

SYNTHESIS AND SPECTRAL CHARACTERIZATION OF SOME NOVEL *N*-ACYL-PIPERIDIN-4-ONES

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ABSTRACT

A collection of novel *N*-acyl-*t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-ones **1-4** are synthesized, characterized by melting point, one-dimensional NMR (¹H and ¹³C) and two-dimensional NOESY and ¹H-¹³C COSY spectrum. The spectra reveal the presence of two isomeric forms i.e., E and Z isomers for **1-4**. The effect of varying the substituents at nitrogen on the ¹H and ¹³C chemical shifts have been analyzed in detail.

Keywords: NMR spectra, ¹H NMR, ¹³C NMR, *N*-acyl-piperidin-4-ones

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INTRODUCTION

Among the family of heterocyclic compounds, the nitrogen-containing six-membered heterocycles, the piperidine structural was the most dominant and very prevalent element in nature and often found to be naturally occurring bioactive compounds such as alkaloids¹. Piperidin-3-one derivatives are used as precursors for the synthesis of antimalarial agents Febrifugine and Isofebrifugine². Piperidin-4-ones mostly display varied and potent biological properties such as Antiviral, Antitumour³, Analgesic⁴, Antimicrobial⁵, Fungicidal⁵, Herbicidal, Insecticidal, Antihistaminic, Anti-inflammatory and Anticancer. CNS stimulant and recent reports suggest that compounds containing piperidin-4-one moiety elicit excellent activity when aromatic substitutions are present at 2- and/or 6-positions.

Mannich reaction is one of the multicomponent reactions for the carbon-carbon and carbon-hetero atom sequential bond formation. Mannich type condensation involving aromatic aldehydes, ammonium acetate and ketones having two active methylene groups, resulting in the formation of 2,6-diarylpiperidin-4-ones, was first reported by Noller and Baliah⁶. In the course of developing biologically active molecules, we have recently reported the synthesis and conformational studies of *N*-acyl-*t*(3)-methyl-2,6-difurylpiperidin-4-ones⁷ and *N*-acyl-*t*(3)-isopropyl-2,6-difurylpiperidin-4-one oxime derivatives⁸. In the present study *N*-acyl-*t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-ones (**1-4**) synthesized and analyzed by ¹H, ¹³C, ¹H-¹³C COSY and NOESY spectrum.

EXPERIMENTAL

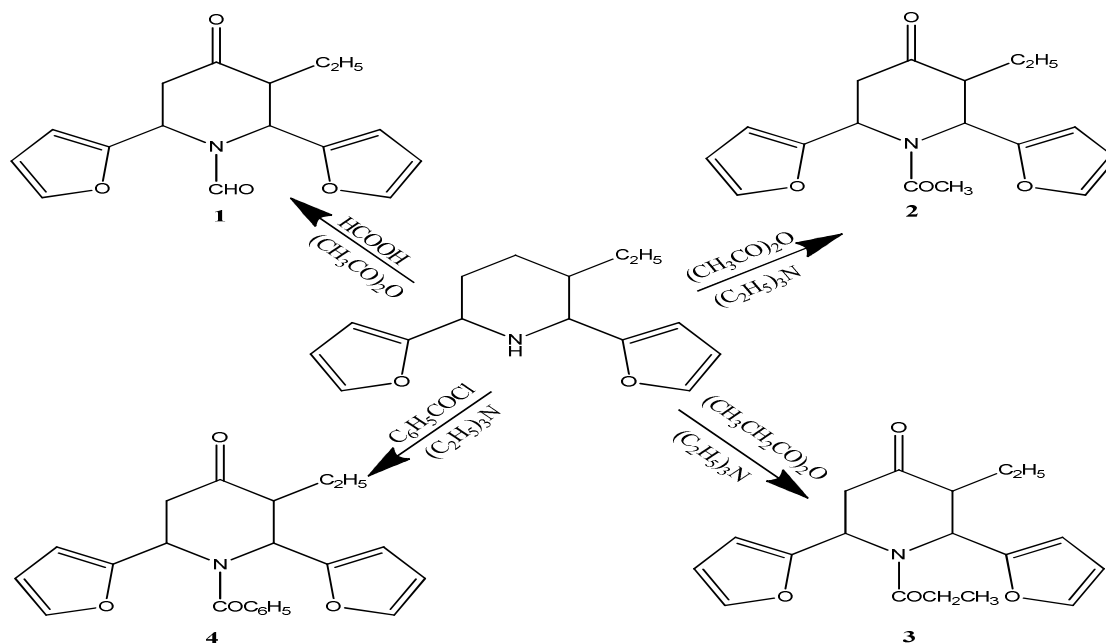
¹H and ¹³C NMR spectra were recorded on a Bruker AMX 400 NMR spectrometer operating at 400 and 100.6 MHz for ¹H and ¹³C respectively. The NOESY and ¹H-¹³C COSY spectra were recorded on a Bruker DRX 500 NMR spectrophotometer.

