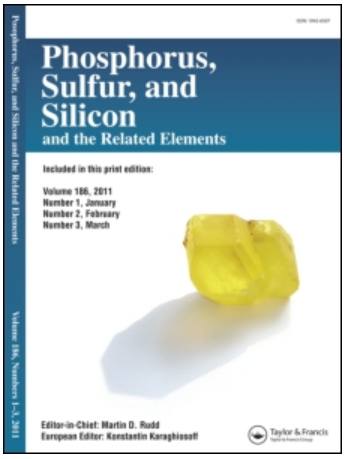

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Synthesis of 2([Methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl]imino)-1,3-thiazolan-4-ones and Their Mannich Bases

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*Isoxazolyl chloroacetamides (**2**) were obtained from 4-amino-3-methyl-5-styryl-isoxazoles (**1**) on reaction with chloroacetyl chloride. Cyclocondensation of **2** with NH_4SCN yielded 2([-methyl-5-(E)-2-aryl-1-ethenyl]-4-isoxazolylimino)-1,3-thiazolan-4-ones(**3**). Mannich reaction of **3** with formaldehyde and secondary amines gave isoxazolyl thiazolidinone Mannich bases (**4** and **5**).*

Keywords Isoxazolyl chloroacetamides; isoxazolyl thiazolidinones; Mannich bases

INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life; hence, they have attracted considerable attention in the design of biologically active molecules and advanced organic materials. Among a wide variety of heterocycles that have explored for developing pharmaceutically important molecules, thiazolidinones constitute an important group due to their wide variety of biological activities such as antitubercular,[1] anticonvulsant,[2] antifungal,[3] antitumor,[4] antimicrobial activities,[5] and are also used in the treatment of arthritis.[6] They have also been utilized as hypolipidemics and hypocholesteremics.[7] Thiazolidnone herbicides are the potent inhibitors of glucose incorporation into cell wall.[8] Besides this, they are proved to be calcium antagonists with both calcium overload inhibitors and antioxidant activity.[9]

Mannich bases are reported to possess potent antibacterial, antifungal, and anti-HIV activities.[10] Similarly, isoxazole unit constitutes an easily accessible nucleus that is present in a number of natural and

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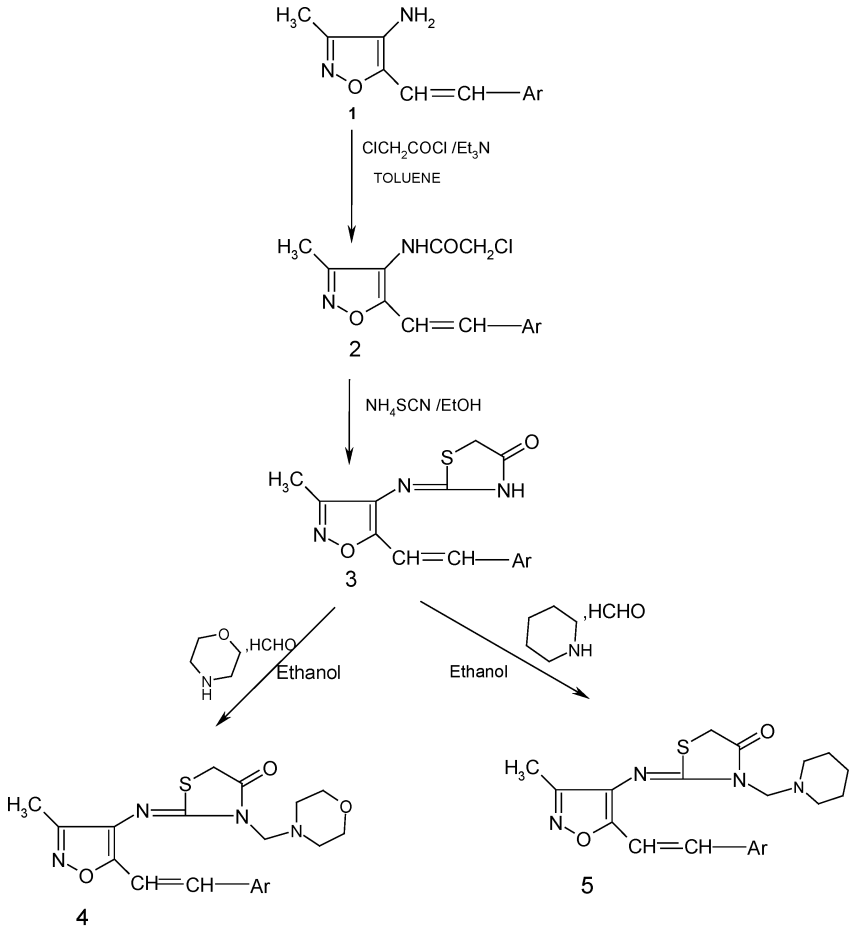
pharmacological compounds[11] and displays a wide range of organic reactivities and could be used as an effective means of preparing new molecular scaffolds.[12] Isoxazoles have been repeatedly shows as useful synthons in organic synthesis.[13]

