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Strategic Approach to 8-Azacoumarins

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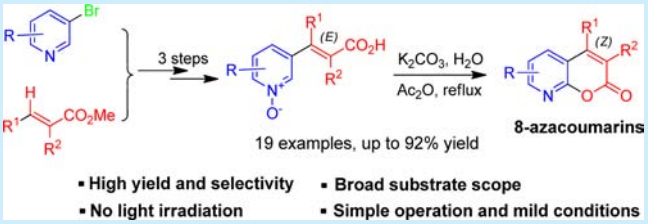
Supporting Information

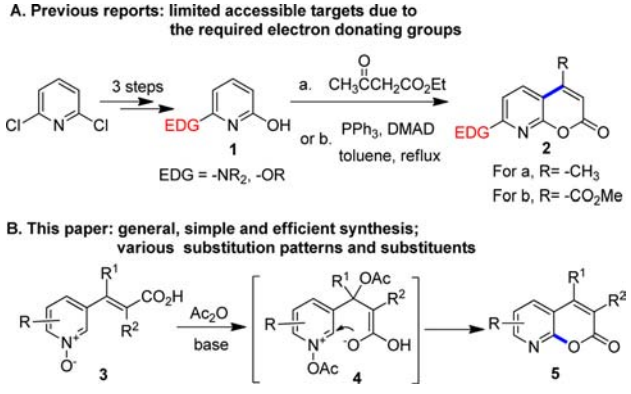
ABSTRACT: 8-Azacoumarins have emerged as a promising class of compounds but are rarely explored due to challenging access. A novel, general, and practical method is provided for this class of compounds. The key lactonization step employs *trans*-acrylic acid attached pyridine *N*-oxides as the starting material, with acetic anhydride as both the activation agent and the solvent. Multiple transformations were involved in this reaction, including conjugate addition, nucleophilic aromatic substitution, and elimination. These studies provide the basis for access to 8-azacoumarins, enabling future work including the discovery and development of novel coumarin-type drugs, fluorescent probes, photolabile protecting groups, and other active molecules.



Natural and synthetic coumarins (benzo-α-pyrone) are some of the most promising targets due to their wide range of biological properties, including anticancer,[1] anticoagulant,[2] anti-HIV,[3] anti-inflammatory,[4] and antibacterial[5] activities. Furthermore, coumarins have been widely applied in fluorescent probes[6] and caging chemistry[7] recently. However, the application of coumarins in both medicinal and photochemistry is restricted due to their low aqueous solubility and insufficient potency. One of the most successful strategies to increase the hydrophilicity and produce similar biological properties relies on isostere replacement of a phenyl with a pyridyl, leading to 8-azacoumarins. Compared to other strategies, this strategy has the advantage that no additional hydrophilic functionalities need to be introduced to the core structure. Indeed, the successful applications of this strategy have been reported.[8] Several promising 8-azacoumarin-type photolabile protecting groups have been prepared and characterized by Tamamura et al.[8] Those azacoumarins show dramatically enhanced water solubility and photolytic efficiency compared to that of their coumarin analogues.

The substitution of a phenyl by a pyridyl has been used not only to improve hydrophilicity but also to improve metabolic stability.[9] Therefore, 8-azacoumarins have emerged as a promising class of compounds. However, not enough study of azacoumarins has been performed, most likely because access to this scaffold is challenging. According to the few reported approaches, this scaffold was prepared by electrophilic aromatic substitution reactions (S_EAr), using 2-hydroxyl-6-EDG (electron-donating groups) substituted pyridines as the starting material under acidic[10] or PPh_3 activation conditions (Scheme 1A).[8,11] Few 8-azacoumarins, however, were prepared by this method. Due to the inherent poor nucleophilicity of pyridines, this method is only suitable for those electron-rich pyridines, resulting in a limited number of accessible targets.

Scheme 1. Synthetic Approaches to 8-Azacoumarins



To address the problem, we sought to design a new method for the synthesis of 8-azacoumarins (**5**) that would greatly extend the substrate scope. Instead of forming a carbon−carbon bond by S_EAr, the scaffold was constructed by forming a carbon−oxygen bond through nucleophilic aromatic substitution reactions (S_NAr). The method is based on a novel synthetic strategy by which the easily accessible pyridine *N*-oxides[12] (**3**) served as the key precursor (Scheme 1B). Due to the inherent enhanced electrophilic character of the C2 position in **3**, it is attacked by the carboxyl oxygen anion under Ac_2O activation conditions, leading to the desired azacoumarin products **5**. To the best of our knowledge, this general approach based on *N*-oxide chemistry is unprecedented.

