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Unexpected hydrazine- and hydroxylamine-induced transformations of aza-14-crown-4 incorporating 4-oxopiperidine-3-carboxylate moiety

Dat T. Nguyen,[a] Hieu H. Truong,[b] Nhung T. Dao,[a] Van T. T. Tran,[a] Olga S. Gorchakova[c] and Anh T. Le*[a]

[a] *Faculty of Chemistry, VNU University of Science, Vietnam National University, Hanoi, Thanh Xuan, 100000 Hanoi, Vietnam. E-mail: huschemical.lab@gmail.com*
[b] *Peoples Friendship University of Russia (RUDN University), 117198 Moscow, Russian Federation*
[c] *'Sanofi-aventis group' Representative office in Russia, 125009 Moscow, Russian Federation*

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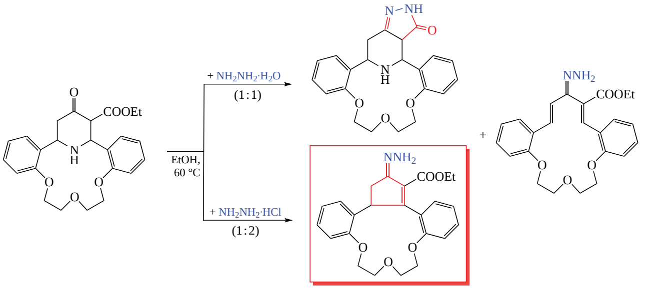
Reactions of aza-14-crown-4 incorporating 4-oxopiperidine-3-carboxylate moiety with hydrazine and hydroxylamine proceed at the functional groups. One unexpected product, cyclopenteno-13-crown-3 ether derivative, is formed when hydrazine hydrochloride is used, its formation occurring *via* deamination of the piperidine followed by the Nazarov reaction of the intermediate hydrazono diene. According to the QSAR through ADMET calculation, the synthesized compounds may show high potential for biological studies.



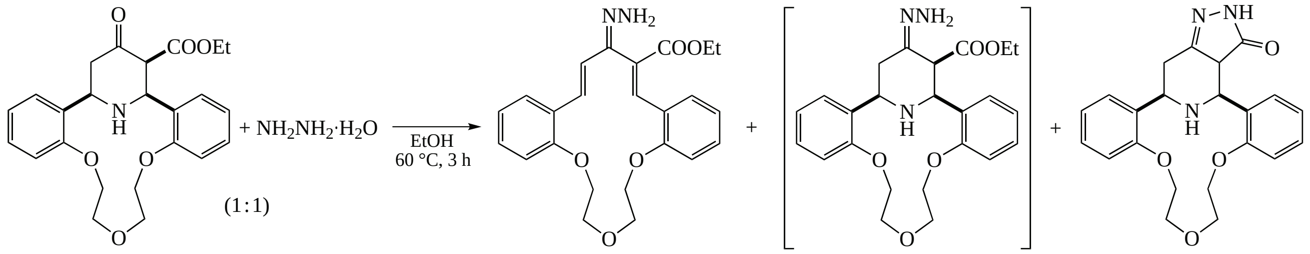
Keywords: azacrown ether, piperidone, Nazarov reaction, hydrazone, cyclopenteno-13-crown-3 ether.

4-Piperidones (see reviews[1,2]) possess two active centers, C=O and NH groups, which facilitates the introduction of other substituents into the piperidine ring affording potential pharmacologically active compounds.[3] Typical transformations of piperidones include nucleophilic addition of phenylthiosemicarbazide,[4–6] hydroxylamine,[7,8] amines,[9,10] hydrazine,[11] aromatic aldehydes,[12] *N*-alkylation reaction,[13] *N*-acylation reaction[14–16] and *O*-acylation reaction.[14] As a part of our ongoing research concerning azacrown compounds,[17–20] this study describes the condensation of azacrown compound **1** bearing 4-oxopiperidine-3-carboxylate moiety with hydroxylamine and hydrazine (Scheme 1). Typically, such reactions would convert piperidone into oxime and hydrazone derivatives, respectively. However, in herein experiments the formation of other derivatives such as pyrazole or (cyclopent-2-en-1-ylidene)hydrazine was detected. This abnormal pathway arises from the contribution of a neighboring ethoxycarbonyl substituent at the α-position to the oxo group in piperidone. Interstingly, in our previous publication we also demonstrated that the presence of β-oxo ester fragment combined with piperidone ring caused unusual transformation of piperidone into tetrahydropyridines.[21,22]

