DOI: 10.31276/VJSTE.2025.0038

Investigating the preparation of oxime derivatives of azacrown ethers containing piperidine-4-one heterocycles under microwave irradiation

Tung H. To[1*], Hieu D. Nguyen[2]

[1]*University of Science and Technology of Hanoi, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet Street, Nghia Do Ward, Hanoi, Vietnam*
[2]*Institute of Chemistry, Vietnam Academy of Science and Technology, 18 Hoang Quoc Viet Street, Nghia Do Ward, Hanoi, Vietnam*

Received 13 May 2025; revised 11 June 2025; accepted 22 June 2025

Abstract:

The use of multi-component reactions to simultaneously synthesise crown ethers and nitrogen-containing heterocycles is a synthetic approach that has attracted significant interest. With nitrogen heterocycles embedded in their structures, azacrown ethers can participate in various reactions to modify their structures for diverse applications. Herein, the preparation of azacrown ethers containing the piperidine heterocycle, based on a modified Petrenko-Kritschenko condition, is reported. The oximation of azacrown compounds was investigated under conventional reflux conditions and microwave irradiation at different temperatures. Physicochemical analyses, including ^{1}HNMR, ^{13}CNMR, and HRMS, were employed to elucidate the structures of the synthesised compounds. The experimental data demonstrated that microwave irradiation is an effective approach for oximation, reducing the reaction time to 20 minutes at 80°C and affording high yields (89-92%).

Keywords: **azacrown ethers, microwave irradiation, oxime derivatives, piperidine.**

Classification numbers: **2.2, 2.3**

1. Introduction

Piperidine-containing compounds hold a prominent position in medicinal chemistry. Their structural framework is versatile and widely utilised in the research, design, and development of new pharmaceuticals across a broad range of therapeutic areas. The piperidine ring serves as a crucial heterocyclic scaffold, contributing significantly to the bioactivity of numerous drugs and natural alkaloids [1-4]. Among piperidine derivatives, piperidine-4-ones are of particular interest because they can be prepared via multi-component condensations, one of the most efficient methods for generation of this heterocycle. A well-known example is the Petrenko-Kritschenko reaction, which is commonly used for the preparation of piperidone derivatives [5]. Recently, there have been reports based on modified Petrenko-Kritschenko conditions, where the synthesis of piperidone heterocycles is carried out simultaneously with crown-ether cyclisation, resulting in new derivatives bearing both heterocyclic moieties. This combination has yielded novel crown ethers with fascinating biological activities, such as α-glucosidase inhibitory activity [6, 7]; cytotoxicity on cancer cell lines [8-10], and anti-microbial effects [11].

The potential of piperidine-4-one compounds extends far beyond these applications. Owing to the presence of the carbonyl (C=O) group, functionalisation could be performed to introduce new biological properties or enhance existing ones, demonstrating their immense versatility. One modification that has garnered significant attention is the oximation reaction, particularly for enhancing antimicrobial properties. Jayaraman and colleagues explored the synthesis of oxime derivatives from piperidone compounds, which were subsequently tested for antimicrobial activity. These derivatives showed positive effects against a range of bacterial and fungal strains [12]. Additionally, a study conducted by Park's group reported a series of substituted piperidin-4-one oxime ethers, which demonstrated good antibacterial and antifungal properties; some compounds were more active than the positive control (the reference drug *amphotericin B*) [13].

In this work, we describe a new approach to prepare oxime derivatives of azacrown ethers containing piperidine-4-one heterocycles under microwave irradiation. These azacrown ethers were synthesised using the modified Petrenko-Kritschenko reaction involving the condensation of a dialdehyde podand with β-ketoesters and an amine source.

[*] *Corresponding author: Email: to-hai.tung@usth.edu.vn*

2. Materials and methods

2.1. Materials

The organic reagents and solvents were purchased from commercial sources and used without further purification. All reactions were conducted in oven-dried glassware. Thin-layer chromatography (TLC) analyses were performed on commercially prepared silica gel plates (Merck, F254) and visualised under a UV lamp (λ=254 nm). Nuclear magnetic resonance (NMR) spectra, including ^{1}HNMR, ^{13}CNMR, and DEPT-^{13}CNMR, were recorded in deuterated solvents (dimethyl sulfoxide, DMSO-d_6 or chloroform-*d*) on Bruker Avance Neo 600 spectrometers (600 and 150 MHz, respectively) and Bruker Avance 500 spectrometers (500 and 125 MHz, respectively). Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), with solvent resonance as the internal standard. Mass spectra were obtained using a Thermo Q-Exactive Quadrupole-Orbitrap mass spectrometer equipped with an electrospray ionisation source operating in positive mode. Microwave synthesis experiments were performed using an Anton Paar Microwave Synthesis Reactor MONOWAVE 400. G30 vials served as reaction vessels. Temperature control was achieved via an infrared sensor. Melting points were determined in open capillary tubes using a Buchi Melting Point M-560 apparatus.

