

SYNTHESIS OF 2-ALKENYL- 4H-3, 1-BENZOXAZIN-4 –ONE UNDER ACIDIC AND BASIC MEDIA

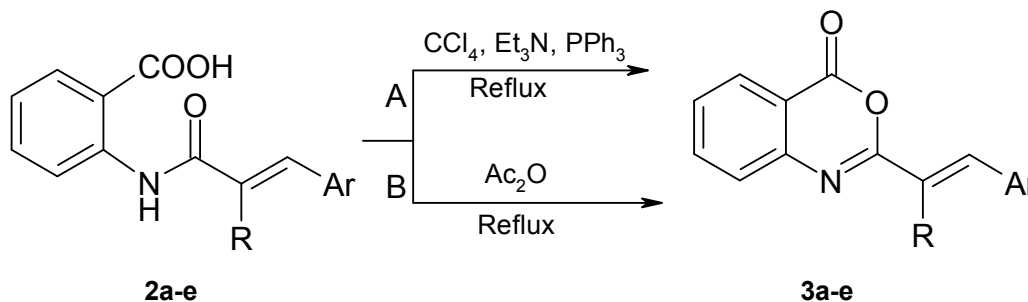
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ABSTRACT

Direct one pot synthesis of 4H-3, 1-benzoxazin-4-ones bearing vinyl substituents at C-2 position by two different and straightforward methods is described. The salient features of this method include a simple procedure, mild conditions, easy purification inexpensive and availability of starting materials and high yields.

KEYWORDS Anthranilic acid, Cinnamyl chloride, Triphenylphosphine.



Scheme-I

INTRODUCTION

4H-3,1-benzoxazin-4-one derivatives are very useful precursors for the development of molecules of biological interest [I-III]. They are indeed useful intermediates in organic synthesis affording through reaction with nitrogen nucleophiles [IV-VIII]. To name just a few, 4H-3, 1-benzoxazin-4-one derivatives have found applications in pharmacology, 2-vinyl-4H-3, 1-benzoxazin-4-one has shown inhibitory activity against human leukocyte elastase [IX], 2-aryl substituted 4H-3, 1-benzoxazin-4-ones is evaluated as specific inhibitors of the tissue factor (TF)/Factor 4a induced pathway [X]. However, common substituents such as, alkyl, or aryl groups at C-2 position were synthesized and the structures and the properties of their derivatives

were investigated, but the synthesis of alkenyl substituted 4H-3, 3-benzoxazin-4-one has been comparatively less studied.

RESULTS AND DISCUSSION

The derivatives of 4H-3, 1-benzoxazin-4-one bearing vinyl substituent at C-2 position were synthesized by two different methods. In the first method, the substituted benzoxazines were prepared by ring closing of the amides in the presence of triethylamine, triphenylphosphine and carbon tetrachloride which was called a basic media. In the second method benzoxazines were prepared in the presence of acetic anhydride and THF or toluene was used as a solvent. The yields are good in both cases. The starting materials were prepared according to the procedure which is reported in the literature.

The structure of all the compounds 3a-e are confirmed by their IR spectra which do not contain the absorption band of OH carboxylic acid and amide, N-H, C=O bands, but contain the bands of the carbonyl group at 1760 cm^{-1} and C=N band at 1600 cm^{-1} .

The $^1\text{H NMR}$ spectrum of the compound 3a (R=H, Ar=Ph) exhibits two doublets at 6.80 and 7.85ppm which are due to the vinylic protons with the coupling constant of $J_{\text{H,H}} = 16.35$ and 16.40 Hz . This indicates that only one geometrical isomer is formed in the reaction, and also this coupling constant is indicative that the stereochemistry around the carbon-carbon double bond is consistent with the E stereoisomer. Since only one stereoisomer was formed it looks like the barrier interconversion of E to Z isomer is high under the experimental conditions used.

The $^{13}\text{C NMR}$ spectrum of this compound 3a (R=H, Ar=Ph) exhibits carbonyl group at 159.24ppm and the other ^{13}C are at 157.28, 140, 141.48, 136.49, 134.59, 130.26, 128.95, 128.58, 128.11, 127.95, 126.88, 118.79, and 116.89. The mass spectrum revealed the molecular ion peak at m/z 249 and the base peak at 248(M-1). Elemental analysis of all the products is consistent with proposed structures.

