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Facile cyclization of 2-arylethynyl aniline to 4(1*H*)-cinnolones: a new chemodosimeter for nitrite ions

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ABSTRACT

2-Arylethynyl anilines undergo very fast reaction (5 min) with nitrite ions in aqueous acidic media to produce 4(1H)-cinnolones which exhibit yellow color and UV absorbance at 391 nm. This reaction is irreversible and has been successfully tested for the detection of nitrite ions in water at ppm concentration. Thus, 2-phenylethynyl aniline serves as a chemodosimeter. An efficient and general method for the synthesis of 4(1H)-cinnolones has been developed based on this reaction.

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The nitrite contamination in food, beverages, and drinking water is of growing concern¹ as nitrite reacts with dietary components in the stomach to generate toxic and carcinogenic nitroso-amines.² Another potential danger of entry of nitrite ions in the blood stream is its capability to convert oxyhemoglobin into methemoglobin and thereby interfering with oxygen transport in the blood.³ As defined by US Environmental Protection Agency (EPA) the maximum content of nitrite ions in drinking water should not exceed 1 ppm.⁴ Thus, even a trace amount of nitrite is harmful to human health.

Various methods have been developed to detect the presence of nitrite ions, based on organic chromophores,⁵ florophores,⁶ and ion chromatography⁷ among others.⁸ However, these methods usually require sophisticated and expensive instruments and thus restrict their use in rural areas. Thus an easy-to-use colorimetric sensor is more helpful for an on-the-spot survey. Recently, a noncross-linking colorimetric nitrite sensor using 4-aminothiophenol modified gold nanorods^{9a} and gold nanoparticle probes^{9b} have been reported. We report herein a new chemodosimeter, 2-arylethynyl aniline which undergoes fast reaction with nitrite ions to form 4(1H)-cinnolones displaying a yellow color (Scheme 1). Although application of chemodosimeter in sensing other ions such as CN⁻ and F⁻ is common¹⁰ similar use for the nitrite ions is rare.

In a typical experiment,¹¹ 2-phenylethynyl aniline was treated with $NaNO_2/HCl(2 N)$ at 0–5 °C to produce 3-phenyl-4(1*H*)-cinnolones with an immediate change of color to yellow from colorless.

The change of color is clearly visible up to 10 ppm concentration of nitrite ions.



Scheme 1. Reaction of nitrite with 2-arylethynyl aniline.



Figure 1. UV spectroscopic studies for nitrite sensing (L = 2-phenylethynyl aniline, 10^{-4} M in H₂O).





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Figure 2. Fluorescence studies for nitrite sensing (L = 6-methoxy-2-naphthylethy-nyl aniline, 10^{-6} M in H₂O).

The end products, 3-phenyl-4(1*H*)-cinnolones show a characteristic UV absorption at 391 nm (Fig. 1). We next turned our attention on fluorescence studies. It was found that starting compound, 2-phenylethynyl aniline as well as the product, 3-phenyl-4(1*H*) cinnolone is not fluorescence active. However, we discovered that

Table 1

Synthesis of 3-aryl-cinnolones



Figure 3. Colorimetric studies for nitrite sensing (L = 2-phenylethynyl aniline, 10^{-4} M in H₂O).

6-methoxy-2-naphthylethynyl aniline shows strong fluorescence emission at 401 nm (excitation at λ_{max} 315 nm), whereas the corresponding cinnolone obtained by reaction with nitrite was completely fluorescence inactive (Fig. 2).

This property was successfully utilized for the detection of nitrite ions at a very low concentration (<1 ppm). The effect of a wide variety of other ions including F⁻, Cl⁻, Br⁻, I⁻, N₃⁻, PO₄³⁻, OAc⁻, SCN⁻, SO₄²⁻, and NO₃⁻ has also been investigated in the sensing process of nitrite by this reaction.

Remarkably, in an experiment in absence of nitrite ion none of these ions even at a higher concentration (1000 ppm) shows any change of color (Fig. 3) or UV absorption at 391 nm (Fig. 1) or quenching of fluorescence emission at 401 nm (Fig. 2). The presence of these ions in the test sample containing nitrite ion also



 Table 1 (continued)



^a Yields refer to those of pure isolated products characterized by spectroscopic data (IR, ¹H NMR, ¹³C NMR and HRMS).

does not interfere in the detection process. For an on-the-spot survey when a paper strip soaked with 2-phenylethynyl aniline and aqueous HCl was quenched with a drop of sample, the presence of nitrite was immediately reflected by a change of color to yellow. The presence of other ions has absolutely no effect.

