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Synthesis and Characterization of Some New N-(Substituted 4-Methylene-2-oxo-4*H*-benzo[e][1,3]oxazin-3-yl)isonicotinamide

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The N-(substituted 4-methylene-2-oxo-4*H*-benzo[e][1,3]oxazin-3-yl)isonicotinamide were synthesized by condensation of isonicotinic acid hydrazide derivatives with triphosgene. The structures of all the synthesized compounds have been elucidated by microanalysis and IR, NMR, MS spectroscopic measurements.

Key Words: Isoniazid, 2-Hydroxyacetophenone derivative, Hydrazides, Microwave irradiation, Triphosgene, 1,3-Benzoxazines.

INTRODUCTION

Tuberculosis is a chronic infectious disease caused by mycobacteria of the 'tuberculosis complex', including *Mycobacterium bovis*, *Mycobacterium africanum* and *Mycobacterium tuberculosis*. Tuberculosis now kills more adults than all other infectious diseases combined. Active tuberculosis is usually treated with isoniazid in association with one or more other anti tuberculosis drugs but multi-drug resistant tuberculosis (MDR-TB) and recently extensively drug resistant tuberculosis (XDR-TB) has become a serious and unsolved public health problem[1-6]. Isoniazid discovered in 1952 is still the most important drug for treatment of tuberculosis. The full therapeutic possibilities of hydrazides were realized after the discovery of isoniazid. Hydrazides and their derivatives have been described as useful synthons of various heterocyclic rings[7]. A large number of hydrazides and their derivatives are reported to possess a broad spectrum of biological activities[8,9]. Thus, these were found to be useful especially in the treatment of inflammatory and autoimmune diseases, osteoarthritis, respiratory diseases, tumors, cachexia, cardiovascular diseases, fever, hemorrhage and sepsis[10]. Hydrazides and derivatives exhibited antifungal[8], psychotropic[9], antituberculous[11], antiparasite[8,12], bacteriostatic[13-16], antiviral[16], insecticidal[9] and anticancer[17] activities. Much research has been carried out with the aim to finding therapeutic values of 1,3-benzoxazines moiety since their discovery. A large number of substituted 1,3-benzoxazines derivatives are prepared and tested for variety of biological activities. Such as antimycobacterial activity[18]. We have recently reported the use of triphosgene for the cyclization of hydrazones of 2-acetyl-1-naphthol and 1-acetyl-2-naphthol to give naphthoxazine and spiro naphthoxazine[19]. Here we report the cyclization reaction of hydrazides with triphosgene.

EXPERIMENTAL

Melting points are uncorrected and were determined on Gallenkamp-melting point apparatus. IR spectra were recorded on a Perkin-Elmer 883 spectrophotometer. NMR spectra were recorded on Jeol ECP 400 (400 MHz) in $CDCl_3$ and expressed as δ in ppm. Mass spectra were recorded on Shimadzu QP-5050A GC/MS system. Microwave irradiations were carried out in a domestic microwave oven (Panasonic model N-N-(20002 W) output of 1000 W. TLC was performed on (TLC plates silica gel 60 F_{245} pre-coated 20 cm × 20 cm layer thickness 0.25 mm).

General procedure for the preparation of hydrazides (3a-e): A solution of the appropriate isonicotinic acid hydrazide (isoniazid) (3.65 mmol), 2-hydroxy-acetophenone (7.28 mmol) in absolute ethanol (3 mL). After irradiation in a microwave oven at 250 Watt for 2-3 min. The separated solid was collected by filtration and recrystallized from ethanol.

