Scientific article
UDC 547.867.4

SYNTHESIS OF CONDENSED MORPHOLINE-CONTAINING SYSTEMS BY REDUCTIVE OR OXIDATIVE HETEROCYCLISATION

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Keywords:
N-(2-nitro-4-R-phenyl)morpholines, 3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazines, reductive heterocyclisation, oxidative heterocyclisation

Abstract. *The article examines the reduction of N-(2,4-dinitrophenyl)morpholine in acidic medium by tin (II) chloride. Under these conditions there is a formation of a mixture of products of reduction, chlorination and heterocyclisation reactions. The authors developed a method for the preparation of condensed 3,4-dihydro-1H-benzo[4,5]imidazo[2,1-c][1,4]oxazines by reduction of (2-nitro-4-R-phenyl)morpholine into 5-R-2-piperidin-1-ylanilines followed by oxidative heterocyclisation with supramuravic acid.*

For citation:
Savina, L.I. & Sokolov, A.A. (2023) Synthesis of condensed morpholine-containing systems by reductive or oxidative heterocyclisation, *From Chemistry Towards Technology Step-By-Step,* 4(3), pp. 69-75 [online]. Available at: http://chemintech.ru/index.php/tor/issue/view/2023-4-3

Introduction

Azaheterocycles are frequent structural components in pharmaceuticals and other biologically active compounds [1, 2]. The most common among saturated heterocycles are piperidine, piperazine, and pyrrolidine [1, 3]. At the same time, condensed bi- and tricyclic systems containing morpholine and aromatic rings are much less common due to the difficulties in their synthesis. Although a number of them exhibit high biological activity [4-9]. It greatly increases the cost of such substances and prevents the production of a wide range of useful compounds based on them.

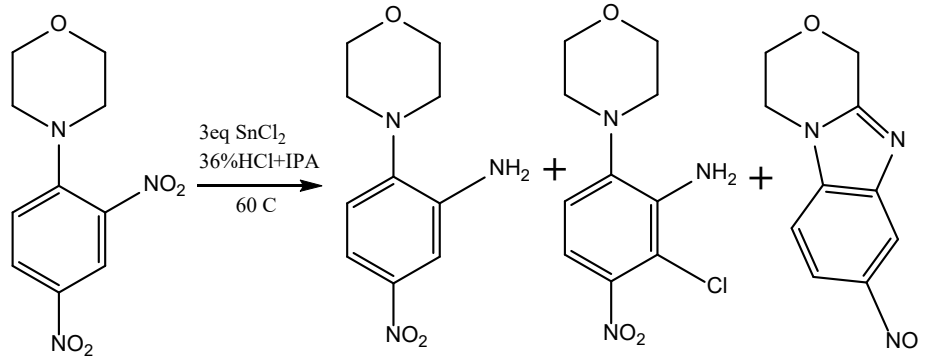
The reductive heterocyclisation of nitroaromatic compounds having morpholine as a substituent or the oxidative heterocyclisation of anilines seems to be a convenient and simple way to solve this problem.

The purpose of this study is to develop methodologies for the preparation of tricyclic condensed morpholine derivatives - 3,4-dihydro-1H-benzo[4,5]imidazo[2,1-*c*][1,4]oxazines.

Main body

At the first stage, we have studied the possibility of reductive heterocyclisation of nitroaromatic structures, allowing us to achieve the purpose of the study at one stage.

We have chosen the available and inexpensive N-(2,4-dinitrophenyl)morpholine (**1**) as a model compound. Additionally, we used tin (II) chloride as the reducing agent. Previously it was successfully used for the heterocyclisation of pyridine- and piperidine-containing systems [10]. We use isopropyl alcohol as a solvent for the substrate and 36% HCl solution for the metal salt of variable valence, and synthesized it at a temperature of 60 °C and a ratio of **1**: $SnCl_2$ = 1:3. We added the reducing agent to the flask with the substrate for 2.5 hours, and stirred it for 0.5 hours. Having finished the reaction, we neutralized the mixture and extracted it with hot chloroform. Having expelled the solvent, we obtained a dry residue which we analyzed by ^{1}H NMR spectroscopy. We found that the product is a mixture of three substances.



The first substance contained a broad singlet from two protons of the primary amino group (5.36 ppm.). We also observed three aromatic protons and two signals from the morpholine cycle. We identified the substance as 2-morpholine-5-nitroaniline (**2**) and obtained it in pure form by reduction of **1** in 8% HCl solution at 40 °C (Fig. 1).