The dialdehyde podand (*1,5-bis(2-formylphenoxy)-3-oxapentane*) was prepared following the procedure described in the previous study [14].

2.2. Synthesis of azacrown ethers containing the piperidine heterocycle (4a-d)

General procedure: A mixture of 1,5-bis(2-formylphenoxy)-3-oxapentane (**1**) (3.0g; 9.5 mmol; 1.0 eq. mol); β-ketoesters (**2a-d**) (11.5 mmol; 1.2 eq. mol) and ammonium acetate (**3**) (1.10g; 14.3 mmol; 1.5 eq. mol) in 30 ml of isopropanol was stirred at the ambient temperature for 18 h. After the completion of reaction (monitored by TLC), the precipitate was filtered on Buchner funnel and washed several times with isopropyl alcohol. The crude products were recrystallised in ethanol-dichloromethane (DCM) mixture to obtain the pure product.

2.2.1. 22-ethoxycarbonyl-8,11,14-trioxa-25 azatetracyclo [19.3.1.0^{2,7}.0^{15,20}]pentacosa-2,4,6,15(20),16,18-hexene-23-one ***(4a)***

White solid; 60% (2.41 g); m.p 200-201(°C). **^{1}HNMR** (600 MHz, $CDCl_3$) δ 7.24-7.17 (m, 4H Ar); 6.89 (td, *J*=7.5, 1.1 Hz, ^{1}HNMR Ar); 6.84 (td, *J*=7.5, 1.1 Hz, ^{1}HNMR Ar); 6.82 (d, *J*=8.2 Hz, ^{1}HNMR Ar); 6.80 (d, *J*=8.2 Hz, ^{1}HNMR Ar); 4.32 (br.s, ^{1}HNMR); 4.26 (d, *J*=9.7 Hz, ^{1}HNMR); 4.15-4.11 (m, 5H Ether); 4.05-4.01 (m, 4H, 2H Ether; -OCH_2CH_3); 3.90 (dt, *J*=10.3, 6.0 Hz, 1H); 3.84 (td, *J*=9.7, 2.8 Hz, 1H); 3.31 (t, *J*=13.0 Hz, 1H); 2.64 (dd, *J*=14.2, 2.8 Hz, 1H); 1.65 (s, 1H, NH[25]); 1.06 (t, *J*=7.1 Hz, 3H,-CH_2CH_3). **^{13}CNMR** (125 MHz, $CDCl_3$) δ 204.93; 169.20; 157.09; 157.01; 129.40; 129.25; 128.60; 121.15; 120.87; 111.23; 111.16; 70.04; 69.96; 66.61; 66.54; 62.74; 60.75; 46.96; 14.13. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{24}H_{28}NO_6$ 426.19166, found 426.19095.

2.2.2. 22-tert-butyloxycarbonyl-8;11;14-trioxa-25-azate tracyclo[19.3.1.0$^{2;7}$.0$^{15;20}$]pentacosa-2;4;6;15(20);16;18-hexene-23-one ***(4b)***

White solid; 65% (2.70 g); m.p 207-209(°C). **^{1}HNMR** (600 MHz, $CDCl_3$) δ 7.24-7.16 (m, 4H); 6.88 (t, *J*=7.4 Hz, 1H); 6.85 (t, *J*=7.4 Hz, 1H); 6.80 (t, *J*=8.2 Hz, 2H); 4.24 (br.s, 1H); 4.16-4.09 (m, 6H); 4.04 (d, *J*=10.4 Hz, 2H); 3.90 (dt, *J*=10.2, 6.0 Hz, 1H); 3.85 (td, *J*=9.7, 2.8 Hz, 1H); 3.28 (t, *J*=13.0 Hz, 1H), 2.61 (dd, *J*=14.2, 2.8 Hz, 1H); 1.66 (br.s, 1H); 1.27 (s, 9H). **^{13}CNMR** (125 MHz, $CDCl_3$) δ 205.18; 168.29; 157.12; 157.09; 129.33; 129.19; 128.73; 121.11; 120.66; 111.20; 111.12; 81.23; 70.08; 70.01; 66.58; 66.56; 63.64; 46.94; 27.96. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{26}H_{32}NO_6$ 454.22296, found 454.22238.

