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Note

Synthesis and characterization of new isoxazoles derived from benzosuberones

Venkateswarlu Peesapati* & Srinivas Bathini

Industrial Chemistry Research Lab, Center for Environment, I.S.T, J.N.T.University, Kukatpally, Hyderabad 500 072, India

E-mail: vpeesapati@yahoo.com

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6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-bezo[a]cyclohepten-5-ones **2a-g,** are obtained by the condensation of 3-methyl benzocyclohepten-5-one **1** with appropriate aromatic aldehydes on reaction with hydroxylamine hydrochloride in alkaline medium to give 9-methyl-3-phenyl-3a,4,5,6-tetrahydro-3H-benzo [6,7] cyclohepta [*c*] isoxazole derivatives **3a-g**.

Keywords: Isoxazoles, benzosuberones

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Literature survey reveals that various oxazoles, isoxazoles and their N-bridged heterocyclic derivatives possess a wide spectrum of pharmacological properties. Furthermore, a large number of isoxazoline derivatives have been found to exhibit antifungal and anticonvulsant activity[1-5]. Prompted by these observations and in continuation of our work on the synthesis of biologically active nitrogen and sulfur containing heterocycles[6], we report in this paper the conversion of 6-arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-5-ones **2a-g** into derivatives of a new heterocyclic system containing isoxazoline moiety.

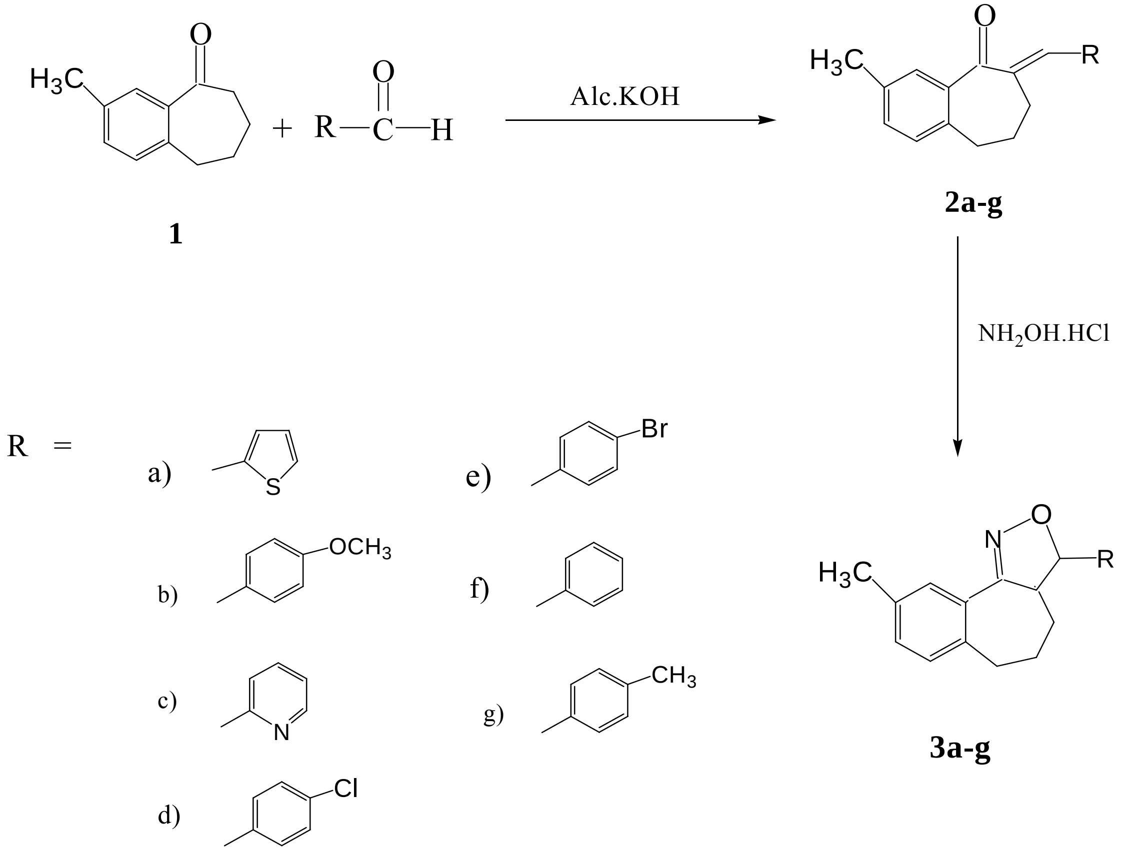
6-Arylidene-3-methyl-6,7,8,9-tetrahydro-5*H*-benzo[a]cyclohepten-5-ones **2a-g** were obtained by the condensation of 3-methyl-6,7,8,9-tetrahydro-5*H*-benzo [a] cyclohepten-5-ones[7] **1** with appropriate aromatic aldehydes. In the enones **2a-g**, the olefinic proton =CH-Ar appeared at δ 7.80 in their ^{1}H NMR spectra.

