

Syntheses and Biological Activity of Some Novel Mannich Bases

FREDDY H. HAVALDAR* and SUSHIL KUMAR J. MISHRA
*Nadkarny-Sacasa Research Laboratory, Department of Chemistry,
St. Xavier's College, Mumbai-400 001, India*

3-Bromo-4-methoxybenzoyl hydrazine (1) was reacted with phenyl isothiocyanate to yield 1-(3'-bromo-4'-methoxybenzoyl)-4-phenylthiosemicarbazide (2) which on cyclization in alkaline medium afforded 3-(3'-bromo-4'-methoxyphenyl)-4-phenyl-1,2,4-triazolin-5-thione (3). The cyclized compound (3) on aminomethylation with formaldehyde and different amines furnished 3-(3'-bromo-4'-methoxyphenyl)-1-(substituted aminomethyl)-4-phenyl-1,2,4-triazolin-5-thiones (4a-e). The structures of the newly synthesized compounds have been established by analytical and spectral methods. These compounds have also been screened for their biological activity.

Key Words: Synthesis, Mannich bases, Biological activity.

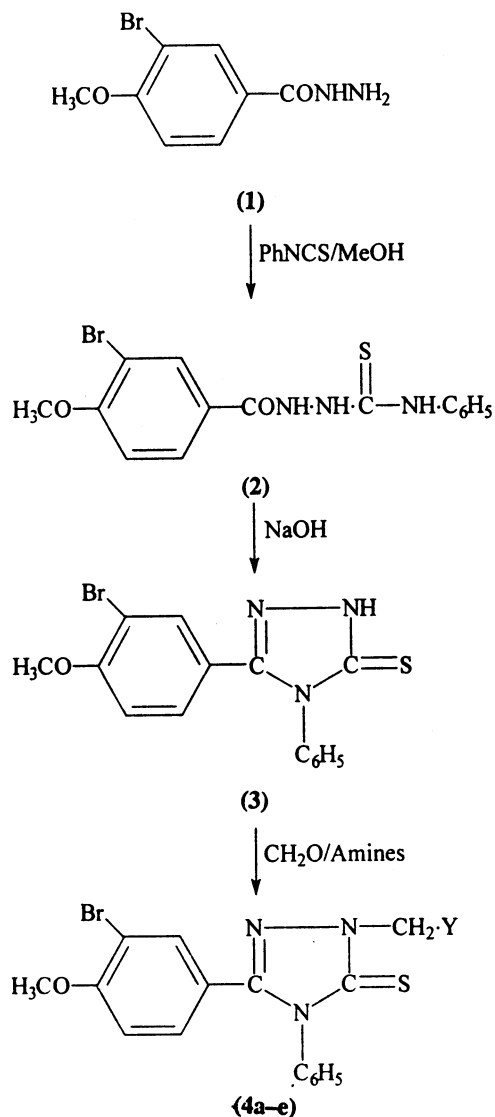
INTRODUCTION

Mannich bases¹ having 1,2,4-triazolin-5-thione moiety are found to possess good anti-leishmanial activity. Mannich bases^{2, 3} are employed as intermediates in chemical syntheses and are found to be potential analgesic and antibiotic drugs. Thus Mannich reaction has become an important method for the syntheses of medicinally important compounds. These reports prompted us to synthesize some new Mannich bases possessing better biological activity.

RESULTS AND DISCUSSION

The starting compound, 3-bromo-4-methoxybenzoyl hydrazine⁴ (1) required for the preparation of the target compounds, was prepared from methyl ester of 4-methoxybenzoic acid by bromination and subsequent hydrazinolysis. The hydrazide (1) was reacted with equimolar proportion of phenyl isothiocyanate using methanol as solvent to give 1-(3'-bromo-4'-methoxybenzoyl)-4-phenylthiosemicarbazide (2). The compound (2) was cyclized in presence of sodium hydroxide solution to yield 3-(3'-bromo-4'-methoxyphenyl)-4-phenyl-1,2,4-triazolin-5-thione (3). The aminomethylation of the compound (3) with formaldehyde and different amines afforded 3-(3'-bromo-4'-methoxyphenyl)-1-(substituted aminomethyl)-4-phenyl-1,2,4-triazolin-5-thiones (4a-e) (Scheme-1). The characteristic properties of the compounds (4a-e) are presented in Table-1.