The starting compound *t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-one was prepared by the general procedure reported by Noller and Baliah⁶. A mixture of ammonium acetate (0.05 mol), furfuraldehyde (0.1 mol) and pentan-2-one (0.05 mol) in distilled ethanol was heated first to boiling and then stirred under the cold condition for 1 hr. Then the reaction mass was added 200 mL ether and 20 mL of concentrated hydrochloric acid. The hydrochloride salt was precipitated out and filtered the salt and washed with 40 mL mixture of ethanol and ether (1:1). The base was liberated by addition of aqueous ammonia followed by dilution with chilled water. The compound was recrystallized from benzene-

petroleum ether mixture. Yield: 70% m.p. 40°C.

The *N*-formyl derivative **1** was prepared from parent piperidin-4-one by the procedure reported in the literature⁹. Charged 50 mL of acetic anhydride into a 250ml 4 neck RB flask followed by cooled the contents to 0 - 5°C. Then added 25 mL of formic acid over a period of 30 minutes. Raised the temperature to 50-60°C and maintained for 1 hr. After maintenance reduced the temperature to 0-5°C. Then slowly added the solution of parent piperidin-4-one (dissolved in benzene) at 0-5 °C, then increased the temperature to 25-30°C and maintained the contents till the completion of the reaction. After completion of the reaction, the reaction mass washed with 10% Na₂CO₃ solution. Finally, the product isolated from the organic layer. Yield: 70%, m.p. 95°C.

The other *N*-acyl derivatives **2-4** were prepared as per the procedure reported in the literature¹⁰. Charged benzene into a 250ml 4 neck RB flask, then added 1.0 mole of parent piperidin-4-one and stirred the reaction mass to 5 -10 minutes. Then slowly added 1.0 mole of acetic anhydride/propanoic anhydride/benzoyl chloride followed by 0.5 moles of triethyl amine at 25-30 °C. Then raised to reflux temperature and maintained the reaction mass up to completion of the reaction. After completion of the reaction, the reaction mass washed with 10% NaCl solution. Then the product is isolated from the organic layer. **2**: Yield: 50-60%, m.p. 80°C **3**: Yield: 40-50%; m.p. 70°C, **4**: Yield: 70 %; m.p. 125°C.



Scheme-1

RESULTS AND DISCUSSION

The *N*-formyl-*t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-one **1**, *N*-acetyl-*t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-one **2**, *N*-propanoyl-*t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-one **3** and *N*-benzoyl-*t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-one **4** were synthesized and analyzed by ¹H, ¹³C, NOESY and ¹H-¹³C COSY spectrum. At room temperature, the signals of the spectrum are very broad. The well-resolved signals are obtained at lower temperatures only (+15, 0, -15 and -30°C). The ¹H and ¹³C NMR spectra reveal the presence of two isomers obtained at lower temperatures. The two isomers in **1-4** suggest the presence of restricted rotation around N-C bonds and establishment of equilibrium between two rotamers with the coplanar orientation of acyl group. The two isomers are labeled as *Z* [carbonyl group is *syn* to ethyl group at C(3)] and *E* [carbonyl group is *anti* to ethyl group at C(3)] isomers (Figure - 1).