2.2.3. 22-isopropyloxycarbonyl-8;11;14-trioxa-25-azate tracyclo[19.3.1.0$^{2;7}$.0$^{15;20}$]pentacosa-2;4;6;15(20);16;18-hexene-23-one ***(4c)***

White solid; 60% (1.25 g); m.p 213.0-214.7(°C). **^{1}HNMR** (600 MHz, $CDCl_3$) δ 7.23-7.16 (m, 4H); 6.88 (t, *J*=7.4 Hz, 1H); 6.83 (t, *J*=7.5 Hz, 1H); 6.81 (d, *J*=8.4 Hz, 1H); 6.79 (d, *J*=8.2 Hz, 1H); 4.91 (hept, *J*=6.3 Hz, 1H); 4.29 (br.s, 1H); 4.23 (d, *J*=9.7 Hz, 1H); 4.14-4.08 (m, 5H); 4.03 (d, *J*=10.4 Hz, 2H); 3.89 (dt, *J*=10.2, 6.1 Hz, 1H); 3.83 (td, *J*=9.8, 2.8 Hz, 1H); 3.29 (t, *J*=13.2 Hz, 1H); 2.62 (dd, *J*=14.2, 2.8 Hz, 1H); 1.75 (s, 1H); 1.10 (d, *J*=6.3 Hz, 3H); 0.98 (d, *J*=6.2 Hz, 3H). **^{13}CNMR** (150 MHz, $CDCl_3$) δ 204.88; 168.66; 157.06; 157.03; 129.35; 129.18; 128.62; 121.09; 120.71; 111.19; 111.09; 69.98; 69.91; 68.14; 66.56; 66.51; 62.81; 46.91; 21.68; 21.59. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{25}H_{30}NO_6$ 440.20731, found 440.20685.

2.2.4. 22-benzyloxycarbonyl-8;11;14-trioxa-25-azatetracyclo[19.3.1.0$^{2;7}$.0$^{15;20}$]pentacosa-2;4;6;15(20);16;18-hexene-23-one ***(4d)***

Light orange solid; 55% (1.27 g); m.p 205.0-206.3(°C). **^{1}HNMR** (600 MHz, $CDCl_3$) δ 7.27-7.25 (m, 3H), 7.22 (dd, *J*=8.1, 1.7 Hz, 1H), 7.19 (dd, *J*=8.2, 1.7 Hz, 1H), 7.17 (d, *J*=7.3 Hz, 1H), 7.13 (d, *J*=7.4 Hz, 1H), 7.09-7.07 (m, 2H),

6.88 (t, *J*=7.4 Hz, 1H), 6.79 (td, *J*=8.5, 2.7 Hz, 3H), 5.05 (d, *J*=12.4 Hz, 1H), 4.99 (d, *J*=12.5 Hz, 1H), 4.34 (s, 2H), 4.13 - 4.07 (m, 5H), 4.01 (d, *J*=8.5 Hz, 2H), 3.86 (td, *J*=9.9, 2.6 Hz, 1H), 3.82 (dt, *J*=9.8, 4.9 Hz, 1H), 3.31 (t, *J*=13.2 Hz, 1H), 2.64 (dd, *J*=14.2, 2.8 Hz, 1H), 1.67 (s, 1H). **^{13}CNMR** (125 MHz, $CDCl_3$) δ 204.65; 169.08; 156.99; 156.89; 135.74; 129.33; 129.17; 128.43; 128.40; 128.03; 127.98; 121.05; 120.92; 111.14; 111.08; 69.89; 69.83; 66.50; 66.43; 66.37; 62.60; 46.82. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{29}H_{30}NO_6$ 488.20731, found 488.20682.

2.3. Synthesis of oxime derivatives of azacrown ethers containing the piperidine heterocycle (6a-d)

Conventional heating method: A mixture of compounds (**4a)** (0.30 g; 1.0 eq. mol) and hydroxylammonium chloride ($NH_2OH.HCl$) (**5**) (2.1 eq. mol) was dissolved in 20 ml acetonitrile and refluxed for 30 minutes. When the reaction finished (checked by the TLC), the reaction mixture was cooled to room temperature and the precipitate was filtered on Buchner funnel. After that, the obtained precipitate was dissolved in DCM with 1 ml of triethylamine and stirred for 30 minutes. The organic layer was washed several times with water, dried with $MgSO_4$ and the solvent was evaporated to obtain a white solid. The product was recrystallised in an ethanol-DCM mixture to obtain the pure product **(6a)**.

Microwave irradiation method: A mixture of compounds (**4a-d)** (0.30 g; 1.0 eq. mol) and hydroxylammonium chloride ($NH_2OH.HCl$) (**5**) (2.1 eq. mol) was dissolved in 10 ml acetonitrile. Reactions were carried out under the microwave irradiation at two temperature conditions: 80°C for 20 minutes and 100°C for 10 minutes. After the reaction was completed, the precipitate was filtered using a Buchner funnel. The obtained precipitate was dissolved in DCM with 1 ml of triethylamine and stirred for 30 minutes. The organic layer was washed several times with water; dried with $MgSO_4$, and the solvent was evaporated to obtain a white solid. The product was recrystallised in an ethanol-DCM mixture to obtain the pure product **(6a-d)**.