Table -I. Synthesis of benzoxazin-4-ones

Compound	Ar	R	Mp ($^{\circ}\text{C}$)	Yield(%) ^a	Yield(%) ^b
3a	C ₆ H ₅	H	139-141	95	93
3b	C ₆ H ₅	CH ₃	148-150	94	89
3c	C ₆ H ₅	Ph	158	96	92
3d	4-CH ₃ -C ₆ H ₄	H	128	95	93
3e	furyl	H	158	96	93

^a Reaction conditions: CCl₄, Et₃N, PPh₃, Reflux

^b Reaction conditions: Ac₂O, Reflux

EXPERIMENTAL SECTION

GENERAL: IR spectra were recorded on a Matson 1000 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were obtained with a Bruker DRX-500 spectrometer and 127.77 MHz respectively using CDCl_3 or DMSO-d_6 solvent and TMS as an internal standard. Mass spectra were recorded on a MS- QP2000A Shimadzu mass spectrometer operating at an ionization potential of 70 ev. Melting points were determined on a Gallenkamp heating stage and are uncorrected. Elemental analyses were performed by National Iranian Oil Company Lab using a Heracus CHN-O- Rapid analyzer.

Commercially available reagents were used as received (Merck, Fluka), THF and toluene was dried over sodium. cinnamoyl chlorides were prepared as was reported in literature [9]. Prior to each method for the synthesis of each of the compounds were presented in the text.

General procedure for preparation of the amides

2-[(E)-3-phenyl-propenoyl 2-amino] benzoic acid (2a). To a solution containing anthranilic acid (30 mmol) in 15 ml THF, cinnamyl chloride (20 mmol) was added dropwise and then the mixture was refluxed for an additional 2 hours. The product was formed as a yellow solid after filtering the mixture and washing the solid with glacial acetic acid. (m.p=181°C).

General procedures for preparation of the benzoxazin-4-ones

Preparation of 2-[(E)-2-phenyl-1-ethenyl]-4H-3, 1-benzoxazin-4-one (3a):

Method A: To a solution of (2 mmol) amide (2a) in 15 ml carbontetrachloride 5 mmol triethylamine and 5 mmol triphenylphosphin was added respectively. The solution mixture was refluxed for 2 hours the solvent was removed under reduced pressure the solid product was purified by recrystallization from ethanol to afford (3a) as a yellow solid.

Method B: To a solution of (1.34 g, 5 mmol) amide (2a) in 5 ml anhydrous toluene (0.5 ml, 5 mmol) acetic anhydride was added dropwise and the reaction mixture was stirred for 24 hours at ambient temperature. The precipitate was collected by filtration, washed with hexane and purified by column chromatography (hexane: ethyl acetate 70/30).

IR spectrum (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 1772 (C=O), 1653 (C=N), 1593 (C=C); ^1H NMR (CDCl_3/TMS) (δ : ppm): 6.80 (1H, d, $^3J_{\text{H,H}}$ 16.3Hz), 7.40-7.44 (3H, m, Ph), 7.49 (1H, dd), 7.58-7.62 (3H, m), 7.80 (1H, td), 7.85 (1H, d, $^3J_{\text{H,H}}$ 16.20 Hz), 8.21 (1H, td); ^{13}C NMR (δ : ppm) 116.89, 134.59, 147.07, 157.28 (4C), 118.79, 126.86, 127.95, 128.11, 128.58, 128.95, 130.26, 136.49, 141.48 (9CH), 159.24 (C=O). MS (m/z, %): 249 (M^+ , 57%), 248 (100%), 220 (31%), 119 (39%), 103 (50%). Anal. Calcd for $\text{C}_{16}\text{H}_{11}\text{NO}_2$: C, 77.10; H, 4.45; N, 5.62% found: C, 77.21; H, 4.52; N, 5.67%

2-[(E)-1-methyl-2-phenyl-1-ethenyl]-4H-3, 1-benzoxazin-4-one (3b):

IR (KBr, $\nu_{\text{max}}/\text{cm}^{-1}$): 1765 (C=O), 1592 (C=N), 1480 (C=C); 262(100%), 234(35%), 115(59%); ^1H NMR (CDCl_3/TMS) (δ)(ppm): 2.35(3H, s, CH_3), 7.33(1H, t, $^3J_{\text{H,H}}$ 7.20 Hz), 7.40-7.50 (5H, m, Ph), 7.64 (1H, d, $^3J_{\text{H,H}}$ 8 Hz), 7.79(1H, td, $^3J_{\text{H,H}}$ 8.20 Hz, $^4J_{\text{H,H}}$ 1.34 Hz), 7.92(1H, s), 8.20(1H, dd, $^3J_{\text{H,H}}$ 7.80 Hz, $^4J_{\text{H,H}}$ 1 Hz); ^{13}C NMR(CDCl_3/TMS) (δ)(ppm): 14.28(CH_3), 116.85, 128.07, 136, 147, 158.73(5C), 127.24, 128.11, 128.40, 128.42, 128.48, 129.86, 136.38, 137.54(8CH), 156.62(C=O); MS(m/z, %), 263(M^+ , 55%),