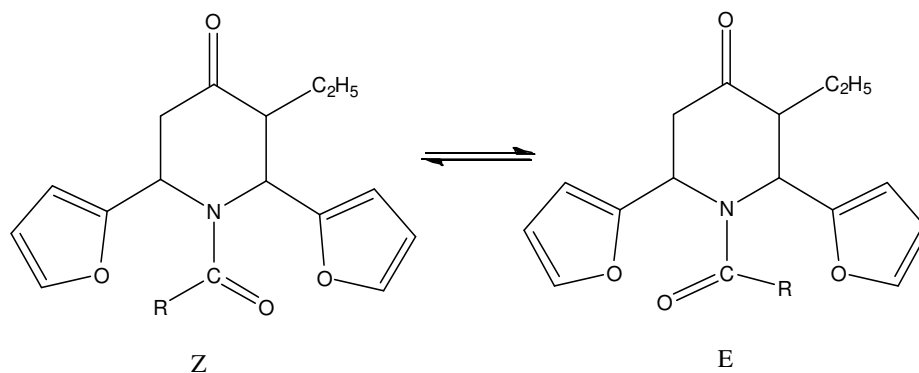


Fig.-1

The two isomers can be easily separated based on the height of the peaks. The proton signals of two isomers were confirmed by NOESY spectrum at -30°C for **1** and ^1H - ^{13}C COSY spectrum at -30°C for **2-4**. Table-1 displayed the ^1H NMR values and the coupling constant values for **1-4**. The ^{13}C NMR values of **1-4** are displayed in Table-2. The ^1H and ^{13}C NMR values of parent *t*(3)-ethyl-*r*(2),*c*(6)-di(2'-furyl)piperidin-4-one are reported in literature¹¹.

Table-1: ^1H NMR values (ppm) of *N*-acyl-3-ethylpiperidin-4-ones (**1-4**)

Compd.	H(2)	H(3)	H(5)	H(6)	Alkyl protons	Acyl protons	Aromatic protons	
1	E	4.90 (s)	2.88-2.91	2.88-2.91	6.11(t, 5.07; 10.14 ^b)	1.00(t, 7.30) (CH_2CH_3) 1.71-1.83 (CH_2CH_3)	8.45	5.91(2H), 5.95(2H), 6.04(2H), 6.08(2H), 7.04(2H), 7.11(2H)
	Z	5.93 (d, 3.19)	2.88-2.91	2.92-3.01	5.23 (d, 5.84)	1.00(t, 7.30) (CH_2CH_3) 1.71-1.83 (CH_2CH_3)	8.58	
2	E	5.25 (s)	2.80-2.87	2.95 (dd, 8.23, 15.27)	6.45 (d, 7.92)	1.03(t, 7.53) (CH_2CH_3) 1.77-1.80 (CH_2CH_3)	2.51	5.84(1H), 5.87(2H), 5.89(1H), 6.03(2H), 6.07(1H), 7.01(1H), 7.04(1H), 7.08(1H), 7.12(1H)
	Z	6.27 (s)	2.80-2.87	3.10 (dd, 8.20, 15.54)	5.56 (d, 7.88)	1.00(t, 7.54) (CH_2CH_3) 1.85-1.91 (CH_2CH_3)	2.55	
3	E	5.17 (s)	2.64-2.80	2.64-2.80	6.32 (d, 7.52)	0.86(t, 7.21) (CH_2CH_3) 1.60-1.62 (CH_2CH_3)	1.15 (t, 6.93) (COCH_2CH_3) 2.55*, 2.64-2.80 (COCH_2CH_3)	5.66(1H), 5.70(2H), 5.72(1H), 5.86(2H), 5.90(2H), 6.85(1H),

						H ₃	6.87(1H), 6.90(1H), 6.94(1H)
Z	6.14 (s)	2.64- 2.80	2.92 (dd, 7.89,1 5.37) 2.64- 2.80	5.47 (d,7.38)	0.83(t,7.18) (CH ₂ CH ₃) 1.69-1.73 (CH ₂ CH ₃)	1.15(t,6.9 3) (COCH ₂ C H ₃) 2.64-2.80 (COCH ₂ C H ₃)	
4 E	5.23 (s)	2.73- 2.78	2.94- 3.07 2.89(d,15.3 4)	6.55 (d,6.95)	0.81(t,7.31) (CH ₂ CH ₃) 1.81-1.94 (CH ₂ CH ₃)	-	5.89(1H), 5.94- 5.97(3H), 6.07- 6.09(4H), 7.10(1H), 7.12(2H), 7.15(1H), 7.46-7.47, 7.73(COC ₆ H ₅)
Z	6.31 (s)	2.73- 2.78	2.94- 3.07	5.48 (d,7.33)	1.04(t,7.29) (CH ₂ CH ₃) 1.61-1.68 (CH ₂ CH ₃)	-	

Analysis of Chemical Shifts

The deshielding effects observed due to *N*-acylation in **1-4** are displayed in Table - 3. The deshielding magnitude observed on H(2) in the *Z* isomers (*syn α* protons) are roughly same as those observed on H(6) in the *E* isomers (*syn α* protons) and the magnitude of deshielding is ≈ 2 ppm in **1-4**. The deshielding magnitude of *syn α* protons higher than the *syn α* axial protons. Moreover, the deshielding magnitude of *anti α* protons is also higher (≈ 1 ppm) than the *anti α* axial protons.