2.3.1. 22-ethoxycarbonyl-23-hydroxyimino-8;11;14-trioxa-25-azatetracyclo[19.3.1.$0^{2;7}$.$0^{15;20}$]pentacosa-2;4;6;15(20);16;18-hexene ***(6a)***

White solid; m.p 212.0-215.0(°C).

Under reflux conditions: Reaction yield was 90% (0.28 g).

Under microwave conditions: Reaction yield at 80°C was 92% (0.29 g) and at 100°C was 84% (0.26 g).

^{1}HNMR (600 MHz, DMSO-d_6) δ 10.78 (s, 1H), 7.24-7.19 (m, 3H), 7.13 (br.s, 1H), 6.92 (d, *J*=8.2 Hz, 2H), 6.86 (t, *J*=7.5 Hz, 1H), 6.83 (t, *J*=7.4 Hz, 1H), 4.14-4.06 (m, 2H), 4.04-3.79 (m, 10H), 3.71 (br.s, 2H), 3.22 (d, *J*=14.4 Hz, 1H), 2.53 (br.s, 1H), 0.93 (t, *J*=7.1 Hz, 3H). **^{13}CNMR** (151 MHz, DMSO-d_6) δ 170.13; 156.81; 154.88; 129.67; 128.85; 128.64; 120.30; 119.93; 111.36; 69.17; 66.62; 66.42; 59.43; 51.73; 28.84; 13.84. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{24}H_{29}N_2O_6$ 441.20256, found 441.20215.

2.3.2. 22-tert-butyloxycarbonyl-23-hydroxyamino-8;11;14-trioxa-25-azatetracyclo[19.3.1.$0^{2;7}$.$0^{15;20}$] pentacosa-2;4;6;15(20);16;18-hexene ***(6b)***

White solid; m.p 222.5-224(°C). Under microwave conditions: Reaction yield at 80°C was 89% (0.28 g) and at 100°C was 52% (0.16 g).

^{1}HNMR (600 MHz, DMSO-d_6) δ 10.65 (s, 1H), 7.26-7.19 (m, 3H), 7.15 (br.s, 1H), 6.93 (d, *J* =8.1 Hz, 1H), 6.92 (d, *J*=8.0 Hz, 1H), 6.86 (t, *J*=7.4 Hz, 1H), 6.84 (t, *J*=7.4 Hz; 1H), 4.13-4.06 (m, 2H), 4.04-3.77 (m, 8H), 3.69 (br.s, 2H), 3.22 (d, *J*=14.5 Hz, 1H), 2.47 (br.s, 1H), 1.14 (s, 9H). **^{13}CNMR** (150 MHz, DMSO-d_6) δ 169.09; 156.90; 156.77; 154.93; 129.74; 128.70; 128.54; 120.25; 119.74; 111.31; 111.22; 79.24; 69.16; 66.52; 66.35; 52.58; 28.70; 27.52. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{26}H_{33}N_2O_6$ 469.23386, found 469.23334.

2.3.3. 22-isopropyloxycarbonyl-23-hydroxyimino-8;11;14-trioxa-25-azatetracyclo[19.3.1.$0^{2;7}$.$0^{15;20}$] pentacosa-2;4;6;15(20);16;18-hexene ***(6c)***

White solid; m.p 184.8-185.7(°C). Under microwave conditions: Reaction yield at 80°C was 89% (0.28 g) and at 100°C was 72% (0.22 g).

^{1}HNMR (600 MHz, DMSO-d_6) δ 10.72 (s, 1H), 7.26-7.18 (m, 3H), 7.12 (br.s, 1H), 6.93 (d, *J*=8.1 Hz, 2H), 6.86 (t, *J*=7.2 Hz, 1H), 6.82 (t, *J*=7.2 Hz, 1H), 4.67 (br.s, 1H), 4.13-4.09 (m, 2H), 4.05-3.79 (m, 8H), 3.71 (br.s, 2H), 3.21 (d, *J*=14.5 Hz, 1H), 1.00 (d, *J*=6.4 Hz, 3H), 0.83 (br.s, 3H). **^{13}CNMR** (150 MHz, DMSO-d_6) δ 169.12; 156.62; 156.57; 154.56; 129.71; 128.38; 128.21; 120.02; 119.54; 111.21; 111.13; 68.77; 66.36; 66.31; 66.26; 51.59; 28.40; 21.03; 20.95. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{25}H_{31}N_2O_6$ 455.21821, found 455.21774.

