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Studies on arylfuran derivatives
Part VII. Synthesis and characterization of some Mannich bases carrying halophenylfuryl moieties as promising antibacterial agents

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Abstract

A series of 4-[5-(halophenyl)-2-furfurylidene)]amino-3-mercapto-5-substituted-1,2,4-triazoles (**3**) were synthesized. Aminomethylation of **3** with formaldehyde and a secondary amine furnished Mannich bases, **4**. Both Schiff bases and Mannich bases were characterized on the basis of IR, NMR, mass spectra1 data and elemental analysis. All the newly synthesized compounds were tested for their antibacterial activities. Some of them carrying morpholino and *N*-methylpiperazino residues were found to be promising antibacterial agents.

Keywords: Arylfuran derivatives; Schiff bases; Mannich bases; Antibacterial activity

1. Introduction

Triazoles are reported to possess significant antibacterial, antifungal and anthelminthic activities [1–5]. Further, arylfuran-2-carboxaldehyde derivatives are also found to possess antibacterial activity [6–8]. This gave a great impetus to the search for potential pharmacologically active drugs carrying arylfuran substituents. It is also reported that the introduction of halogen atom augments the antimicrobial properties of the system [9].

In recent years, Mannich bases have gained importance due to their application in pharmaceutical chemistry. They have been encountered with antibacterial, antiviral, antifungal, antimalarial and CNS depressant activities [10,11]. Many Mannich bases of 1,2,4-triazoles carrying *N*-methylpiperazine substituents possess protozoacidal and bactericidal activities. Hence, in continuation of our work on arylfuran derivatives [12–14] with enhanced therapeutic values and in order to modify the structure of nitrofuran drugs [15,16], we decided to synthesize a series of aminomethyl-3-substituted-4-(5-aryl-2-furfurylidene) amino-1,2,4-triazole-5-thiones (**4**) starting from the respective Schiff bases (**3**).

2. Chemistry

p-Chlorophenylfurfural and *p*-bromophenylfurfural were synthesized through the Meerwein reaction [17]. 3-Alkyl-substituted 4-amino-5-mercapto-*s*-triazoles (**1**) were prepared according to Baeyer's procedure [18] by refluxing thiocarbohydrazide with suitable aliphatic carboxylic acids. 3-Aryl-4-amino-5-mercapto-*s*-triazole was prepared by adopting the procedure of Reid and Heindel [19], viz. hydrazinolysis of the corresponding potassium aroyl dithiocarbazinates. In order to study the structure activity relationships, two halo substituents (X = Cl and Br) and three secondary amines, viz. morpholine, *N*-methylpiperazine and piperidine were used for the present investigation.

The triazoles (**1**) were condensed with *p*-halophenylfurfural (**2**) in the presence of a few drops of concentrated sulfuric acid as a catalyst to produce Schiff bases (**3**) in rather good yields. These Schiff bases (**3**) were then reacted with secondary amines in the presence of formaldehyde in ethanol or dimethylformamide–ethanol media to produce Mannich bases (**4**) (Scheme 1). The structures of Schiff bases (**3**) and Mannich bases (**4**) were established on the basis of elemental analysis, IR, NMR and mass spectral data. The characterization data of these compounds are given in Tables 1 and 2, respectively.