The second substance differed from **2** by the presence of only two rather than three aromatic protons in the form of *ortho*-arranged doublets with a "roof effect" shifted to a weaker field relative to 2-morpholine-5-nitroaniline. Thus, the molecule lacked a hydrogen atom at the carbon C6 of the benzene ring. This is possible when it is substituted by an atom/group of atoms, for example, by a halogen. 6-Chloro-2-morpholin-5-nitroaniline (**3**), further synthesized in pure form by reduction of **1** in 36% HCl solution at 60 °C with tin (II) chloride addition without doping, corresponded to such spectral data (Fig. 2).

The third substance, in comparison to **2** and **3**, did not contain a signal from the amino group. In addition, only six protons of the morpholine fragment were observed in the aliphatic region instead of eight. At the same time, the chemical shifts of the hydrogen nuclei of the azagederocycle were more differentiated compared to those of **2** and **3** - there were three signals. One of them shifted significantly to a weaker field (up to 5.01 m.d.), which was also characteristic of hydrogen nuclei at the C1 atom in another condensed tricyclic system - 1,2,3,3,4-tetrahydropyrido[1,2-*a*]benzimidazoles [10]. The peaks of all three aromatic protons were shifted to the weak-field region by 0.74-0.90 ppm relative to substance **2**. We identified the compound as 8-nitro-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-*c*][1,4]oxazine (**4**) and synthesised further in pure form by oxidative heterocyclisation. ^{1}H-^{1}H NOESY (Fig. 3) and ^{13}C NMR spectra were recorded for the heterocycle in addition to ^{1}H NMR (Fig. 3).

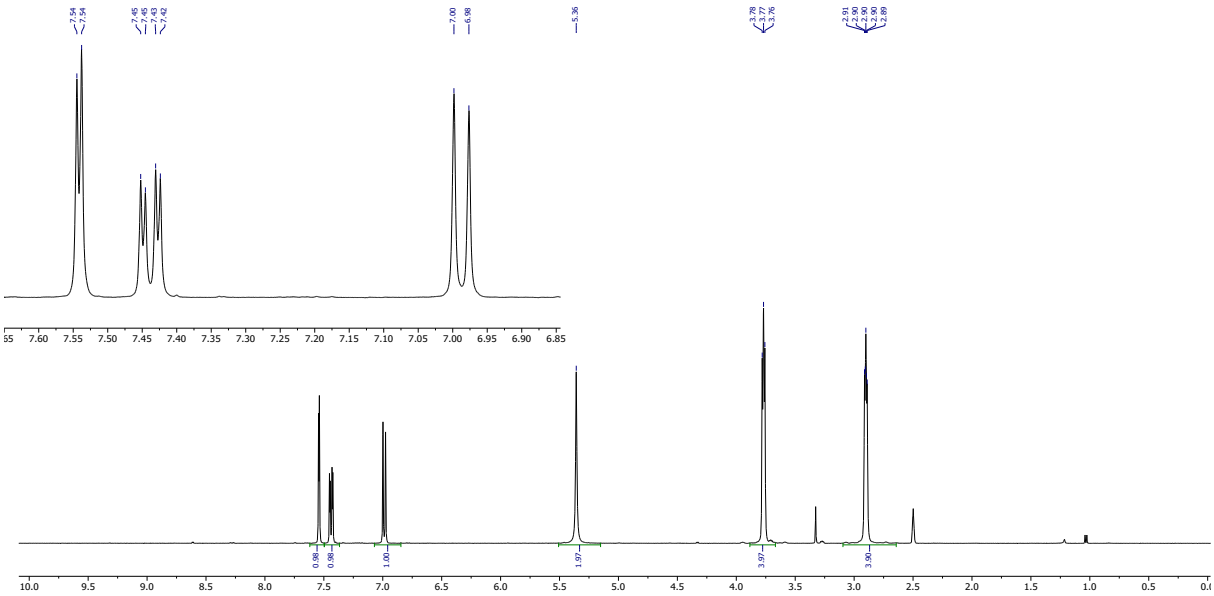


Fig. 1. [1]H NMR spectrum of 2-morpholine-5-nitroaniline (Bruker DRX 400, SF = 400 MHz, solvent and internal standard DMSO-d_6)

