

SYNTHESIS OF TETRACYCLIC CARBAZOLE DERIVATIVES

R. Balamurali and K. J. Rajendra Prasad*

Department of Chemistry, Bharathiar University, Coimbatore -641 046, India

Abstract

Mixed aldol condensation of 1-oxo-1,2,3,4-tetrahydrocarbazoles **1a-e** with thiophene-2-carbaldehyde yielded 2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazoles **2a-e**. Treatment of **2a-e** with hydrazine hydrate and hydroxylamine hydrochloride afforded 4,5-dihydrothienyl-2*H*-pyrazolino[3,4-*a*]carbazoles **3a-e** and 4,5-dihydro-3-thienylisoxazolo[3,4-*a*]carbazoles **4a-e** respectively. All the newly synthesized compounds were characterized by spectral and analytical data.

Introduction

In recent years carbazole nucleus have received considerable interest owing to its significant and diverse biological activities.¹⁻³ Further the discovery of tetracyclic pyridocarbazole derivatives like ellipticine and olivacine and their antitumour activity have induced numerous synthetic routes towards them.⁴⁻⁶ But in literature only scant reports are available on the synthesis of other tetracyclic carbazole derivatives.⁷⁻¹² As well, thienyl substituted nitrogen heterocyclic compounds are expected to exhibit interesting pharmacological activities as it contains both sulphur and nitrogen atoms. In conjugation with the above said facts, we aimed to derive a simple synthetic route for 3-thienyl-2*H*-pyrazolino[3,4-*a*]carbazole and 3-thienylisoxazolo[3,4-*a*]carbazole derivatives.

Experimental

General Information

Melting points were determined using Mettler FP₅ apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8000 infrared spectrometer. ¹H-NMR were recorded on Varian AMX 400 FT-NMR spectrometer using tetramethylsilane as internal reference in CDCl₃ and chemical shifts are quoted in parts per million (ppm). Mass spectra were recorded on a Jeol-JMS-D 300 mass spectrometer. Microanalyses were performed on a Perkin Elmer Model 240 CHN analyser.

General Procedure

Reaction of 1-oxo-1,2,3,4-tetrahydrocarbazoles with thiophene-2-carbaldehyde

A mixture of 1-oxo-1,2,3,4-tetrahydrocarbazole (4 mmol) and thiophene-2-carbaldehyde (4 mmol) was treated with 4% alcoholic potassium hydroxide (15 mL) and stirred at room temperature for 8 h. The precipitated crystalline product was filtered off and was washed with 50% ethanol. The products were crystallized from methanol.

Reaction of 2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazoles with hydrazine hydrate.

A mixture of respective 2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazole (1 mmol) and hydrazine hydrate (0.5mL) in absolute ethanol (20mL) was refluxed for 6 h. The excess solvent was removed under pressure to yield the crude product which was extracted with chloroform, washed with water and the combined organic layers were dried over anhydrous sodium sulphate. Evaporation of the solvent followed by crystallization with petroleum ether yielded the corresponding 4,5-dihydro-3-thienyl-2H-pyrazolo[3,4-a]carbazoles.

Reaction of 2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazoles with hydroxylamine hydrochloride

A mixture of 2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazole (1 mmol) and hydroxylamine hydrochloride (1gm) in pyridine (10 mL) was refluxed for 12 h. The reaction mixture was then poured into crushed ice, the resulting semi-solid separated was extracted with chloroform, subsequently washed with dilute hydrochloric acid and water. The combined organic layers were dried over anhydrous sodium sulphate. Removal of the solvent yielded the crude product, which was purified by column chromatography using petroleum ether-ethyl acetate (98:2) mixture as eluant. The products were recrystallized from the same solvent mixture.

Results and discussion

In order to achieve our synthetic target, we opted 1-oxo-1,2,3,4-tetrahydrocarbazoles¹³ 1a-e as basic synthons. Mixed aldol condensation¹⁴ of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole (1a) with thiophene-2-carbaldehyde (scheme 1) under basic conditions yielded 8-methyl-2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazole (2a). The structure of 2a was established on the basis of spectral and microanalysis data. In the IR spectrum, carbonyl absorption was decreased (1637 cm^{-1}) indicating the formation of

α,β -unsaturated carbonyl group. In the $^1\text{H-NMR}$ spectrum, the resonance at δ 7.92 is characteristic of thienylic proton and disappearance of C_2 proton resonance confirmed the mixed aldol condensation reaction of **1a** with thiophene-2-carbaldehyde. The structure of the condensation product was attested by microanalysis and mass spectral data. In the mass spectrum (table 1) the molecular ion peak appeared at m/z 293 (6.8%) and the base peak at m/z 29. A similar series of compounds **2b**, **2c**, **2d** and **2e** were obtained from **1b**, **1c**, **1d** and **1e** (scheme 1, table 1 and 2).