Our literature survey revealed that when one biodynamic heterocyclic system was coupled with another, a molecule with enhanced biological activity[14,15] was produced. The chemistry of these linked heterocycles has been a fascinating field of investigation in medicinal chemistry as they have been found to exhibit enhanced biological profile.[16] In view of these observations, and also as a sequel to our search for biologically active nitrogen and sulfur heterocycles[17] linked to isoxazole rings, we planned to synthesize isoxazolyl thiazolidinone Mannich bases, which may be useful as bioactive compounds.

RESULTS AND DISCUSSION

The starting material, 4-amino-3-methyl-5-styrylisoxazoles[18] (**1**) were secured by reduction of 3-methyl-4-nitro-5-styrylisoxazoles[19] with stannous chloride and conc. hydrochloric acid. The reaction of 4-amino-3-methyl-5-styrylisoxazoles (**1**) with chloroacetyl chloride in the presence of trimethyl amine in dry benzene furnished *N*-1-[3-methyl5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl]-2-chloro acetamides (**2**). Compounds **2** on cyclocondensation with ammonium thiocyanate in refluxing ethanol afforded 2-([3-methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl]imino)1,3-thiazolan-4-ones (**3**). Compounds **2** displayed characteristic absorption bands in the IR spectra around 1675 cm^{-1} and 3310 cm^{-1} due to —C=O and —NH—functional groups respectively. ^1H NMR spectra of 2 exhibited a singlet around δ4.2 due to —CH_2—proton and a broad singlet around δ9.8 due to —NH—proton. The IR spectra of isoxazolyl thiazolidinones (**3**) exhibited strong absorption bands around 3160 and 1650 cm^{-1} due to —NH—and —C=O functional groups respectively. ^1H NMR spectra of 3 recorded in $CDCl_3$ confirmed the structural assignments. The newly formed thiazolan-4-one ring CH_2 protons resonated as a sharp singlet around δ4.0, whereas NH proton signal appeared at δ9.0

The isoxazolyl thiazolidinones (**3**) on reaction with 37% formaldehyde and morpholine/piperidine-hydrochloride in ethanol yielded Mannich bases *viz*., 2-([3-methyl-5-[(*E*)-2-aryl-1-ethenyl]-4-isoxazolyl] amino-3-morpholino methyl/ piperidino methyl)-1,3-thiazolan-4-ones (**4**) and (**5**), respectively. Compounds (**4**) and (**5**) have shown strong absorption band in the IR spectra around 1720 cm^{-1} due to C=O group. The NH functional group absorption band which appeared at 3160 cm^{-1} in its precursor, was absent in compounds **4** and **5**. Moreover, in the ^1H



2,3,4 and **5a** Ar, = C_6H_5
2,3,4 and **5b** Ar, = 4-$CH_3C_6H_4$
2,3,4 and **5c** Ar, = 4-$CH_3OC_6H_4$
2,3,4 and **5d** Ar, = 4-ClC_6H_4
2,3,4 and **5e** Ar, = 2-ClC_6H_4

SCHEME 1

NMR spectra of compounds **4** and **5** the signal at δ9.0, which is present in its precursor (**3**) was not present. This indicates that the NH group is involved in Mannich reaction in preference to methylene group.

