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Synthesis of new pyrido1,4-oxazin derivatives from 2-amino-3-hydroxypyridine and activated acetylenic compound

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Abstract: The reaction of 2-amino-3-hydroxypyridine with acetylenic ester or dibenzoylacetylene leads to pyrido1,4-oxazines in 95-98% yields.

Keywords: Pyrido1,4-Oxazin, 2-Amino-3-hydroxypyridine, Acetylenic ester, Dibenzoylacetylene.

Introduction

The development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the main objectives of organic synthesis. Nitrogen heterocycles are of special interest because they constitute an important class of natural and nonnatural products, many of which exhibite useful biological activities. Investigation of the 1,4-oxazine or pyrido 1,4-oxazine heterocycles has shown that they possess varied biological properties such as analgesic, anticonvulsant, antitubercular, antibacterial and anticancer activity [1-4]. Particular attention has been paid to these compounds since the discovery of the non-nucleoside reverse transcriptase inhibitor trifluoromethyl-1,4-oxazine-2-one, which shows high activity against a variety of HIV-1 mutant strains [5]. In addition, pyrido 1,4-oxazine derivatives have exhibited therapeutic potential for the treatment of Parkinson's disease [6-10]. Furthermore, they can be used as intermediates in the synthesis of *N*-substituted aminoalcohols or in enantioselective syntheses of chiral amines but only very few synthesis of pyrido 1,4-oxazines [11-13], are reported.

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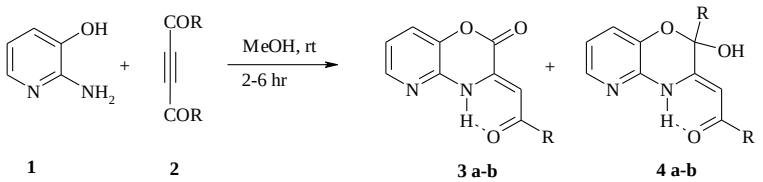
Results and discussion

In the course of our research program on the facile synthesis of heterocycles in mild conditions [14-16], herein we report the results of our studies involving the reactions of 2-amino 3-hydroxypyridin **1** and activated acetylenes **2** which constitutes a synthesis of pyrido 1,4-oxazines derivatives **3** (Scheme **1 and** Table **1**).

The structures of compounds **3a-3b** and **4a-4b** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR. For example, the ^{1}H NMR spectrum of **3a** exhibited a three singlet as methoxy (δ 3.69), vinyl proton (δ 6.04) and amine proton (δ 12.10) along with multiplets for the remaining aromatic protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 10 distinct resonances which further confirmed the proposed structure. The IR spectrum of **3a** displayed characteristic ester and aromatic bands. The ^{1}H NMR and ^{13}C NMR spectra of **3b** and **4a-4b** were similar to those for **3a** except for the ester moieties and hydroxyl or aromatic group respectively, which exhibited characteristic resonances in appropriate regions of the spectrum.

A possible mechanism for the formation of **3** and **4** are shown in (Scheme **2**). Although there is no experimental verification of this. The first step maybe

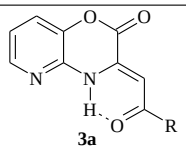
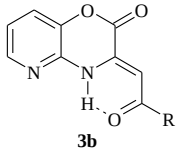
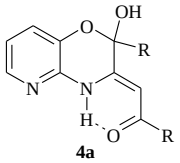
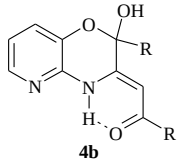
involves the addition of amine group [17] of **1** to the acetelinic compound **2** and formation of 1:1 adduct **5**. Then the carbonyl group of the closer benzoyl moiety is attacked by the hydroxy group to produce **3** or **4**.



1 **2** **3 a-b** **4 a-b**

Scheme 1: Synthesis of pyrido 1,4-oxazines derivatives.

