ONE-POT SYNTHESIS OF 7-FLUORO-5-METHYL-4H-1,4-BENZOTHIAZINES

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Abstract : One-pot synthesis of 4H-1,4-benzothiazines involving the condensation and oxidative cyclisation of 2-amino-5-fluoro-3-methyl benzenethiol with β-diketones/ β-ketoesters in dimethyl sulfoxide is reported.

Introduction

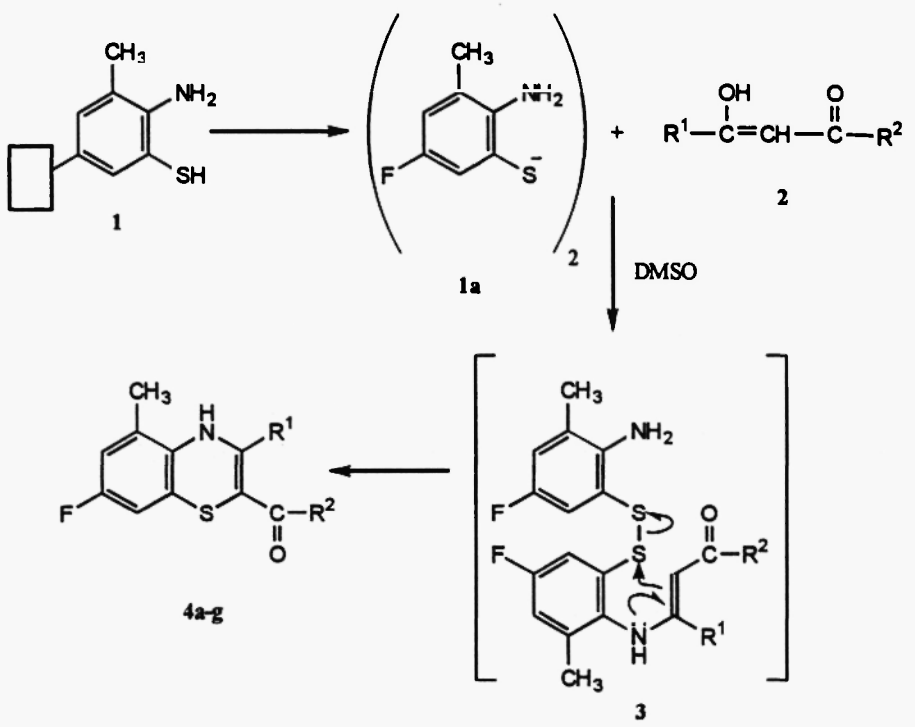
1,4-Benzothiazines resemble structurally to phenothiazines in having a fold along nitrogen-sulphur axis which is considered a structural specificity to impart a wide specturm of biological activities to phenothiazines. 1,4-Benzothiazines are anticipated to possess biological activities similar to phenothiazines (1-9). In our research programmes to develop new drugs it has been considered worthwhile to synthesize title compounds.

Experimental

Melting points of the synthesized compounds are uncorrected. The purity has been checked by thin layer chromatography. Characterization of synthesized compound was done by spectral studies. The infrared spectra were recorded on Nicolet-Magna IR Spectrophotometer model 550 using KBr disc. NMR spectra were recorded on 90 MHz Jeol FX90 FT NMR using TMS as internal standard.

1. Preparation of 4H-1,4-benzothiazines(4a-g)

To the stirred suspension of β-diketones/β-ketoesters **2** in dimethyl sulfoxide (5 ml.) was added 2-amino-5-fluoro-3-methyl benzenethiol **1** and the mixture was



$R^1 = CH_3$
$R^2 = OCH_3$, $-OC_2H_5$, C_6H_4-Cl(*p*), CH_3,
C_6H_4-OCH_3(*m*), C_6H_4-CH_3(*p*), C_6H_3-Cl_2 (*m*, *p*)

Scheme-1

refluxed for 20-30 minutes. The reaction mixture was concentrated and washed with petroleum ether and crystallized from methanol (Scheme-1). Analytical data of synthesized compounds is tabulated in table 1.

Result and discussion

The condensation and oxidative cyclisation of 2-amino-5-fluoro-3-methylbenzenethiol 1 with β-diketones / β-ketoesters 2 in dimethyl sulfoxide is believed to involve the formation of a enaminoketone intermediate 3. Under experimental conditions 2-aminothiophenols are readily oxidized to bis(2-aminophenyl) disulphides which cyclize to 4H-1,4-benzothiazines 4 by scission of sulphur-sulphur bond due to high reactivity of 2-position of enaminoketone system towards nucleophilic attack. IR and NMR data of synthesized benzothiazines are included in tables 2 and 3 respectively.