Isonicotinic acid[1-(2-hydroxy-phenyl)ethylidene]-hydrazide (3a): This compound was prepared from 2-hydroxy-acetophenone and isoniazid. Yield *ca.* 94 %, yellowish white powder, m.p. 237-238 ºC; IR (KBr, ν_{max}, cm^{-1}): 1551 (C=N), 1700 (C=O), 3235 (NH), 3345 (OH); ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 6.86-7.63 (m, 4H, $H_{aromatic}$), 7.83 (d, 2H, J = 5.88 Hz, 3,5-pyridine-H), 8.77 (d, 2H, J = 5.84 Hz, 2,6-pyridine-H), 11.57 (s, 1H, NH), 13.20 (s, 1H, OH); ^{13}C

NMR (100 MHz,$CDCl_3$): δ 14.81, 117.89, 119.14, 119.75, 122.55 ($C_{3,5\text{-pyridine}}$), 129.25, 132.10, 140.64, 150.71 ($C_{2,6\text{-pyridine}}$), 155.29, 158.54 (C=N), 163.53 (C=O); MS: m/z (%) 255 (M^+, 92), 241, 240, 231, 156, 114, 109, 91, 81, 65, 51,29; Anal. calcd. (%) for $C_{14}H_{13}N_3O_2$: C, 65.87; H, 5.13; N, 16.46. Found (%): C, 65.52; H, 5.22; N, 16.38.

Isonicotinic acid [1-(5-chloro-2-hydroxy-phenyl)-ethylidene]hydrazide (3b): This compound was prepared from 5-chloro-2-hydroxyacetophenone and isoniazid. Yield *ca.* 91 %, yellowish white powder, m.p. 234-235 ºC; IR (KBr, ν_{max}, cm^{-1}): 3351 (OH), 3216 (NH),1557(C=N),1705 (C=O); ^{1}H NMR: 2.54 (s, 3H, CH_3), 6.94-7.66 (m, 3H, $H_{aromatic}$), 7.85 (d, 2H, *J* = 5.84 Hz, 3,5-pyridine-H) , 8.80 (d, 2H, *J* = 5.88 Hz, 2,6-pyridine-H), 11.67 (s, 1H, NH), 13.29 (s, 1H, OH); ^{13}C NMR: 14.96, 119.72, 121.27, 122.60 ($C_{3,5\text{-pyridine}}$), 122.74, 128.50, 131.59, 140.51, 150.73 ($C_{2,6\text{-pyridine}}$), 158.02, 158.54 (C=N), 163.71 (C=O); MS: m/z (%) 291 (M + 2, 92), 289 (M + 1, 49), 276, 241, 231, 156, 114, 109, 91, 81, 65, 51, 29; Anal. calcd. (%) for $C_{14}H_{12}N_3O_2Cl$: C, 58.04; H, 4.17; N, 14.50. Found (%): C, 58.50; H, 4.10; N, 14.26.

Isonicotinic acid [1-(3,5-dichloro-2-hydroxy-phenyl)-ethylidene]hydrazide (3c): This compound was prepared from 3,5-di-chloro-2-hydroxyacetophenone and isoniazid. Yield *ca.* 86 %, brown powder, m.p. 287-288 ºC; IR (KBr, ν_{max}, cm^{-1}): 3344 (OH), 3075 (NH), 1649 (C=N), 1693 (C=O); ^{1}H NMR: 2.51 (s, 3H, CH_3), 7.64-7.70 (m, 2H, $H_{aromatic}$), 7.87 (d, 2H, *J* = 5.88 Hz, 3,5-pyridine-H), 8.81 (d, 2H, *J* = 5.88 Hz, 2,6-pyridine-H), 11.67 (s, 1H, NH), 13.29 (s, 1H, OH); ^{13}C NMR: 15.01, 119.75, 121.20, 122.64 ($C_{3,5\text{-pyridine}}$), 127.59, 131.25, 140.50, 150.76 ($C_{2,6\text{-pyridine}}$), 158.34 (C=N), 163.98 (C=O); MS: m/z (%) 327 (M + 4, 8), 325 (M + 2, 4), 323 (M + 1, 9), 310, 278, 265, 182, 109, 91, 81, 65, 51, 29; Anal. calcd. (%) for $C_{14}H_{11}N_3O_2Cl_2$: C, 51.87; H, 3.42; N, 12.96. Found (%): C, 51.23; H, 3.16; N, 12.56.