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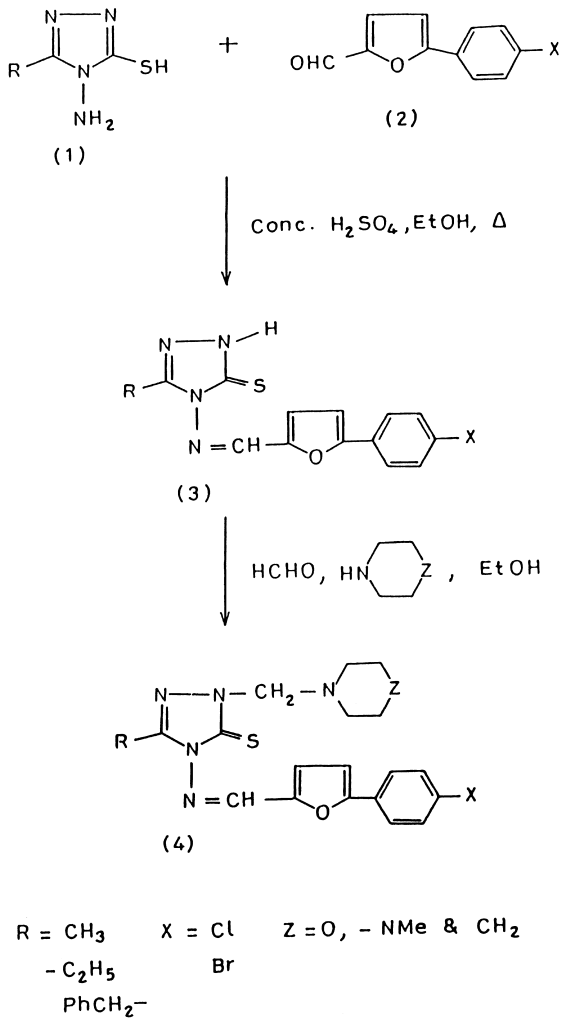


Scheme 1.

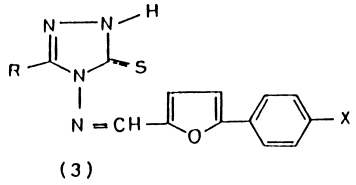
The reaction proceeds via the formation of immonium salt which subsequently attacks the N-1 of triazole giving rise to regioselective Mannich bases.

The IR spectrum of compound **3a** showed an absorption band at 1612 cm^{-1} indicating the presence of C=N in the ring. Thus the formation of an iminomethine functional group in the compound was indicated. The absorption band observed at 3096 cm^{-1} could be attributed to an NH/SH functional group, while the absorption band appearing at 738 cm^{-1} was due to the 1,4-disubstituted phenyl ring.

In the PMR spectra of hydrazones **3b** and **3d**, a sharp, singlet corresponding to one proton characteristic of the –N=CH– group was observed at δ 10.05. A downfield signal appearing at δ 13.42 is attributable to the –N=CH–SH moiety indicating the easy thione–thiol tautomerism. The AB coupling of the protons of the *para* substituted phenyl ring resulted in the formation of two doublets at δ 7.85 ($J = 8.0$ Hz) and 7.25 ($J = 8.0$ Hz) respectively, while the two β protons of the furan ring resonated as two doublets at δ 7.11 ($J = 3.7$ Hz) and 6.83 ($J = 3.7$ Hz) respectively integrating for two protons. The methyl protons of **3d** appeared as a sharp singlet at δ 1.32 ($J = 7.4$ Hz) and the ethyl protons of **3b** appeared as a triplet and a quartet at δ 1.32 ($J = 7.4$ Hz) and 2.44 ($J = 7.4$ Hz), respectively.

The mass spectra of compounds **3a** and **3d** were found to be consistent with the assigned structures. Molecular ions of these Schiff bases were observed at *m/z* 318/320 and 362/364, respectively, corresponding to the molecular formulae $C_{14}H_{11}ClN_4OS$ and $C_{14}H_{11}BrN_4OS$, respectively. The base peaks, however, were observed at *m/z* 203/205 and *m/z* 247/249, respectively, which indicate the formation of molecular ions of *p*-chlorophenylfuronitrile and *p*-bromophenylfuronitrile during the frag-

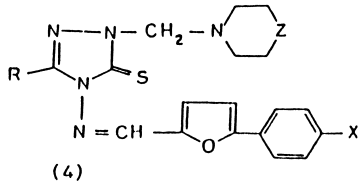
Table 1
Characterization data of 4-(5-aryl-2-furfurylidene)amino-3-mercapto-5-substituted-*S*-triazoles (**3**)[a]



