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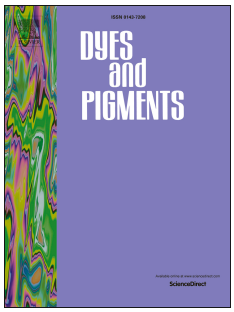

A mild acid-free one-pot reaction for synthesis of new phenanthridine dyes

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PII: S0143-7208(16)30358-8

DOI: 10.1016/j.dyepig.2016.07.041

Reference: DYPI 5375

To appear in: *Dyes and Pigments*

Received Date: 29 April 2016

Revised Date: 29 June 2016

Accepted Date: 31 July 2016

Please cite this article as: Qin X, Ding G, Luo Z, Wang Z, Zhang S, Li H, Gao F, A mild acid-free one-pot reaction for synthesis of new phenanthridine dyes, *Dyes and Pigments* (2016), doi: 10.1016/j.dyepig.2016.07.041.

A mild acid-free one-pot reaction for synthesis of new phenanthridine dyes

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Abstract

A series of new phenylphenanthridin dyes have been synthesized in the yields of 52~75% by a mild strategy in one-pot reaction. This is the first successful attempt to perform efficient soft acid-free reaction for phenanthridine ring construction. A large substrate scope was well demonstrated.

Keywords: Phenanthridine; Mild condition; Acid-free; One-pot reaction

1. Introduction

The phenanthridine family is widely found in medicinal chemistry and material science because of the biological activity and the presence in a variety of significant natural products and synthetic dye-stuffs [1]. So far, various synthetic strategies have been developed such as Bischler–Napieralski cyclization and Heck cyclization for the robust synthesis of phenanthridines [2]. However, the reported approaches remain the extreme difficulties including the multi-step routes, the limited substrate scopes, the use of metal catalysts or the weak generalities/limited diversities [3-5]. Therefore, there is a great demand to develop a simple, convenient protocol for expeditious synthesis of phenanthridine derivatives.

Phenanthridine could be accessed by Pictet-Spengler reaction under various reaction conditions such as Lewis acids [6], Bronsted acids [7], tandem threefold reaction condition [8]. In 2009, Youn and the coworker found the trifluoroacetic acid (TFA)-mediated coupling reaction of

2-arylanilines with arylaldehydes for the synthesis of phenanthridines [9]. Some efforts were devoted to improve the reaction conditions [10], however, strong acid catalysis was still required.

In this letter, we describe a new entry for the efficient synthesis of phenylphenanthridine dyes by an acid-free one-pot reaction at room temperature under air atmosphere. In this way, 2'-amino-1,1'-biphenyl-3-ol reacts with different benzaldehydes to yield the target phenylphenanthridine dyes. To the best of our knowledge, this is the first successful attempt to perform one-pot reaction at mild acid-free conditions for synthesis of phenanthridine dyes.

2. Results and discussion

The substrate **1** (shown in **Scheme 1**) was obtained by directly condensing 3-hydroxyphenylboronic acid and 2-bromo aniline via Suzuki reaction without protecting amino group in 90% isolated yield, which was used to undergo the reaction with benzaldehydes at room temperature under air atmosphere. The isolated major products and the yields of the above reactions are listed in **Table 1**. It is shown that phenanthridine dyes **2** are the major products with the yields from 52% to 75% produced by various benzaldehydes, while the condensed products **3** could be isolated as the minor products (~ 10%) only in some reactions, such as 2'-amino-1,1'-biphenyl-3-ol reacted with the 2-methoxybenzaldehyde (**Scheme 1(a)**).

Insert Scheme 1

Figure 1(a) gives the representative ^{1}H-NMR spectra of the phenanthridine dye **P1**. There are two separated peaks at 8.615 ppm of ^{1}H-NMR chemical shift, suggesting the absence of imino

group. The ^{1}H-NMR spectral integration area ratio of different hydrogen atoms is consistent with that of the numbers of hydrogen atoms.

Insert Figure 1

The molecular structures of the yielded phenanthridine dyes were further confirmed by single crystals obtained by the vapor diffusion of n-hexane into the solution in dichloromethane. The typical X-ray single crystal diffraction of **P1** shows the presence of phenanthridine ring, which is defined by the small torsion angle of C6-C7-C8-C13 (1.06°). Hence, the fused three aromatic rings (A, B, C) are almost in a plane. In addition, we notice a dihedral angle of 58.95° between the fused three aromatic rings (A, B, C) and aromatic ring D (**Figure 2(a)**).