Isonicotinic acid [1-(2-hydroxy-5-methyl-phenyl)-ethylidene]hydrazide (3d): This compound was prepared from 2-hydroxy-5-methylacetophenone and isoniazid. Yield *ca.* 91 %, pale yellow powder, m.p. 163-165 ºC; IR (KBr, ν_{max}, cm^{-1}): 3340 (OH), 3220 (NH), 1650 (C=N) 1698 (C=O); ^{1}H NMR: 2.27 (s, 3H, CH_3C=N), 2.51 (s, 3H, CH_3), 6.81-7.45 (m, 3H, $H_{aromatic}$), 7.85 (d, 2H, *J* = 5.88 Hz, 3,5-pyridine-H), 8.80 (d, 2H, *J* = 5.88 Hz, 2,6-pyridine-H), 11.57 (s, 1H, NH), 12.98 (s, 1H, OH); ^{13}C NMR: 14.86 (CH_3C=N), 20.76, 117.71, 119.41, 125.57 ($C_{3,5\text{-pyridine}}$), 127.59, 129.29, 32.78, 140.74, 150.73($C_{2,6\text{-pyridine}}$), 157.11, 160.06 (C=N), 163.50 (C=O); MS: m/z (%) 269 (M + 1, 100), 252, 241, 231, 156, 114, 109, 91, 81, 65, 51, 29; Anal. calcd. (%) for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found (%): C, 66.21; H, 5.26; N, 15.10.

Isonicotinic acid [1-(2-hydroxy-5-methoxy-phenyl)-ethylidene]hydrazide (3e): This compound was prepared from 2-hydroxy-5-methoxyacetophenone and isoniazid. Yield *ca.* 89 %, yellow powder, m.p. 248-251 ºC; IR (KBr, ν_{max}, cm^{-1}): 3331 (OH), 3229 (NH), 1659 (C=N) 1701(C=O); ^{1}H NMR: 2.54 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.85-7.15 (m, 3H, $H_{aromatic}$), 7.86 (d, 2H, *J* = 5.88 Hz, 3,5-pyridine-H), 8.80 (d, 2H, *J* = 5.88 Hz, 2,6-pyridine-H), 11.56 (s, 1H, NH), 12.66 (s, 1H, OH); ^{13}C NMR: 15.00, 56.15 (OCH_3), 113.57, 118.49, 118.57, 119.83, 122.57 ($C_{3,5\text{-pyridine}}$), 140.71, 150.73 ($C_{2,6\text{-pyridine}}$), 152.04, 153.24, 159.70 (C=N), 163.53 (C=O); MS: m/z (%) 285 (M + 1, 64), 254, 241, 231, 156, 114, 109, 91, 81, 65, 51, 29; Anal. calcd. (%) for $C_{15}H_{15}N_3O_3$: C, 65.45; H, 5.49; N, 17.43. Found (%): C, 65.20; H, 5.20; N, 17.49.

General procedure for the preparation of (4a-e): A solution of the appropriate hydrazide (**3a**) (3 mmol) and 1 mL of triethylamine in 25 mL of dichloromethane was stirred under nitrogen atmosphere. Triphosgene (1.5 mmol) in 10 mL of dichloromethane was added drop wise over a period of 15 min. The mixture was stirred at room temperature for 1 h and then refluxed for 3 h. Water was added, the organic layer was separated followed by extraction of the aqueous layer with dichloromethane (30 mL). The combined organic layers were dried over magnesium sulfate and evaporated to dryness. The resulting solid was crystallized from ethyl ether.

N-(4-Methylene-2-oxo-4*H*-benzo[e][1,3]oxazin-3-yl)-isonicotinamide (4a): This compound was prepared from **3a**. Yield *ca.* 79 %, colourless solid, m.p. 210-212 ºC; IR (KBr, ν_{max}, cm^{-1}): 1612 (=CH_2), 1673 (C=O_{amide}), 1726 (C=O), 3310 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.04 (d, *J* = 2.5 Hz, 1H), 5.10 (d, *J* = 2.5 Hz, 1H), 7.20-7.90 (4H, $H_{aromatic}$), 8.23 (d, 2H, *J* = 5.90 Hz, 3,5-pyridine-H), 9.00 (d, 2H, *J* = 5.90 Hz, 2,6-pyridine-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.56, 111.51, 120.69, 122.94, 125.18, 127.47, 128.12, , 129.31, 134.67, 138.69, 146.16, 148.05, 164; MS: m/z (%) 281 (M + 1, 64), 254, 236, 241, 231, 156, 114, 109, 106, 91, 81, 65, 51, 29; Anal. calcd. (%) for $C_{15}H_{11}N_3O_3$: C, 64.05; H, 3.94; N, 14.94. Found (%): C, 64.20; H, 3.22; N, 14.41.