The reaction of azacrown **1** with 1 equiv. hydrazine hydrate (see Scheme 1) at 60 °C for 3 h was supposed to give three products, namely, hydrazone **2′**, deamination product **2** and the product of intramolecular cyclization of pyrazolo[4,3-*c*]-piperidine chemotype **3**. Surprisingly, mostly anticipated hydrazone **2′** was not detected in the reaction mixture (LC-MS study using ESI soure at positive mode, see Online Supplementary Materials). Apparently, it underwent deamination into hydrazono diene **2** and intramolecular cyclization into fused pyrazolone **3**. The silica gel column chromatopraphy afforded first compound **2** (white crystals, mp 225–227 °C, 27% yield) followed by pyrazolone derivative **3** (25% yield). Increasing the amount of hydrazine hydrate over azacrown **1** as well as prolongation of the reaction time do not change the ratio of products **2** and **3**.

The IR spectra of compounds **2**, **3** contained the absorption bands for NH, NH_2 and C=O groups around 3300 (NH and NH_2) and 1739 cm^{-1} (C=O). Their ^1H NMR spectra were in good agreement with the structures of **2**, **3**. The proton for the NH group of the pyrazolone fragment of compound **3** resonates as a singlet at 8.31 ppm.

Unexpected result has been obtained when azacrown **1** was heated with a twofold excess of hydrazine hydrochloride (ethanol, 60 °C, 1 h). Along with compound **2** (40%), another



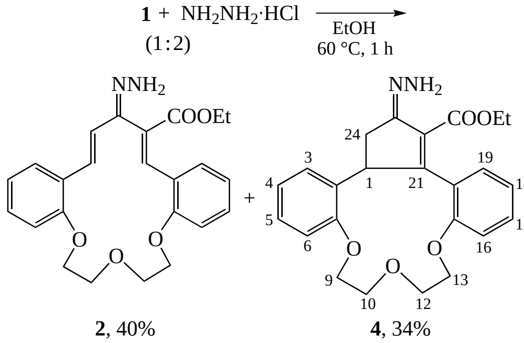
1

2, 27%
m/*z* 422.18

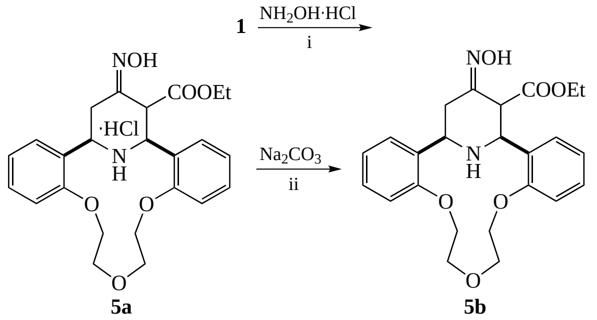
2′
m/*z* 439.21

3, 25%
m/*z* 393.17

Scheme 1



Scheme 2



Scheme 4 *Reagents and conditions:* i, $NH_2OH·HCl$, EtOH, reflux, 40 min; ii, Na_2CO_3 (5% aq.), pH 11, EtOAc extraction.

product with interesting structure, hydrazono cyclopenteno-13-crown-3 **4** (34%) was also formed (Scheme 2). Prolongation of the reaction time to 6 h and increasing amount of hydrazine hydrochloride led to the total conversion of diene **2** into cyclopentene **4**. Alternatively, when compound **1** and hydrazine hydrochloride were mixed in a 1 : 1 molar ratio, the reaction gave mostly product **2** with minority of **4**.

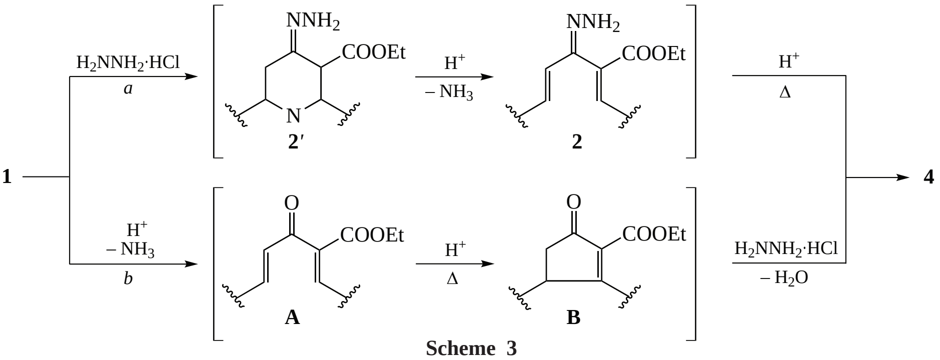
The structure of compound **4** was confirmed by spectrometry. Its HRMS spectrum contains clear peak for $[M+H]^+$ at *m/z* 423.2100. The IR spectrum shows a strong absorption band at 1732 cm^{-1} for the ethoxycarbonyl group and two bands at 3305 cm^{-1} (NH_2), 1665 and 1631 cm^{-1} (C=C–C=N). In the ^1H NMR spectrum, the cyclopentenone protons resonate at 2.73 and 3.80–4.25 ppm.