Table 1 : Physical data of 4H-1,4-benzothiazines

Compound 4	Molecular formula	Mpt °C	Yield %	% C Found (Calcd.)	% H Found (Calcd.)	% N Found (Calcd.)
a	$C_{12}H_{12}FNO_2S$	135	46	57.10 (56.91)	4.76 (4.74)	5.50 (5.53)
b	$C_{13}H_{14}FNO_2S$	170	48	58.12 (58.42)	5.22 (5.24)	5.26 (5.24)
c	$C_{17}H_{13}FClNOS$	148	55	61.01 (61.16)	3.91 (3.89)	4.17 (4.19)
d	$C_{12}H_{12}FNOS$	192	40	60.55 (60.75)	5.08 (5.06)	5.92 (5.90)
e	$C_{18}H_{16}FNOS$	96	50	66.00 (65.65)	4.88 (4.86)	4.23 (4.25)
f	$C_{18}H_{16}FNOS$	105	55	68.82 (69.00)	5.08 (5.11)	4.50 (4.47)
g	$C_{17}H_{12}FCl_2NOS$	102	48	55.20 (55.43)	3.24 (3.26)	3.79 (3.80)

Table 2 : Infrared spectral data of 4H-1,4-Benzothiazines

Compound 4	N-H A	C=O B	C-H C	C-O-C D	C-F E	C-Cl F
a	3390	1595	1450 1350	1240 1050	840	
b	3400	1600	1420 1380	1260 1040	800	
c	3380	1640	1450 1360		830	780
d	3400	1650	1450 1380		800	
e	3395	1590	1440 1375	1260 1030	810	
f	3340	1620	1450 1330		850	
g	3400	1600	1440 1350		890	756

Table 3 : NMR spectra data of 4H-1,4-benzothiazines

Compound 4	Solvent	δ (ppm)	Hydrogen	Multiplicity	Assignment
a	DMSO-d6	8.02	1	Singlet	N-H Proton
		7.52-6.53	2	Multiplet	Aromatic Protons
		2.3	3	Singlet	OCH_3 Protons of $COOCH_3$ at C_2
		2.02	3	Singlet	CH_3 Protons at C_3
		1.80	3	Singlet	CH_3 Protons at C_5
b	DMSO-d6	8.40	1	Singlet	N-H Proton
		7.92-7.16	2	Multiplet	Aromatic Protons
		4.43-4.12	2	Quartet	OCH_2 Protons of $COOC_2H_5$ at C_2
		2.78	3	Singlet	CH_3 Protons at C_3
		2.06	3	Singlet	CH_3 Protons at C_5
		1.45-1.20	3	Triplet	CH_3 Protons of $COOC_2H_5$ at C_2
c	DMSO-d6	8.17	1	Singlet	N-H Proton
		7.73-6.53	6	Multiplet	Aromatic Protons
		2.22	3	Singlet	CH_3 Protons at C_3
		1.84	3	Singlet	CH_3 Protons at C_5
d	DMSO-d6	7.90	1	Singlet	N-H Proton
		7.60-7.0	2	Multiplet	Aromatic Protons
		2.53	3	Singlet	CH_3 Protons of $COCH_3$ at C_2
		2.12	3	Singlet	CH_3 Protons C_3
		1.83	3	Singlet	CH_3 Protons at C_5
e	DMSO-d6	8.08	1	Singlet	N-H Proton
		7.44-7.13	6	Multiplet	Aromatic Protons
		3.89	3	Singlet	OCH_3 Protons of $COC_6H_4OCH_3$ (*m*) at C_2
		3.01	3	Singlet	CH_3 Protons at C_3
		2.53	3	Singlet	CH_3 Protons at C_5
f	DMSO-d6	8.24	1	Singlet	N-H Proton
		7.73-6.68	6	Multiplet	Aromatic Protons
		2.53	3	Singlet	CH_3 Protons of $COC_6H_4CH_3$ (*p*) at C_2
		2.12	3	Singlet	CH_3 Protons at C_3
		1.77	3	Singlet	CH_3 Protons at C_5
g	DMSO-d6	8.40	1	Singlet	N-H Proton
		7.7-6.03	5	Multiplet	Aromatic Protons
		2.3	3	Singlet	CH_3 Protons at C_3
		1.2	3	Singlet	CH_3 Protons at C_5

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