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A straightforward access to 2-hydroxyoxazino[3,2-*f*]phenanthridines from phenanthridine, oxalylacetylenes and water

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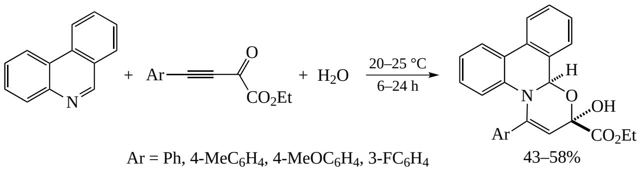
Phenanthridine is readily annulated at room temperature with dihydro-1,3-oxazine ring under the action of oxalylacetylene ethyl ester to diastereoselectively deliver (*R,*R**)-2-hydroxy-4-aryl-2*H*,13b*H*-[1,3]oxazino[3,2-*f*]-phenanthridines in up to 58% yield. According to quantum chemical calculations, among the possible transformations of the 1,3(4)-dipole phenanthridine/oxalylacetylene intermediate, protonated with water, the preferred route leading to the target product is attack of the hydroxyl anion at the carbonyl moiety, followed by closing of the oxazine ring. The calculated stability of oxazinophenanthridine with respect to the oxazinoquinoline derivative in terms of Δ*G*, and the higher C^6–O bond order in the former are confirmed by experimental results of differences between the reactions of phenanthridine and quinoline with aryloxalylacetylenes in water.**

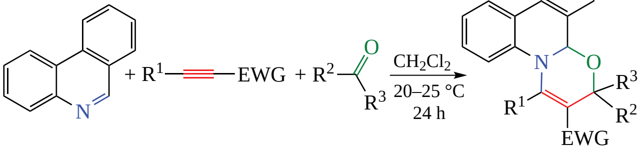


Ar = Ph, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 3-FC$_6$H$_4$

Keywords: alkynes, annulation, diastereoselectivity, 1,3-dipolar intermediates, hemiacetals, phenanthridine, 1,3-oxazines, quantum chemical calculations.

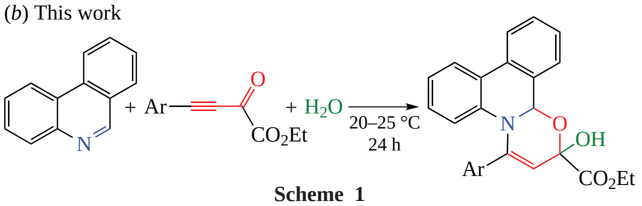
Condensed dihydro[1,3]oxazines are of interest due to their rich potential as drug precursors and their properties valuable for materials science. 1,3-Oxazino(iso)quinolines are patented as antimalarial agents.[1] The 1,3-oxazinopyridine fragment is a structural motif of nitrogen-doped carbon nanodots, which are very promising for application in optoelectronics, biomedicine, and bioimaging.[2] Due to the high biological and material significance of dihydro[1,3]oxazine[3] derivatives, the development of their construction is an urgent challenge. One of the most widely used approaches to dihydro[1,3]oxazines conjugated with a heterocyclic system is the interception of 1,3-dipole intermediates, adducts of azines with electron-deficient acetylenes or arynes and various carbonyl electrophiles.[4] The phenanthridine cycle, a common structural unit of many biologically active compounds,[5] was successfully involved in this reaction [Scheme 1(*a*)].[6]

(*a*) Previous works



EWG = CO$_2$Me, CO$_2$Et, CO$_2$Bu^i, C(O)CO$_2$Et
R^1 = H, Ph, CO$_2$Me, CO$_2$Et, CO$_2$Bu^i
R^2 = H, CF$_3$, PhC≡C
R^3 = Ar, OEt, CO$_2$Et

(*b*) This work



Scheme 1

Recently, we were able to improve this approach by limiting the number of reagents to two: 1-ethoxyoxalyl-2-phenylacetylene in the reaction with phenanthridine sequentially played the role of C≡C and C=O electrophiles to afford annulated 1,3-oxazinophenanthridine in 66% yield functionalized with ethynyl, ester and oxalyl groups.[7] This work presents a new method for the annulation of the phenanthridine ring by the 1,3-oxazine cycle under the action of electron-deficient oxalylacetylenes and water participating in the reaction as both a reagent and a medium [see Scheme 1(*b*)].

