A convenient synthesis of functionalised pyrimido[4,5-*a*]carbazoles

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Abstract

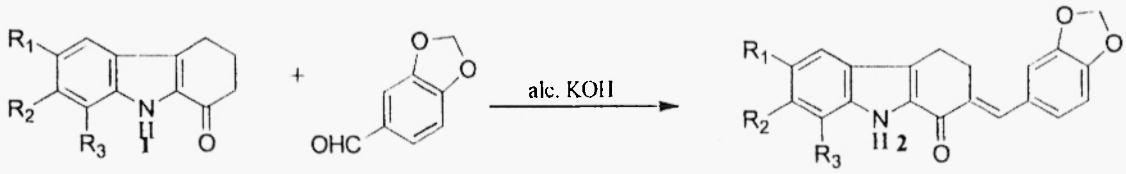
A convenient new synthesis of 2-amino-5,6-dihydro-4-(3',4'-methylenedioxy)phenylpyrimido[4,5-*a*]carbazoles 3 by the base catalysed reaction of 2-(3',4'-methylenedioxy)benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles 2 are described. The plausible mechanism for the formation of compounds has been proposed.

Introduction

Research carried out in recent years showed that carbazoles exhibit significant and diverse biological activities[1-5]. These alkaloids show definite antitumour characteristics. However a major drawback in using these classes of compounds as drugs is their notorious insolubility in water. This makes it extremely difficult to administer the drug in intravenous form. However, incorporation of amino groups into these systems will enhance the hydrophilicity of the molecule and therefore enhance its water solubility[6]. In addition to this, a large number of reports are available in which heterocyclic pyrimidines especially with a amino group have pharmacological as well as chemotherapeutic properties[7]. Hence based on the above mentioned facts we decided to synthesis some new pyrimidocarbazoles with amino group.

In achieving our target we opted 1-oxo-1,2,3,4-tetrahydrocarbazoles as precursors. Mixed aldol reaction[8] of 8-methyl-1-oxo-1,2,3,4-tetrahydrocarbazole 1a with 3,4-methylenedioxybenzaldehyde under basic condition gave 8-methyl-2-(3',4'-methylenedioxy)benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazole 2a. The IR spectrum exhibited a sharp and strong absorption band at 1652cm^{-1} characteristic of α,β-unsaturated carbonyl group and a band at 3267cm^{-1} ascribable to NH group. The disappearance of C_2 proton signal and the appearance of benzylic proton signal at δ 7.71 in its ^{1}H-NMR spectrum proved mixed aldol reaction of 1a with 3,4-methylenedioxybenzaldehyde to give 2a. The C_3 and C_4 methylene protons resonated as two multiplets at δ 3.07 and δ 3.25 respectively while that of methyl group and carbazole NH as a singlet at δ 2.52 and as a broad singlet at δ 8.84 respectively. The -O-CH$_2$-O- proton appeared as a singlet at δ 6.02. Further, it exhibited a multiplet at δ 6.86-7.69 which was accounted as resonance of six aromatic protons. The elemental analysis was compatible with the molecular formula $C_{21}H_{17}NO_3$ (Scheme-I).

