SYNTHESIS OF TETRACYCLIC CARBAZOLE DERIVATIVES

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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 FP_5 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8000 infrared spectrometer. ^{1}H-NMR were recorded on Varian AMX 400 FT-NMR spectrometer using tetramethylsilane as internal reference in $CDCl_3$ 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-2*H*-pyroazolino[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-tetrahydrocarbazoles[13] 1a-e as basic synthons. Mixed aldol condensation[14] 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}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 2c 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 hydrate[15] 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}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 $C_{18}H_{17}N_3S$. On the basis of the aforesaid data, the product was attested to be 9-methlyl-4,5-dihydro-3-thienyl-2*H*-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 hydrochloride[16] 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 $C_{18}H_{14}N_2OS$. Based on the above mentioned spectral data the structure of the product was assigned as

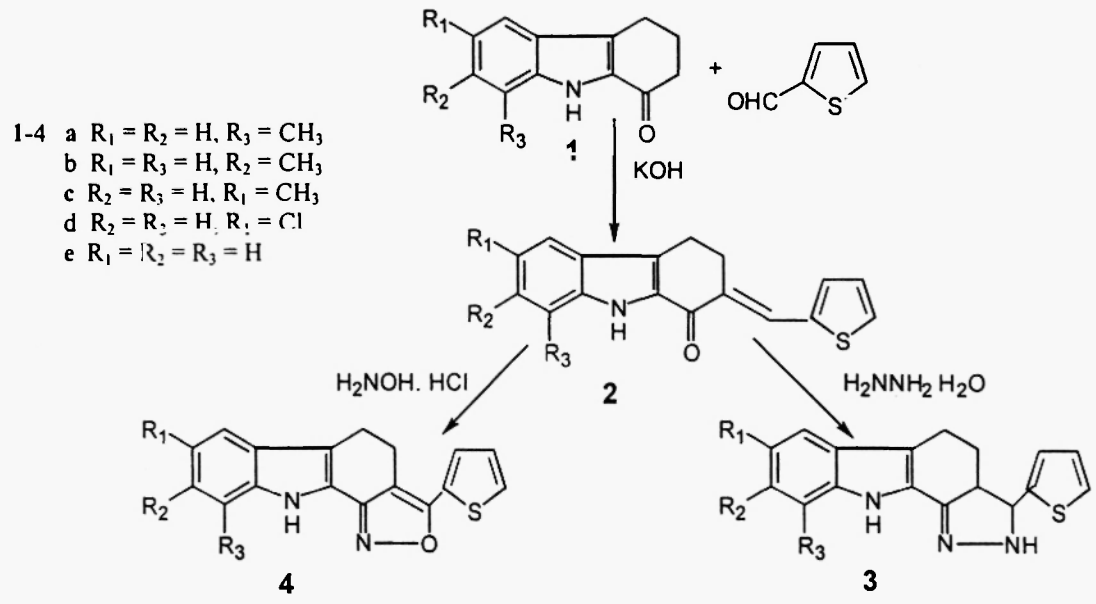
Table 1. Characterisation data of compounds 2a-e, 3a-e and 4a-e

Compound 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
2a	260	78	3293 1637	$C_{18}H_{15}NOS$ (293.36)	73.75 (73.78)	05.03 (05.11)	04..70 (04.77)
2b	258	76	3286 1635	$C_{18}H_{15}NOS$ (293.36)	73.71 (73.78)	05.04 (05.11)	04.71 (04.71)
2c	235	75	3290 1627	$C_{18}H_{15}NOS$ (293.36)	73.74 (73.78)	05.01 (05.11)	04.74 (04.77)
2d	270	72	3230 1631	$C_{17}H_{12}NOSCl$ (313.80)	65.01 (65.06)	03.76 (03.82)	04.39 (04.46)
2e	224	75	3275 1634	$C_{17}H_{12}NOS$ (279.36)	72.93 (73.09)	04.60 (04.69)	04.95 (05.01)
3a	210	70	3295 3178 1608	$C_{18}H_{17}N_3S$ (307.41)	70.30 (70.35)	05.47 (05.53)	13.65 (13.68)
3b	227	67	3285 3170 1618	$C_{18}H_{17}N_3S$ (307.41)	70.32 (70.35)	05.50 (05.53)	13.62 (13.68)
3c	198	68	3290 3175 1620	$C_{18}H_{17}N_3S$ (307.41)	70.27 (70.35)	05.49 (05.53)	13.60 (13.68)
3d	247	60	3315 3172 1624	$C_{17}H_{14}N_3SCl$ (327.83)	62.19 (62.22)	04.21 (04.27)	12.69 (12.81)
3e	210	65	3300 3172 1610	$C_{17}H_{15}N_3S$ (293.39)	65.52 (65.59)	05.08 (05.11)	14.28 (14.33)
4a	273	59	3335 1625	$C_{18}H_{14}N_2OS$ (306.38)	70.52 (70.58)	04.48 (04.57)	09.09 (09.15)
4b	217	57	3245 1620	$C_{18}H_{14}N_2OS$ (306.38)	70.49 (70.58)	04.52 (04.57)	09.12 (09.15)
4c	220	56	3230 1618	$C_{18}H_{14}N_2OS$ (306.38)	70.54 (70.58)	04.51 (04.57)	09.10 (09.15)
4d	235	52	3285 1610	$C_{17}H_{11}N_2OSCl$ (328.82)	62.10 (62.19)	03.91 (03.96)	08.49 (08.53)
4e	242	60	3275 1627	$C_{17}H_{12}N_3OS$ (292.36)	69.81 (69.86)	03.98 (04.10)	09.52 (09.58)

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

Compound No.	^{1}H nmr($CDCl_3$) δ (ppm)
2a	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)
2b	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)
2c	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)
2d	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)
2e	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)
3a	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)
3b	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)
3c	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)
3d	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)
3e	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)
4a	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)
4b	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)
4c	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)
4d	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)
4e	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 2c afforded the corresponding isoxazolo[3,4-*a*]carbazole derivatives, 4b, 4c, 4d and 4e (scheme 1, table 1 and 2).

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