The synthesis of pyridine *N*-oxides **3** was completed in three steps (Scheme 2).[13] The Heck reaction[14] of commercially

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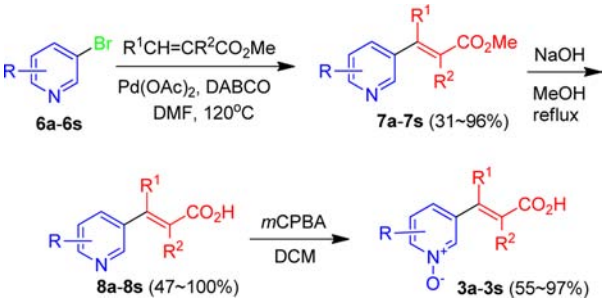
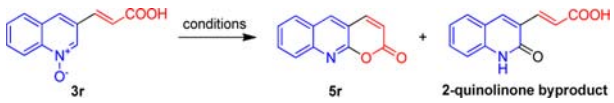
Scheme 2. Synthesis of the *N*-Oxide Precursors



available 3-bromopyridine derivatives **6** with methyl acrylate derivatives provided the *E*-isomer **7** stereoselectively,[15] which was hydrolyzed and chemoselectively oxidized to afford **3** in good yields.

The lactonization reaction of quinoline *N*-oxide (**3r**) was selected as the model reaction for the optimization of the reaction condition (Table 1). Based on our previous findings,[16]

Table 1. Reaction Optimization for the Lactonization[a]



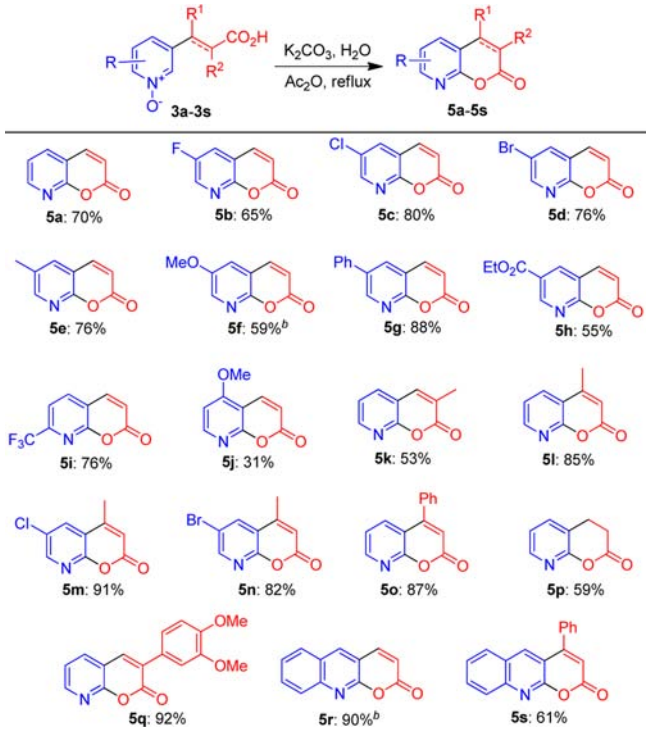
entry	additive	base	solvent	*t* (°C)	yield (%)
1	PyBroP	NaOAc	DCE	reflux	n/a
2[b]			Ac_2O	reflux	<10
3[b]		NaOAc	Ac_2O	120	15
4		NaOAc	Ac_2O	120	51
5[c]		NaOAc	Ac_2O	120	n/a
6[b]		Et_3N	Ac_2O	120	61
7		Na_2CO_3	Ac_2O	120	41
8[b]		K_2CO_3	Ac_2O	reflux	61
9[b,d]		K_2CO_3	Ac_2O	120	65
10		K_2CO_3	Ac_2O	120	90
11		K_2CO_3	TFAA	reflux	n/a

[a]Unless otherwise noted, all reactions were conducted at 0.20 M concentration with *N*-oxide (150 mg, 1.0 equiv), base (3.0 equiv), and H_2O (7.0 equiv). [b]No water was added. [c]14.0 equiv of H_2O was added. [d]Reaction run at 0.10 M.

2-quinolinone product should be formed under PyBrop (bromotripyrrolidinophosphonium hexafluorophosphate) activation conditions. This condition was first chosen, as the 2-quinolinone product might be cyclized in situ to afford the desired product. However, several spots, including the 2-quinolinone byproduct, were detected (entry 1, Table 1). Gratifyingly, the desired product was detected utilizing Ac_2O as both the activating reagent and the solvent under reflux conditions (entry 2). It is found that both base and water are critical for this transformation. The yield of the reaction was improved with sodium acetate (entry 3), and dramatic improvement was observed when water was added to the reaction mixture (51% yield, entry 4). However, an excess amount of water was detrimental to the product yield (entry 5). A careful screening of base/quantity of water (entries 6−10) led to the identification of the optimum condition for this reaction (90% yield, entry 10). It is worth noting that the double bond geometry is converted from *trans* to *cis* in this transformation without any photoirradiation.[17] Ac_2O seems to be the only appropriate solvent as no product could be detected using trifluoroacetic anhydride (TFAA) as the solvent (entry 11).