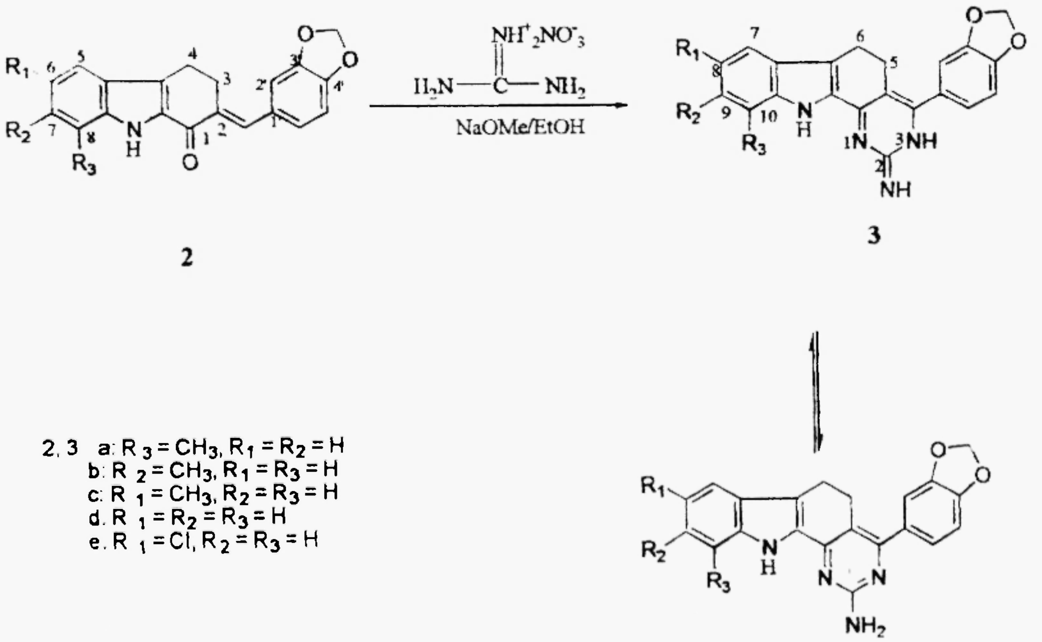
Scheme-I



1,2 a: $R_3 = CH_3, R_1 = R_2 = H$
b: $R_2 = CH_3, R_1 = R_3 = H$
c: $R_1 = CH_3, R_2 = R_3 = H$
d: $R_1 = R_2 = R_3 = H$
e: $R_1 = Cl, R_2 = R_3 = H$

Further, treatment of 8-methyl-2-(3',4'-methylenedioxy)benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazole 2a and guanidine nitrate with sodium methoxide in ethanol at 90°C for 36 hours afforded 2-amino-10-methyl-5,6-dihydro-2-(3',4'-methylenedioxy)phenylpyrimido[4,5-*a*]carbazole 3a in 66% yield after purification over silica gel column. The IR spectrum showed 3 prominent absorptions at 3387, 3306, and 3188 cm^{-1} which were assigned to three different N-H strechings . In the proton NMR spectrum, the proton integration revealed the ratio of the amino and imino forms to be 2:1. The two broad singlets at δ 5.31 and δ 10.49 corresponding to N_3-H and C_2=NH of imino form and a broad singlet at δ 6.65 corresponding to amino form respectively. Further, two multiplets were observed at δ 3.01 and δ 3.41 which correspond to C_5 and C_6 protons.Two protons of methylenedioxy group appeared as a singlet at δ 6.10, an aromatic cluster between δ 6.99 to δ 8.22 corresponding to 6 protons, a broad singlet at δ 9.10 corresponding to indole NH were also observed. The elemental analysis was compatible with the molecular formula $C_{22}H_{18}N_4O_2$ (Scheme-II). A series of similar reactions were carried out with 2-arylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles 2b-e and similar results were obtained were obtained. The peaks at m/e 340, 313, 356, and 324 are obtained by the loss of neutral molecules like O_2, HCHO, etc. as depicted in the mass fragmentation pattern (Scheme-IV).