In summary, we have prepared novel Mannich bases carrying isoxazole and thiazolidinone moieties. In view of potential activity of these

TABLE I Data of Compounds (2a–e)* and (3a–e)*

Compd.	M.p. (°C)	Yield (%)	Mol. formula (m.wt.)	Found (calcd.) % C	H	N	S
2a	125	60	$C_{14}H_{13}N_2ClO_2$ (276)	60.79 (60.86)	4.75 (4.71)	10.08 (10.14)	—
2b	105	65	$C_{15}H_{15}N_2ClO_2$ (290)	62.01 (62.06)	5.09 (5.17)	9.58 (9.65)	—
2c	110	60	$C_{15}H_{15}N_2ClO_3$ (306)	58.79 (58.82)	4.92 (4.90)	9.21 (9.15)	—
2d	135	72	$C_{14}H_{12}N_2Cl_2O_2$ (310)	54.23 (54.19)	3.91 (3.87)	9.01 (9.03)	—
2e	143	67	$C_{14}H_{12}N_2Cl_2O_2$ (310)	54.08 (54.19)	3.79 (3.87)	9.08 (9.03)	—
3a	80	65	$C_{15}H_{13}N_3O_2S$ (299)	60.15 (60.20)	4.37 (4.34)	14.01 (14.04)	10.62 (10.70)
3b	72	87	$C_{16}H_{15}N_3O_2S$ (313)	61.28 (61.34)	4.71 (4.79)	13.48 (13.41)	10.25 (10.22)
3c	76	82	$C_{16}H_{15}N_3O_3S$ (329)	58.39 (58.35)	4.59 (4.55)	12.67 (12.76)	9.69 (9.72)
3d	107	79	$C_{15}H_{12}N_3ClO_2S$ (333)	54.11 (54.05)	3.51 (3.60)	12.55 (12.61)	9.69 (9.60)
3e	112	75	$C_{15}H_{12}N_3ClO_2S$ (333)	54.01 (54.05)	3.69 (3.60)	12.57 (12.61)	9.62 (9.60)

*Compounds **2a–e** were recrystallized from aqueous methanol and **3a–e** from ethanol.

compounds, we predict that the newly synthesized Mannich bases may be drug candidates, and the activity data will be published elsewhere.

EXPERIMENTAL

All the melting points were determined on a Cintex melting point apparatus and are uncorrected. Analytical TLC was performed on Merck precoated 60 F_{254} silica gel plates. Visualization was done by exposing to Iodine vapor IR spectra (KBr pellet) were recorded on Perkin-Elmer BX series FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on a Varian Gemini 300 MHz spectrometer. Chemical shift values are given in ppm (δ) with tetramethylsilane as internal standard. Mass spectral measurements were carried out by EI method on a Jeol JMC-300 spectrometer at 70 eV. Elemental analyses were performed on a Carlo Erba 106 Perkin-Elmer model 240 analyzer.

The 4-Amino-3-methyl-5-styrylisoxazoles[18] (**1**) were prepared according to the literature procedure.

N 1-[3-Methyl-5-[(*E)-2-aryl-1-ethenyl]-4-isoxazolyl]-2-chloroacetamides (2)

4-Amino-3-methyl-5-styrylisoxazole (**1**) (0.01 mol), chloroacetyl chloride (0.01 mol), and triethylamine (0.5 ml) were taken in dry benzene. The contents were refluxed with stirring for 4–6 h. The precipitated triethyl-amine hydrochloride was removed by filtration. The gummy product obtained after the removal of solvent at ambient temperature was triturated with methanol. Recrystallization of the product was effected from aqueous methanol (Tables I and III).

2-([3-Methyl-5-[(*E)-2-phenyl-1-ethenyl]-4-isoxazolyl]imino)1,3-thiazolan-4-ones (3)

A mixture of compound **2** (0.01 mol) and NH_4SCN (0.015 mol) were taken in ethanol and refluxed on a water bath for 4–6 h. After completion of the reaction (monitored with TLC), the reaction mixture was concentrated by rotary evaporator and the residue was washed thoroughly with cold water and it was purified by recrystallization from ethanol (Tables I and III).