2.3.4. 22-benzyloxycarbonyl-23-hydroxyimino-8;11;14-trioxa-25-azatetracyclo[19.3.1.$0^{2;7}$.$0^{15;20}$]pentacosa-2;4;6;15(20);16;18-hexene ***(6d)***

White solid; m.p 175.6-177.3(°C). Under microwave conditions: Reaction yield at 80°C is 89% (0.28 g) and at 100°C is 72% (0.22 g).

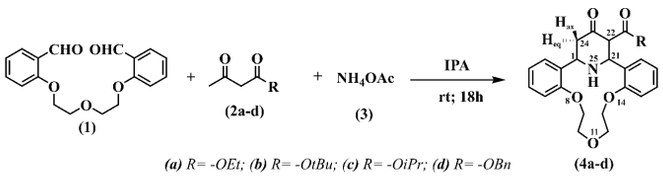
^{1}HNMR (600 MHz, DMSO-d_6) δ 10.82 (s, 1H), 7.26-7.21 (m, 6H), 7.10 (br.s, 1H), 6.98 (br.s, 2H), 6.93 (t, *J*=9.4

Hz, 2H), 6.87 (t, *J*=7.2 Hz, 1H), 6.80 (t, *J*=7.3 Hz, 1H), 5.03 (d, *J*=12.9 Hz, 1H), 4.83 (d, *J*=13.1 Hz, 1H), 4.14-3.89 (m, 8H), 3.86-3.64 (m, 4H), 3.26 (d, *J*=14.0 Hz, 1H), 2.55 (br.s, 1H). **^{13}CNMR** (151 MHz, DMSO-d_6) δ 170.17; 156.77; 154.88; 136.00; 129.59; 128.88; 128.58; 128.20; 127.49; 127.00; 120.24; 120.05; 111.38; 111.30; 69.07; 66.60; 66.38; 64.80; 51.59; 28.74. **HR-ESI-MS** *m/z* $[M+H]^+$ calculated for $C_{29}H_{31}N_2O_6$ 503.21821, found 503.21814.

3. Results and discussion

3.1. Synthesis of azacrown ethers

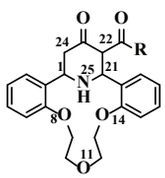
The multi-component condensation based on the Soldatenkov condition [15, 16] is a modification of the synthesis of γ-piperidone derivatives by the Petrenko-Kritschenko reaction. Instead of using two equivalent molars of arylaldehyde as in the conventional method, a dialdehyde podand bearing a polyethyl ether bridge is employed as the starting material, serving as the basis to generate crown ethers or heterocrown ethers. In this work, the condensation between 1,5-bis(2-formylphenoxy)-3-oxapentane and β-keto esters, in the presence of ammonium acetate as the amine source, simultaneously forms the piperidine and cyclises to obtain the azacrown ethers (Scheme 1).



Scheme 1. The general procedure to prepare azacrown ethers containing piperidine heterocycles.

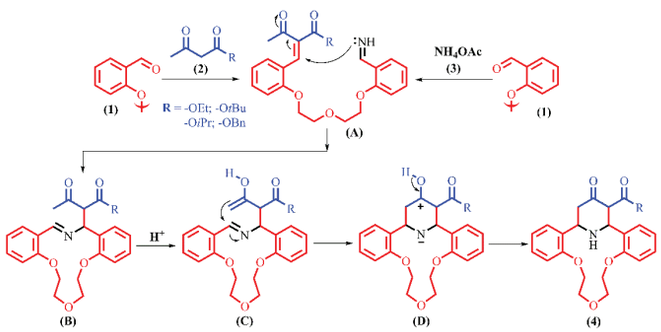
We first carried out the reaction of ethyl acetoacetate (**2a**), used as the model compound, with dialdehyde podand (**1**) and NH_4OAc (**3**) in isopropyl alcohol at ambient temperature. After one hour, a light-yellow solid precipitated. The reaction was monitored by TLC and was finished after 18 h. The obtained product **4a** was purified by recrystallisation from the ethanol-DCM mixture and its structure was confirmed by ^{1}HNMR and DEPT ^{13}CNMR. The analysis of the recorded spectra demonstrated the formation of a piperidine product. In the ^{1}HNMR spectrum, characteristic signals for the piperidine ring appeared as two peaks corresponding to the *axial* and *equatorial* protons in the methylene group at the 24-position. A doublet of doublets at 2.63 ppm was assigned for H^{24}_{ex} with two *J*-coupling constants: 14.2 Hz for the geminal coupling (^2J) and 2.8 Hz for the vicinal coupling (^3J). The other broad triplet peak at 3.31 ppm corresponded to H^{24}_{ax} with a coupling constant of 13.0 Hz. Besides that, the peak of NH^{25} was found at 1.65 ppm as a broad singlet. These assignments were further substantiated with the DEPT ^{13}CNMR spectrum. Two carbonyl group signals appeared at 204.9 ppm (C=O ketone) and 169.2 ppm (C=O ester). Resonance peaks of aromatic and polyether moieties as well as signals corresponding to piperidine ring could be found completely on the spectra, thereby confirming the structure of desired compound. The HRMS (ESI) data collected in the positive mode showed a pseudomolecular ion peak at *m/z* 426.19095 corresponding to the formula of compound **4a** $[C_{24}H_{27}NO_6+H]^+$. All the available data were confirmed with high confidence for the formation of azacrown ether containing piperidine product **4a.** This process was then successfully applied to the other β-keto esters as summarised in Table 1. All characterisations of the obtained products showed structural similarities to that of model compound **4a**. It should be noted that the three compounds (**4b-d**) were synthesised for the first time and were determined accordingly.