In a typical experiment, 8-methyl-2-thienyl-1-oxo-1,2,3,4-tetrahydrocarbazole **2a** was treated with hydrazine hydrate¹⁵ in ethanol at reflux condition (scheme 1). This yielded a single product, which was recrystallised from petroleum-ether. In the IR spectrum of the product, the carbonyl absorption was lost. Strong absorptions at 1608, 3295 and 3178 cm^{-1} were ascribable to a -C=N and two -N-H stretching vibrations respectively. The $^1\text{H-NMR}$ spectrum exhibited a three proton singlet at δ 2.45 for the methyl group protons, four multiplets at δ 2.34, 2.50, 2.83 and 3.09 assignable for C_4 , C_{3a} , C_5 and C_3 protons respectively, a broad doublet at δ 4.85 is accountable for the pyrazolino -N-H proton, the aromatic protons resonated as a multiplet between the region δ 6.97- 7.50 and a broad singlet at δ 8.97 for the carbazole -N-H . In the mass spectrum the molecular ion peak appeared at m/z 307 (100%). Further the elemental analysis agreed well with the molecular formula $\text{C}_{18}\text{H}_{17}\text{N}_3\text{S}$. On the basis of the aforesaid data, the product was attested to be 9-methyl-4,5-dihydro-3-thienyl-2H-pyrazolino[3,4-*a*]carbazole **3a**. Generality of the above reaction was tested with **2b**, **2c**, **2d** and **2e**. In all the cases the corresponding pyrazolino[3,4-*a*]carbazole derivatives **3b**, **3c**, **3d** and **3e** were realized (scheme 1, table 1 and 2).

In an another experiment **2a** was treated with hydroxylamine hydrochloride¹⁶ in dry pyridine. This yielded a single product, which was purified by column chromatography. The product in its IR spectrum recorded two absorptions at 3335 and 1625 cm^{-1} which are ascribable for -N-H and -C=N stretching vibrations respectively. The proton NMR spectrum registered a three proton singlet at δ 2.45 for methyl group protons, two multiplets centered at δ 3.05 and δ 3.32 for the C_4 and C_5 protons, an aromatic cluster between δ 7.05-7.54 and a broad singlet at δ 9.75 for the -N-H proton. The mass spectrum showed molecular ion peak at m/z 306 (23%). The elemental analysis agreed well with the molecular formula $\text{C}_{18}\text{H}_{14}\text{N}_2\text{OS}$. Based on the above mentioned spectral data the structure of the product was assigned as

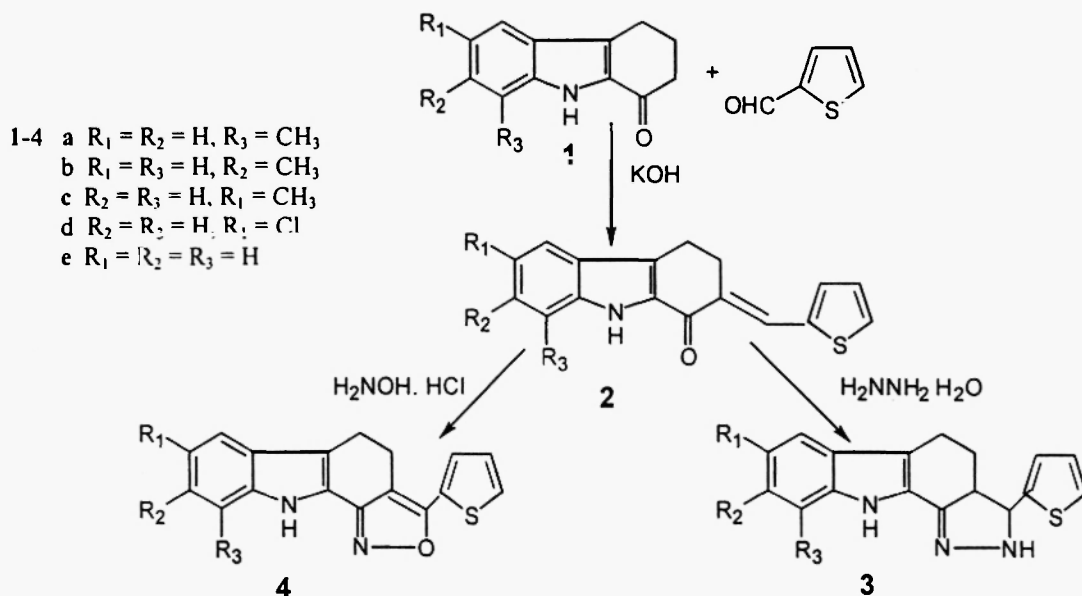
Table 1. Characterisation data of compounds 2a-e, 3a-e and 4a-e

