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Mendeleev Commun., 2020, **30**, 12–14

Mendeleev Communications

Cyanoacetylene-driven base catalyzed synthesis of dihydropyrimidophenanthridinones from phenanthridine and water

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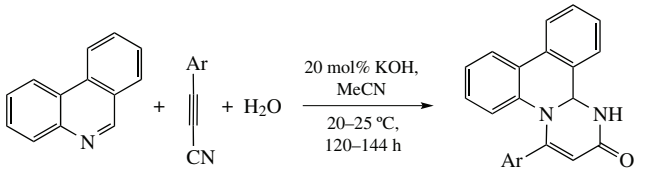
DOI: 10.1016/j.mencom.2020.01.004

3-Arylpropynenitriles are readily annulated with phenanthridine in the KOH/H_2O/MeCN system at room temperature to afford 4-aryl-1,13b-dihydropyrimido[1,2-*f*]phenanthridin-2-ones. The moderate yield of the products can be rationalized by the anionic oligomerization of an intermediate zwitterion adduct of the reactants. The reaction represents a single-stage access to a new family of pharmaceutically prospective compounds.

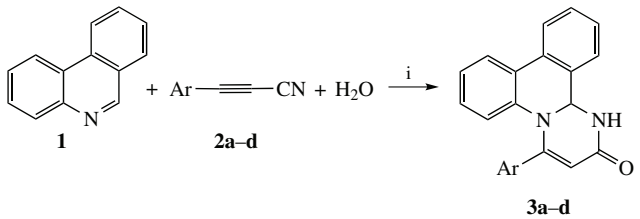


Ar = H, Me, Et, OEt

Keywords: alkynes, annulation, nucleophilic addition, phenanthridine, zwitterions.

Phenanthridine derivatives have attracted considerable attention[1] due to their broad spectrum of biological activity and the presence of this scaffold in a variety of natural alkaloids.[2–5] Important representatives in this class are ethidium salts used as DNA intercalators[6] as well as fagaronine[7] and trispheridine, which exert excellent antiproliferative effects on both human and mouse cell lines.[8] On the other hand, pyrimidinone as a δ-lactam moiety is a key pharmacophore scaffold in a number of commercially important drugs for the treatment of HIV (Raltegravir),[9] erectile dysfunction (Viagra, Udenafil)[10] and herpes (Aciclovir).[11] Therefore, the synthesis of molecular ensembles containing both these structural motifs represents a challenge for organic and medicinal chemistry. Noteworthy, pyrimidophenanthridinone tetracyclic moiety is the important structural part of the alkaloid jadomycine N.[12]

An approach to the functionalized tetracyclic phenanthridine-tailored systems is the annulation of phenanthridine with acetylenecarboxylates and a third component. This allowed one to synthesize phenanthridines annulated with pyrrole,[13–15] pyridine[16] and oxazine[17–20] cycles. The annulation of phenanthridine with cyanoacetylenic alcohols opened a straightforward route to cyanomethylidene-containing oxazolophenanthridines (60–74%, based on phenanthridine consumed).[21] In the last decades, such electron-deficient acetylenes as substituted 3-arylpropynenitriles attract a special attention due to their availability,[22,23] extraordinary electrophilicity[24,25] and high multifaceted synthetic potential of the cyano substituent.[26–28]



1 **2a–d** **3a–d**

3	Ar	Time/h	Isolated yield (%)	Yield based on consumed **1** (%)
a	Ph	120	33	68
b	4-MeC_6H_4	144	33	62
c	4-EtC_6H_4	144	12	50
d	4-$EtOC_6H_4$	144	26	72

Scheme 1 *Reagents and conditions*: i, **1** (1 equiv.), **2** (1 equiv.), H_2O (5 equiv.), MeCN, 20–25 °C.

In this work, we propose a simple straightforward approach to pyrimidophenanthridinones **3**, based on activation of phenanthridine **1** by 3-arylpropynenitriles **2** followed by the tandem transformations involving cyano function and hydroxide anions (Scheme 1).†

The selected experiments demonstrated the relationship between product yield and the reaction conditions exemplified by phenanthridine **1** and 3-phenylpropynenitrile **2a** (Table 1).