Compound no.	X	R	M.p. (°C)	Yield (%)	Molecular formula	Anal. % N found (calc.)
3a	Cl	CH_3	288	84	$C_{14}H_{11}ClN_4OS$	17.75 (17.61)
3b	Cl	C_2H_5	243	86	$C_{15}H_{13}ClN_4OS$	17.12 (16.87)
3c	Cl	$PhCH_2$	235	81	$C_{20}H_{15}ClN_4OS$	14.49 (14.20)
3d	Br	CH_3	284	85	$C_{14}H_{11}BrN_4OS$	15.69 (15.46)
3e	Br	C_2H_5	240	87	$C_{15}H_{13}BrN_4OS$	15.24 (14.89)

[a]IR (ν cm^{-1}): **3a**, 3096 (NH/SH), 1612 (C=N), 738 (*p*-ArH); **3d**, 3056 (NH/SH), 1598 (C=N), 724 (*p*-ArH). ^{1}H NMR (90 MHz, DMSO-d_6): **3b**, δ, 13.42 (s, 1H, –N=C–SH), 10.05 (s, 1H, –N=CH–), 7.85 (d, 2H, *p*-chlorophenyl, $J = 8.0$ Hz), 7.25 (d, 2H, *p*-chlorophenyl, $J = 8.0$ Hz), 7.11 (d, 1H, furan 4H, $J = 3.7$ Hz), 6.83 (d, 1H, furan 3H, $J = 3.7$ Hz), 2.44 (q, 2H, CH_2, $J = 7.4$ Hz), 1.32 (t, 3H, CH_3, $J = 7.4$ Hz). **3d**, δ, 13.42 (s, 1H, –N=C=SH), 10.05 (s, 1H, –N=CH–), 7.65 (d, 2H, *p*-bromophenyl, $J = 8.4$ Hz), 7.45 (d, 2H, *p*-bromophenyl, $J = 8.4$ Hz), 7.19 (d, 1H, furan 4H, $J = 3.7$ Hz), 6.99 (d, 1H, furan 3H, $J = 3.7$ Hz), 1.21 (s, 3H, CH_3). Mass: **3a**, *m/z* 318/320 (M^+, 57.1%); **3d**, *m/z* 362/364 (M^+, 8.8%).

Table 2
Characterization data of 1-aminomethyl-3-substituted-4-(5-aryl-2-furfurylidene)amino-1,2,4-triazole-5-thiones (**4**)[a]



(4)

Compound no.	X	R	Z	Molecular formula	Yield (%)	M.p. (°C)	Anal. %N found (calc.)
4a	Cl	CH_3	O	$C_{19}H_{20}ClN_5O_2S$	61	176–178	16.85 (16.79)
4b	Cl	CH_3	NMe	$C_{20}H_{23}ClN_6OS$	59	260–262	19.29 (19.53)
4c	Cl	CH_3	CH_2	$C_{20}H_{22}ClN_5OS$	60	160–162	16.69 (16.86)
4d	Cl	C_2H_5	O	$C_{21}H_{22}ClN_5O_2S$	68	148–150	15 74 (15.80)
4e	Cl	C_2H_5	NMe	$C_{21}H_{25}ClN_6OS$	59	145–147	18.69 (18.92)
4f	Cl	C_2H_5	CH_2	$C_{21}H_{24}ClN_5OS$	62	150–152	16.10 (16.32)
4g	Cl	$PhCH_2$	O	$C_{25}H_{24}ClN_5O_2S$	72	138–140	14.02 (14.20)
4h	Cl	$PhCH_2$	NMe	$C_{26}H_{27}ClN_6OS$	78	124–126	16.38 (16.60)
4i	Cl	$PhCH_2$	CH_2	$C_{26}H_{26}ClN_5OS$	69	122–123	14.04 (14.26)
4j	Br	CH_3	O	$C_{19}H_{20}BrN_5O_2S$	63	196–198	15.06 (15.18)
4k	Br	CH_3	NMe	$C_{20}H_{23}BrN_6OS$	61	178–180	17.38 (17.72)
4l	Br	CH_3	CH_2	$C_{20}H_{22}BrN_5OS$	52	167–169	15.43 (15.25)
4m	Br	C_2H_5	O	$C_{20}H_{22}BrN_5O_2S$	79	148–150	14.56 (14.74)
4n	Br	C_2H_5	NMe	$C_{21}H_{25}BrN_6OS$	64	138–140	17.39 (17.21)
4o	Br	C_2H_5	CH_2	$C_{21}H_{24}BrN_5OS$	65	149–151	14.68 (14.80)