Cycloaddition of **2a-g** with hydroxylamine hydrochloride in alkaline medium yielded 9-methyl-3-phenyl-3a,4,5,6-tetrahydro-3H-benzo [6,7]cyclohepta[c] isoxazole derivatives **3a-g** (**Scheme I)**. The IR spectra of **3a-g** exhibited a band due to -C-O-N- (1246-1261 cm^{-1}) and C=N (1600-1610 cm^{-1}) respectively, which indicates the presence of isoxazoline ring. Similarly, the absence of C=O band proves the formation of the ring. Further, in their ^{1}H NMR spectra, disappearance of the olefinic proton (=CH-Ar) at δ 7.80 and appearance of a doublet at δ 3.30-3.40 (1H, d, J = 4.3-5.0 Hz, -CH-Ar) and δ 2.85-3.00 (1H, m, isoxazoline bridge proton –CH) confirms the presence of oxazoline ring. The aryl protons resonate as multiplets in the range of δ 6.80-7.55. The proton signals of methyl group and aliphatic protons appeared in the expected region[8].

Experimental Section

Melting points were determined using Gallankamp apparatus and are uncorrected. IR spectra were recorded on a FT-IR 1605 Perkin-Elmer; ^{1}H NMR in $CDCl_3$ on a Varian FT-80A spectrometer with TMS as an internal standard; and mass spectra on a VG-micromass 7070H mass spectrometer. TLC was run on silica gel G coated plates and iodine vapour as visualizing agent.

9-Methyl-3-thiophene-3a,4,5,6-tetrahydro-3H-benzo[6,7]cyclohepta[c] isoxazole (3a-g) General procedure. A mixture of **2a-g** (0.00068 mole) and hydroxylamine hydrochloride (0.00068 mole) in 2% ethonolic sodium hydroxide solution (5 mL) was heated under reflux for 3 hr. The progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed under reduced pressure and the residue was added to ice water (15 mL). The resulting solution was neutralised with dilute hydrochloric acid and extracted with chloroform (20 mL). Upon evaporation, the organic layer gave the crude product, which was purified by preparative TLC using 10% ethyl acetate-petroleum ether afforded products **3a-g**. Physical, analytical and spectral data of **3a-g** are given in **Table I**.