Table – 2: ¹³C NMR values (ppm) of *N*-acyl-3-ethylpiperidin-4-ones (**1-4**)

Compd.	C(2)	C(3)	C(4)	C(5)	C(6)	Alkyl carbons	Acyl carbons	Aromatic carbons
1 E	55.92	52.25	208.25	37.79	44.71	11.32 (CH ₂ CH ₃)	163.03	151.28, 151.06, 150.92, 150.46 C(2') and C(2'')
Z	48.73	52.25	208.38	38.65	51.26	24.30 (CH ₂ CH ₃) 11.62 (CH ₂ CH ₃) 24.19 (CH ₂ CH ₃)	163.36	142.63, 142.43, 142.25, 142.12 C(5') and C(5'') 110.48, 110.37, 110.16, 110.06 C(3') and C(3'') 108.33, 107.95, 107.88, 107.65 C(4') and C(4'')
2 E	55.99	52.51	208.73	38.29	46.04	11.83 (CH ₂ CH ₃)	22.38 (COCH ₃)	152.20, 152.02, 151.82, 151.27 C(2') and C(2'')
Z	49.75	52.51	208.73	38.74	51.25	24.76 (CH ₂ CH ₃) 11.83 (CH ₂ CH ₃) 24.39 (CH ₂ CH ₃)	171.53 (COCH ₃) 22.38 (COCH ₃) 171.63 (COCH ₃)	142.24, 142.11, 142.01 C(5') and C(5'') 110.42, 110.13 C(3') and C(3'') 107.97, 107.57 C(4') and C(4'')

3	E	54.74	52.56	208.86	38.40	46.25	11.85 (CH ₂ CH ₃)	9.55 (COCH ₂ CH ₃)	152.35, 152.14, 151.85, 151.36 C(2') and C(2'') 142.21, 142.09, 141.95, 142.85 C(5') and C(5'') 110.43, 110.31, 110.09, 110.03 C(3') and C(3'') 107.91, 107.75, 107.49 C(4') and C(4'')
	Z	49.94	52.56	208.99	38.76	50.07	24.40 (CH ₂ CH ₃) 11.78 (CH ₂ CH ₃) 24.76 (CH ₂ CH ₃)	26.66 (COCH ₂ CH ₃) 174.45 (COCH ₂ CH ₃) 9.55 (COCH ₂ CH ₃) 26.66 (COCH ₂ CH ₃) 174.58 (COCH ₂ CH ₃)	
4	E	56.43	53.60	208.75	38.49	46.72	11.73 (CH ₂ CH ₃)	173.00	152.10, 151.81, 151.10 C(2') and C(2'') 142.90, 142.68, 142.02 C(5') and C(5'') 135.34, 130.17, 128.83, 127.35, 126.90 (COC ₆ H ₅) 110.49, 110.41 C(3') and C(3'') 108.54, 108.03 C(4') and C(4'')
	Z	50.82	52.77	208.75	39.37	52.61	24.25 (CH ₂ CH ₃) 12.03 (CH ₂ CH ₃) 24.68 (CH ₂ CH ₃)	173.00	

With a view to determining the ¹³C substituent parameters of the formyl, acetyl and benzoyl substituents at nitrogen in the six-membered ring compounds, the chemical shifts of *N*-formylpiperidine¹², *N*-acetyl piperidine¹³ and *N*-benzoylpiperidine¹⁴ are compared with that of the parent piperidine and the parameters are displayed in Table-4. It is seen from Table -4 that *syn* α carbons are shielded to 5-7 ppm due to *N*-acylation. The *anti* α, *syn* β, *anti* β and γ carbons are also shielded to 1-3 ppm.