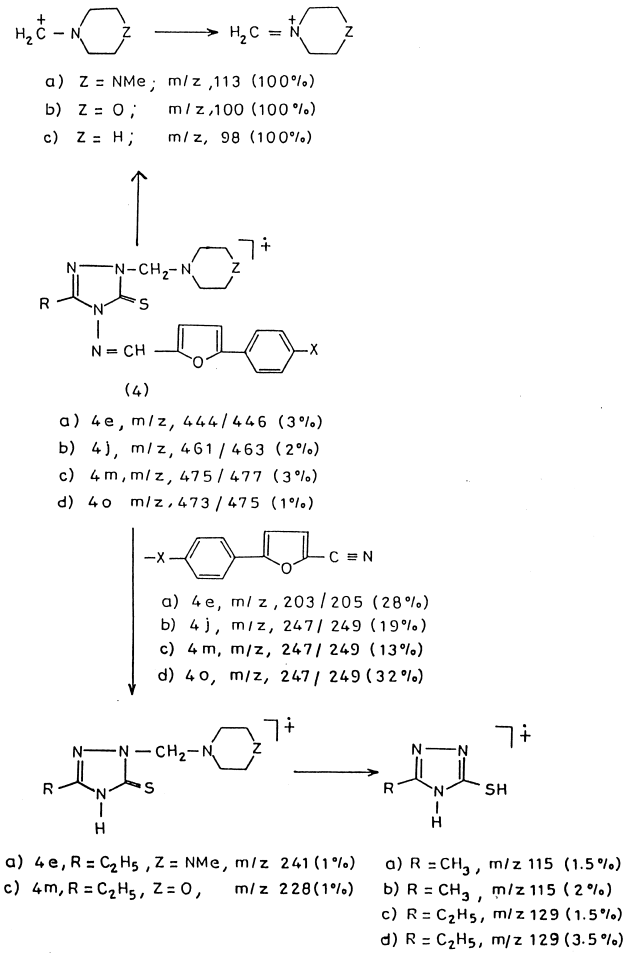
[a] IR (ν cm^{-1}): **4a**, 1612 (C=N), 1278 (C=S) 724 (*p*-ArH); **4c**, 1598 (C=N), 1278 (C=S), 724 (*p*-ArH); **4d**, 1600 (C=N), 1278 (C=S), 738 (p-ArH); **4e**, 1612 (C=N), 1278 (C=S), 724 (*p*-ArH); **4g**, 1598 (C=N), 1278 (C=S), 724 (*p*-ArH). ^{1}H NMR (270 MHz, DMSO-d_6): (δ ppm), **4a**, 9.91 (s, 1H, –N=CH–), 8.15 (d, 2H, $J = 8.2$ Hz, *p*-chlorophenyl), 7.75 (d, 2H, $J = 8.2$ Hz, *p*-chlorophenyl), 7.65 (d, 1H, $J = 3.5$ Hz, furan 4H), 7.45 (d, 1H, furan 3H, $J = 3.5$ Hz), 5.15 (s, 2H, $-NCH_2N-$), 3.68 (t, 4H, $-CH_2O-$, $J = 7.4$ Hz), 2.65 (t, 4H, $-CH_2-O-CH_2-$, $J = 7.4$ Hz), 1.31 (s, 3H, CH_3). **4b**, 9.75 (s, 1H, –N=CH–), 7.89 (d, 2H, *p*-chlorophenyl, $J = 8.5$ Hz), 7.58 (d, 2H, *p*-chlorophenyl, $J = 8.5$ Hz), 7.51 (d, 1H, furan 4H, $J = 3.3$ Hz), 7.36 (d, 1H, furan 3H, $J = 3.3$ Hz), 5.01 (s, 2H, $-NCH_2N-$), 3.35 (s, 3H, $-NCH_3$), 2.66 (t, 4H, $-CH_2-O-CH_2-$, $J = 7.4$ Hz), 2.37 (t, 4H, $-CH_2-N(Me)-CH_2-$, $J = 7.4$ Hz), 1.34 s, 3H, CH_3). **4e**, 9.76 (s, 1H, –N=CH–), 7.88 (d, 2H, *p*-chlorophenyl, $J = 8.5$ Hz), 7.59 (d, 2H, *p*-chlorophenyl, $J = 8.5$ Hz), 7.43 (d, 1H, furan 4H, $J = 3.6$ Hz), 7.36 (d, 1H, furan 3H, $J = 3.5$ Hz), 5.02 (s, 2H, $-NCH_2N-$), 3.35 (s, 3H, $-NCH_3$), 2.74 (q, 2H, CH_2, $J = 7.3$ Hz), 2.67 (t, 4H,$-CH_2-N-CH_2-$, $J = 7.3$ Hz), 2.51 (t, 4H, $-CH_2-N$ (Me)–CH_2, $J = 5.4$ Hz), 1.23 (t, 3H, CH_3, $J = 7.4$ Hz). Mass, **4e**, *m/z* 444/446 (M^+, 3%), 203/205 (*p*-chlorophenylfuronitrile, 28%), 113 (*N*-methylpiperazinomethyl cation, 100%). **4j**, *m/z* 461/463 (M^+, 2%), 247/249 (*p*-bromophenylfuronitrile, 19%), 100 (morpholinomethyl cation, 100%). **4m**, *m/z* 475/477 (M^+, 3%), 460 ($M^+ - CH_3$), 247/249 (*p*-bromophenylfuronitrile 13%), 100 (morpholinomethyl cation, 100%). **4o**, *m/z* 473/475 (M^+, 1%), 247/249 (*p*-bromophenylfuronitrile, 32%), 98 (piperidinomethyl cation, 100%).