Screening for biological activity: The compounds (4a-e) synthesized were screened *in vitro* for their antibacterial activity against *Staphylococcus aureus*,



Scheme-I

Escherichia coli, *Bacillus subtilis* and *Salmonella typhosa* by the ditch-plate technique⁵ and for antifungal activity against *Aspergillus niger*, *Candida albicans*, *Cryptococcus neoformans* and *Thielaviopsis paradoxa* by paper disc diffusion method 6 using concentrations of 2 and 5 mg/mL. Nutrient agar was employed as culture medium and DMF was used as solvent control for both antibacterial and antifungal activity. The results of such studies are given in Table-2.

TABLE-1
CHARACTERIZATION DATA OF 3-(3'-BROMO-4'-METHOXYPHENYL)-1-(SUBSTITUTED AMINOMETHYL)-4-PHENYL-1,2,4-TRIAZOLIN-5-THIONES (4a-e)

Compd.	Y	m.f.	m.p. (°C)	Yield (%)	Analysis % N	
					Requires	Found
4a	Anilino	C ₂₂ H ₁₉ N ₄ OSBr	180	74	12.00	12.03
4b	4-Methoxyanilino	C ₂₃ H ₂₁ N ₄ O ₂ SBr	102	76	11.27	11.31
4c	N-methylanilino	C ₂₃ H ₂₁ N ₄ OSBr	95	58	11.64	11.66
4d	Morpholino	C ₂₀ H ₂₁ N ₄ O ₂ SBr	90	92	12.15	12.18
4e	Piperidino	C ₂₁ H ₂₃ N ₄ OSBr	80	87	12.20	12.25

TABLE-2
BIOLOGICAL ACTIVITY DATA

Antibacterial activity								
Compd.	<i>S. aureus</i>		<i>E. coli</i>		<i>B. subtilis</i>		<i>S. typhosa</i>	
	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL
4a	-	+	-	-	-	-	+	+
4b	-	-	-	+	+	+	-	-
4c	-	+	-	-	-	-	-	+
4d	-	-	+	+	+	+	-	-
4e	+	+	+	++	-	+	+	++

Antifungal activity								
Compd.	<i>A. niger</i>		<i>C. albicans</i>		<i>C. neoformans</i>		<i>T. paradoxa</i>	
	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL	2 mg/mL	5 mg/mL
4a	+	+	-	+	-	-	+	+
4b	-	-	-	+	+	+	-	-
4c	-	-	-	+	-	-	-	-
4d	+	++	+	+	+	++	-	+
4e	-	+	+	+	+	+	+	+

Inhibition zone diameter in mm: (-) <11 mm; (+) 11-14 mm; (++) 15-18 mm

EXPERIMENTAL

All the melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm⁻¹) were recorded on SHIMADZU 8201 PC FTIR spectrophotometer. ¹H NMR spectra were recorded on a Varian 300 MHz NMR spectrophotometer using CDCl₃ as solvent and TMS as internal standard (chemical shifts in δ ppm). The purity of the compounds was monitored by thin layer chromatography.

1-(3'-Bromo-4'-methoxybenzoyl)-4-phenylthiosemicarbazide (2)

3-Bromo-4-methoxybenzoyl hydrazine (1) (3.43 g, 0.014 mol) was dissolved in 40 cm³ hot methanol. Phenyl isothiocyanate (1.67 cm³, 0.014 mol) was added to the clear solution and the reaction mixture was refluxed for 0.5 h. The solid separated on cooling was filtered and crystallized from petroleum ether (60-

80°C); yield (4.42 g, 83%); m.p. 190°C; Found: C, 47.40; H, 3.75; N, 11.08; C₁₅H₁₄N₃O₂SBr requires: C, 47.37; H, 3.68; N, 11.05%; IR (cm⁻¹) (KBr) 3320 ν(N—H), 3150 ν(C—H, aromatic), 2960 ν(C—H), 1630 ν(C=O), 1550, 1500, 1360 ν(C=C, aromatic), 1280 ν(C—O), 1160–820 ν(C—C), 1050 ν(C—N), 1020 ν(C=S), 500 ν(C—Br).