Table 1. Synthesis of azacrown ethers containing piperidine derivatives.



Compound	R	Yield (%)	m.p (°C)	R_f*
4a	-OC_2H_5	45	200.0-201.0	0.61
4b	-O*t*Bu	54	207.0-209.0	0.67
4c	-O*i*Pr	60	213.0-214.7	0.65
4d	-OBn	38	205.0-206.3	0.68

*Solvent system: Ethyl acetate/n-Hexane=2/1 (v/v).

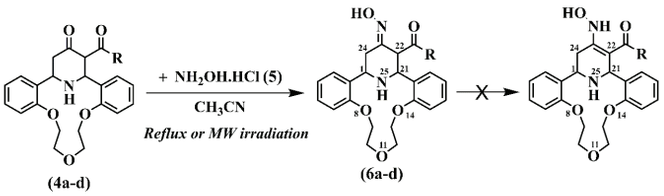


Scheme 2. The proposed mechanism for the formation of azacrown ethers according to the Petrenko-Kritschenko reaction.

A plausible mechanism of this reaction is shown in the Scheme 2. The formation of intermediate **A** follows the original mechanism involving aldehyde groups of podand (**1**), β-keto esters (**2**), and NH_4OAc (**3**). Intramolecular condensation occurs between the imine group and the α, β-unsaturated carbonyl group in the podand to form intermediate **B**. In the presence of CH_3COOH acid, which is released from the first step, there is an enol-keto tautomerism

generating the enol **C**. The intramolecular cyclisation occurs *via* intermediate **D** to generate the desired product (**4**).

3.2. Synthesis of oxime derivatives



(a) R= -OEt; (b) R= -OtBu; (c) R= -OiPr; (d) R= -OBn

Scheme 3. Synthesis of oxime derivatives of piperidone azacrown ethers.

Due to the presence of C=O ketone in the structure, it is possible to synthesise derivatives of azacrown ethers based on the condensation reaction with this group. Nitrogen-containing compounds are potential candidates, which could form the new products throughout the imine or enamine linkages. In this work, oxime derivatives were chosen for initial investigation. Firstly, the reaction between azacrown ethers **4a** and hydroxylammonium chloride ($NH_2OH.HCl$) was carried out under the reflux condition with CH_3CN as the solvent (Scheme 3). After the reaction was completed (1 hour) (monitored by TLC), a white precipitate formed, which was the HCl salt of the desired products. The basification with triethyl amine was conducted to obtain the base-form product **6a** with a yield of 90%. The formation of oxime derivative was confirmed by NMR-spectrum analysis of the purified compound. In both NMR spectra, the characteristic resonance signals of azacrown ether structure remained beside the specific signals of oxime groups: the proton of -OH group at 10.78 ppm in the ^{1}HNMR and the carbon of -C=N group at 154.8 ppm. The disappearance of the C=O peak at 204.9 ppm was evidence that the reaction only took place at the ketone position. Moreover, there was no observation of the double bond rearrangement in the -C=N group to create the conjugated system with an ester moiety because there was no peak at around 90 ppm (C^{22} position) in ^{13}CNMR, which is a specific signal for this formation [17]. The result of the HR-MS measurement also confirmed the formation of oxime products: a pseudomolecular ion peak at *m*/*z* 441.20215, which corresponds to the formula of compound **6a** $[C_{24}H_{28}N_2O_6+H]^+$.