Scheme I

Table I — Physical and spectral data of the compounds **3a-g**

Compd	m.p. °C	Yield (%)	(Mol.formula) (mol.wt)	Found (Calcd) %			IR (cm^{-1})	^{1}H NMR (δ, ppm)
				C	H	N		
3a	70-72	68	$C_{17}H_{17}NOS$ (283)	72.04 (72.08	5.98 6.00	4.90 4.94)	1259 (-C-O-N), 1605 (C=N).	1.80-1.95 (2H, m, 4-CH$_2$), 2.00- 2.15 (2H, m, 5-CH$_2$), 2.35 (3H, s, 9-CH$_3$), 2.55-2.78 (2H, m, 6-CH$_2$), 2.85-3.10 (1H, m, 2-CH), 3.45-3.55 (1H, d, J=4.5 Hz, 3-CH) and 6.80-7.55 (6H, m, Ar-CH).
3b	132-135	70	$C_{20}H_{21}NO_2$ (307)	78.14 (78.17	6.82 6.84	4.53 4.56)	1246 (-C-O-N), 1609 (C=N).	1.60-1.78 (2H, m, 4-CH$_2$), 1.95-2.10 (2H, m, 5-CH$_2$), 2.40 (3H, s, 9-CH$_3$), 2.65-2.75 (2H, m, 6-CH$_2$), 2.90-3.05 (1H, m, 3-CH), 3.30-3.38 (1H, d, J=4.3 Hz, 2-CH), 3.80 (3H, s, OCH$_3$) and 6.80-7.50 (7H, m, Ar- CH).
3c	80	72	$C_{18}H_{18}N_2O$ (278)	77.65 (77.69	6.44 6.47	10.03 10.07)	1261 (-C-O-N), 1607 (C=N).	1.62-1.80 (2H, m, 4-CH$_2$), 1.95-2.10 (2H, m, 5-CH$_2$), 2.40 (3H, s, 9-CH$_3$), 2.60-2.78 (2H, m, 6-CH$_2$) 2.90-3.05 (C=N). (1H, m, 3-CH), 3.32-3.40 (1H, d, J=4.5 Hz, 2-CH), 6.80-7.50 (6H, m, Ar-CH) and 8.30 (1H, d, N=CH).

—*Contd*

Table I — Physical and spectral data of the compounds **3a-g**—*Contd*

Compd	m.p. °C	Yield (%)	(Mol.formula) (mol.wt)	Found (Calcd) %			IR (cm^{-1})	^{1}H NMR (δ, ppm)
				C	H	N		
3d	91-92	69	$C_{19}H_{18}NOCl$ (311)	73.28 (73.31	5.75 5.78	4.47 4.50)	1250 (-C-O-N), 1610 (C=N).	1.60-1.75 (2H, m, 4-CH$_2$), 1.95-2.10 (2H, m, 5-CH$_2$), 2.40 (3H, s, 2.50- 2.70 (2H, m, 6-CH$_{2)}$ 2.85-3.00 (1H, m, 3-CH), 3.30-3.40 (1H, d, J=4.5 Hz, 2-CH), and 6.95-7.55 (7H, m, Ar-CH).
3e	118	63	$C_{19}H_{18}NOBr$ (357)	63.83 (63.86	5.01 5.04	3.89 3.92)	1252 (-C-O-N), 1610 (C=N).	1.60-1.70 (2H, m, 4-CH$_2$), 1.90-2.10 (2H, m, 5-CH$_2$), 2.40 (3H, s, 9-CH$_3$) 2.55-2.75 (2H, m, 6-2.82-3.00 (1H, m, 3-CH), 3.30-3.38(1H, d, J=5.0 Hz, 2-CH) and 6.90-7.55 (7H, m, Ar-CH).
3f	72	70	$C_{19}H_{19}NO$ (277)	82.28 (82.31	6.81 6.85	5.03 5.05)	1250 (-C-O-N), 1609 (C=N).	1.50-1.60 (2H, m, 4-CH$_2$), 2.00-2.35 (3H, s, 9-CH$_3$), 2.50-2.60 (2H, m, 5- CH$_2$), 2.60-2.70 (2H, m, 6-CH$_2$), 2.80-2.90 (1H, m, 3-CH), 3.40-3.50 (1H, d, J=5.0 Hz, 2-CH), 6.90-7.80 (8H, m, Ar-CH).
3g	78	59	$C_{20}H_{21}NO$ (291)	82.43 (82.47	7.00 7.20	4.78 4.81)	1248 (-C-O-N), 1608 (C=N).	1.50-1.63 (2H, m, 4-CH) , 1.72-1.90 (2H, m, 5- CH$_2$), 2.20-2.40 (6H, s, 9- CH$_3$ & Ar-CH$_3$), 2. 60-2.80 (2H, m, 6-CH$_2$), 2.90-3.32 (1H, m, 3-CH), 3.40-3.50 (1H, d, J=4.5 Hz, 2-CH) and 6.92-7.4 (7H, m, Ar-CH).

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