With the optimized conditions in hand, the scope of the lactonization with a range of pyridine and quinoline derivatives was examined (Scheme 3).[18] We were pleased to observe modest

Scheme 3. Substrate Scope for the Lactonization of Various Heterocyclic *N*-Oxides[a]



[a]Unless otherwise noted, all reactions were conducted at 0.20 M concentration with *N*-oxide (1.0 equiv), K_2CO_3 (3.0 equiv), and H_2O (7.0 equiv) in Ac_2O at reflux. [b]Reaction run at 120 °C.

to excellent yields in all cases examined, with excellent regioselectivity (C2 vs C4). In none of these instances did we observe the C4-lactonized regioisomeric products. There is no general conclusion about the effects of electron density on pyridine/quinoline *N*-oxide reactivity. Those electron-rich substrates afford yields similar to those of electron-poor substrates (**3f** vs **3h**). Remarkably, those examples containing a carboxylic ester (**3h**) or reactive halide (**3b**−**3d**, **3m**, **3n**) were also effective in the transformation, suggesting a general compatibility with base-sensitive functionality. It is worth noting that **5p** was synthesized successfully, indicating that the carbon−carbon double bond of the substrate is not essential for this lactonization reaction.

The formation of azacoumarins (**5**) from *N*-oxides (**3**) in Ac_2O under basic conditions implies a complex reaction manifold. Remarkably, it seems that the double bond geometry was converted from *trans* to *cis* directly. Two possible reaction pathways leading to **5** are depicted in Scheme 4. In pathway 1, the activated pyridine acetate **9** is formed in the first step. Subsequent conjugate addition of acetate anion or hydroxide furnishes isomeric intermediates **10** and **10′**. Nucleophilic attack of the carboxyl oxygen anion to the C2 position of **10** affords lactone **11**. Finally, rearomatization of **11** under basic conditions followed by elimination affords **5**. Water could improve the yield of the reaction probably by dissolving more K_2CO_3 in the

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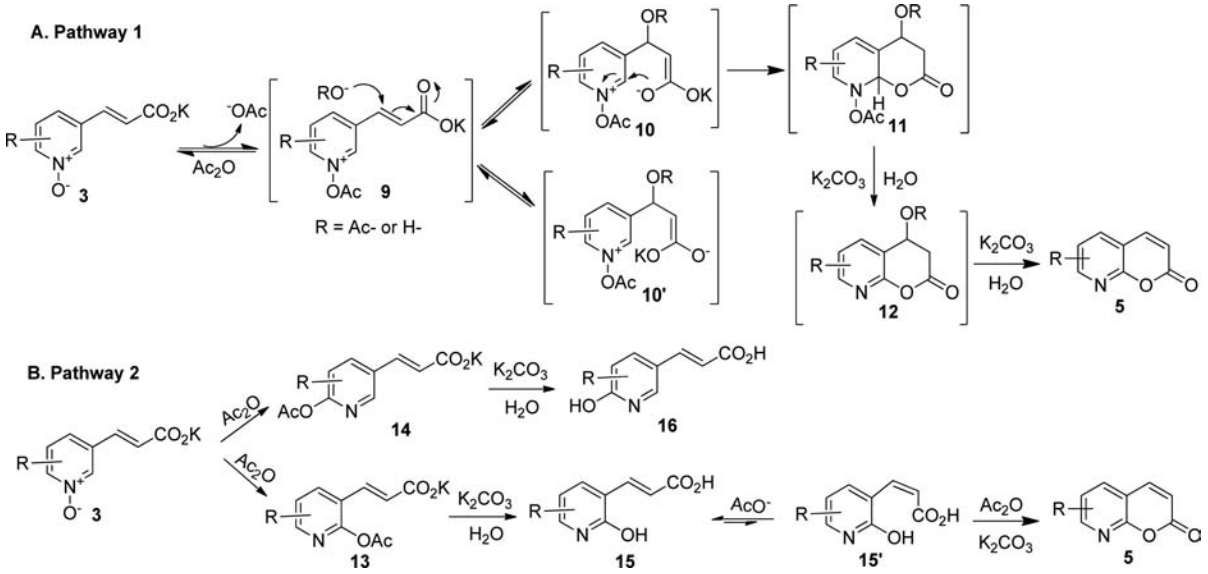
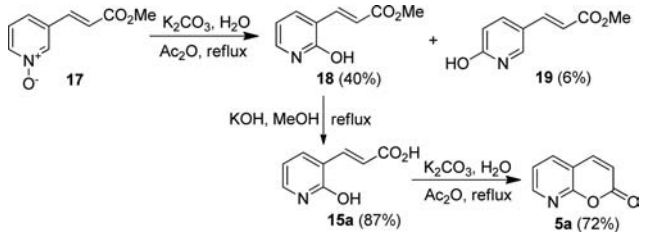
Scheme 4. Proposed Reaction Mechanism



