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Versatile acenaphtho[1,2-*b*]pyrrol-carbonitriles as a new family of heterocycles: diverse S_NAr^H reactions, cytotoxicity and spectral behavior

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Abstract—The diverse reactivity of highly electron-deficient 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile **1** is attractive for the preparation of derivatives bearing different substituents via S_NAr^H reaction with N, O, S nucleophiles. These derivatives were versatile, possessing potential antitumor activities and displaying tunable fluorescence spectral behavior.

1. Introduction

Heterocycles are important constituents, which commonly exist in biologically active natural products and synthetic compounds of medicinal interest.[1] It is an efficient method to develop versatile heterocyclic precursors or leading compounds that can be diversely and conveniently functionalized to access large amounts of derivatives for pharmacological and cytotoxic investigations as well as for SAR (structure–activity relationship) establishment.[2] Thus, it is not surprising that novel heterocyclic families have been receiving special attention in drug discoveries.

On the other hand, many electron-deficient polycyclic chromophoric systems[3] have been demonstrated to play an important role in some valuable antitumor agents, such as the anthraquinone ring system in daunomycin, mitoxantron, and doxorubicin, naphthalimide in amonafide and acridine in DACA (Fig. 1).[3–6] Thus, in the current search for potential antitumor agents, a majority of attention has been devoted to the discovery of novel electron-deficient heterocycles, which can be easily derived or functionalized.

Among the multitude of reported organic heterocyclic compounds, acenaphtho-heterocycles have been once neglected. Less attention has been focused on the synthesis and functionalization of acenaphtho-heterocycles.[7] Recently, we have reported a new acenaphtho-heterocycle precursor **1**, 8-oxo-8*H*-acenaphtho[1,2-*b*]pyrrol-9-carbonitrile, characteristic of a flat and highly electron-deficient heteroaromatic system. Some S_NAr^H reaction could easily occur between **1** and primary aliphatic amines in very mild conditions. Meanwhile, amino derivatives of **1** were typical intramolecular charge transfer (ICT) fluorophores.[8]

As a novel electron-deficient heterocycle, its derivation and potential is prospective. Thus, we further synthesized a variety of derivatives mainly with basic amino chains and expected that these compounds might possess promising bioactivities. Meanwhile, we also anticipated that the introduction of nitrogen, oxygen, sulfur nucleophiles with different electron-donating ability might give birth to a diversity of spectral behaviors.

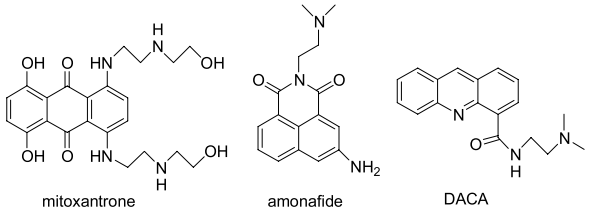

Figure 1. Structures of some available chromophores as antitumor agents.

Keywords: S_NAr^H reaction; Nucleophiles; Acenaphtho-heterocycles.
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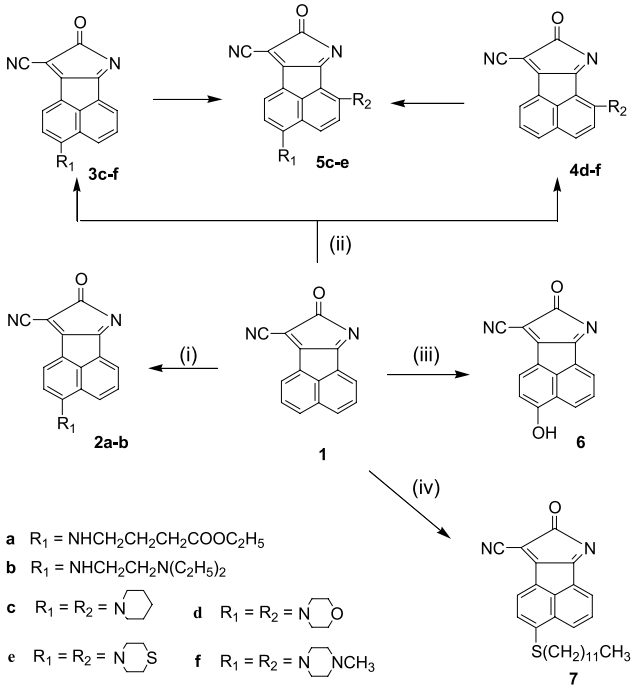
2. Results and discussion

2.1. Chemistry

Precursor **1** was prepared according to our previous publication.[8] Compounds **2–5** were synthesized according to Scheme 1. 3-Substituted products **2a–b** were formed as the sole product from the reaction of **1** with excess primary aliphatic amines at room temperature. Different results were observed in the reaction of **1** with alicyclic secondary amines under the same conditions. Besides 3-substituted products **3c–f**, 6-substituted products **4d–f** and 3,6-disubstituted products **5c–e** were also obtained. The formation of **4d–f** and **5c–e** is beyond what we had expected. Given adequate time, mono-substituted products **3c–f** and **4d–f** could be totally converted into 3,6-disubstituted products. Table 1 displays the ratio of 3-substituted to 6-substituted products.