mentation of parent, molecular ions, analogous to our earlier observations of the mass spectra of arylfuran heterocycles [12].

In the IR spectrum of the Mannich base **4c**, the absorption band at 1598 cm^{-1} corresponds to C=N of the ring, while the absorption band appearing at 1278 cm^{-1} could be attributed to the C=S functional group.

In the NMR spectrum of compound **4a**, the $-NCH_2N-$ protons resonated as a singlet at δ 5.15 integrating for two protons. The signal due to the methyl protons of the triazole moiety appeared at δ 1.31 as a singlet. The $-CH_2-O-CH_2-$ protons of the morpholine residue appeared as a triplet at δ 3.68 ($J = 7.4$ Hz), while the $-CH_2-N-CH_2-$ protons of the morpholine residue resonated as a triplet at 2.65 ($J = 7.4$ Hz). The aromatic proton signals of the *p*-chlorophenyl group appeared as two doublets at δ 8.15 ($J = 8.2$ Hz) and 7.75 ($J = 8.2$ Hz), respectively, integrating for four protons. The two β protons of the furan ring appeared as two doublets at δ 7.65 ($J = 3.5$ Hz) and 7.45 ($J = 3.5$ Hz), respectively, integrating for two protons. The signal of the –N=CH– proton was seen as a singlet at δ 9.91. The NMR spectral data of some of Mannich bases are given in Table 2.

The mass spectra of Mannich bases **4e**, **4j**, **4m** and **4o** conformed with the assigned structures. The molecular ion peaks were observed at *m/z* 444/446, 461/463, 475/477 and 473/475 which correspond to the molecular formulae $C_{21}H_{25}ClN_6OS$, $C_{19}H_{20}BrN_5O_2S$, $C_{20}H_{22}BrN_5O_2S$ and $C_{21}H_{24}BrN_5OS$, respectively. These molecular ions underwent fragmentations to produce ions at *m/z* 113, 100 and 98 as base peaks which correspond to *N*-methylpiperazinomethyl, morpholinomethyl and piperidinomethyl cations, respectively. The peaks appearing at *m/z* 203/205 and 247/249 were ascribed to the formation of *p*-chlorophenylfuronitrile and *p*-bromophenylfuronitrile. The mass spectral fragmentation patterns of these Mannich bases along with their relative abundances of daughter ions are given in Scheme 2.



Scheme 2.