Calcd: C, 77.5; H, 4.9 and N, 5.3%. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_2$: C, 77.5; H, 4.9; N, 5.3% found: C, 77.4; H, 5.1; N, 5.1%

2- [(E)-1, 2-diphenyl-etheny]-4H-3, 1-benzoxazin-4-one (3c):

IR(KBr, $\nu_{\max}/\text{cm}^{-1}$): 1756(C=O), 1617(C=N), 1592(C=C); ^1H NMR(CDCl_3/TMS)(δ)(ppm): 7.00-7.24(5H, m, Ph), 7.27-7.45(5H, m, Ar), 7.48(1H, d, $^3J_{\text{H,H}}$ 7.6Hz), 7.52(1H, td, $^3J_{\text{H,H}}$ 8Hz), 7.75(1H, td, $^3J_{\text{H,H}}$ 7.50Hz), 8.05(1H, s), 8.23(1H, dd, $^3J_{\text{H,H}}$ 8Hz, $^4J_{\text{H,H}}$ 1.2Hz); ^{13}C NMR(CDCl_3/TMS)(ppm): 116.67, 129.36, 136.17, 136.26, 147.02, 158.31(6C), 127.60, 128.13, 128.20, 128.56, 128.74, 129.00, 130.18, 130.32, 130.67, 132.60, 134.85, 135.50, 136.17, 138.39, 138.88(15CH), 159.61(C=O); CHN analysis: Found: C, 80.8; H, 4.8; and N, 4.1%; calcd for $\text{C}_{22}\text{H}_{15}\text{NO}_2$: C, 81.2; H, 4.6 and N, 4.3%. MS(m/z, %): 326($\text{M}^+ + 1$, 80%), 325(M^+ , 96%), ($\text{M}^+ - \text{H}$, 100%), 296(38%), 248(60%), 178(98%), 146(45%), 90(45%);

2-[(E)-2-(4-methyl phenyl)-1-ethenyl]-4H-3, 1-benzoxazin-4-one (3d):

IR (KBr, $\nu_{\max}/\text{cm}^{-1}$): 1760(C=O), 1635(C=N), 1598(C=C); ^1H NMR (CDCl_3/TMS)(δ)(ppm): 2.38 (3H, s, Me), 6.72 (1H, d, $^3J_{\text{H,H}}$ 16Hz), 7.20 (1H, d, $^3J_{\text{H,H}}$ 7Hz), 7.45-7.51 (3H, m, Ar), 7.80 (1H, d, $^3J_{\text{H,H}}$ 16Hz), 8.20 (1H, d, $^3J_{\text{H,H}}$ 7.8Hz). ^{13}C NMR (CDCl_3/TMS) (δ) (ppm): 21.42 (CH_3), 116.83, 136.43, 140.76, 147.13, 157.51 (5C), 117.67, 126.75, 127.95, 128.0, 128.54, 129.67, 131.88, 142.02 (8C), 159.27(CO); MS (m/z, %): 263(M^+ , 72%), 262($\text{M}^+ - \text{H}$, 100%), 234(26%), 145(26%), 115(47%); CHN Analysis, Found: C: 77.2, H: 5.1 and N: 5.1%; calcd for $\text{C}_{17}\text{H}_{13}\text{NO}_2$: C: 77.5, H: 4.9 and N: 5.3%.

2-[(E)-(3-furyl)-1-ethenyl]-4H-3, 1-benzoxazin-4-one (3e):

IR(KBr, $\nu_{\max}/\text{cm}^{-1}$): 1760 (C=O), 1636 (C=N), 1602 (C=C); ^1H NMR (CDCl_3/TMS) (δ) (ppm): 6.51 (1H, dd, $^3J_{\text{H,H}}$ 3Hz, $^4J_{\text{H,H}}$ 1.7Hz), 6.69(1H, d, $^3J_{\text{H,H}}$ 12.5Hz), 7.48(1H, td, $^3J_{\text{H,H}}$ 7.2Hz, $^4J_{\text{H,H}}$ 0.9Hz), 7.59, 7.63 (3H, m), 8.20 (1H, dd, $^3J_{\text{H,H}}$ 9Hz, $^4J_{\text{H,H}}$ 1.2Hz); ^{13}C NMR(CDCl_3/TMS)(δ)(ppm): 116.76, 147.12, 151.16, 157.32(4C), 112.49, 114.97, 116.36, 126.78, 128.32, 128.56, 136.47, 145.06 (CH), 159.93 (C=O). Ms (m/z, %): 239 (M^+ , 100), 211(45), 121(54), 90(37).

CONCLUSION

In conclusion we have demonstrated that the benzoxazinone derivatives were prepared by two different facile reactions.

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