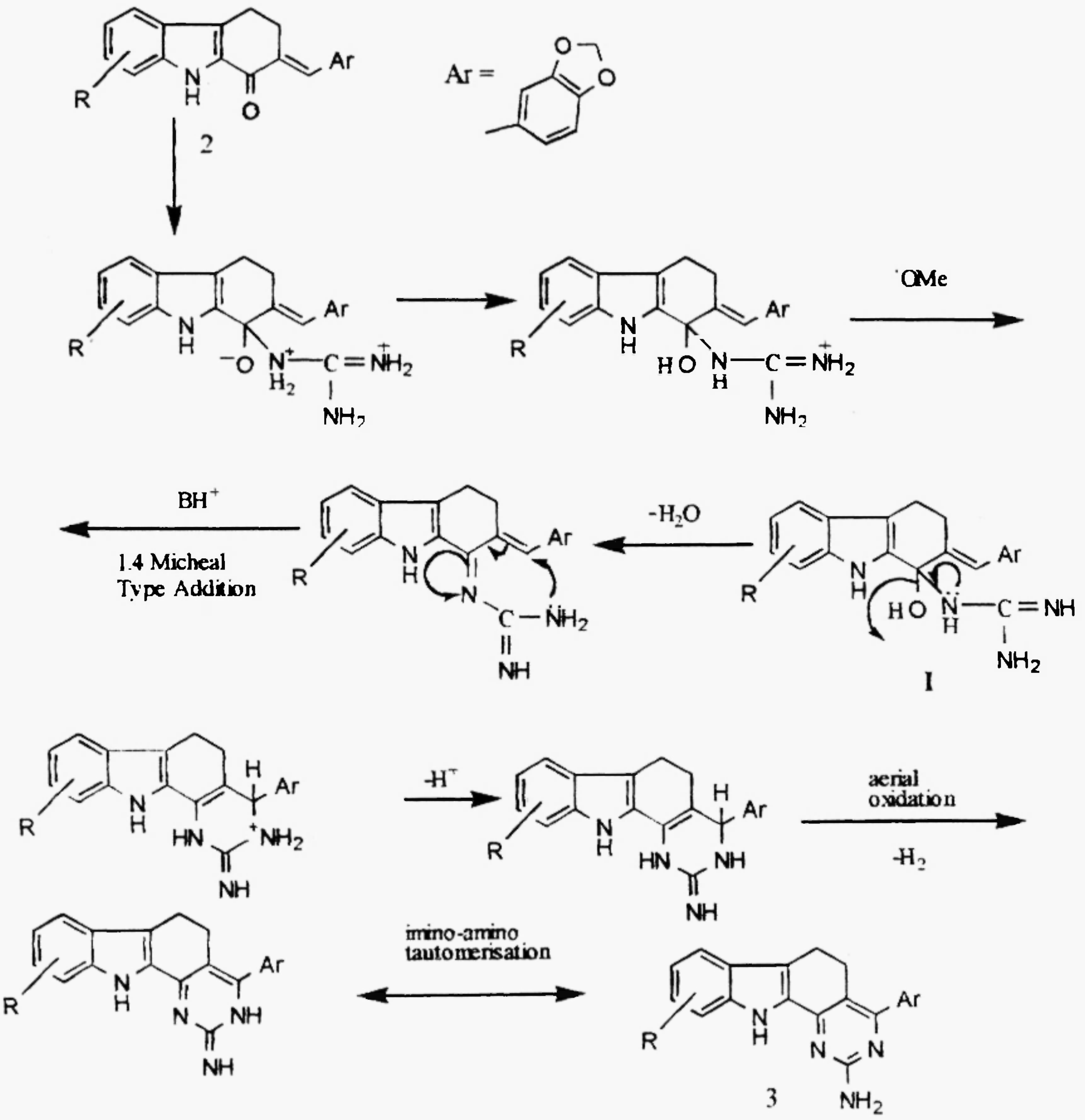
SCHEME-II



2, 3 a: $R_3 = CH_3, R_1 = R_2 = H$
b: $R_2 = CH_3, R_1 = R_3 = H$
c: $R_1 = CH_3, R_2 = R_3 = H$
d. $R_1 = R_2 = R_3 = H$
e. $R_1 = Cl, R_2 = R_3 = H$

The following mechanism has been proposed for the formation of pyrimido[4,5-*a*]carbazoles 3. Amino group of guanidine nitrate reacts with carbonyl group of 2-arylidiene derivative 2 to give the Schiff's base I, which subsequently will undergo intramolecular 1,4 – Michael type addition followed by ariel oxidation and imino-amino tautomerisation to afford the product 3.