The formation of 6-substituted isomer of **3c** was very slow and it was quickly converted into disubstituted product **5c**, thus the isomer could not be obtained. Disubstituted product of **3f** and **4f** was unstable and could not be obtained either.

The distinction between alicyclic secondary and primary amines is possibly attributed to steric hindrance from *peri*-hydrogen. Generally, nucleophilic amines preferentially attack the most electron-deficient carbon at 3-position, namely *peri*-position of naphthalene. Unlike primary aliphatic amine, when alicyclic secondary amine attacks the carbon at 3-position, it bears steric hindrance from another *peri*-hydrogen (namely 4-position). As a result, sub-electron-deficient carbon at 6-position becomes a competing



Scheme 1. Synthesis and yield: (i) 4 equiv corresponding primary amines, CH_3CN, rt, 1.0–2.0 h (**2a** 45%, **2b** 42% yield); (ii) 4–6 equiv corresponding secondary amines, CH_3CN, rt, 1.0–12 h (**3c** 49%, **3d** 30%, **3e** 35%, **3f** 30%, **4d** 18%, **4e** 12%, **4f** 16%, **5c** 48%, **5d** 45%, **5e** 45%, yield); (iii) 0.2 equiv K_2CO_3, H_2O, DMSO, rt, 1.0 h (**6** 38% yield); (iv) $CH_3(CH_2)_{11}SH$, reflux, 72 h (**7** 42% yield).

Table 1. Ratio of 3-substituted to 6-substituted products

Entry	Nucleophiles	Yields of **3** and **4** (%)	Ratio of **3** to **4**[a]
1	Morpholine	48 (**3d** and **4d**)	30:18
2	Thiomorpholine	47 (**3e** and **4e**)	35:12
3	4-Methyl-piperazine	46 (**3f** and **4f**)	30:16

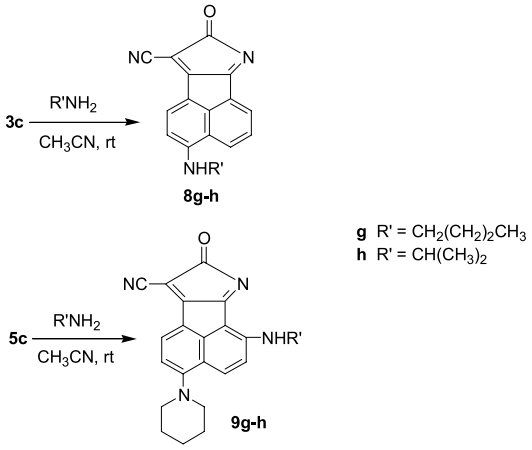
[a] The ratio was calculated according to isolated yields.

reactive site. Thus, for alicyclic secondary amine, 6-substituted and 3,6-disubstituted products are obtained. But for primary aliphatic amines, due to the absence of steric hindrance from *peri*-hydrogen, 3-carbon is the most preferential reactive site. Moreover, once the 3-substituted products of primary amines are formed, the hydrogen on nitrogen of amino substituents possibly departs under excess of amines in reaction system and a nitrogen anion forms. Such strong electron-donating ability of nitrogen anion greatly decreases the electron-deficient features of the system and thus 3-substituted products could not be attacked by the second nucleophiles.

Interestingly, we further found that alicyclic secondary amino substituents of 3-substituted and 3,6-disubstituted products could be easily replaced by aliphatic primary amines to give **8g–h**[8] or **9g–h** with different amino substituents, respectively (Scheme 2). Thus, some di-substituted products with different amino groups could be obtained.

Here, there are four unusual characteristics for the S_NAr^H reaction concluded in this case: (1) there are two active sites for S_NAr^H reaction in one molecule;[9] (2) regioselectivities for S_NAr^H reaction depend on the nature of nucleophiles; (3) two hydrogen atoms in one aromatic conjugation system is simultaneously replaced;[9a] (4) mono-substituted derivatives could be transformed to other derivatives by nucleophilic substitution or further S_NAr^H reaction. Since few phenomena alike for S_NAr^H were reported, such reactions possibly provided some particular and precious examples.

In order to further extend reaction prospect of precursor **1**, reactions of hydroxyl group and *n*-dodecyl thiol with **1** were successfully carried out (Scheme 1). Similar to



Scheme 2. Reaction of alicyclic amino derivatives with primary aliphatic amines. Synthesis and yield: 3 equiv RNH_2, CH_3CN, rt, 1–2 h (**8g** 75% yield; **8h** 78% yield; **9g** 70% yield; **9h** 72% yield).