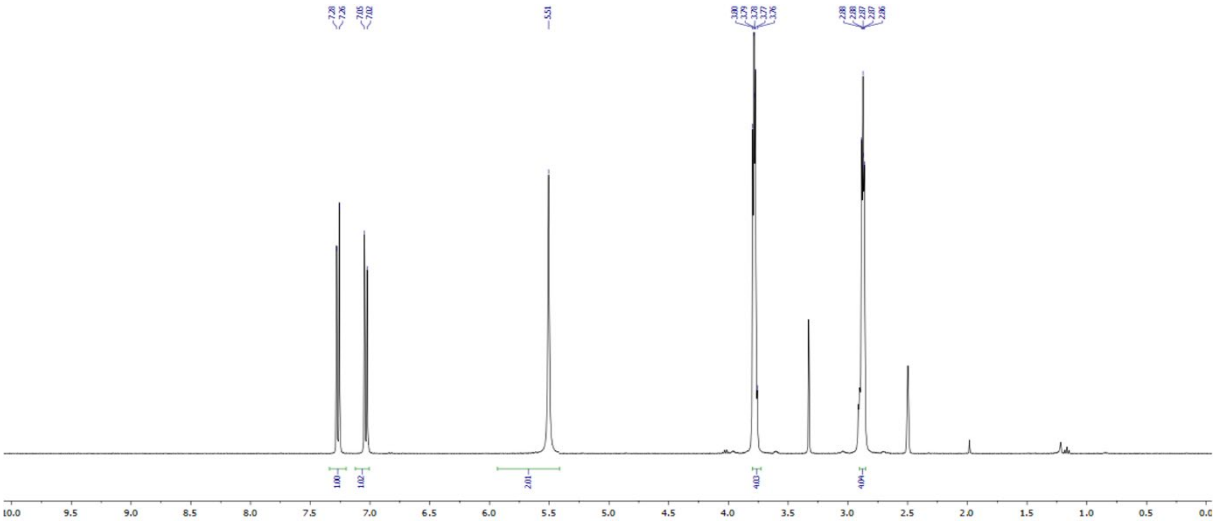


Fig. 2. [1]H NMR spectrum of 6-chloro-2-morpholine-5-nitroaniline (Bruker DRX 400, SF = 400 MHz, solvent and internal standard DMSO-d_6)

We observed 10 signals in the carbon spectrum of the tricyclic condensed product: three in the aliphatic range from 43.1-65.1 ppm, and seven signals in the aromatic range with chemical shift values from 110.0 to 153.1 ppm. At the same time, four peaks had reduced intensity characteristic of quaternary carbon atoms.

Therefore, the reduction of N-(2,4-dinitrophenyl)morpholine under the above conditions resulted in the formation of reduction, halogenation, and heterocyclisation products in amounts of 21, 62 and 17%, respectively. To increase the proportion of the desired substance **4**, we varied the amount of reducing agent introduced as well as the temperature, and acid concentration. We found that decreasing the mass of tin(II) chloride added increased the relative yield of **4**, but unreacted substrate remained in the reaction mass makes isolation difficult. Decreasing the temperature and/or HCl concentration helped to reduce the amount of the heterocyclisation product.