Insert Figure 2

Table 1 shows that the main target phenanthridine dyes and the yields are not greatly varied by different electron-rich or -deficient benzaldehydes. The unhydrogenated phenanthridines are the major products while the aromatic aldehydes are substituted by electron-donating groups. In addition, the substituted positions of the groups in the benzaldehydes caused negligible effects on the reaction (**Table 1**, **P2**, **P3**, **P10**).

It is noticed that the hydrogenated phenanthridines become the predominant products as the benzaldehydes carry the strong electron-withdrawing groups such as nitro and cyano groups, while the unhydrogenated phenanthridines are the minor products (**Scheme 1(b), Table 1**). On the other hand, the hydrogenated phenanthridines can be converted into unhydrogenated

phenanthridines as the temperature was raised (under reflux), which indicates the presence of a large reaction energy barrier.

Insert Table 1

The chemical structures of the hydrogenated phenanthridines were identified by ^{1}H & ^{13}C-NMR spectra. As shown in **Figure 1(b)**, the ^{1}H-NMR chemical shifts of 5.565 ppm and 6.712 ppm in **P11** can be assigned to -NH- and its adjacent -CH- groups, respectively. X-ray single crystal diffraction of **P11** further confirms the structures of hydrogenated phenanthridines (**Figure 2(b)**).

It is found that the phenanthridine dyes could be produced by this reaction in a variety of organic solvents. However, a much longer reaction time (75 hr) was required in aprotic solvents such as benzene, tetrahydrofuran and acetonitrile, which only produced a dramatic low yields of phenanthridines (< 10%), and a higher yields of the main condensed products (60~75%).

As discussed, a shorter time (18 hr) and a higher yield of the reaction were found in alcoholic solvents, particularly in methanol and ethanol solvents. However, the phenanthridine dyes were obtained in lower yields in *n*-propanol and *n*-butyl alcohol solvents (30~40%). Furthermore, the yields of phenanthridine dyes reached ~30% as the reaction was performed in mixed solvents of methanol or ethanol and tetrahydrofuran (1:1, v:v) with a longer time (46 hr).

In addition, the reaction time could be reduced by the increase of the reaction temperature, while the yields of the phenanthridine dyes were not increased remarkably. It is further observed that the same reaction occurred under oxygen or argon atmosphere in ethanol or methanol. It is also found that the target phenanthridine dyes were produced as well in toluene containing

trifluoroacetic acid under the reflux for 2 hr.

Insert Scheme 2

In light of these experimental results, we propose a tentative mechanism for an acid free one-pot reaction using 3-hydroxybiphenyl-2-amine as the substrate (**Scheme 2**). Firstly, the amine and the aldehyde are easily condensed to yield the imine product, followed by the attack of the double bond to the protonated imine, and rearrangement occurred, towards cyclization leading to dihydrophenanthridines, which is followed by deprotonation and oxidation to yield the final phenanthridine dyes. It is worthy pointing out that the cyclization may also go through the different mechanisms, for instance, 6pi-electrocyclization with subsequent oxidation.

3. Conclusions

To be closing, we present an acid free one-pot reaction under the mild conditions for the efficient synthesis of a variety of phenanthridines. The molecular structures of the yielded phenanthridines were characterized by ^{1}H & ^{13}C NMR spectroscopy, MS, IR spectra as well as X-ray diffraction analyses. Further work is being performed in our laboratory to investigate the new interesting intriguing biological and optical activities of these dye molecules and will be reported in due course.

Supplementary date

The synthesis and characterization of the major products including NMR spectral data, IR spectral data, elementary analysis as well as high resolution mass spectral data (HRMS) of the products (**P1~P13**) are provide in the **Supplementary date**, and the document is available free of charge from the website of this journal.

The supplementary crystallographic data for this work are contained in file numbered by 1472575-1472576, which are free available http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge crystallographic data center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033. The crystallographic data are also provided in the **Supplementary date**.

Acknowledgements

The authors greatly appreciate Chongqing Natural Science Foundation CSTC2012jjB50007 and CSTC2010BB0216. H. Li is grateful to the Postdoctoral Science Foundation of China for financial supporting (Grant No. 22012T50762 & 2011M501388). This work was also supported by the Graduate Student Innovation Foundation of Chongqing University (CDJX11131146).