It was experimentally established that phenanthridine **1** reacted with oxalylacetylenes **2a–d** and water under mild conditions (20–25 °C) to diastereoselectively deliver 2-hydroxy-1,3-oxazinophenanthridines **3a–d** in 43–58% yields (Scheme 2).[†] The reaction was conducted under catalyst- and metal-free

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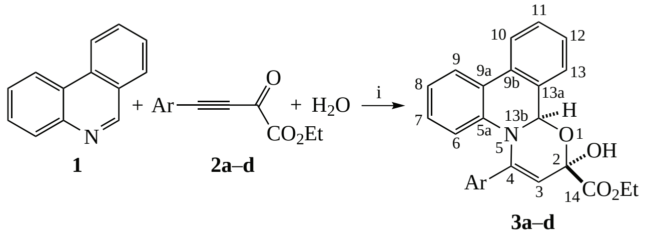
[†] A mixture of phenanthridine **1** (0.5 mmol), acetylene **2** (0.5 mmol) and water (45 mg, 2.5 mmol) was stirred at 20–25 °C for appropriate time. The solvents were removed under reduced pressure, and further column chromatography afforded oxazinophenanthridine **3**.

For the characteristics of compounds **3a–d**, see Online Supplementary Materials.



3a–d	Ar	Time/h	Isolated yield (%)	Yield based on consumed **1** (%)
a	Ph	6	43	83
b	4-MeC_6H_4	24	48	60
c	4-$MeOC_6H_4$	24	31	75
c[a]	4-$MeOC_6H_4$	24	58	63
d[a]	3-FC_6H_4	24	43	64

Scheme 2 *Reagents and conditions*: i, **1** (1 equiv.), **2** (1 equiv.), H_2O (55 equiv.), 20–25 °C; [a] for homogenization of reaction mixture MeCN was used.

(biomimetic, ecologically benign) conditions (room temperature, water). The reaction duration was controlled by IR spectroscopy until disappearance of the C≡C band in the region 2198–2220 cm^{-1} for initial acetylenes **2**, which commonly took 24 h. It was found for 4-methoxyphenyloxalylacetylene **2c** that due to its poor solubility in water, the addition of acetonitrile for homogenization had a positive effect on the yield of product **3c** (31% *vs.* 58%). In the case of acetylenes **2a** and **2b**, the reaction was performed in a two-phase system (without MeCN addition). Thus, 1-aryl-2-oxalylacetylenes containing both donor (H, 4-Me, 4-MeO) and acceptor (3-F) substituents in the aromatic part were successfully involved in the studied reaction.

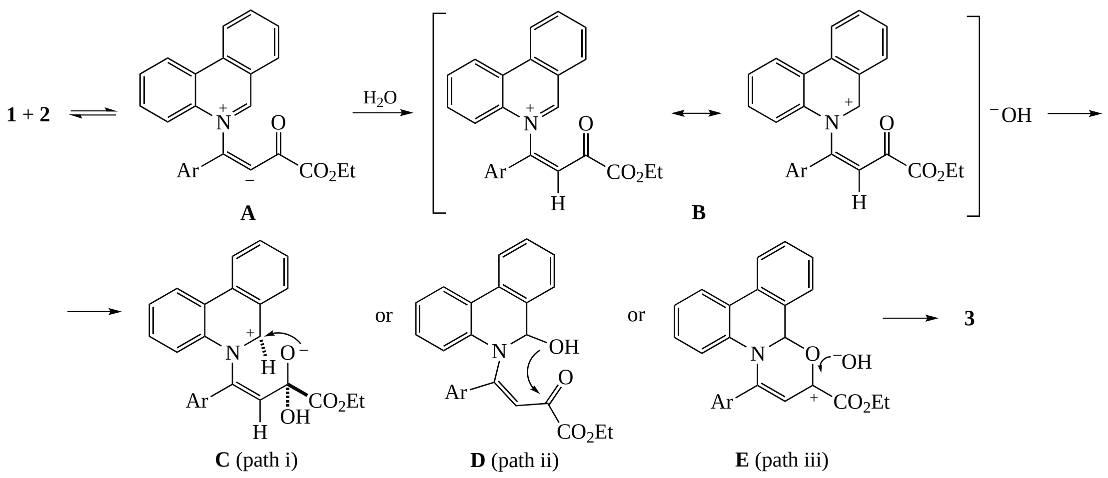
The structure of oxazinophenanthridines **3** was established using NMR spectroscopic data. Despite the presence of two chiral centers in the molecule, only one set of signals is observed in the ^{1}H NMR spectra indicating the formation of one diastereomer. The relative configuration was attributed by analogy to compounds with similar skeletons based on quinoline and trifluoroacetylphenylacetylene.[8] NMR data confirm configuration retention for a wide range of compounds. Characteristic signals are singlets of OH (4.61–4.64 ppm), H-3 (5.96–6.11 ppm) and H-13b (5.95–6.09 ppm) in the ^{1}H NMR and C-14 (170.0–170.4 ppm), C-2 (92.7–93.0 ppm) and C-13b (81.2–81.3 ppm) in the ^{13}C NMR spectra. This suggests that the synthesized compounds **3** have the *R**,*R**-configuration with *dr* ~100.