Table 1: pyrido 1, 4-oxazines derivatives.

entry	R	Product	3:4	time (hr)	Yield%
1	OMe	 **3a**	98:0	2	98
2	OEt	 **3b**	97:0	3	97
3	Ph	 **4a**	0:99	5	99
4	4-Me-Ph	 **4b**	0:95	6	95

Conclusion

In summary, we have reported a new procedure for the synthesis of biologically active pyrido 1,4-oxazine derivatives *via* reaction of activated acetylenes and 2-amino-3-hydroxypyridine in excellent yield.

Experimental

General procedure:

All compounds were obtained from Fluka or Merck and were used without further purification. Dibenzoylacetylen (DBA) was prepared according to the literature procedure [21]. M.p. Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C- NMR spectra: Bruker DRX-500 AVANCE instrument; in DMSO (d6) at 500, 125 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

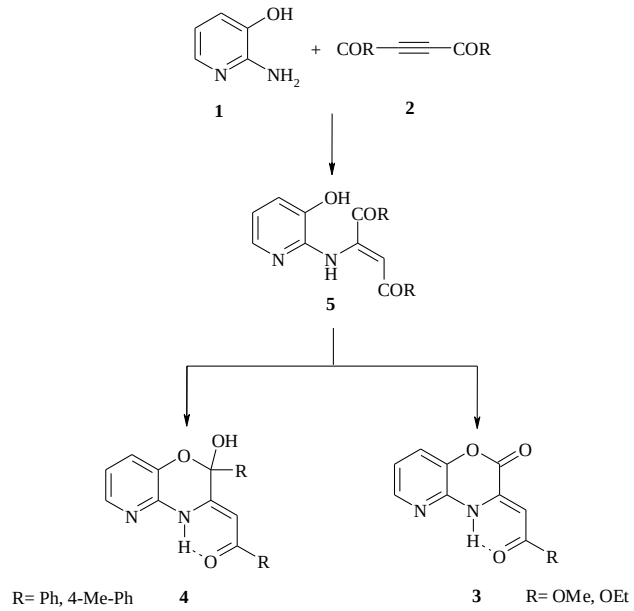
General procedure for preparation of (**3** and **4**):

To a stirred solution of **1** (2 mmol) in 3 mL MeOH was added (2 mmol) activated acetylene at rt. The reaction mixture was then sntirred for 2-6 h. The precipitate was filtered off and washed with cooled methanol to get pure product **3** or **4**.

*Methyl 2-[2-oxo-2 H-pyrido[2,3b][1,4]oxazin-3(4H)-ylidine]acetate (**3a**):*

Pale yellow powder, mp 119–122 °C, 0.215 g, yield 98%. IR (KBr) (vmax/cm^{-1}): 3188 (NH), 1722, 1688, 1616, 1195, 800. Anal. Calcd for $C_{10}H_8N_2O_4$ (220.18): C, 54.55; H, 3.66; N, 12.72. Found (%): C, 54.71; H, 3.73; N, 12.85. ^{1}HNMR: δ 3.69 (3H, s, OCH_3), 6.04 (1H, s, CH), 7.10 (1H, dd, J= 8.0, 4.8 Hz, CH), 7.56 (1H, dd, $^{3}J_{=}$ 8.0, 1.3 Hz, CH), 8.05 (1H, dd, $^{3}J_{=}$ 4.8, 1.3

Hz, CH), 12.10 (1H, br s, NH) ppm. ^{13}C NMR: δ 51.2 (OCH_3), 98.6 (CH), 119.3 (CH), 122.8 (CH), 136.20 (C), 139.1(C), 142.7 (CH), 150.9 (C), 155.4 (C=O), 163.6 (C=O) ppm.



Scheme 2: Proposed mechanism for the formation of 3 and 4.