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The captions of Figures 1~2

Figure 1 ^{1}H-NMR spectra of **P1** and **P11**

Figure 2 An ORTEP (30% thermalellipsoids) plot of **P1** and **P11** with the numbering

The captions of Schemes 1~2

Scheme 1 Synthesis of phenanthridine dyes with different electron donating or accepting substrates by one-pot reaction

Scheme 2 Postulated mechanism of a mild acid-free one-pot reaction

The caption of Table 1

Table 1 The one-pot synthesis results of phenanthridine dyes.[a]

Figures

Figure 1

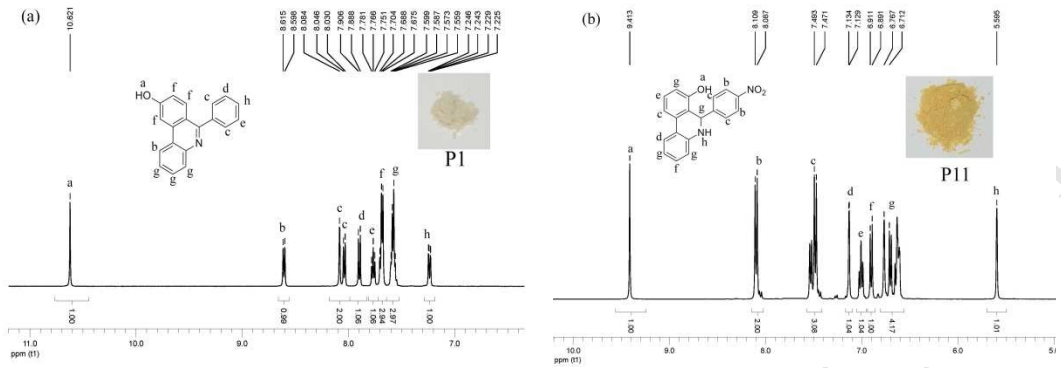
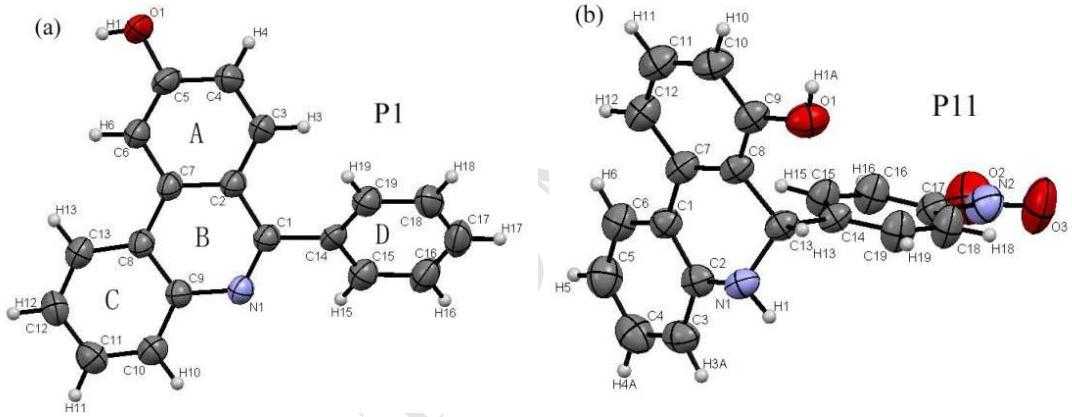


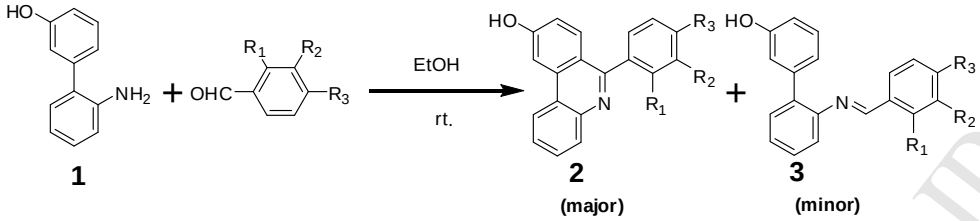
Figure 2



Schemes

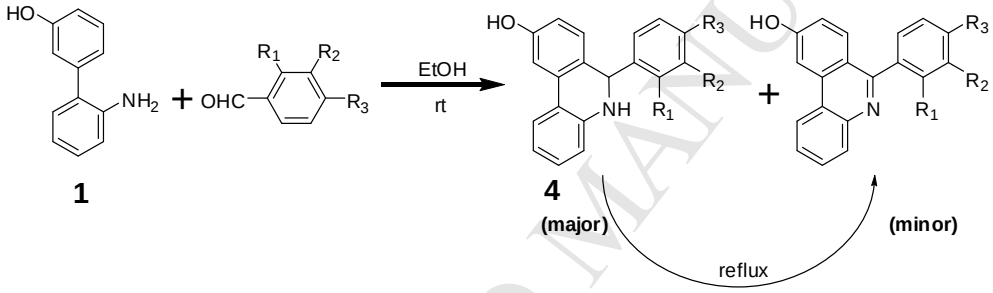
Scheme 1

(a)