N-(6-Chloro-4-methylene-2-oxo-4*H*-benzo[e][1,3] oxazin-3-yl)isonicotinamide (4b): This compound was prepared from **3b**. Yield *ca.* 66 %, colourless solid, m.p. 280-282 ºC; IR (KBr, ν_{max}, cm^{-1}): 16110 (=CH_2), 1670 (C=O_{amide}), 1722 (C=O), 3311 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, *J* = 2.5 Hz, 1H), 5.10 (d, *J* = 2.5 Hz, 1H), 7.28-7.93 (3H, $H_{aromatic}$), 8.21 (d, 2H, *J* = 5.90 Hz, 3,5-pyridine-H), 9.01 (d, 2H, *J* = 5.90 Hz, 2,6-pyridine-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.52, 111.54, 121.01, 122.10, 124.11, 127.27, 128.22, , 129.33, 134.77, 138.70, 146.26, 148.06,164.11; MS: m/z (%) 317 (M + 2, 23), 315 (M + 1, 77), 280, 254, 236, 241, 231, 156, 114, 109, 106, 91, 81, 65, 51, 29; Anal. calcd. (%) for $C_{15}H_{10}N_3O_3Cl$: C, 57.07; H, 3.19; N, 13.31. Found (%): C, 57.20; H, 3.20; N, 13.31.

N-(6,8-Dichloro-4-methylene-2-oxo-4*H*-benzo[e][1,3]-oxazin-3-yl)isonicotinamide (4c): This compound was prepared from **3c**. Yield *ca.* 64 %, white powder, m.p. 190-193 ºC; IR (KBr, ν_{max}, cm^{-1}): 1609 (=CH_2), 1674 (C=O_{amide}), 1725 (C=O), 3312 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, *J* = 2.5 Hz, 1H), 5.112 (d, *J* = 2.5 Hz, 1H), 7.27-7.95 (2H, $H_{aromatic}$), 8.20 (d, 2H, *J* = 5.90 Hz, 3,5-pyridine-H), 9.01 (d, 2H, *J* = 5.90 Hz, 2,6-pyridine-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 87.98, 111.74, 121.08, 122.13, 124.13, 127.29, 128.20, 129.38, 134.71, 138.77, 146.29, 148.09,164.41; MS: m/z (%) 351 (M + 2, 44), 349 (M + 1, 55), 314, 280, 254, 241, 231, 156, 114, 109, 106, 91, 81, 65, 51; Anal. calcd. (%) for $C_{15}H_9N_3O_3Cl_2$: C, 51.45; H, 2.59; N, 12.00. Found (%): C, 51.21; H, 2.60; N, 12.05.

N-(6-Methyl-4-methylene-2-oxo-4*H*-benzo[e][1,3]-oxazin-3-yl)isonicotinamide (4d): This compound was prepared from **3d**. Yield *ca.* 72 %, white powder, m.p. 290-291 ºC; IR (KBr, ν_{max}, cm^{-1}): 1615 (=CH_2),1677 (C=O_{amide}),

1728 (C=O), 3316 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, *J* = 2.5 Hz, 1H), 5.112 (d, *J* = 2.5 Hz, 1H), 7.33-7.92 (3H, $H_{aromatic}$), 8.27 (d, 2H, *J* = 5.90 Hz, 3,5-pyridine-H), 9.12 (d, 2H, *J* = 5.90 Hz, 2,6-pyridine-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.22, 111.64, 121.11, 122.18, 124.23, 127.33, 128.45, 129.70, 134.64, 138.69, 146.31, 148.12, 164.12; MS: m/z (%) 295 (M + 1, 40), 280, 254, 241, 232, 156, 114, 109, 106, 91, 81, 65, 29; Anal. calcd. (%) for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23. Found (%): C, 65.23; H, 4.61; N, 14.15.

