Journal of Fluorine Chemistry, 31 (1986) 19–24

Received: March 23, 1985; accepted: September 18, 1985

SYNTHESIS OF 6-TRIFLUOROMETHYL-4H-1,4-BENZOTHIAZINES AS POSSIBLE ANTICANCER AGENTS

R.R. GUPTA and RAKESH KUMAR

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

SUMMARY

The synthesis of 6-trifluoromethyl-4H-1,4-benzothiazines is reported by the condensation and oxidative cyclization of 2-amino-4-trifluoromethylbenzenethiol hydrochloride with β-dicarbonyl compounds. All the newly synthesized compounds have been characterized by elemental analyses, IR, NMR and Mass spectral studies.

INTRODUCTION

Dibenzothiazines of varying structural complexity have become well known in recent years and find a number of applications in medicine as antipsychotics [1-3], anti-inflammatory [4], antihistaminic [5] and anticancer agents [6-9].

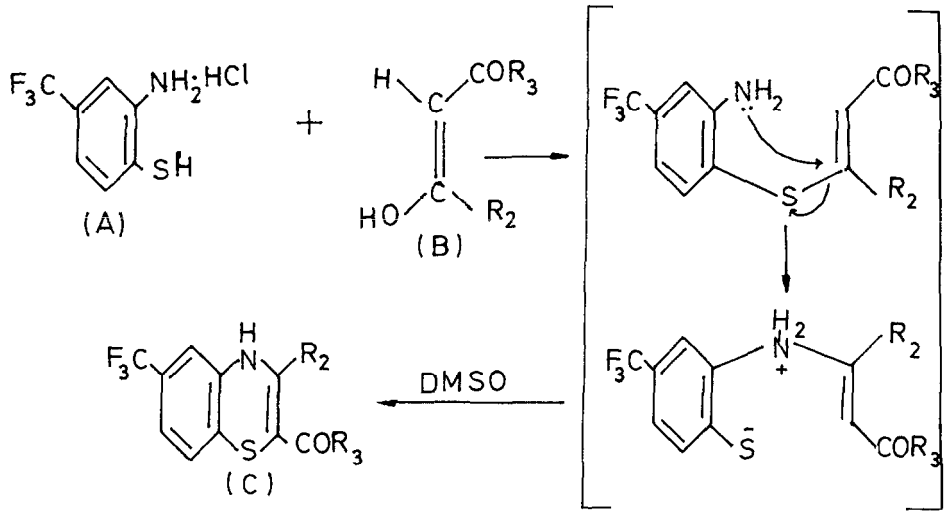
Fluoro derivatives are known to be particularly effective medicinal agents. At the moment 5-fluoro-uracil and 5-fluorotryptamine are most effective anticancer agents and from drug design point of view trifluoromethyl substituted 1,4-benzothiazines should be effective antitumour agents.

The introduction of a trifluoromethyl group in the phenothiazines (analogues of 4H-1,4-benzothiazines) [10-15] at the meta position (relative to the nitrogen atom) causes marked differences in biological [16] and other substituents leads to increased lipid solubility in membranes which enhance the rate of absorption and transport *in vivo*.

0022-1139/86/$3.50

Keeping in view all these observations it was considered worthwhile and interesting to synthesize 4H-1,4-benzothiazines having trifluoromethyl groups at a position meta to the nitrogen atom by a convenient method, so that they could be made available for screening their anticancer activities.

In the present communication, 6-trifluoromethyl-4H-1,4-benzothiazines have been synthesized by a single step and convenient method involving the condensation and oxidative cyclization of 2-amino-4-trifluoromethylbenzenethiol hydrochloride with ß-dicarbonyl compounds in presence of DMSO. The reaction is believed to proceed through the formation of an intermediate enaminoketone as shown in the Scheme 1.



Scheme 1 Intermediate

where R_2 = CH_3, C_6H_5, H ; R_3 = CH_3, OC_2H_5, C_6H_5, C_6H_4Cl-p, H.

RESULTS AND DISCUSSION

All the melting points are uncorrected. The purity of all the synthesized compounds was tested by TLC. The infrared spectra were obtained on a Perkin-Elmer spectrophotometer Model 577 in KBr discs over the range of 4000-400 cm^{-1}. Nmr spectra were recorded at 60 MHz on a Perkin-Elmer Model EM 360 in $CDCl_3$ and

DMSO d_6, using TMS as an internal standard. Mass spectra were recorded on a Jeol, JMSD-300 mass spectrometer at 70 ev and 100 μ amp ionizing current.