Scheme-III



Scheme-IV

Mass fragmentation pattern of compound **3a**

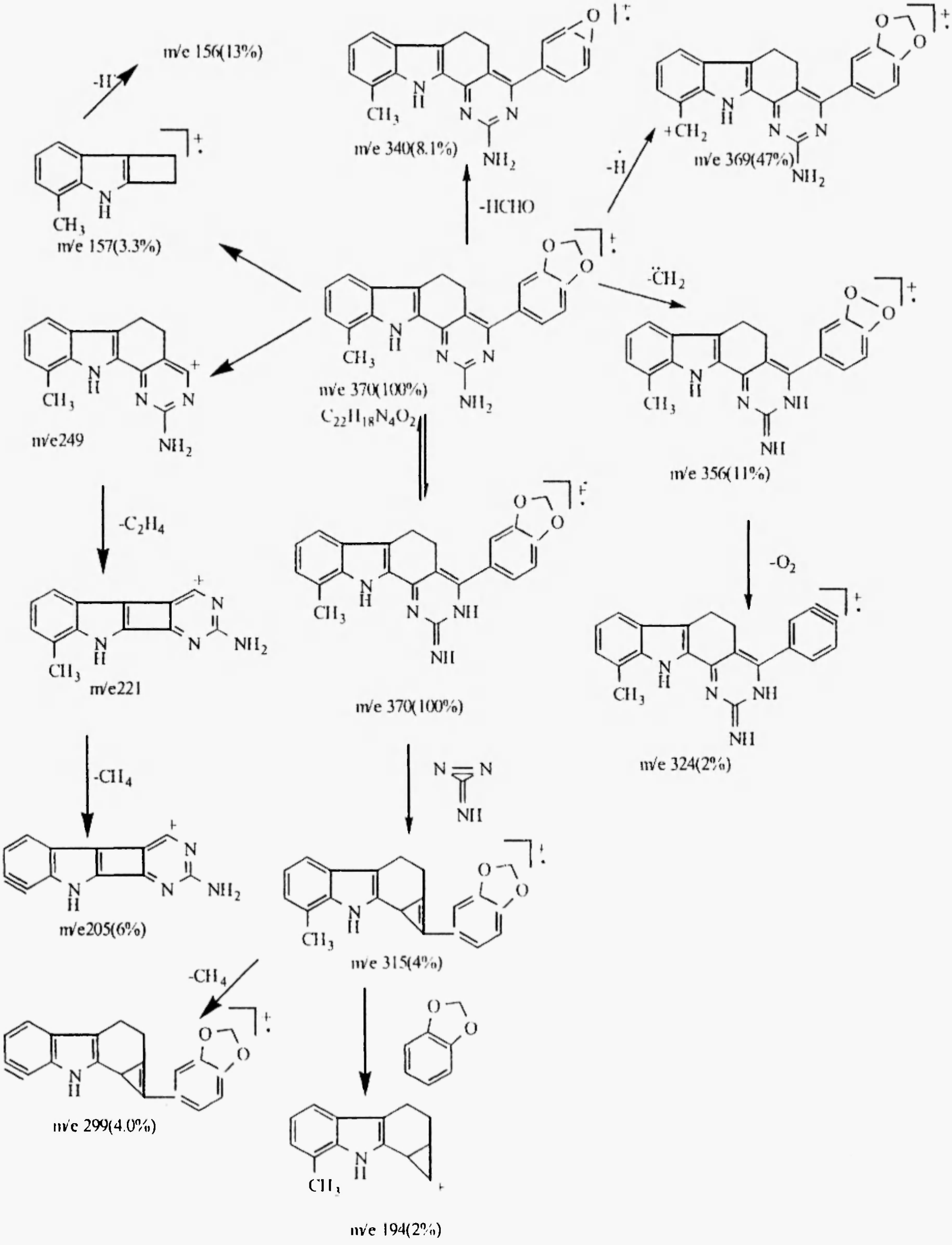


Table 1. Physical and spectral data of 2-(3',4'-methylenedioxy)benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles 2