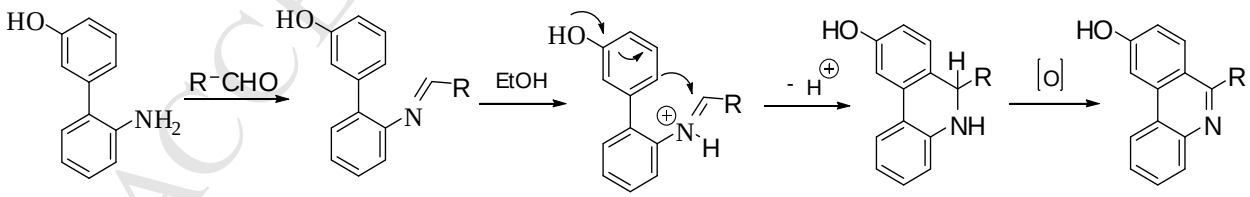
P1:R_1=R_2=R_3=-H
P2:R_1=R_2=-H, R_3=-OCH_3
P3:R_1=R_3=-H, R_2=-OCH_3
P4:R_1=-H, R_2=R_3=-OCH_3
P5:R_3=-H, R_1=R_2=-OCH_3
P6:R_1=R_2=-H, R_3=-$N(Me)_2$
P7:R_1=R_2=-H, R_3=-$N(Et)_2$
P8:R_1=R_2=-H, R_3=-F
P9:R_1=R_2=-H, R_3=-Cl
P10:R_2=R_3=-H, R_1=-OCH_3

(b)



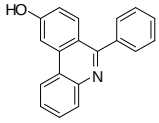
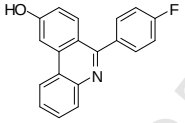
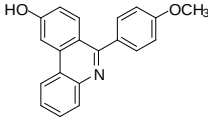
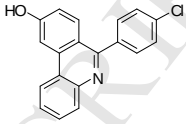
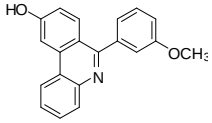
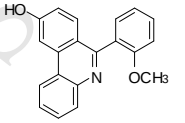
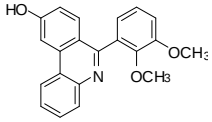
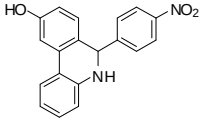
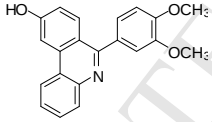
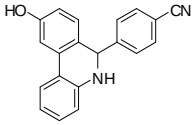
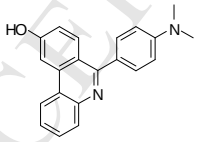
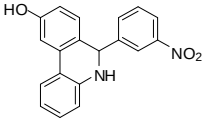
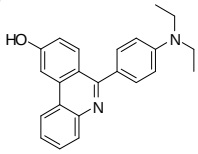
P11:R_1=R_2=-H, R_3=-NO_2
P12:R_1=R_2=-H, R_3=-CN
P13:R_1=R_3=-H, R_2=-NO_2

Scheme 2



Tables

Table 1

Entry	Aldehyde	Product	Yield(%)	Entry	Aldehyde	Product	Yield(%)
P1	PhCHO		75%	P8	4-FC_6H_4CHO		54%
P2	4-$MeOC_6H_4CHO$		70%	P9	4-ClC_6H_4CHO		52%
P3	3-$MeOC_6H_4CHO$		68%	P10	2-$MeOC_6H_4CHO$		65%
P4	2,3-$MeOC_6H_4CHO$		67%	P11	4-$NO_2C_6H_4CHO$		68%
P5	3,4-$MeOC_6H_4CHO$		72%	P12	4-CNC_6H_4CHO		55%
P6	4-$(Me)_2NC_6H_4CHO$		63%	P13	3-$NO_2C_6H_4CHO$		60%
P7	4-$(Et)_2NC_6H_4CHO$		62%				

[a] Performed under the experimental conditions: **1** (1 equiv.), aromatic aldehyde (1.05 equiv.) in ethanol at 25°C, 18 hr under air atmosphere.

Highlights

- The mild acid-free one-pot reaction strategy for efficient synthesis of phenanthridines dyes
- A large scope of the substrates well used for this approach
- The chemical structures of the yielded phenanthridines well identified by various characterizations
- The roles of alcoholic solvents well demonstrated by the experiments