reaction media. In pathway 2, based on the known *N*-oxide chemistry,[19] intermediate **13** and regioisomer **14** would be formed irreversibly in refluxing Ac_2O. Subsequent basic hydrolysis produces 6-pyridone byproduct (**16**) and 2-pyridone intermediate **15**, which would be converted to the *cis* isomer **15′** under the reversible acetate anion conjugate addition conditions. Finally, lactonization of **15′** by Ac_2O activation of the carboxylic acid group offers **5**.

Pathway 1 is more reasonable than pathway 2. First, no 6-pyridone byproduct **16a** (R = H) was detected in the reaction media. Regioisomeric products (2- and 6-pyridones) are usually formed in Ac_2O-mediated *N*-oxide rearrangement reactions.[19] Indeed, both **18** and **19** were isolated (6.4:1 ratio) when **17**, the methyl ester analogue of **3a** (R = H), was subjected to the lactonization reaction conditions (Scheme 5). Second, it is

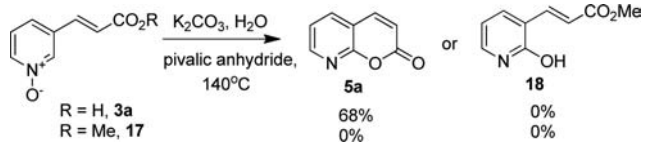
Scheme 5. Synthesis of Pyridone Intermediates



rational to assume that the yield for **15a** from **3a** is similar to the yield (40%) for **18** from **17**. If the reaction proceeds via pathway 2, the yield for **5a** from **3a** should be lower than 40% as the formation of **5a** involves the irreversible formation of **15a** in the first step. Therefore, pathway 2 is unlikely to occur as the yield (70%) for **5a** is much higher than the yield for **15a**. Subsequent hydrolysis of **18** led to **15a**, which was converted to **5a** as expected under the lactonization reaction conditions (Scheme 5).

Pathway 1 was further evidenced by reactions in Scheme 6. When the solvent was switched from Ac_2O to pivalic anhydride, **5a** was obtained in 68% yield, whereas no reaction was detected with **17**. Pathway 2 is unlikely to happen due to the lower nucleophilicity of pivalic anhydride. Considering that the yield

Scheme 6. Lactonization Reactions in Pivalic Anhydride



for **5a** was similar to that in Ac_2O (68% vs 70%), the lactonization reaction should proceed via pathway 1.

Several azacoumarins were chosen to evaluate their aqueous solubility and fluorescent properties. As expected, **5e** showed hydrophilicity higher than that of 6-Me-coumarin (Table 2). The

Table 2. Hydrophilic Properties of 6-Me-Coumarin and 5e

compd	log P^a	$C_s{}^b$ (mM)
6-Me-coumarin	2.31	2.6
5e	1.69	6.2

[a]Calculated by ChemBioDraw Ultra 12.0. [b]Concentration at saturation in PBS (0.1% DMSO).

log *P* value of **5e** was lower, and the C_s value was 2-fold higher than that of 6-Me-coumarin. Fluorescent properties of **5d**, **5e**, and the coumarin analogues were measured in PBS (Table 3). To

Table 3. Fluorescent Properties of Compounds 5d and 5e

compd	$\lambda_{ex}{}^a$ (nm)	$\lambda_{em}{}^b$ (nm)	Φ^c
5d[d]	367	441	0.122
5e[d]	368	435	0.070

[a]Excitation maxima. [b]Emission maxima. [c]Quantum yields were calculated by using quinine in 0.1 N H_2SO_4 (Φ = 0.577) as the standard. [d]100 μM in PBS.

our delight, both **5d** and **5e** exhibited fluorescence, characterized by large Stokes shifts, whereas no fluorescence was detected for 6-Br-coumarin or 6-Me-coumarin. These preliminary data indicate that 8-azacoumarins are a promising class of fluorescent probes.

In conclusion, we have presented a facile and general synthesis of 8-azacoumarins, which have emerged as a promising class of

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compounds but are rarely explored. Starting from commercially available 3-bromopyridine derivatives, most target compounds were prepared in four consecutive steps in modest to excellent yields. Multiple transformations were involved in the key lactonization reaction, including conjugate addition, S_NAr, and elimination. Notably, a compound library of 8-azacoumarins, readily accessible by this procedure, would be valuable resources in efforts to develop molecules with potential applications in medicinal chemistry. This is currently under study in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03771.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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