Compound	m.p.[a] (°C) solvent	Yield(%)	IR[b] (v)	MS(70ev) [c]m/e(M⁺)	Molecular formula	Analysis[d] Calcd	Found	^{1}H NMR[e]
2a	172	82	3267 1652	331	$C_{21}H_{17}NO_3$	C 76.11 H 05.17 N 04.22	76.09 05.13 04.19	2.52(s,3H,C[illegible]$-CH_3$), 3.07(m,2H,C_3-H_2), 3.25(m,2H, C_4-H_2), 6.02(s,2H, $-O-CH_2-O-$), 6.85-7.09(m,6H,aromatic H), 7.71(s,1H,benzylic CH), 8.84(b s, 1H,carbazolo NH)
2b	148	84	3257 1644	331	$C_{21}H_{17}NO_3$	C 76.11 H 05.17 N 04.22	76.12 05.16 04.23	2.49(s,3H,C_7-CH_3), 3.09(m,2H,C_3-H_2), 3.24(m,2H, C_4-H_2), 6.01(s,2H, $-O-CH_2-O-$), 6.79-7.11(m,6H,aromatic H), 7.71(s,1H,benzylic CH), 8.84(b s, 1H,carbazolo NH)
2c	153	79	3263 1643	331	$C_{21}H_{17}NO_3$	C 76.11 H 05.17 N 4.22	76.03 05.12 04.21	2.52(s,3H,C_6-CH_3), 2.99(m,2H,C_3-H_2), 3.15(m,2H, C_4-H_2), 6.02(s,2H, $-O-CH_2-O-$), 6.88-7.25(m,6H,aromatic H), 7.59(s,1H,benzylic CH), 8.89(b s, 1H,carbazolo NH)
2d	183	81	3251 1643	317	$C_{20}H_{15}NO_3$	C 74.98 H 05.75 N 04.41	74.95 05.78 04.39	3.07(m,2H,C_3-H_2), 3.12(m,2H, C_4-H_2), 6.02(s,2H, $-O-CH_2-O-$), 6.85-7.25(m,7H,aromatic H), 7.59(s,1H,benzylic CH), 8.89(b s, 1H,carbazolo NH)
2c	169	78	3227 1636	351	$C_{20}H_{14}NO_3Cl$	C 68.29 H 04.01 N 03.98	68.26 03.99 03.91	3.01(m,2H,C_3-H_2), 3.15(m,2H, C_4-H_2), 6.06(s,2H,$-O-CH_2-O-$), 6.88-7.25(m,6H,aromatic H), 7.59(s,1H,benzylic CH), 9.00(b s, 1H,carbazolo NH)

PE: Petroleum ether: 60-80°C, EA: Ethyl acetate.

[a] Uncorrected, measured using Mettler FP5 apparatus.

[b] Recorded on a Shimadzu FTIR-8201(PC) spectrometer and only noteworthy absorption levels (in reciprocal centimeters) are listed.

[c] Recorded on a Jeol-JMS-D 300 Mass spectrometer.

[d] Satisfactory microanalysis were obtained on Carlo Erba 1106 and Perkin Elmer Model 240 CHN analyzers.

[e] NMR spectra were recorded on Varian AMX400 FT-NMR spectrometer using tetramethylsilane as internal reference in $CDCl_3$.

Table 2. Physical and spectral data of 2-amino-5,6-dihydro-4-(3',4'-methylenedioxy)phenylpyrimido[4,5-*a*]carbazoles 3