Comp- ound No.	m.p. °C	Yield (%)	Ir (KBr) max cm ⁻¹	Molecular formula	Analysis observed C, H and N (Calcd C, H, N) (%)		
					C	H	N
<u>2a</u>	260	78	3293	C ₁₈ H ₁₅ NOS	73.75	05.03	04..70
			1637	(293.36)	(73.78)	(05.11)	(04.77)
<u>2b</u>	258	76	3286	C ₁₈ H ₁₅ NOS	73.71	05.04	04.71
			1635	(293.36)	(73.78)	(05.11)	(04.71)
<u>2c</u>	235	75	3290	C ₁₈ H ₁₅ NOS	73.74	05.01	04.74
			1627	(293.36)	(73.78)	(05.11)	(04.77)
<u>2d</u>	270	72	3230	C ₁₇ H ₁₂ NOSCl	65.01	03.76	04.39
			1631	(313.80)	(65.06)	(03.82)	(04.46)
<u>2e</u>	224	75	3275	C ₁₇ H ₁₂ NOS	72.93	04.60	04.95
			1634	(279.36)	(73.09)	(04.69)	(05.01)
<u>3a</u>	210	70	3295	C ₁₈ H ₁₇ N ₃ S	70.30	05.47	13.65
			3178	(307.41)	(70.35)	(05.53)	(13.68)
			1608				
<u>3b</u>	227	67	3285	C ₁₈ H ₁₇ N ₃ S	70.32	05.50	13.62
			3170	(307.41)	(70.35)	(05.53)	(13.68)
			1618				
<u>3c</u>	198	68	3290	C ₁₈ H ₁₇ N ₃ S	70.27	05.49	13.60
			3175	(307.41)	(70.35)	(05.53)	(13.68)
			1620				
<u>3d</u>	247	60	3315	C ₁₇ H ₁₄ N ₃ SCl	62.19	04.21	12.69
			3172	(327.83)	(62.22)	(04.27)	(12.81)
			1624				
<u>3e</u>	210	65	3300	C ₁₇ H ₁₅ N ₃ S	65.52	05.08	14.28
			3172	(293.39)	(65.59)	(05.11)	(14.33)
			1610				
<u>4a</u>	273	59	3335	C ₁₈ H ₁₄ N ₂ OS	70.52	04.48	09.09
			1625	(306.38)	(70.58)	(04.57)	(09.15)
<u>4b</u>	217	57	3245	C ₁₈ H ₁₄ N ₂ OS	70.49	04.52	09.12
			1620	(306.38)	(70.58)	(04.57)	(09.15)
<u>4c</u>	220	56	3230	C ₁₈ H ₁₄ N ₂ OS	70.54	04.51	09.10
			1618	(306.38)	(70.58)	(04.57)	(09.15)
<u>4d</u>	235	52	3285	C ₁₇ H ₁₁ N ₂ O SCi	62.10	03.91	08.49
			1610	(328.82)	(62.19)	(03.96)	(08.53)
<u>4e</u>	242	60	3275	C ₁₇ H ₁₂ N ₃ OS	69.81	03.98	09.52
			1627	(292.36)	(69.86)	(04.10)	(09.58)