The reaction was carried out in KOH/H_2O/MeCN system at room temperature for 120 h. The reaction progress was followed by IR spectroscopy and TLC. In the absence of KOH, no reaction occurred (Table 1, entry 1). The optimal alkali loading which provided 33 and 32% yield of pyrimidophenanthridinone **3a** was 20 mol% (entries 3, 4). At elevated temperature (55–60 °C), the reaction expectedly proceeded faster (5 h instead of 120 h), however, the yield of the target product **3a** considerably dropped to 15% (entry 6). Upon 5-fold dilution of the reaction mixture with MeCN, along with the target compound **3a**, a product of composition **1**:**2a**:H_2O = 1:3:1, namely compound **4**, was

† *4-Phenyl-1,13b-dihydropyrimido[1,2-f]phenanthridin-2-one* **3a**. A mixture of phenanthridine **1** (90 mg, 0.5 mmol), acetylene derivative **2a** (64 mg, 0.5 mmol), H_2O (45 mg, 2.5 mmol) and KOH (6 mg, 20 mol%) in MeCN (0.1 ml) was stirred at 20–25 °C for 120 h. The solvents were removed *in vacuo*, the subsequent column chromatography afforded pyrimidophenanthridin-2-one **3a** (53 mg, 33%) as a light-beige powder, mp 251–253 °C (EtOH). Starting phenanthridine **1** (47 mg, conversion 48%) was recovered. For details and syntheses of compounds **3b–d**, see Online Supplementary Materials.

Table 1 Relationship between the yield of product **3a** and the reaction conditions.[a]

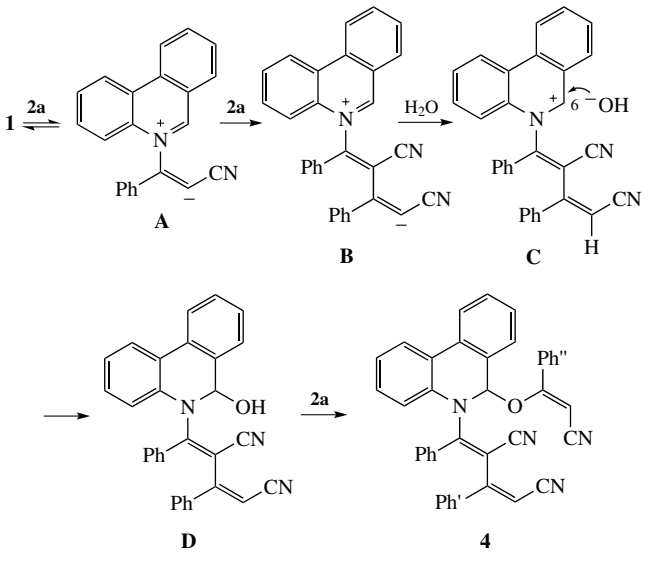
Entry	KOH (mol%)	Conversion of **1** (%)	Conversion of **2a** (%)	Yield of **3a** (%)[b]
1	none	5	10	0
2	10	15	30	traces
3	20	48	100	33 (68)
4	20[c]	71	100	32 (45)
5	30	44	100	25 (57)
6[d]	20	41	100	15 (37)
7[e]	20	31	100	14[f] (45)
8[g]	20	100	58	38[h]

[a] **1** (0.5 mmol), **2a** (0.5 mmol), H_2O (2.5 mmol), MeCN (0.1 ml), 20–25 °C, 120 h. [b] Yields in parentheses are based on phenanthridine **1** consumed. [c] NaOH was used. [d] 55–60 °C, 5 h. [e] 0.5 ml MeCN. [f] 1 : 3 : 1 adduct **4** was also isolated in 12% yield. [g] **2a** (1.5 mmol). [h] Phenanthridine-terminated oligoenes were also isolated.

isolated in 12% yield (entry 7, Scheme 2). To increase the conversion of phenanthridine **1**, we used the threefold molar excess of acetylene **2a** that provided the complete conversion of the former, but the yield was improved by 5% only. Instead, a mixture of phenanthridine terminated oligoenes of the type **4** was isolated (entry 8), their composition was not investigated in detail.

For the assembly of the pyrimidophenanthridinone scaffold, the following reaction conditions can be accepted as optimal: molar ratio **1**:**2**:H_2O = 1 : 1 : 5, 20 mol% KOH, 20–25 °C. These conditions were employed for reaction of other 3-arylpropynenitriles **2b–d** with phenanthridine **1** (see Scheme 1).† The yields of products **3** based on the phenanthridine **1** consumed were 50–72%. The modest yields (12–33%) of the products **3** and incomplete conversion of phenanthridine **1** originate from the anionic oligomerization of the intermediates and starting propynenitriles **2**. This is supported by the formation of 1 : 3 : 1 adduct **4** when excess of acetylene **2a** has been applied (see Table 1, entry 7).