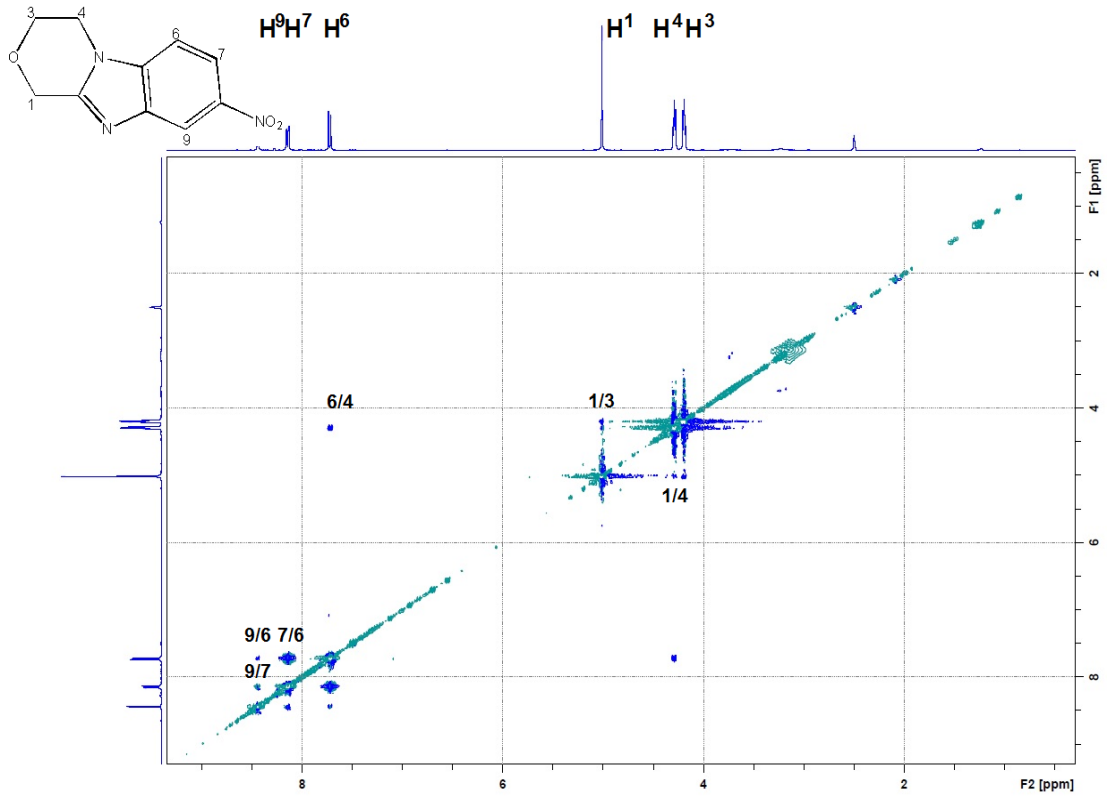
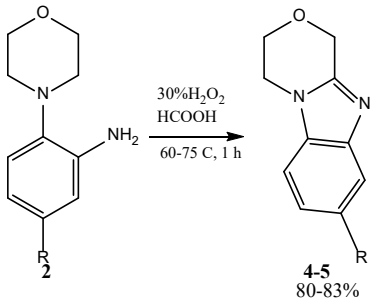


Fig. 3. ^{1}H-^{1}H NOESY NMR spectrum of 8-nitro-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-$_c$][1,4]oxazine (Bruker DRX400, SF = 400 MHz, solvent and internal standard DMSO-*d6*)

These results demonstrated the inefficiency of the method under study for the synthesis of condensed morpholine derivatives. Therefore, we tried a two-step approach to their preparation. At the first stage we performed reduction of compound **1** into **2**, followed by oxidative heterocyclisation at the second stage. We conducted it with supra formic acid, formed by mixing a 30% solution of hydrogen peroxide with concentrated formic acid. We synthesized the reaction at 60 °C by addition of HCOOH to peroxide followed by stirring at 75 °C for 60 minutes. Analysis of the reaction product showed the presence of the required **4** in the amount of 83%. In order to confirm the applicability of the proposed methodology, we obtained 8-bromo-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-*c*][1,4]oxazine (**5**), which spectral data were in agreement with the literature [11].



This study allowed us to refine the methodology for the preparation of benzimidazoles containing a morpholine moiety condensed with them.

The substances synthesized as a result of this study are interesting as substrates for further structural modification in order to obtain biologically active substances.

Experimental part

We determined the melting points on a PolyTherm A device at a heating rate of 3 °C/min and did not adjust. NMR spectra were recorded on a Bruker DRX-400 for solutions. We used the signals of residual solvent protons in the ^{1}H NMR (DMSO δ 2.50 ppm. or chloroform δ 7.26 ppm.) and ^{13}C NMR (DMSO δ 40.5 ppm. or chloroform δ 77.4 ppm.) spectra as a reference for counting chemical shifts. We used standard Bruker techniques to capture the two-dimensional spectra. The mixing time in NOESY spectra was 0.3 s.

Methods for the synthesis of 2-morpholine-5-nitroaniline

We added N-(2,4-dinitrophenyl)morpholine with a mass of 0.500 g (0.002 mol) to a 100 ml three-neck flask equipped with a stirrer, thermometer, and Liebich refrigerator and dissolved it in 20 ml of isopropyl alcohol under heating. We added 0.671 g (0.003 mol) of tin (II) chloride anhydrous tin (II) chloride to a 50 ml cup and added 20 ml of 8% hydrochloric acid to it. We warmed up both solutions to a temperature of 50 °C. When the temperature was reached, we added the reducing agent once into the flask and conducted the reaction for 0.5 hours. After the synthesis was completed, we put the reaction mixture from the flask into a 250 ml cup. We added a piece of ice and 25% aqueous ammonia solution to pH = 7-8 while stirring. We then extracted three times with 30 ml of boiling chloroform. We put the combined extract to a distillation flask and distilled off the solvent.