The 4(1H)-cinnolines, have received considerable attention in recent times because of their promising biological activities.¹² Surprisingly, a few methods have been available for the synthesis of cinnolines.¹³

The direct method for the synthesis of cinnolones is rare. We have found only one report of their synthesis by electrochemical reduction of cinnolines.¹⁴ Considering the importance of cinnolones, we standardized the basic reaction of 2-phenylethynyl aniline and nitrite toward a general procedure¹⁵ for the synthesis of 4(1H)-cinnolones. Several 2-arylethynyl anilines which are obtained by the Sonogashira coupling of 2-iodoanilines and aryl acetylenes in water by a standard procedure,¹⁶ were converted into the corresponding 3-aryl-4(1*H*)-cinnolones by this procedure.¹⁵ The results are summarized in Table 1. A variety of substituted phenyl and naphthyl-ethynyl anilines participate in this reaction and several functional groups such as Cl, CN, and OMe are compatible with the reaction conditions. The reactions in this two-step procedure starting from 2-iodoanilines to 3-aryl-4(1H)-cinnolones were carried out in aqueous medium and a minimum amount of relatively safe¹⁷ ethyl acetate was used for extraction and crystallization. The compounds are obtained in high purity on recrystallization and were characterized by spectroscopic data (IR, ¹H NMR, ¹³C NMR and HRMS).



Scheme 2. Possible reaction pathway.

In general, the reactions are very fast, clean and high yielding. The possible reaction pathway involves diazotization of the ethynyl anilines followed by hydration of ethynyl moiety and subsequent cyclization to provide the 4(1H)-cinnolones, as outlined in Scheme 2.

In conclusion, we have developed a simple tool for sensing nitrite ions selectively in presence of other ion contaminants by visual color change, UV absorption, and fluorescence emission, based on a key reaction of 2-arylethynyl aniline and nitrite in acidic aqueous medium. This kit is also effective on a paper strip for an on-the-spot survey without any instrument at low concentration of nitrite ions (10 ppm). This reaction has been utilized to develop a general procedure for the synthesis of 4(1*H*)-cinnolones which are pharmaceutically very important. To the best of our knowledge, this is the first direct method for the synthesis of 4(1*H*)-cinnolones. In addition, the significant advantages of high yield, fast reaction, reaction in aqueous media, and ambient temperature make this procedure very attractive.

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Supplementary data

Supplementary data (copies of ¹H NMR and ¹³C NMR spectra of all products listed in Table 1) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.098.

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- 11. General procedure for the detection of nitrite ions: An aqueous nitrite solution $(10^{-4} \text{ M}, 2 \text{ mL})$ was added to an aqueous HCl (4 N) solution of 2-phenylethynyl aniline (2 mL, $0.5 \times 10^{-4} \text{ M})$ in a cubet and shaken well. UV study was carried out with this solution. For fluorescence studies a similar experiment was performed using a 10^{-6} M solution (2 mL) of 6-methoxynaphthyl-2-ethynyl aniline.
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- 15. General experimental procedure: representative procedure for the synthesis of 3-phenyl-1H-cinnolin-4-one: To 2 N acidic suspension (2 mL) of 2-phenylethynyl-phenylamine (193 mg, 1 mmol), NaNO₂ (103 mg, 1.5 mmol) was added in portions at 0–5 °C. The reaction mixture was stirred at 0–5 °C for 5 min followed by further 5 min at room temperature. The reaction mixture was extracted with EtOAc (2 × 5 mL), dried, concentrated and was left at room temperature to give 3-phenyl-1H-cinnolin-4-one as a pale yellow solid (204 mg, 92%), IR (KBr) 756, 1305, 1477, 1546, 2860, 2929 cm⁻¹; ¹H NMR (DMSO-d₆, 300 MH2) δ 7.36–7.46 (m, 4H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.77 (t, *J* = 7 Hz, 1H), 8.09–8.17 (m, 3H), 13.70 (k, 1H); ¹³C NMR (DMSO-d₆, 75 MH2) δ 117.0, 124.0, 125.2, 125.3, 128.4 (2C), 128.8 (2C), 134.1, 135.5, 141.3, 146.0, 169.8; HRMS Calcd for C₁₄H₁₀N₂0 (M*+H): 223.0871. Found: 223.0868.
 - This procedure was followed for all the reactions listed in Table 1. The products in entries 3 and 6 of Table 1 are known¹⁴ and were identified by comparison of their spectra with those reported. The products in entries 2, 4, 5, 7 and 8 in Table 1 were not reported earlier and were characterized by their spectroscopic data (IR, ¹H NMR, ¹³C NMR and HRMS) which are provided below in order of their entries.

In general, these cinnolones are very high melting $(300 \,^{\circ}\text{C})$ and attempts to determine the melting points on an electrical bath leads to decomposition.