In addition to the traditional reflux conditions, the oximation was also investigated under microwave irradiation, which has been previously applied to synthesise conventional crown ethers [18, 19]. Compound **6a** was synthesised under two temperature conditions for microwave irradiation: 80 and 100°C. At the lower temperature, the reaction finished after 20 minutes and afforded the oxime product in a 92% reaction yield, which was similar to this one under the reflux condition. When the reaction was irradiated at 100°C, the desired product formed in just 10 minutes, however, the reaction yield decreased to about 84%. It could be seen that conducting the reaction at a higher temperature under microwave irradiation condition reduced the reaction time but also generated more by-products, which were observed in the reaction-monitoring TLC. Besides that, the colour of the reaction mixture changed to deep yellow after irradiation, which was also indirect evidence for the formation of undesired compounds. This procedure was applied to synthesise other oxime derivatives of azacrown ethers **6b-d**, which were investigated with the two temperature conditions mentioned above. Structure determination of the synthesised compounds was conducted by NMRs and showed the same specific data to confirm the generation of oxime groups as well as the remains of the carbon skeleton of azacrown ethers. Upon deeper analysis of the experimental findings, there was an observed trend in oxime synthesis: the reaction yield decreased with increasing reaction temperature under irradiation condition (Fig. 1). This factor also reduced the reaction time, namely 20 minutes for 80°C condition and 10 minutes for 100°C. Notably, compound **6b** containing the *tert*-butyl group exhibited a significant yield decrease of 37%.

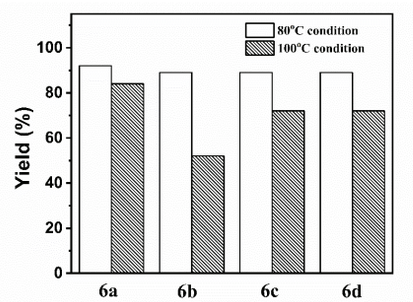


Fig. 1. Reaction yields of oximation with two temperature conditions under the microwave irradiation.

We propose that at higher temperatures, the oxime products undergo a further transformation, such as the intramolecular cyclisation between the =N-OH group and the ester groups to form an isoxazole heterocycle [20]. Compared with a previous study employing ultrasonic energy for the oximation of azacrown ethers, our microwave-assisted method requires less reaction time (20 minutes versus 30 minutes of ultrasonic irradiation) and achieves significantly higher reaction yields (around 90% compared to 50% with the ultrasonic method) [21]. We note that there was a difference in temperature between the two methods; the temperature using microwaves was set at 80°C, which is 10°C higher that used in the ultrasonic process.

4. Conclusions

To conclude, new azacrown ethers containing the piperidine heterocycle were synthesised via the modified Petrenko-Kritschenko piperidone synthesis, achieving good yields (55-65%). Moreover, an effective approach using microwave irradiation, alongside the traditional reflux method, was explored for the synthesis of oxime derivatives. The optimal conditions were 80°C and 20 minutes of irradiation, resulting in the highest synthesis efficiency (89-92%). Although reaction time could be reduced, irradiation at 100°C decreased overall oximation yields (52-84%) and led to the formation of more by-products. All synthesised compounds were structurally characterised by physical methods, including NMR spectroscopy and HR-MS.

CRediT author statement

Tung H. To: Methodology, Investigation, Formal analysis, Supervision, Funding acquisition, Writing - Original draft; Writing - Reviewing & Editing; Hieu D. Nguyen: Investigation.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

[1] M.M. Abdelshaheed, I.M. Fawzy, H.I.E. Subbagh, et al. (2021), "Piperidine nucleus in the field of drug discovery", *Future Journal of Pharmaceutical Sciences*, **7(1)**, DOI: 10.1186/s43094-021-00335-y.

[2] S. Mitra, U. Anand, N.K. Jha, et al. (2022), "Anticancer applications and pharmacological properties of piperidine and piperine: A comprehensive review on molecular mechanisms and therapeutic perspectives", *Front. Pharmacol.*, **12**, DOI: 10.3389/fphar.2021.772418.

[3] Q.S. Chen, J.Q. Li, Q.W. Zhang (2023), "Application of chiral piperidine scaffolds in drug design", *Pharmaceutical Fronts*, **5(1)**, DOI: 10.1055/s-0043-1764218.

[4] N.A. Frolov, A.N. Vereshchagin (2023), "Piperidine derivatives: Recent advances in synthesis and pharmacological applications", *Int. J. Mol. Sci.*, **24(3)**, DOI: 10.3390/ijms24032937.

[5] Z. Wang (2010), *Comprehensive Organic Name Reactions and Reagents*, John Wiley & Sons, Inc., DOI: 10.1002/9780470638859.

[6] D.T. Nhung, N.N. Tram, P.T.T. Tam, et al. (2023), "Synthesis, α-glucosidase inhibitory activity, and molecular docking studies of tri(benzo)-5-azacrownophanes with a γ-piperidone moiety", *ChemistrySelect*, **8(25)**, DOI: 10.1002/slct.202300860.