2-([3-Methyl-5-[(*E)-2-phenyl-1-ethenyl]-4-isoxazolyl]imino-3-(morpholino methyl)-1,3-thiazolan-4-ones (4)

A solution of 0.5 ml of 37% formaldehyde and morpholine (0.01 mol) were added dropwise with vigorous stirring to a suspension of isoxazolyl thiazolidinones **(3)** (0.01 mol) in 20 ml of ethanol. The reaction mixture was refluxed for 5–7 h. After completion of the reaction (monitored with TLC), the reaction mixture was concentrated by rotary evaporator. The crude solid obtained was purified by column chromatography to afford isoxazolyl thiazolidinone morpholino Mannich bases (Tables II and III).

2-([3-Methyl-5-[(*E*)-2-phenyl-1-ethenyl]-4-isoxazolyl]imino-3-(piperidino methyl)-1,3-thiazolan-4-ones (5)

A mixture of compound **3** (0.01 mol), 1 ml of 37% formaldehyde and piperidine hydrochloride (0.02 mol) were taken in ethanol (20 ml) and the contents were refluxed for 3–5 h. After completion of the reaction (monitored by TLC), the reaction mixture was allowed to cool and poured into ice-cold water. The separated solid was purified by recrystallization with aqueous methanol, to afford isoxazolyl thiazolidinone piperidino Mannich bases (Tables II and III).

TABLE II Physical Data of Compounds (4a–e)* and (5a–e)*

Compd.	M.p. (°C)	Yield (%)	Mol. formula (m.wt.)	Found (calcd.) % C	H	N	S
4a	70	67	$C_{20}H_{22}N_4O_3S$ (398)	60.18 (60.30)	5.58 (5.52)	14.12 (14.07)	8.01 (8.04)
4b	68	81	$C_{21}H_{24}N_4O_3S$ (412)	61.19 (61.16)	5.75 (5.82)	13.51 (13.59)	12.74 (12.69)
4c	65	84	$C_{21}H_{24}N_4O_4S$ (428)	58.80 (58.87)	5.53 (5.60)	13.01 (13.08)	7.53 (7.47)
4d	98	79	$C_{20}H_{21}N_4ClO_3S$ (432)	55.59 (55.55)	4.78 (4.86)	12.88 (12.96)	7.36 (7.40)
4e	105	75	$C_{20}H_{21}N_4ClO_3S$ (432)	55.48 (55.55)	4.88 (4.86)	12.91 (12.96)	7.48 (7.40)
5a	180	69	$C_{21}H_{24}N_4O_2S$ (396)	63.55 (63.63)	6.09 (6.06)	14.01 (14.04)	8.15 (8.08)
5b	171	76	$C_{22}H_{26}N_4O_2S$ (410)	64.31 (64.39)	6.39 (6.34)	13.58 (13.65)	7.82 (7.80)
5c	165	81	$C_{22}H_{26}N_4O_2S$ (426)	61.99 (61.97)	6.02 (6.10)	13.17 (13.14)	7.48 (7.51)
5d	195	85	$C_{21}H_{23}N_4ClO_2S$ (430)	58.65 (58.60)	5.28 (5.34)	13.09 (13.02)	7.38 (7.44)
5e	201	72	$C_{21}H_{23}N_4ClO_2S$ (430)	58.52 (58.60)	5.39 (5.34)	13.00 (13.02)	7.51 (7.44)

*Compounds **4a–e** were purified by column chromatography and **5a–e** were recrystallized from aq. ethanol.