Table 2 ^1H -NMR data of compounds 2a-e, 3a-e and 4a-e

Compound No.	^1H nmr(CDCl_3) δ (ppm)
<u>2a</u>	2.50 (s, 3H, C Me), 3.14 (m, 2H, 2H-3), 3.35 (t, 2H, 2H-4) 7.05-7.48 (m, 6H, aromatic H), 7.92 (s, 1H, thienylic H), 8.83 (b s, 1H, NH)
<u>2b</u>	2.53 (s, 3H, C Me), 3.10 (m, 2H, 2H-3), 3.31 (t, 2H, 2H-4) 7.07-7.56 (m, 6H, aromatic H), 7.89 (s, 1H, thienylic H), 8.72 (b s, 1H, NH)
<u>2c</u>	2.45 (s, 3H, C Me), 3.13 (m, 2H, 2H-3), 3.35 (m, 2H, 2H-4) 7.13-7.50 (m, 6H, aromatic H), 7.96 (s, 1H, thienylic H), 8.93 (b s, 1H, NH)
<u>2d</u>	3.12 (t, 2H, 2H-3), 3.36 (t, 2H, 2H-4), 7.14-7.65 (m, 6H, aromatic H), 7.96 (s, 1H, thienylic H), 8.93 (b s, 1H, NH)
<u>2e</u>	3.02 (t, 2H, 2H-3), 3.26 (t, 2H, 2H-4), 7.25-7.63 (m, 7H, aromatic H), 7.80 (s, 1H, thienylic H), 9.21 (b s, 1H, NH)
<u>3a</u>	2.34 (m, 2H, 2H-4), 2.45 (s, 3H, C Me), 2.50 (m, 1H, 1H-3a) 2.83 (m, 2H, 2H-5), 3.09 (m, 1H, 1H-3), 4.85 (b d, 1H, pyrazolino-NH) 6.97-7.50 (m, 6H, aromatic H), 8.97 (b s, 1H, carbazole NH)
<u>3b</u>	2.33 (m, 2H, 2H-4), 2.45 (s, 3H, C Me), 2.64 (m, 1H, 1H-3a) 2.82 (m, 2H, 2H-5), 3.07 (m, 1H, 1H-3), 4.72 (b d, 1H, pyrazolino-NH) 6.81-7.70 (m, 6H, aromatic H), 8.98 (b s, 1H, carbazole NH)
<u>3c</u>	2.35 (m, 2H, 2H-4), 2.47 (s, 3H, C Me) 2.68 (m, 1H, 1H-3a) 2.87 (m, 2H, 2H-5), 3.02 (m, 1H, 1H-3), 4.82 (b d, 1H, pyrazolino-NH), 6.92-7.67 (m, 6H, aromatic H) 9.02 (b s, 1H, carbazole NH)
<u>3d</u>	2.34 (m, 2H, 2H-4), 2.83 (m, 1H, 1H-3a) 3.01 (m, 2H, 2H-5), 3.22 (m, 1H, 1H-3), 4.74 (b d, 1H, pyrazolino-NH), 6.89-7.60 (m, 6H, aromatic H), 9.15 (b s, 1H, carbazole NH)
<u>3e</u>	2.36 (m, 2H, 2H-4), 2.87 (m, 1H, 1H-3a) 3.07 (m, 2H, 2H-5), 3.23 (m, 1H, 1H-3), 4.72 (b d, 1H, pyrazolino-NH), 6.89-7.55 (m, 7H aromatic H), 9.00 (b s, 1H, carbazole NH)
<u>4a</u>	2.52 (s, 3H, C Me), 3.07 (t, 2H, 2H-4), 3.26 (t, 2H, 2H-5) 7.10-7.52 (m, 6H, aromatic H), 8.95 (b s, 1H, NH)
<u>4b</u>	2.45 (s, 3H, C Me), 3.00 (t, 2H, 2H-4), 3.16 (t, 2H, 2H-5) 7.05-7.54 (m, 6H, aromatic H), 9.75 (b s, 1H, NH)
<u>4c</u>	2.53 (s, 3H, C Me), 3.07 (t, 2H, 2H-4), 3.26 (t, 2H, 2H-5) 7.05-7.68 (m, 6H, aromatic H), 9.11 (b s, 1H, NH)
<u>4d</u>	2.95 (t, 2H, 2H-4), 3.20 (t, 2H, 2H-5) 7.04-7.55 (m, 6H, aromatic H), 9.92 (b s, 1H, NH)
<u>4e</u>	3.08 (t, 2H, 2H-4), 3.27 (t, 2H, 2H-5) 7.16-7.68 (m, 7H, aromatic H), 9.24 (bs, 1H, NH)

Scheme 1



9-methyl-4,5-dihydro-3-thienylisoxazolo[3,4-a]carbazole **4a**. Extension of the above reaction to **2b**, **2c**, **2d** and **2e** afforded the corresponding isoxazolo[3,4-a]carbazole derivatives, **4b**, **4c**, **4d** and **4e** (scheme 1, table 1 and 2).

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