Apparently, compound **2′** is deaminated under acidic conditions into divinyl derivative **2**, which would undergo the Nazarov cyclization[23–26] into **4** (Scheme 3, pathway *a*). However, another way for formation of **4** as a result of deamination of **1** into divinyl ketone **A** followed by its Nazarov cyclization into cyclopentanone **B** with final formation of hydrazone **4** (pathway *b*) should not be excluded.[27–29] The present electron-withdrawing β-oxo ester group would polarize the whole conjugated system, which should facilitate the Nazarov cyclization leading to compound **4**.[28]

When $NH_2NH_2·HCl$ was replaced by $NH_2OH·HCl$, compound **5a** was readily crystallized as a hydrochloride from the cooling reaction mixture (yield 79%, Scheme 4). After treatment with Na_2CO_3 and filtering, oxime **5b** was obtained as a free base. Due to the fact that oxygen is less nucleophilic than nitrogen, possible isoxazoline or Nazarov cyclization product are not formed (see Online Supplementary Materials, Scheme S1). The formation of **5b** is confirmed by the disappearance of one vibration for the piperidone C=O group in the IR spectrum. Vibration of OH group displays a strong and broad band at 3379 cm^{-1}. ^1H NMR and mass spectra also support the **5b** structure.

Compounds **2–5** may be interesting not only for studying their application in coordination chemistry but also for virtual evaluation of their bioactivity. The qualitative structure–activity relationships (QSAR) of azacrownophanes **1–5** was studied by physicochemical calculations (Table 1) using the SwissADME web server (http://www.swissadme.ch/) and the Molsoft web server (http://molsoft.com/mprop/).[30] Six compounds including starting **1** do not violate the Lipinski's rule and have the same Bioavailability Score of 0.55. The gastrointestinal (GI) absorption of all substances are high. Values of the blood–brain barrier (BBB) score are less than 6.0, which means that the compounds are low toxic. The drug likeness scores (DLS) are in the range from –0.54 to 0.23 in which compounds **2** and **3** showed negative value (–0.54 and –0.31, respectively) whereas compound **4** exhibited the highest value (0.23). Interestingly, the synthesized compounds are predicted as good inhibitors of three major CYP isoenzymes (CYP2D6, CYP3A4 and CYP2C9).

In conclusion, a series of new compounds was successfully prepared from the reaction between crown derivative **1** and



Scheme 3

Table 1 Some physicochemical parameters of synthesized compounds.

Compound	MW	log*P*	log*S*	HBD number[a]	HBA number[b]	DSL	BBB score	BS[c]	Inhibitor	GI absorption	Lipinski's rule violation
1	425.18	2.57	–4.06	1	7	0.01	2.71	0.55	CYP2D6, CYP3A4	High	0
2	422.47	2.02	–4.48	2	6	–0.54	3.14	0.55	CYP3A4	High	0
3	393.17	2.22	–3.51	2	6	–0.31	2.93	0.55	CYP2D6, CYP3A4	High	0
4	422.18	2.73	–4.50	2	6	0.23	3.13	0.55	CYP2C9, CYP3A4	High	0
5a	461.94	0.00	–4.78	1	7	0.01	2.67	0.55	CYP3A4	High	0
5b	440.19	3.12	–4.30	2	8	0.03	2.45	0.55	CYP2D6, CYP3A4	High	0

[a] Number of H-bond donors. [b] Number of H-bond acceptors. [c] Bioavailability score.

hydrazine and hydroxylamine with the yield from 29 to 79%. Oxime derivatives **5a**,**b** were obtained in higher yield in comparison with deamination product **2** and pyrazolo[4,3-*c*]-piperidinoaza-14-crown-4 compound **3**. Interestingly, when using hydrazine as salt of an acid in 2 : 1 molar ratio to azacrown ether **1**, cyclopenteno-13-crown-3 **4** was unexpectedly formed *via* the mechanism of Nazarov reaction. Some ADMET parameters were recorded and indicated that the synthesized compounds are good sources for further biological studies.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2023.09.037.

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