TABLE III Spectral Data of Compounds 2,3,4, and 5

Compd.	IR (ν_{max} cm^{-1}) C=O	–NH–	^{1}HNMR (δ ppm)	Mass spectra Mass spectra m/z (%) $[M+H]^+$
2a	1692	3320	2.3 (s, 3H, isoxazole-CH_3), 4.2 (s, 2H, CH_2), 6.8 (d, 1H, CH =CH), 7.0 (d, 1H, CH =CH), 7.1–7.5 (m, 5H, Ar-H), and 9.9 (bs, 1H, NH)	277 (71)
2b	1675	3290	2.3 (s, 3H, isoxazole- CH_3), 2.4 (s, 3H, CH_3), 4.1 (s, 2H, CH_2), 6.8 (d, 1H, CH =CH), 7.0 (d, 1H, CH = CH), 7.1–7.5 (m, 4H, Ar-H), and 9.9 (bs, 1H, NH)	291 (66)

TABLE III Spectral Data of Compounds 2,3,4, and 5 *(Continued)*

Compd.	IR (ν_{max} cm^{-1}) C=O	IR (ν_{max} cm^{-1}) –NH–	^{1}HNMR (δ ppm)	Mass spectra Mass spectra m/z (%) $[M+H]^+$
2c	1679	3295	2.2 (s, 3H, isoxazole- CH_3), 3.7 (s, 3H, OCH_3), 4.2 (s, 2H, CH_2), 6.9 (d, 1H, CH =CH), 7.1 (d, 1H, CH =CH), 7.2–7.6 (m, 4H, Ar-H), and 9.5 (bs, 1H, NH)	307 (62)
2d	1681	3326	2.2 (s, 3H, isoxazole- CH_3), 4.1 (s, 2H, CH_2), 6.8 (d, 1H, CH =CH), 7.0 (d, 1H, CH =CH), 7.2–7.6 (m, 4H, Ar-H), and 9.4 (bs, 1H, NH)	311 (65)
2e	1682	3310	2.2 (s, 3H, isoxazole-CH_3), 4.2 (s, 2H, CH_2), 6.9 (d, 1H, CH =CH), 7.1 (d, 1H, CH =CH), 7.3–7.7 (m, 4H, Ar-H), and 9.2 (bs, 1H, NH)	311 (60)
3a	1672	3280	2.2 (s, 3H, isoxazole-CH_3), 4.0 (s, 2H, CH_2), 6.9 (d, 1H, CH =CH), 7.1–7.7 (m, 5H, Ar-H & 1H, CH =CH), and 9.0 (bs, 1H, NH)	300 (69)
3b	1665	3210	2.2 (s, 3H, isoxazole-CH_3), 2.4 (s, 3H, CH_3), 3.9 (s, 2H, CH_2), 6.8 (d, 1H, CH =CH), 7.0–7.5 (m, 4H, Ar-H & 1H, CH =CH), and 8.2 (bs, 1H, NH)	314 (42)
3c	1685	3310	2.3 (s, 3H, isoxazole-CH_3), 3.8 (s, 3H, OCH_3), 4.0 (s, 2H, CH_2), 6.9 (d, 1H, CH =CH), 7.1–7.6 (m, 4H, Ar-H & 1H, CH =CH), and 9.9 (bs, 1H, NH)	330 (52)
3d	1674	3250	2.2 (s, 3H, isoxazole-CH_3), 4.1 (s, 2H, CH_2), 6.9 (d, 1H, CH =CH), 7.1–7.6 (m, 4H, Ar-H & 1H, CH =CH), and 9.3 (bs, 1H, NH)	334 (46)
3e	1660	3190	2.3 (s, 3H, isoxazole-CH_3), 4.1 (s, 2H, CH_2), 6.8 (d, 1H, CH =CH), 7.0–7.5 (m, 4H, Ar-H & 1H, CH =CH), and 8.6 (bs, 1H, NH)	334 (73)

(Continued on next page)