3-(3'-Bromo-4'-methoxyphenyl)-4-phenyl-1,2,4-triazolin-5-thione (3)

1-(3'-Bromo-4'-methoxybenzoyl)-4-phenylthiosemicarbazide (2) (3.80 g, 0.01 mol) was dissolved in 50 cm³ of 5 per cent sodium hydroxide. The reaction mixture was refluxed for 0.5 h, cooled to room temperature and then neutralized with dilute hydrochloric acid. A white crystalline compound obtained was filtered, washed with cold water and crystallized from N,N-dimethylformamide; yield (2.90 g, 80%); m.p. 260°C; Found: C, 49.76; H, 3.35; N, 11.63. C₁₅H₁₂N₃OSBr requires: C, 49.72; H, 3.31; N, 11.60%; IR (cm⁻¹) (KBr) 3050 ν(N—H), 2900 ν(C—H, aromatic), 2800 ν(C—H), 1610 ν(C=N), 1500, 1470, 1420 ν(C=C, aromatic), 1280 ν(C—O), 1180–820 ν(C—C), 1050 ν(C—N), 1010 ν(C=S), 570 ν(C—Br).

3-(3'-Bromo-4'-methoxyphenyl)-1-(substituted aminomethyl)-4-phenyl-1,2,4-triazolin-5-thiones (4a–e)

3-(3'-Bromo-4'-methoxyphenyl)-4-phenyl-1,2,4-triazolin-5-thione (3) (0.91 g, 0.0025 mol) was dissolved in 10 cm³ N,N-dimethylformamide. A slight excess of formaldehyde (0.083 cm³, 0.003 mole) and appropriate amine (0.0025 mol) was added with vigorous stirring. The reaction mixture was refluxed for about 1 h, then cooled and poured into crushed ice. The crystalline product obtained was filtered, washed with water and recrystallized from N,N-dimethylformamide (4e); IR (cm⁻¹) (KBr) 3050 ν(C—H, aromatic), 2936 ν(C—H), 1605 ν(C=N), 1500, 1416, 1327 ν(C=C, aromatic), 1274 ν(C—O), 1156–814 ν(C—C), 1053 ν(C—N), 1016 ν(C=S), 569 ν(C—Br); NMR (CDCl₃) δ 1.6 (m, 6H, —CH₂—CH₂—CH₂ of piperidine), 2.8 (t, 4H, —CH₂—N—CH₂), 3.9 (s, 3H, —OCH₃), 5.2 (s, 2H, —N—CH₂—N), 7.2–8.1 (m, 8H, ArH).

The characterization data of compounds (4a–e) have been given in Table-1.

REFERENCES

1. R.S. Varma, Vinita Bajpai and A. Kapil, *Indian J. Heterocyclic Chem.*, **10**, 17 (2000).
2. J.R. Dimmock, S.K. Raghavan, B.M. Logan and G.E. Bigam, *J. Med. Chem.*, **18**, 249 (1983).
3. H. Bundgaard, *Methods in Enzymology*, **112**, 347 (1985).
4. B.S. Holla, K.N. Poojary, B. Kalluraya and P.V. Gowda, *Indian J. Heterocyclic Chem.*, **5**, 273 (1996).
5. C.H. Collins and P. M. Lyne, *Microbiological Methods*, 3rd Edn., Butterworths, London, p. 424 (1970).
6. H.W. Seeley and P.J. Van Denmark, *Microbes in Action*, W.H. Freeman & Co., USA (1972).