N-(6-Methoxy-4-methylene-2-oxo-4*H*-benzo[e][1,3]-oxazin-3-yl)isonicotinamide (4e): This compound was prepared from **3e**. Yield *ca.* 74 %, white powder, m.p. 223-225 ºC; IR (KBr, ν_{max}, cm^{-1}): 1614 (=CH_2), 1679 (C=O_{amide}), 1721 (C=O), 3310 (NH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.05 (d, *J* = 2.5 Hz, 1H), 5.11 (d, *J* = 2.5 Hz, 1H), 7.35-7.94 (3H, $H_{aromatic}$), 8.20 (d, 2H, *J* = 5.90 Hz, 3,5-pyridine-H), 9.15 (d, 2H, *J* = 5.90 Hz, 2,6-pyridine-H), ^{13}C NMR (100 MHz, $CDCl_3$): δ 88.21, 111.63, 121.10, 122.19, 124.11, 127.13, 128.10, 129.71, 134.60, 138.01, 146.82, 148.11,164.92; MS: m/z (%) 311 (M + 1, 40), 310, 254, 241, 232, 156, 114, 109, 106, 91, 81, 29; anal. calcd. (%) for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.20; N, 13.50. Found (%): C, 61.43; H, 4.51; N, 13.15.

RESULTS AND DISCUSSION

A series of hydrazides **3** was prepared from the reaction of isonicotinic acid hydrazide (isoniazid) **1** with 2-hydroxy-acetophenone derivative **2** under microwave irradiation (**Scheme-I**).

Synthesis of hydrazides **3** compounds **3a-e** (Table-1) show in their IR spectra absorbance for the hydroxyl group at about 3350 cm^{-1}. Other major bands at 3235, 1700 and 1550 cm^{-1} which are attributed to ν(NH), ν(C=O) and ν(C=N), respectively. In ^{1}H NMR spectra the methyl group appears as a singlet about δ = 2.55 ppm. The signals at about δ = 13.20 ppm and δ = 11.57 ppm represent OH and NH, respectively. Upon addition of D_2O the intensities of both OH and NH protons significantly decrease, confirming the assignment. The ^{13}C NMR spectra showed the methyl group at 14.81 ppm. The signals at δ = 163.71 ppm and δ = 158.54 ppm represent C=O and C=N, respectively.

TABLE-1
HYDRAZIDES **3** DERIVATIVES

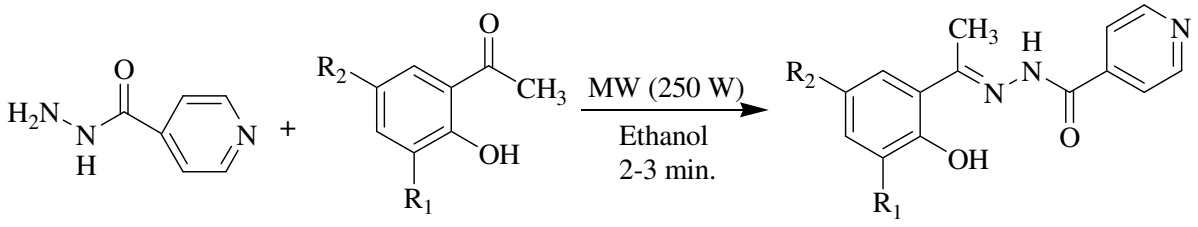
R_1	R_2	Product	Yield (%)
H	H	**3a**	94
H	Cl	**3b**	91
Cl	Cl	**3c**	86
H	CH_3	**3d**	91
H	OCH_3	**3e**	89

Although **3** could exist as E or Z isomers, it was used in the next step without investigating its stereochemistry. Previous work on the cyclization of similar hydrazones to give the benzotriazepine ring system did not investigate the stereo-chemistry of the hydrazones[20-22]. Nevertheless, in present case, if the cyclization proceeds *via* the enamine form as shown in **Scheme-III**, the C=N will be broken and its stereochemistry will be lost.