2-morpholine-5-nitroaniline (**2**). Yield 0.40 g (91%). T_{melt} = 146.5–148.5 °C. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm., J /Hz): 2.64-3.09 (m, 4H, morpholine), 3.67-3.88 (m, 4H, morpholine), 5.36 (s, 2H, NH_2), 6.99 (d, 1H, H^3, J 8.7 Hz), 7.44 (dd, 1H, H^4, J 8.7 Hz, 2.7 Hz), 7.54 (d, 1H, H^6, J 2.7 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): 50.5, 66.9, 108.8, 112.8, 119.2, 143.4, 144.0, 144.7.

Methods for the synthesis of 6-chloro-2-morpholine-5-nitroaniline

We added N-(2,4-dinitrophenyl)morpholine with a mass of 1.000 g (0.004 mol) to a 250 ml three-neck flask equipped with a stirrer, thermometer, and Liebich refrigerator and dissolved it in 40 ml of isopropyl alcohol under heating. At the same time, we put 2.708 g (0.012 mol) of tin (II) chloride anhydrous in a 100 ml cup and added 40 ml of 36% hydrochloric acid solution to it. We got both solutions to a temperature of 60 °C. When the temperature was reached, we added the reducing agent once into the flask and conducted the reaction for 0.5 h, after that the reaction mixture was cooled, alkalized it to pH = 7-8 with aqueous ammonia, extracted with hot chloroform 5 times 30 ml each, tin (IV) hydroxide was filtered off under vacuum. Chloroform was distilled off. The dry residue obtained was purified by recrystallization in isopropyl alcohol.

6-chloro-2-morpholine-5-nitroaniline (**3**). Yield 0.76 g (75%). T_{melt} = 162–165 °C. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm, J /Гц): 2.87 (m, 4H, morpholine), 3.76 (m, 4H, morpholine), 5.51 (s, 2H, NH_2), 7.04 (d, 1H, H^3, J 8.6 Hz), 7.27 (d, 1H, H^4, J 8.6 Hz).

Synthesis methods of 8-R-3,4-dihydro-1*H*-benzo[4,5]imidazo[2,1-*c*][1,4]oxazine

We put 5-R-2-morpholin-4-ylaniline (0.004 mol) into a 100 ml three-necked flask equipped with a stirrer, thermometer, and Liebich refrigerator, we dissolved in 6 mL of formic acid and spiked with 2 ml of 30% hydrogen peroxide solution for 6 minutes. We heated the solution obtained to a temperature of 60 °C at which an exothermic reaction occurred, and then

heated to 75 °C and stirred for 1 hour. After that we cooled the reaction mixture, alkalized it to pH = 7-8 with aqueous ammonia, extracted with hot chloroform three times with 30 ml each. Chloroform was distilled off. The dry residue obtained was purified by recrystallization in chloroform.

8-nitro-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-*c*][1,4]oxazine (**4**). Yield 0.82 g (83%). T_{melt} = 203–205 °C. NMR spectrum ^{1}H (DMSO-d_6, δ, ppm., *J* /Hz): 4.16 (t, 2H, morpholine, *J* 5.2 Hz), 4.29 (t, 2H, morpholine, *J* 5.2 Hz), 5.01 (s, 2H, morpholine), 7.73 (d, 1H, H^6, *J* 8.9 Hz), 8.15 (dd, 1H, H^7, *J* 8.9 Hz, 2.2 Hz), 8.44 (d, 1H, H^9, *J* 2.2 Hz). ^{13}C{^{1}H} NMR (DMSO-d_6, 100 MHz): 43.1, 63.8, 65.1, 110.0, 115.4, 118.1, 139.2, 142.3, 143.8, 153.1.

8-brom-3,4-dihydro-1H-benzo[4,5]imidazo[2,1-*c*][1,4]oxazine (**5**). Yield 0.79 g (80%). T_{melt} = 208-209 °C. NMR spectrum ^{1}H ($CDCl_3$, δ, ppm., *J* /Hz): 4.11-4.22 (m, 4H, morpholine), 5.01 (s, 2H, morpholine), 7.19 (d, 1H, H^6, *J* 8.6 Hz), 7.36 (dd, 1H, H^7, *J* 8.6 Hz, 1.4 Hz), 7.84 (d, 1H, H^9, *J* 1.4 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 42.2, 63.9, 65.5, 110.0, 115.6, 122.5, 125.5, 133.1, 144.1, 149.1.

This work was conducted with the financial support of grant No MK-3459.2022.1.3 from the President of the Russian Federation for state support of young Russian scientists - candidates of science.

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Received 08.09.2023
Approved 15.09.2023
Accepted 19.09.2023