Journal of Fluorine Chemistry, 28 (1985) 381–385

Received: October 25, 1984; accepted: January 10, 1985

SYNTHESIS OF NEW FLUORINATED 4H-1,4-BENZOTHIAZINES AS POSSIBLE ANTICANCER AGENTS

R.R. GUPTA, RAKESH KUMAR and R.K. GAUTAM

Department of Chemistry, University of Rajasthan, Jaipur-302004 (India)

SUMMARY

A single-step synthesis for ring-fluorinated 4H-1,4-benzothiazines is reported by the condensation and oxidative cyclization of β-diketones with 2-amino-5-fluorobenzenethiol. The reaction is believed to proceed via an enaminoketone system.

INTRODUCTION

Benzothiazines find a number of applications in chemotherapy [1-7], dyes [8] and industry [9-12]. Such a wide spectrum of applications of benzothiazines has stimulated our interest to synthesize fluorinated 4H-1,4-benzothiazines via a simple and convenient method.

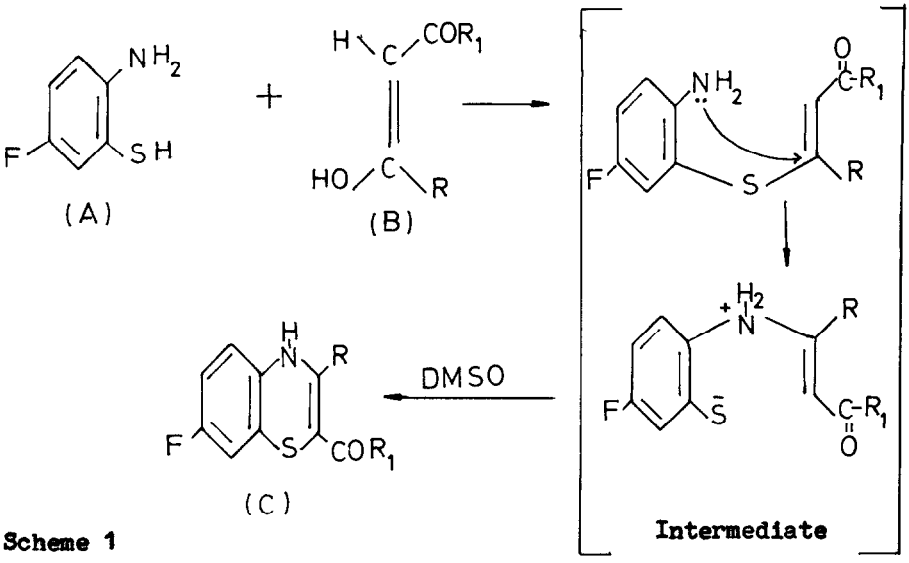
Fluorinated phenothiazines [13-16] (analogues of 4H-1,4-benzothiazines) are most effective drugs and we are designing fluorinated 4H-1,4-benzothiazines as possible anticancer agents.

The tremendous growth in the chemistry of organic fluorine compounds during the last few decades has been due to the unique properties conferred by the fluorine atom on molecules to which it is bonded. 5-Fluoro-uracil and 5-fluorotryptamine are highly effective drugs used in the treatment of cancer.

0022-1139/85/$3.30

Keeping the above observations in view, the present investigation has been undertaken to develop a convenient method for the synthesis of new ring-fluorinated 4H-1,4-benzothiazines, so that they can be made available for screening their anticancer activities.

Condensation of 2-amino-5-fluorobenzenethiol with β-diketones in DMSO under reflux afforded ring-fluorinated 4H-1,4-benzothiazines. The reaction is believed to proceed through the formation of an intermediate enamino-ketone (Scheme 1).



Scheme 1

where R = CH_3, C_6H_5, R_1 = CH_3, OC_2H_5, C_6H_5, C_6H_4Cl-p ,

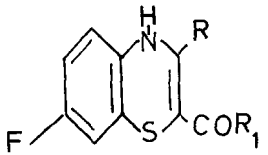
C_6H_4-CH_3-p, $C_6H_4OCH_3$-p.

RESULTS AND DISCUSSION

All the melting points are uncorrected. The purity of the synthesized compounds was tested by thin layer chromatography. The infrared spectra of all the newly synthesized benzothiazines invariably showed an NH absorption in the region 3260-3340 cm^{-1} and carbonyl absorption in the region 1580-1620 cm^{-1}.