3. Experimental

Melting points were determined by capillary method and are uncorrected. The IR spectra (in KBr pellets) were recorded on a Shimadzu FT-IR 157 spectrophotometer. PMR spectra were recorded either on a Perkin–Elmer EM-390 (90 MHz) or on a Bruker WH-200 (270 MHz) spectrometer using TMS as an internal standard. The mass spectra were recorded on a Jeol JMS-D 300 spectrometer operating at 70 eV. The purity of the compounds was checked by thin layer chromatography (TLC) on silica gel plate.

*3.1. 3-Substituted 4-[5-(halophenyl)-2-furfurylidene]-amino-5-mercapto-1,2,4-triazoles (**3**)*

To a suspension of suitably substituted halophenyl furfuraldehyde (**2**; 10 mmol) in dioxane (15 ml), an equimolecular amount of the corresponding amino mercapto triazole (**1**) was added. The suspension was heated until a clear solution was obtained. Then, a few drops of concentrated sulphuric acid were added as a catalyst and the solution was refluxed for 3–4 h on a water bath. The precipitated solid was filtered off and recrystallized from a mixture of dimethylformamide and ethanol (2:1) to yield the title compounds (**3**).

*3.2. 1-Aminomethyl-3-substituted 4-5-[4-halophenyl)-2-furfurylidene]amino-1,2,4-triazole-5-thiones (**4**)*

The Schiff base (**3**; 10 mmol) was dissolved in ethanol or a mixture of ethanol and dimethylformamide (2:1). Then, formaldehyde (40%, 1.5 ml) and secondary amine (10 mmol) in ethanol were introduced to this solution. The mixture was stirred for 1–2 h and kept overnight at room temperature. The resulting solid separated was collected by filtration, washed with ethanol and recrystallized from a mixture of dimethylformamide and ethanol (2:1) to yield the title compounds.

4. Antibacterial activity

The newly synthesized compounds, **4**, were initially screened for their in vitro antibacterial activities against *Escherischia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Bacillus subtilis* according to the disc diffusion method [20]. The minimal inhibitory concentrations (MIC values) of the above compounds were determined by serial dilution method. Furacin was used as a standard drug for comparison. The results of these studies are given in Table 3.

The antibacterial screening data indicate that Mannich base **4b** carrying *N*-methylpiperazine and *p*-chlorophenyl-furyl groups showed excellent antibacterial activity against *S. aureus*, *P. aeruginosa* and *B. subtilis*. The compound **4d** carrying a morpholino moiety exhibited excellent antibacterial activity against *P. aeruginosa* and *B. subtilis*. The compounds **4f** and **4g** also possessed good antibacterial activities against *P. aeruginosa* and *B. subtilis*, respectively. The antibacterial activities of the remaining compounds

Table 3
Antibacterial activity data of 1-aminomethyl-3-substituted-4-[5-aryl-2-furfurylidene]amino-1,2,4-triazole-5-thiones (**4**)

Compound no.	Minimum inhibitory concentration μg/ml			
	E. coli	*S. aureus*	*P. aeruginosa*	*B. subtilis*
4a	25	25	12.5	12.5
4b	12.5	3	6	6
4c	12.5	12.5	12.5	12.5
4d	6	12.5	6	6
4e	6	12.5	12.5	12.5
4f	12.5	12.5	6	12.5
4g	6	25	12.5	6
4h	25	25	12.5	12.5
4j	12.5	12.5	12.5	6
4k	12.5	25	6	6
4l	12.5	12.5	6	12.5
4n	12.5	12.5	6	6
4o	6	12.5	6	6
Furacin (standard)	6	12.5	12.5	12.5

were comparable with that of furacin especially against *S. aureus*, *P. aeruginosa* and *B. subtilis*.

The compounds **4k**, **4l**, **4n**, and **4o** carrying a *p*-bromophenyl group showed excellent antibacterial activity against *P. aeruginosa* and compared with furacin. However, there is no substantial difference of activities observed between two series of compounds carrying *p*-chlorophenylfuryl and *p*-bromophenylfuryl groups.

It was concluded that some of the compounds of the series were found to be promising antibacterial agents and hence deserve further pharmacological investigation.

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