Compound	m.p.[a] (°C) solvent	Yield(%)	IR[b] (ν)	MS(70ev) [c]m/e(M+)	Molecular formula	Analysis[d]		^{1}H NMR[e]
						Calcd	Found	
3a	117	66	3387 3306 3188	370	$C_{22}H_{18}N_4O_2$	C 71.34 H 04.90 N 15.13	71.38 04.82 15.09	2.89(s,3H, C_{10}-CH_3), 3.01(m,2H,C_5-H_2), 3.41(m 2H,C_6-H_2), 5.31(s,1H, pyrimido NH), 6.10(s, 2H -O-CH_2-O-), 6.65(s,2H, C_2-NH_2), 6.99-8.22(m 6H, aromatic H), 9.10(b s,1H, carbazolo NH), 10.49(b s, 1H, C_2=NH). Ratio of Imino: Amino 2:1
3b	103	68	3379 3301 3180	370	$C_{22}H_{18}N_4O_2$	C 71.34 H 04.90 N 15.13	71.28 04.88 15.11	2.84(s,3H, C_9-CH_3), 3.53(m,2H,C_5-H_2), 3.57(m,2H,C_6-H_2), 5.31(s,1H, pyrimido NH), 6.10(s, 2H, -O-CH_2-O-), 6.60(s,2H, C_2-NH_2), 6.71-7.868(m, 6H, aromatic H), 9.25(b s 1H carbazolo NH), 10.15(b s, 1H, C_2=NH). Ratio of Imino: Amino 2:1
3c	110	69	3388 3309 3194	370	$C_{22}H_{18}N_4O_2$	C 71.34 H 04.90 N 15.13	71.29 04.79 15.06	2.79(s,3H, C_8-CH_3), 3.11(m,2H,C_5-H_2), 3.13(m,2H,C_6-H_2), 5.27(s,1H, pyrimido NH), 6.17(s, 2H, -O-CH_2-O-), 6.56(s,2H, C_2-NH_2), 7.03-7.96(m, 6H, aromatic H), 9.14(b s,1H, carbazolo NH), 10.15(b s, 1H, C_2=NH). Ratio of Imino: Amino 2:1
3d	121	72	3369 3316 3140	356	$C_{21}H_{16}N_4O_2$	C 70.71 H 04.49 N 15.68	70.78 04.53 15.72	2.88(m,2H,C_5-H_2), 2.95(m,2H,C_6-H_2), 5.23(s,1H, pyrimido NH), 5.95(s, 2H, -O-CH_2-O-), 6.14(s,2H, C_2-NH_2), 6.92-8.17(m, 7H, aromatic H), 9.30(b s,1H, carbazolo NH), 9.70(b s, 1H, C_2=NH). Ratio of Imino: Amino 3:2
3e	108	70	3379 3297 3166	390	$C_{21}H_{15}N_4O_2Cl$	C 64.48 H 03.82 N 14.29	64.54 03.87 14.34	2.85(m,2H,C_5-H_2), 2.95(m,2H,C_6-H_2), 5.07(s,1H, pyrimido NH), 6.01(s, 2H, -O-CH_2-O-), 6.10(s,2H, C_2-NH_2), 6.70-8.21(m, 6H, aromatic H), 9.10(b s,1H, carbazolo NH), 10.49(b s, 1H, C_2=NH). Ratio of Imino: Amino 2:1

PE: Petroleum ether 60-80°C, EA: Ethyl acetate

[a] Uncorrected, measured using Mettler FP5 apparatus.

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[e] NMR spectra were recorded on Varian AMX400 FT NMR spectrometer using tetramethylsilane as internal reference in $CDCl_3$

Experimental

2-(3',4'-Methylenedioxy)benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazoles 2

A mixture of respective 1-oxo-1,2,3,4-tetrahydrocarbazole (1, 4 mmol) and piperonal (4 mmol) was treated with 4% alc. KOH (15 ml) and was stirred for 48 hours at room temperature. The precipitated crystalline product was filtered off and washed with 50% ethanol. A further crop of condensation product was obtained on neutralisation with acetic acid and dilution with water. The products were crystallised from methanol.

2-Amino-5,6-dihydro-4-(3',4'-methylenedioxy)phenylpyrimido[4,5-*a*]carbazoles 3

A solution of sodium methoxide was prepared from sodium (2 g) and methanol (10 ml). To this 10 ml ethanol was added and then maintained on a water bath until a homogenous solution was formed. To this, the respective 2-(3',4'-methylenedioxy)benzylidene-1-oxo-1,2,3,4-tetrahydrocarbazole (2, 0.001 mol) and guanidine nitrate (0.01 mol) was added and refluxed for 36 hours. The excess solvent was boiled off and was poured into crushed ice. The precipitate was washed with water and dried, which was purified by passing through a silica gel coloum and eluting with pet.ether-ethyl acetate mixture (75:25)

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