TABLE 1

Physical data for fluorinated 4H-1,4-benzothiazines



Comp. No.	R	R_1	M.p. °C	Yield %	Molecular formula	Colour	% Found			% Calcd		
							C	H	N	C	H	N
I	CH_3	CH_3	193	70	$C_{11}H_{10}NSFO$	orange	59.08	4.46	6.31	59.19	4.48	6.27
II	CH_3	C_6H_5	194	65	$C_{16}H_{12}NSFO$	orange	67.24	4.19	4.89	67.36	4.21	4.91
III	CH_3	C_6H_4Cl	217	72	$C_{16}H_{11}NSFClO$	red	60.17	4.35	3.42	60.09	4.38	3.44
IV	CH_3	OC_2H_5	160	60	$C_{12}H_{12}NSFO_2$	yellow	56.78	4.71	5.49	56.91	4.74	5.53
V	CH_3	$C_6H_4OCH_3$	192	68	$C_{17}H_{14}NSFO_2$	dark red	64.63	4.42	4.47	64.76	4.44	4.44
VI	CH_3	$C_6H_4CH_3$	187-8	63	$C_{17}H_{14}NSFO$	red	68.09	4.65	4.72	68.22	4.68	4.68
VII	C_6H_5	C_6H_5	215	50	$C_{21}H_{14}NSFO$	orange	72.48	4.01	4.06	72.62	4.03	4.03

The weak absorption bands in the region 1360-1490 cm^{-1} are attributed to C-CH_3 ring vibrations in all fluorinated benzothiazines. The nmr spectra of these benzothiazines exhibit a signal at τ 0.80-1.5 due to the NH proton and the multiplets in the region τ 2.4-3.8 are due to aromatic ring protons. The mass spectrum showed molecular ion peaks corresponding to their molecular weights. 2-Benzoyl-, p-chlorobenzoyl-, p-methylbenzoyl-, and p-methoxybenzoyl-4H-1,4-benzothiazines show peaks at m/z = M^+-105, 139, 119, 135 (with high intensity, base peak).

EXPERIMENTAL

Preparation of 2-amino-5-fluorobenzenethiol

2-Amino-5-fluorobenzenethiol (m.p. 82°) was prepared by hydrolytic cleavage of 2-amino-6-fluorobenzothiazole in the presence of sodium hydroxide [17] .

Preparation of fluorinated 4H-1,4-benzothiazines

2-Amino-5-fluorobenzenethiol (A ; 0.01 mole) was added to the stirred suspension of β-diketone (B ; 0.01 mole) (acetylacetone, ethylacetoacetate, dibenzoylmethane, benzoylacetone, p-chlorobenzoylacetone, p-methylbenzoylacetone, p-methoxybenzoylacetone) in DMSO (5 ml) and the resulting mixture was heated for 30 minutes. The mixture was cooled down to room temperature and a solid substance separated, which was filtered and crystallized from methanol. The physical and analytical data of synthesized compounds are given in Table 1.

REFERENCES

1 A. Takamizawa and H. Sato, Japan Pat. 7 025 499 (1979); Chem. Abstr., 74 (1979) 3640.
2 N.E. Mackenzie, R.H. Thomson and C.W. Greenhalgh, J. Chem. Soc. Perkin Trans. 1(12) (1980) 2923
3 F. Desimov, A. Dini, R.A. Nicolaus, E. Ramundo, M. Di Rosa and P. Persico, Farmaco-Ed. Sci. 35(4) (1980) 333.

4 J. Krapcho, U.S. Pat.4 078 062 (1978); Chem. Abstr., 89, (1978) 109526.
5 C.F. Turk, P. Egli and J. Krapcho, J. Heterocyclic Chem, 14 (1977) 1135.
6 T.V. Sokolova, K.I. Lopatina, I.V. Zaitseva, R.M. Salimov, N.P. Speranskaya and V.A. Zagorevakii, Khim. Farm. Zh., 10(9) (1976) 42.
7 J. Kropcho, U.S. Pat. Appl. B. 348438; Chem. Abstr., 84 (1976) 180247.
8 M.G. Khristianson and A. Ya II'chenko, Veb. Uspekhi. Fotogr. N., 17 (1976) 175; Chem. Abstr., 85 (1976) 161865.
9 N.E. Mackenzil, R.H. Thomson and C.W. Greenhalgh, J. Chem. Soc. Perkin Trans. (1980) 2923.
10 H. Eilingsfeld, D. Lach, Ger. Offem. 2,536,120 (1977); Chem. Abstr., 86 (1977) 173075.
11 S. Ishige, H. Usui and K. Saeki, Ger. Offen. 2 704 724 (1977); Chem. Abstr., 87 (1977) 144134.
12 H. Nagase, Agric. Chem. Pharm. Bull, 22(1) (1974) 42.
13 A/S. Kefales, Neth. Appl. 7,407,643 (1974); Chem. Abstr., 83 (1975) 10115.
14 H.F. Darling, G.H. Hess, A.C. Capistrano and M.G. Hoermann, Dis. Nerv. Syst. 21 (1960) 409.
15 J.J. Piala, J.J. Hassert, J.P. High and J.C. Buke, Monographs on Therapy, 2 (1957) 214.
16 H.L. Yale, F. Sowinski and J. Bernstein, J. Am. Chem. Soc., 79 (1959) 4375.
17 A. Mackei and J. Raiburn, J. Chem. Soc. (1952) 787.