Since 2-hydroxyoxazinophenanthridines **3** have labile hemiacetal function, diastereoselectivity should be thermodynamic characteristic of the reaction. Quantum-chemical calculations of the enthalpy difference and Gibbs free energy of diastereomers of compound **3a** is in keeping with prediction of a high activation barrier (~30 kcal mol^{-1}) for isomerization of the *R**,*R** isomer to the *R**,*S** one (determined by the $C1^{3b}$–O^1 bond cleavage), which under reaction conditions is unattainable (see Table S1 in Online Supplementary Materials).

Apparently, the assembly of product **3** begins with the formation of 1,3(4)-dipole intermediate **A** by the attack of the nucleophilic nitrogen atom of phenanthridine **1** at the triple bond of oxalylacetylene **2** (Scheme 3). Then, the vinyl carbanionic center of intermediate **A** is protonated with water molecule to give *N*-alkenylphenanthridinium hydroxide **B**. Further development of the scenario assumes three possible routes: i) the attack of the hydroxide anion at the carbonyl group of the oxalylalkenyl fragment with the formation of hemiacetal oxygen-centered anion **C**, followed by the closure of the oxazine ring **3**; ii) the attack of the hydroxide anion at the carbocation position 6 of the phenanthridine ring to deliver hemiaminal **D**, in which the intramolecular nucleophilic addition of the hydroxyl at the carbonyl group completes the formation of product **3**; iii) the attack of the carbonyl group oxygen at the position 6, followed by the addition of hydroxide anion at the emerging carbocationic oxazine intermediate **E**.

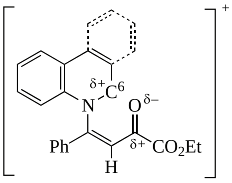
Quantum-chemical calculations of charges and condensed Fukui indices of the cation intermediate **B** show that the positive charge is localized on the carbonyl carbon atom and the C^6 atom of the ring, in support of path i in which the former value is greater than the latter (Table 1). In contrast, the C^6 atom is predicted to be a stronger electrophilic (f^+) center than the carbonyl carbon atom in accordance with condensed Fukui function analysis (path ii). In support of path iii, the carbonyl oxygen atom in the intermediate **B** is negatively charged for successful intramolecular recombination with the positively charged C^6 carbon atom, however the former nucleophilicity is low, f^- is only 0.005. Thus, the charge control of the chemical reaction for cation **B** does not allow one to make a conclusion on the preferred reaction path.

The analysis of frontier HOMO and LUMO orbitals performed at HF/cc-pVTZ level in the adduct **B** (generated from phenanthridine) (see Online Supplementary Materials, Figure S1) indicates that HOMO orbital is localized on phenanthridine π-system, the localization contribution of C^6 atomic orbitals (LCAO) is only 0.07, $E_{\mathrm{HOMO}} = -0.2693$ Ha. The LUMO orbital is mainly localized on CHC(O)C(O) moiety, LCAO of the carbonyl carbon and oxygen atoms as well as C^6 carbon atom is 0.48, 0.07 and 0.40, respectively, $E_{\mathrm{LUMO}} = -0.1362$ Ha. The energy gap ($E_{\mathrm{gap}} = E_{\mathrm{LUMO}} - E_{\mathrm{HOMO}}$) between intramolecular frontier orbitals in the adduct **B** is



Scheme 3

Table 1 CM5 atomic charges and condensed Fukui reactivity indices of cation intermediate **B** obtained using the MP2/cc-pVTZ wave function.