*Ethyl 2-[2-oxo-2 H-pyrido[2,3b][1,4]oxazin-3(4H)-ylidine]acetate (**3b**):*

Pale yellow powder, mp 125–127 °C, 0.226 g, yield 97%. IR (KBr) (νmax/cm^{-1}): 3193 (NH), 1710, 1667, 1610, 1192, 799. Anal. Calcd for $C_{11}H_{10}N_2O_4$ (234.2): C, 56.41; H, 4.30; N, 11.96. Found (%): C, 56.65; H, 4.43; N, 12.14. ^{1}HNMR: δ 1.18 (3H, t, ^3J= 7.1, CH_3), 4.18 (2H, q, ^3J= 7.1, O-CH_2), 6.08 (1H, s, CH), 7.12 (1H, dd, J= 8.0, 4.6 Hz, CH), 7.49 (1H, dd, $^3J_=$ 8.0, 1.1 Hz, CH), 8.12 (1H, dd, $^3J_=$ 4.6, 1.1 Hz, CH), 12.00 (1H, br s, NH) ppm. ^{13}C NMR: δ 14.5 (CH_3), 61.4 (OCH_2), 99.1 (CH), 119.4 (CH), 122.5 (CH), 136.5 (C), 139.3(C), 141.9 (CH), 149.2 (C), 155.6 (C=O), 164.1 (C=O) ppm.

*2-[2-hydroxy-2-phenyl-2H-pyrido[2,3b][1,4]oxazin-3(4H)-ylidine]-1-phenyl-1-ethanone (**4a**):*

Pale yellow powder, mp 165–168 °C, 0.330 g, yield 99%. IR (KBr) (νmax/cm^{-1}): 3200 (NH), 1690, 1672, 1616, 1288, 1190, 985. Anal. Calcd for $C_{21}H_{16}N_2O_3$ (344.37): C, 73.24; H, 4.68; N, 8.13. Found (%): C, 73.40; H, 4.73; N, 8.25. ^{1}HNMR: δ 4.78 (1H, br s, OH), 6.17 (1H, s, CH), 7.15- 7.51 (10 H, m, 10 CH), 7.85 (2 H, d, $^3J_=$ 7.5, Hz, 2CH), 8.15 (1H, dd, $^3J_=$ 4.5, 1.3 Hz, CH), 12.60 (1H, br s, NH) ppm. ^{13}C NMR: δ 91.4 (CH), 96.7 (C), 118.1 (CH), 119.4 (CH), 122.5 (CH), 124.1 (CH), 126.0 (C), 126.5 (2CH), 127.4 (2CH), 128.5 (2CH), 128.7 (2CH), 131.3 (CH), 138.4 (C), 139.1(C), 142.3 (C), 149.8 (C), 189.3 (C=O) ppm.

*2-[2-hydroxy-2-(4-metylphenyl)-2H-pyrido[2,3b][1,4]oxazin-3(4H)-ylidine]-1(4 metylphenyl)-1-ethanone (**4b**):*

Pale yellow powder, mp 165–168 °C, 0.360 g, yield 95%. IR (KBr) (νmax/cm^{-1}): 3200 (NH), 1686, 1670, 1610, 1288, 1179, 967. Anal. Calcd for $C_{23}H_{20}N_2O_3$ (372.4): C, 74.18; H, 5.41; N, 7.52. Found (%): C, 73.95; H, 5.65; N, 7.63. ^{1}HNMR: δ 2.20 (3 H, s, CH_3), 2.43 (3 H, s, CH_3), 4.60 (1H, br s, OH), 6.21 (1H, s, CH), 7.12- 7.18 (3 H, m, 3 CH), 7.50 (2H, t, $^3J_=$ 7.5, 2CH), 7.70- 7.74 (3 H, m, 3 CH), 7.80 (2 H, d, $^3J_=$ 7.5, Hz, 2CH), 8.18 (1H, dd, $^3J_=$ 4.5, 1.3 Hz, CH), 12.50 (1H, br s, NH) ppm. ^{13}C NMR: δ 21.4 (CH_3), 23.4 (CH_3), 91.8 (CH), 96.2 (C), 118.3 (CH), 120.4 (CH), 123.5 (CH), 124.4 (C), 126.8 (C), 126.9 (2CH), 126.6 (2CH), 128.4 (2CH), 128.9 (2CH), 131.1 (C), 139.0 (C), 139.3(C), 142.2 (C), 149.3 (C), 189.1 (C=O) ppm.

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