Treatment of the hydrazides **3a-e** with triphosgene in dichloromethane in the presence of triethylamine gave the N-(substituted 4-methylene-2-oxo-4*H*-benzo[e][1,3]oxazin-3-yl)isonicotinamide **4a-e** (**Scheme-II**, Table-2).

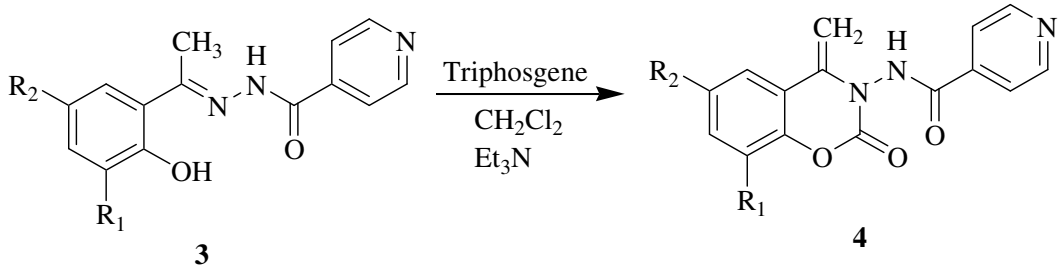
The cyclization of **3** to **4** did not proceed to form a seven membered ring(benzoxadiazepine) in a similar manner to that previously reported for the cyclization of hydrazones of 2-aminobenzophenone into benzotriazepines with phosgene and paraformaldehyde[20,22]. The methyl group in **3** is involved in the cyclization step *via* the formation of the enamine form of **3** which reacts with triphosgene to give the six membered ring product **4** rather than the seven membered ring (benzoxadiazepine) (**Scheme-III**). A similar cyclization across the enol form of acetophenone has previously been reported[22].

Compounds of type **4** show in their IR spectra absorbance for the exocylic double bond ν(=CH_2) at 1612 cm^{-1}. Another