Table-3: Observed deshielding magnitude (ppm) in *N*-acyl-3-ethylpiperidin-4-one derivatives (1-4)

Compd.	H(2)	H(3)	H(5)	H(6)	Alkyl protons	
1	E	+0.98	+(0.13-0.22)	+(0.04-0.07) +(0.19-0.36)	+1.95	+0.20 (CH ₂ CH ₃) +0.12-0.24 (CH ₂ CH ₃) +0.43-0.55 (CH ₂ CH ₃)
	Z	+2.01	+(0.13-0.22)	+(0.08-0.17) +(0.23-0.46)	+1.07	+0.21 (CH ₂ CH ₃) +0.12-0.24 (CH ₂ CH ₃) +0.43-0.55 (CH ₂ CH ₃)
2	E	+1.33	+(0.05-0.18)	+0.11 +(0.05-0.18)	+2.29	+0.23 (CH ₂ CH ₃) +0.49-0.63 (CH ₂ CH ₃) +0.26-0.32 (CH ₂ CH ₃)
	Z	+2.35	+(0.05-0.18)	+0.26 +(0.05-0.18)	+1.40	+0.20 (CH ₂ CH ₃) +0.57-0.63 (CH ₂ CH ₃) +0.26-0.32 (CH ₂ CH ₃)
3	E	+1.25	-0.11 to +0.11	+(0.04-0.2) -0.11 to +0.11	+2.16	+0.06 (CH ₂ CH ₃) +0.32-0.34 (CH ₂ CH ₃)

					+0.01-0.03 (CH ₂ CH ₃)
Z	+2.22	-0.11 to +0.11	+(0.01-0.27) +(0.17-0.36)	+1.31	+0.03 (CH ₂ CH ₃) +0.41-0.45 (CH ₂ CH ₃) +0.10-0.14 (CH ₂ CH ₃)
4 E	+1.31	-0.02 to +0.09	+(0.10-0.23) +(0.14-0.20)	+2.39	+0.01 (CH ₂ CH ₃) +0.53-0.66 (CH ₂ CH ₃) +0.22-0.35(CH ₂ CH ₃)
Z	+2.39	-0.02 to +0.09	+(0.10-0.23) +(0.19-0.38)	+1.32	+0.24 (CH ₂ CH ₃) +0.33-0.40 (CH ₂ CH ₃) +0.02-0.09 (CH ₂ CH ₃)

Table-4: Observed shielding magnitude (ppm) of some simple N-acyl piperidines and N-acyl-3-ethylpiperidin-4-one derivatives (**1-4**)

Compd.	α		β		γ
	syn	anti	syn	anti	
N-Formylpiperidine	40.57 (-7.33)	46.76 (-1.14)	26.66 (-1.24)	24.75 (-3.15)	25.16 (-1.04)
N-Acetylpiperidine	41.58 (-6.32)	46.66 (-1.24)	25.29 (-2.61)	26.08 (-1.82)	24.12 (-2.08)
N-Benzoylpiperidine	42.60 (-5.30)	26.11 (-1.79)	24.60 (-1.60)	26.11 (-1.79)	48.30 (+0.40)
Piperidine	47.90		27.90		26.20

	C(2)	C(3)	C(4)	C(5)	C(6)	Methyl group
1 E	-2.90	-3.92	+0.62	-9.14	-9.40	- 0.46(CH 2CH ₃) +6.13(C H ₂ CH ₃)
Z	-10.09	-3.92	+0.75	-8.28	-2.85	- 0.16(CH 2CH ₃) +6.02(C H ₂ CH ₃)
2 E	-2.83	-3.66	+1.10	-8.64	-8.07	+0.05(C H ₂ CH ₃) +6.59(C H ₂ CH ₃)
Z	-9.07	-3.66	+1.10	-8.19	-2.86	+0.05(C H ₂ CH ₃) +6.22(C H ₂ CH ₃)
3 E	-4.08	-3.61	+1.23	-8.53	-7.86	- 0.07(CH 2CH ₃) +6.23(C H ₂ CH ₃)
Z	-8.88	-3.61	+1.36	-8.17	-4.04	+0.00(C

						H2CH3) +6.59(C H2CH3)
4 E	-2.39	-2.53	+1.12	-8.44	-7.39	- 0.05(CH 2CH3) +6.08(C H2CH3)
Z	-8.00	-3.40	+1.12	-7.56	-1.50	+0.25(C H2CH3) +6.51(C H2CH3)

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