3-*p*-Tolyl-1*H*-cinnolin-4-one (Table 1, entry 2): Yield 90%, pale yellow solid, IR (KBr) 667, 754, 821, 1301, 1477, 1545, 2841, 2887 cm⁻¹; ¹H NMR (DMSO- d_6 , 500 MHz) δ 2.33 (S, 3H), 7.23 (d, *J* = 8 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.77 (t, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 8 Hz, 2H), 8.13 (d, *J* = 8 Hz, 1H), 13.62 (s, 1H); ¹³C NMR (DMSO- d_6 , 125 MHz) δ 21.4, 116.9, 123.8, 125.2, 128.6 (2C), 132.6, 134.0, 138.3, 141.2, 145.9, 169.7; HRMS Calcd for C₁₅H₁₃N₂O (M*+H): 237.101. Found: 237.101.

7-*Chloro-3-p-tolyl-1H-cinnolin-4-one* (Table 1, entry 4): Yield 92%; pale yellow solid; IR (KBr) 819, 1051, 1454, 1537, 1560, 2825, 2885, 2982, 3051 cm⁻¹; ¹H NMR (DMSO- d_{6} , 500 MHz) δ 2.32 (s, 3H), 7.22 (d, J = 8 Hz, 2H), 7.40 (d, J = 8.5 Hz, 1H), 7.65 (s, 1H), 7.96 (d, J = 8 Hz, 2H), 8.11 (d, J = 8.5 Hz, 1H), 13.74 (s, 1H); ¹³C NMR (DMSO- d_{6} , 125 MHz) δ 116.0, 122.3, 125.6, 127.8, 128.7 (2C), 129.0 (3C), 132.2, 138.6, 141.8, 146.5, 169.3; HRMS Calcd for C₁₅H₁₂ClN₂O (M*+H); 271.0638. Found: 271.0633.

3-(4-Chloro-phenyl)-4-oxo-1,4-dihydro-cinnoline-6-carbonitrile (Table 1, entry 5): Yield 95%; pale yellow solid; IR (KBr) 823, 1091, 1300, 1487, 1585, 2231, 3027, 3277 cm⁻¹; ¹H NMR (DMSO-d₆, 500 MHz) δ 7.37 (d, J = 8.5 Hz, 2H), 7.68 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 8.0 (d, J = 8 Hz, 2H), 8.3 (s, 1H), 14.1 (s, 1H), ¹³C NMR (DMSO-d₆, 125 MHz) δ 107.4, 118.8, 123.1, 128.5 (3C), 130.4 (2C), 131.5, 133.4, 134.2, 135.3, 142.6, 145.9, 168.8; HRMS Calcd for C₁₅H₉ClN₃O (M^{*}+H): 282.0434. Found: 282.0429.

3-(2-Methoxynaphthalen-6-yl)cinnolin-4(1H)-one (Table 1, entry 7): Yield 90%; pale yellow solid; IR (KBr) 727, 871, 1201, 1481, 1612, 1629, 3198, 3223 cm⁻¹; ¹H NMR (DMSO- d_6 , 500 MHz) δ 3.93 (S, 3H), 7.26 (d, J = 9 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.43 (S, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 7.43 (S, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.74 (d, J = 7.5 Hz, 1H), 8.94 (d, J = 9 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H), 8.33 (d, J = 8 Hz, 1H), 8.94 (S, 1H), 13C NMR (DMSO- d_6 , 125 MHz) δ 55.3, 106.0, 110.9, 119.3, 121.9, 123.0, 123.3, 126.3, 126.6, 127.0, 127.2, 131.2, 132.0, 132.7, 136.6, 140.7, 142.4, 159.2, 187.5; HRMS Calcd for C₁₉H₁₄N₂O₂ (M*+Na): 325.0953. Found: 325.0954.

7-*Chloro-3*-(4-*methoxy-phenyl*)-1*H*-*cinnolin*-4-*one* (Table 1, entry 8): Yield 92%; pale yellow solid; IR (KBr) 827, 1055, 1300, 1556, 2885, 3054 cm⁻¹; ¹H NMR (DMSO-*d*₆, 500 MHz) δ 3.7 (s, 3H), 7.0 (d, *J* = 8.5 Hz, 2H), 7.23 (d, *J* = 7.5 Hz, 1H), 7.48 (s, 1H), 7.98 (d, *J* = 8 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 2H), 13.90 (s, 1H); ¹³C NMR (DMSO-*d*₆, 125 MHz) δ 55.56, 112.3, 113.9 (2C), 120.7, 121.2, 121.7, 124.1, 128.8, 131.7 (3C), 134.0, 142.8, 161.0; HRMS Calcd for C₁₅H₁₂ClN₂O₂ (M^{*}+H): 287.0587. Found: 287.0583.

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