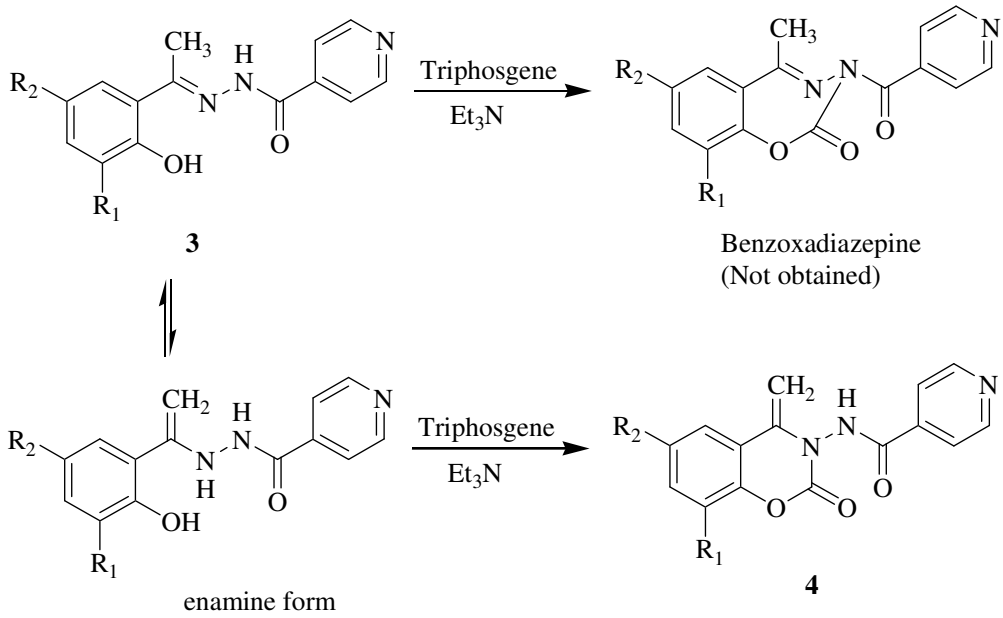
1 **2** **3**

Scheme-I



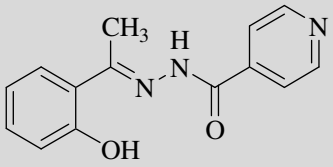
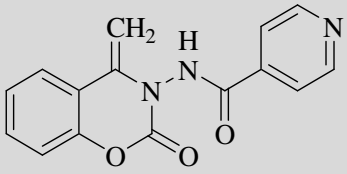
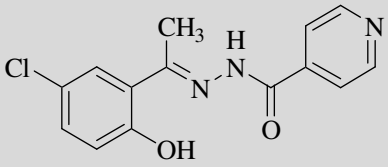
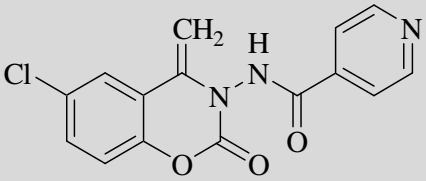
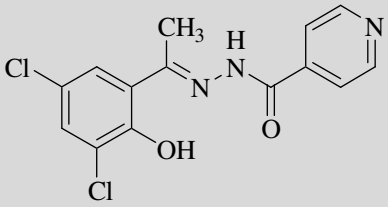
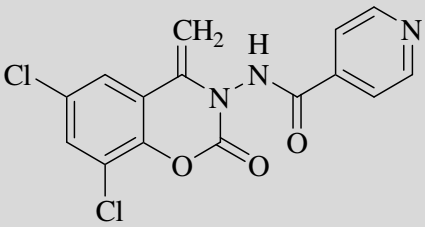
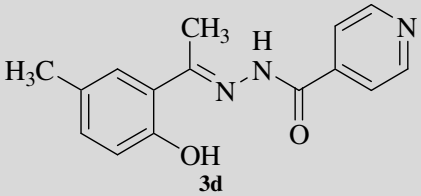
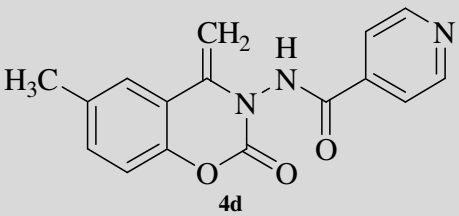
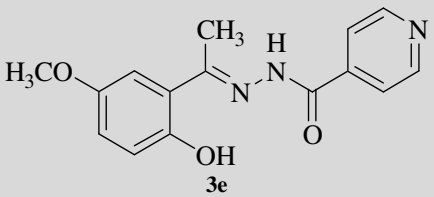
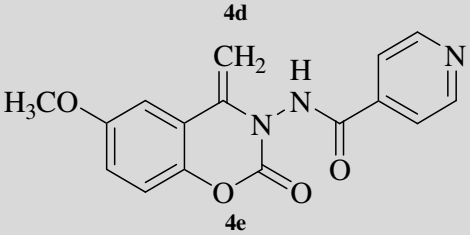
3 **4**

Scheme-II



Scheme-III

TABLE-2
PER CENT YIELD OF THE PRODUCTS **4a-e**

Reagent	Product	Yield* (%)
 **3a**	 **4a**	79
 **3b**	 **4b**	66
 **3c**	 **4c**	64
 **3d**	 **4d**	72
 **3e**	 **4e**	74

*Yields refer to isolated products.

important band occurs at 1673 cm^{-1} attributed to carbonyl-amide carbonyl and NH-amide absorption bands appear at 1726 and 3310 cm^{-1}, respectively. The protons of the latter group appear as two doublets at δ = 5.04 and 5.10 ppm with coupling constants of about 2.5 Hz in the ^{1}H NMR spectra. Furthermore, the ^{13}C NMR spectra show a distinct absorbance for the exocylic methylene group at about 88.56 ppm, which is in agreement with previous studies on related compounds[21,23-25].

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