TABLE III Spectral Data of Compounds 2,3,4, and 5 *(Continued)*

Compd.	IR (ν_{max} cm^{-1}) C=O	IR (ν_{max} cm^{-1}) –NH–	^{1}HNMR (δ ppm)	Mass spectra Mass spectra m/z (%) $[M+H]^+$
4a	1716	—	2.2 (s, 3H, isoxazole-CH_3), 2.7 (t, 4H, CH_2 NCH_2), 3.6 (t, 4H, CH_2-OCH_2), 3.9 (s, 2H, CH_2), 4.7 (s, 2H, NCH_2N), 6.8(d, 1H, CH =CH), 7.0 (d, 1H, CH =CH), and 7.4–7.8 (m, 5H, Ar-H)	399 (42)
4b	1720	—	2.3 (s, 3H, isoxazole-CH_3), 2.5 (s, 3H, CH_3), 2.8 (t, 4H, CH_2NCH_2), 3.7 (t, 4H, CH_2OCH_2), 3.9 (s, 2H, CH_2), 4.8 (s, 2H, NCH_2N), 6.7 (d, 1H, CH =CH), 7.0 (d, 1H, CH =CH), and 7.3–7.8 (m, 4H, Ar-H)	413 (33)
4c	1729	—	2.3 (s, 3H, isoxazole-CH_3), 2.8 (t, 4H, CH_2NCH_2), 3.7 (t, 4H, CH_2OCH_2), 3.9 (s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 4.9 (s, 2H, NCH_2N), 6.8 (d, 1H, CH =CH), 7.1 (d, 1H, CH =CH), and 7.2–7.7 (m, 4H, Ar-H)	429 (53)
4d	1721	—	2.2 (s, 3H, isoxazole-CH_3), 2.7 (t, 4H, CH_2NCH_2), 3.7 (t, 4H, CH_2OCH_2), 4.1 (s, 2H, CH_2), 4.8 (s, 2H, NCH_2N), 6.7 (d, 1H, CH =CH), 7.0 (d, 1H, CH =CH), and 7.2–7.6 (m, 4H, Ar-H)	433 (64)
4e	1725	—	2.1 (s, 3H, isoxazole-CH_3), 2.7 (t, 4H, CH_2NCH_2), 3.8 (t, 4H, CH_2OCH_2), 4.0 (s, 2H, CH_2), 4.7 (s, 2H, NCH_2N), 6.8 (d, 1H, CH =CH), 7.1 (d, 1H, CH =CH), and 7.3–7.7 (m, 4H, Ar-H)	433 (42)
5a	1718	—	1.6 (m, 6H, $(CH_2)_3$), 2.2 (s, 3H, isoxazole-CH_3), 2.8 (t, 4H, CH_2NCH_2), 4.0 (s, 2H, CH_2), 4.6 (s, 2H, NCH_2N), and 6.9–7.8 (m, 5H, Ar-H & 2H, CH =CH)	397 (49)

TABLE III Spectral Data of Compounds 2,3,4, and 5 *(Continued)*

Compd.	IR (ν_{max} cm^{-1}) C=O	IR (ν_{max} cm^{-1}) –NH–	^{1}HNMR (δ ppm)	Mass spectra Mass spectra m/z (%) $[M+H]^+$
5b	1715	—	1.7 (m, 6H, $(CH_2)_3$), 2.1 (s, 3H, isoxazole-CH_3), 2.4 (s, 3H, CH_3), 2.9 (t, 4H, CH_2NCH_2), 3.9 (s, 2H, CH_2), 4.7 (s, 2H, NCH_2N), and 6.9–7.7 (m, 4H, Ar-H & 2H, CH =CH)	411 (54)
5c	1724	—	1.6 (m, 6H, $(CH_2)_3$), 2.3 (s, 3H, isoxazole-CH_3), 2.8 (t, 4H, CH_2NCH_2), 3.7 (s, 3H, OCH_3), 4.1 (s, 2H, CH_2), 4.9 (s, 2H, NCH_2N), and 6.8–7.6 (m, 4H, Ar-H & 2H, CH =CH)	427 (45)
5d	1722	—	1.7 (m, 6H, $(CH_2)_3$), 2.2 (s, 3H, isoxazole-CH_3), 2.6 (t, 4H, CH_2NCH_2), 3.7 (s, 2H, CH_2), 4.7 (s, 2H, NCH_2N), and 6.9–7.6 (m, 4H, Ar-H & 2H, CH =CH)	431 (60)
5e	1720	—	1.5 (m, 6H, $(CH_2)_3$), 2.3 (s, 3H, isoxazole-CH_3), 2.7 (t, 4H, CH_2NCH_2), 3.8 (s, 2H, CH_2), 4.6 (s, 2H, NCH_2N), and 7.0–7.7 (m, 4H, Ar-H & 2H, CH =CH)	431 (69)

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