[7] N.T. Dat, T.T.T. Van, D.T. Nhung, et al. (2024), "Trithiasacrown ethers containing piperidine heterocycle: Synthesis, structural characterisation and evaluation of α-glucosidase inhibitory activity", *ChemistrySelect*, **9(3)**, DOI: 10.1002/slct.202303741.

[8] L.M. Nguyen, H.H. Truong, V.N. Khrustalev, et al. (2020), "Synthesis and biological evaluation of novel phane-structured diasacrowns containing γ-piperidone and pyridine rings", *Mendeleev Communications*, **30(6)**, pp.753-755, DOI: 10.1016/j.mencom.2020.11.021.

[9] N.T. Dao, D.T. Nguyen, L.M. Nguyen, et al. (2021), "Synthesis of dithiacrown ethers and evaluation of their cytotoxic activity", *ChemistrySelect*, **6(40)**, pp.11081-11085, DOI: 10.1002/slct.202102963.

[10] N.T. Dao, V.N. Khrustalev, E.I. Polyakova, et al. (2022), "Synthesis and biological evaluation of asacrownophanes containing tetrahydropyridine or piperidone subunits", *ChemistrySelect*, **7(48)**, DOI: 10.1002/slct.202204392.

[11] N.T. Dao, H.H. Truong, V.B. Luu, et al. (2019), "Synthesis and bioactivity of novel (γ-piperidono)dibenzo-33-aza-14-crown-3 ethers", *Chemistry of Heterocyclic Compounds*, **55(7)**, pp.654-659, DOI: 10.1007/s10593-019-02512-7.

[12] J. Jayabharathi, A. Manimekalai, T.C. Vani, et al. (2007), "Synthesis, stereochemistry and antimicrobial evaluation of t(3)-benzyl-r(2),c(6)-diarylpiperidin-4-one and its derivatives", *European Journal of Medicinal Chemistry*, **42(5)**, pp.593-605, DOI: 10.1016/j.ejmech.2006.11.009.

[13] C. Ramalingan, Y.T. Park, S. Kabilan (2006), "Synthesis, stereochemistry, and antimicrobial evaluation of substituted piperidin-4-one oxime ethers", *European Journal of Medicinal Chemistry*, **41(6)**, pp.683-696, DOI: 10.1016/j.ejmech.2006.02.005.

[14] E.A. Alexandrova, K.A. Lotsman, K.A. Lyssenko, et al. (2019), "Synthesis of novel N,O-macrocyclic ligands, functionalised by phosphine oxide groups", *Chemistry of Heterocyclic Compounds*, **55(9)**, pp.875-881, DOI: 10.1007/s10593-019-02551-0.

[15] A.N. Levov, V.M. Strokina, L.T. Anh, et al. (2006a), "Synthesis of dibensopiperidinoasa-14-crown-4 ethers and their one-step conversion into dibenzo-16-crown-3", *Mendeleev Communications*, **16(1)**, pp.35-36, DOI: 10.1070/MC2006v016n01ABEH002201.

[16] A.N. Levov, V.M. Strokina, A.I. Komarova, et al. (2006b), "Synthesis of dibenzoazacrown ethers including a γ-piperidone moiety", *Chemistry of Heterocyclic Compounds*, **42(1)**, pp.125-126, DOI: 10.1007/s10593-006-0060-z.

[17] T.H. To, D.B. Tran, V.T.T. Ha, et al. (2022), "Electrocatalytic H2 evolution using binuclear cobalt complexes as catalysts", *RSC Advances*, **12(40)**, pp.26428-26434, DOI: 10.1039/D2RA05109E.

[18] M. Canbolat, Ü. Çalışır, B. Çiçek (2022), "Microwave-assisted synthesis of aromatic thiadiazol crown ethers and determination of complexation properties with metal ions by application of Job′s plot method to conductometry", *ChemistrySelect*, **7(29)**, DOI: 10.1002/slct.202200944.

[19] A. Sapmaz, Ü. Çalışır, E. Akkemik, et al. (2023), "Microwave assisted synthesis of benzo-azacrown ethers and *in vitro* inhibition studies on hCA I-II", *Russian Journal of General Chemistry*, **93(2)**, pp.440-448, DOI: 10.1134/S1070363223020275.

[20] N. Agrawal, P. Mishra (2018), "The synthetic and therapeutic expedition of isoxazole and its analogs", *Medicinal Chemistry Research*, **27(5)**, pp.1309-1344, DOI: 10.1007/s00044-018-2152-6.

[21] D.T. Nhung, L.T. Anh, L.V. Boi, et al. (2019), "Ultrasonic irradiation assisted the preparation of γ-piperidone azacrowns and its oxime", *Vietnam Journal of Chemistry*, **57(4e3,4)**, pp.392-396.