The stereoselective formation of the multi-functionalized *N*-(*Z*,*Z*)-butadienyl-6-(*Z*)-ethenyloxy derivative of phenanthridine **4** can be rationalized according to Scheme 2. The intermediate 1,3-dipolar complex **A** of phenanthridine **1** with 3-phenylprop-2-ynenitrile **2a** having *Z*-configuration is captured by the second molecule of compound **2a** to give *Z*-configured carboanion **B**. Its carbanionic center is then neutralized by proton from water, and the subsequent attack of the released hydroxide anion at the positively charged 6-position of the phenanthridine ring in intermediate **C** affords hydroxy derivative **D**. This intermediate is vinylated by the third molecule of acetylene **2a** realizing a stereoselective nucleophilic addition at the triple bond and thereby completing the formation of compound **4**.‡



Scheme 2

A similar carbanionic oligoene chain prolongation (**A** → **C**) was previously observed for the catalyst-free reaction of N-substituted imidazoles with 3-phenylpropynenitrile.[29]

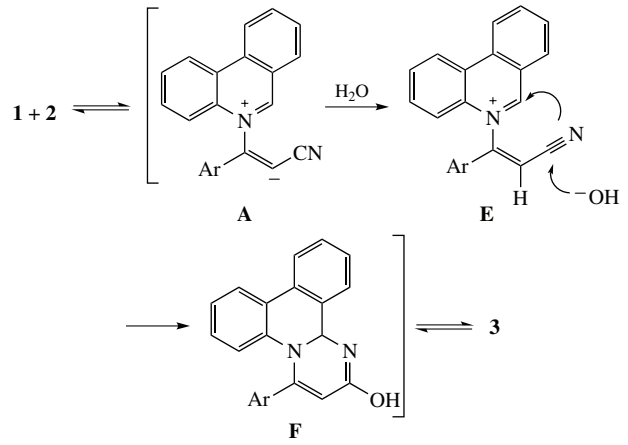
The structure of products **3a–d** and **4** was established using ^{1}H, ^{13}C NMR and IR spectroscopy (see Online Supplementary Materials).

Apparently, the assembly of pyrimidophenanthridinones **3** begins with activation (polarization) of the phenanthridine ring **1** upon its complexation with 3-phenylpropynenitrile **2** to produce 1,3-dipole **A** (Scheme 3). The latter is neutralized at its carbanionic center by a water molecule to afford *N*-alkenylphenanthridinium hydroxide **E**. Next, hydroxide anion attacks the nitrile group. The nitrogen-centered anionic center thus generated is attached to the positively charged 6-position of the phenanthridine ring, thus closing the pyrimidine cycle. Finally, pyrimidophenanthridinol **F** tautomerizes to pyrimidophenanthridinone **3** (see Scheme 3).

The catalytic role of KOH can also be understood in terms of Schemes 2 and 3, which include as an important step the hydroxide anion attack at the C(6) position and CN bond.

3-Arylpropynenitriles activate phenanthridine ring and thereby trigger the tandem transformation involving cyano function and hydroxide anions to deliver highly functionalized dihydropyrimido[1,2-*f*]phenanthridin-2-ones. The modest yield of the annulated product is caused by the oligomerization of phenanthridine/cyanoacetylene intermediates leading to stereoselective formation of multi-functionalized *N*-(*Z*,*Z*)-butadienyl-6-(*Z*)-ethenyloxy derivative of phenanthridine. Thus, a new approach to a novel family of pharmaceutically prospective compounds has been elaborated.

This work was supported by the Russian Foundation for Basic Research (grant no. 18-03-00762-a). The main results were obtained using the equipment of Baikal Analytical Center of



Scheme 3

‡ *(2Z,4Z)-4-({6-[(Z)-2-cyano-1-phenylvinyloxy]phenanthridin-5(6H)-yl}[phenyl]methylidene)-3-phenylpent-2-enedinitrile* **4**. Reaction of phenanthridine **1** (90 mg, 0.5 mmol), acetylene **2a** (64 mg, 0.5 mmol), H_2O (45 mg, 2.5 mmol), KOH (6 mg, 20 mol%) in MeCN (0.5 ml) at 20–25 °C for 120 h, along with pyrimidophenanthridin-2-one **3a** (23 mg, 14%), affords product **4** (12 mg, 12%) as a light-beige powder, mp 148–149 °C (EtOH). Starting phenanthridine **1** (61 mg, conversion 31%) was also recovered. For details, see Online Supplementary Materials.

Collective Using, Siberian Branch of the Russian Academy of Sciences.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2020.01.004.

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Received: 14th June 2019; Com. 19/5950