light yellow solid (isolated 230mg, yield: 0.9%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 2.4 Hz, 1H), 8.24 (dd, J = 8.4, 2.4Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 4.41 (s, 2H), 4.15 – 4.07 (m, 2H), 3.74 (t, J = 5.0 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.47, 147.64, 144.21, 133.85, 130.45, 126.03 , 123.18 , 68.45, 63.93, 49.26; MS: $[M+1]^+$= 257. After the oxidation reaction was performed for 2.5 hours, the reaction mixture was detected by HPLC. HPLC spectrum can be found in supporting information. Retention times for **1**, **1a**, **1b** and **3** are 6.2min., 8.9min., and 6.7min. and 7.7min. respectively.

1a could be prepared according this procedure: a mixture of 4-nitrophenyl morpholine (1.04 g ,5 mmol) and acetic acid(0.09g, 1.5mmol) in 10 ml acetonitrile was heated to 40℃ on a water bath，then sodium hypochlorite (7% activated Cl, 8.34g, 9mmol) was added dropwise. After 4-nitrophenyl morpholine was consumed (TLC), the reaction was quenched by adding aqueous saturated sodium sulfite. After most solvent was removed by evaporation, a large amount of solid was precipitated. This solid was collected by filtration, and dried to obtain **1a**. (yield 88%, purity 98%, HPLC) .

1b can be prepared from **1a** (1.21g, 5mmol) with same procedure as the preparation of **1**. Yield, 86%, HPLC purity 98%.

When the mixture of **1** and acetic acid in acetonitrile was treated with sodium hypochlorite (7% activated Cl), no reaction occured.

4-(4-Aminophenyl)morpholin-3-one (**2**): To a solution of 4-(4-nitrophenyl)morpholin-3-one (11.1 g, 0.05 mol) in 150mL ethanol, anhydrous ferric chloride (1.215 g, 7.5 mmol) and activated carbon (5 g) were added subsequently. Then the reaction was heated to reflux, 15.6 g of hydrazine hydrate (80% aqueous solution, 0.25 mol) was added dropwise in 1h. TLC and HPLC detection showed that this reaction could be completed in 2h. Charcoal was removed by filtration, and the solution was concentrated on a rotatory evaporator to leave a residue, which was recrystallized from acetonitrile to afford pure **2**. White solid (isolated yield: 93%, purity 98%, HPLC); ^{1}H NMR (400 MHz,DMSO-d_6) δ 6.96 (d, J = 5.6 Hz, 2H), 6.56 (d, J = 5.6 Hz, 2H), 5.13 (s, 2H), 4.14 (s, 2H), 3.91 (t, J = 3.2 Hz, 2H), 3.58 (t, J = 3.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.74 , 147.31 , 130.21 , 126.39, 113.65 , 67.68 , 63.51 , 49.58. MS(ES-API） $[M+1]^+$= 193

If the reaction performed in one pot, a yellow solid was formed, the structure was confirmed to be the ring opening product **2a, 2-(2-((4-nitrophenyl)amino)ethoxy) acetohydrazide:** Yellow solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 8.00(d, 2H, J = 9.2 Hz), 7.38 (t, J = 5.2 Hz, 1H), 6.70 (d, 2H, J = 9.2 Hz), 4.27 (s, 2H), 3.93 (s, 2H), 3.60 (t, J = 5.2 Hz, 2H), 3.39 (t, J = 5.2 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.98 , 154.45 , 135.64 , 126.17 , 110.79, 69.28 , 69.01 , 42.04. MS(ES-API） $[M+1]^+$= 255

ASSOCIATED CONTENT

Supporting Information.

Spectrums for some compounds. This material are available free of charge.

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Notes

The authors declare no competing financial interest.

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