B

Cation **B**	CM5 charges/e					Condensed Fukui functions				
	O	C(O)	C_α	N	C^6	f^-(O)	$f^+(C_\alpha)$	f^+(N)	$f^+(C^6)$	f^+[C(O)]
for quinoline	–0.330	0.247	–0.079	–0.230	0.168	0.088	0.067	0.020	0.086	0.076
for phenanthridine	–0.330	0.248	–0.079	–0.230	0.195	0.005	–0.005	0.089	0.168	0.031

0.1331 Ha, while E_{gap} between E_{LUMO} of **B** and E_{HOMO} of HO^- is by 0.086 Ha higher with respect to the former. Basing on the aforementioned results, the possibility of further development of the reaction along path ii, namely, the attack of the hydroxide anion at the C^6 atom is unlikely. Despite the lower E_{gap}, adduct **B** has a center with greater LUMO localization, the carbonyl carbon atom. The formation of covalent bond between C^6 and carbonyl oxygen atoms by intramolecular cyclization is also unlikely (path iii) in view of their low atomic orbital contribution to the corresponding frontier orbitals. Thus, the orbital control of chemical reaction indicates further development of the reaction by the attack of hydroxide anion at the carbonyl carbon atom to form hemiacetal oxygen centered anion **C**, path i.

The diastereoselectivity of the reaction also does not favor the mechanism with the initial generation of oxazine carbocation **E** and its attack by hydroxyl (path iii). The process of nucleophilic addition with the formation of product **3** should occur with equal probabilities and lead to a mixture of two diastereomers, which is not observed experimentally.

The difference between this work and previous studies on the reactivity of pyridines[9] and quinolines[7] with 1-aryl-2-oxalylacetylenes is that the primary 1,3(4)-dipole of type **A** in the case of phenanthridine in the presence of water exhibits basic properties, *viz*. it is protonated with water, while the 1,3(4)-dipoles based on pyridine and quinoline, even in water, are intercepted by the second molecule of oxalylacetylene, acting as nucleophiles. Apparently, the presence of two condensed benzene rings stabilizes the positive charge at position 6 of the pyridine part of the molecule (like in benzyl cation), thus violating the conjugation with the vinyl carbanion, and increasing the basic properties of the latter. Calculations have also shown (see Online Supplementary Materials) that the relative stability of oxazinophenanthridine **3** is by 7.9 kcal mol^{-1} greater with respect to oxazinoquinoline derivative in terms of ΔG, while the C^6–O bond order is decreased from 0.35 to 0.33, respectively.

The systematic studies on the functionalization of the phenanthridine ring under the action of electron-deficient acylacetylenes and water earlier showed that the reaction proceeded in the presence of the base catalyst (20 mol% KOH) when heated in acetonitrile (55–60 °C) to furnish hemiaminal products, *N*-alkenyl-6-hydroxyphenanthridines,[10] like intermediate **D** in Scheme 3. Apparently, in oxazinophenanthridines **3** synthesized here, the ester group, due to the strong acceptor effect, contributes to the stabilization of the cyclic hemiacetal fragment, interfering the oxazine ring cleavage.

In conclusion, a one-pot diastereoselective catalyst- and metal-free approach to new pharmacological attractive hydroxy-1,3-oxazinophenanthridines *via* three-component reaction between phenanthridine, 1-aryl-2-oxalylacetylenes and water has been developed. This approach extents the arsenal of diastereoselective reactions in organic synthesis.[11] According to the data of quantum-chemical calculations, the mechanism of the reaction includes the hydroxyl anion attack at the carbonyl moiety of the 1,3(4)-dipole previously protonated with water, followed by the closure of the oxazine ring. The differences between reactions of phenanthridine and quinoline with aryloxalylacetylenes in water are also explained by calculations, which show the greater relative stability of hydroxy-substituted oxazinophenanthridine with respect to oxazinoquinoline derivative in terms of ΔG, and the higher C^6–O bond order in the former, indicating instability of the latter.

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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.2022.07.004.

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