The N-H stretching vibrations in all the 4H-1,4-benzothiazines are observed in the region 3280-3320 cm^{-1} as sharp peaks and carbonyl absorptions in the region of 1570-1610 cm^{-1}. The bands in the region 1320-1325 cm^{-1} and 1120-1150 cm^{-1} are attributed to $-CF_3$ deformation vibrations. The two sharp absorption bands in the region 1350-1370 cm^{-1} and 1450-1475 cm^{-1} are due to the asymmetric and symmetric C-H deformation vibrations of the $C-CH_3$ groups.

In the nmr spectra a single sharp peak in the region τ 0.80-1.50 is observed in all the compounds from the N-H protons. The signals in the region τ 7.9-8.3 are due to the $C=C-CH_3$ groups. A triplet centered at τ 8.95 and quartet centered at τ 6.0 in benzothiazine-2 are from CH_3 and CH_2 protons of the ester linkages at C_2. The multiplets in the region of τ 2.0-3.6 are due to aromatic ring protons.

The mass spectrum of all the 6-trifluoromethyl-4H-1,4-benzothiazines showed molecular ion peaks in accordance with their molecular weights. 2-Benzoyl and p-chlorobenzoyl-4H-1,4-benzothiazines show peaks at M/e = M^+-105 and 139 ($(C_6H_5CO^+$, $p\text{-}ClC_6H_4CO^+$, base peak) by the loss of a benzoyl and p-chlorobenzoyl group. The 3-methyl-6-trifluoromethyl-2-ethoxycarbonyl derivative gave peaks at M/e = $M^+-C_2H_4$ and $M^+-C_2H_5$. The elimination of ethylene ($M^+-C_2H_4$) is analogous to that reported in mass fragmentation of ethyl benzoate [17].

EXPERIMENTAL

Preparation of 2-amino-4-trifluoromethylbenzenethiol hydrochloride A

2-amino-4-trifluoromethylbenzenethiol hydrochloride was prepared by the reduction of 2,2'-dinitro-4,4'-di(trifluoromethyl) diphenyldisulphide by tin and hydrochloric acid [18]. The former was prepared by the reaction of 2-nitro-4-(trifluoromethyl)chlorobenzene and sodium polysulphide.

TABLE 1

Data for 6-trifluoromethyl-4H-1,4-benzothiazines (1-5)

Comp. No.	R 2	R 3	M.p. °C	Yield %	Colour	Molecular Formula	% Found			% Calcd		
							C	H	N	C	H	N
1	CH_3	CH_3	206	65	Orange	$C_{12}H_{10}NSOF_3$	52.65	3.68	5.10	52.74	3.66	5.12
2	CH_3	OC_2H_5	160	60	Yellow	$C_{13}H_{12}NSO_2F_3$	51.41	3.94	4.59	51.48	3.96	4.62
3	CH_3	C_6H_5	165	58	Red	$C_{17}H_{12}NSOF_3$	60.83	3.54	4.15	60.89	3.58	4.17
4	CH_3	C_6H_4Cl-p	209	62	Red	$C_{17}H_{11}NSOF_3Cl$	55.12	2.95	3.76	55.20	2.97	3.78
5	C_6H_5	C_6H_5	192	50	Red	$C_{22}H_{14}NSOF_3$	66.41	3.50	3.49	66.49	3.52	3.52

Preparation of 6-trifluoromethyl-4H-1,4-benzothiazines C

In a round bottomed flask the 2-amino-4-trifluoromethyl-benzenethiol hydrochloride (A, 0.01 mole) was taken in DMSO (5 ml) and neutralized by adding liquid ammonia. β-Dicarbonyl compound (B, 0.01 mole in DMSO 3 ml) was added to the flask, and the resulting bright yellow solution was stirred and heated for thirty minutes. The colour of the reaction mixture changed from yellow to red in the case of benzothiazines 3-5 and remained deep yellow in the case of benzothiazines 1 and 2. The contents were cooled and poured into a beaker containing crushed ice; filtered and washed well with cold water and extracted from ether. The compounds were recrystallized from methanol. Yields and physical data of 6-trifluoromethyl-4H-1,4-benzothiazines are summarized in the Table 1.

REFERENCES

1 K. Kobayashi, T. Shohmori and M. Kohsaka, Adv. Biosci., 37, (1982) 123; Chem. Abstr., 97 (1982) 104109.

2 M.K. Elsaid, Pharmazie., 36 (1981) 678.

3 M. Gorden, ed, Psychopharmacological Agents, Vol. III, Academic Press, New York, NY, 1974.

4 Ube Industries Ltd., Jpn, Kokai Tokyo Koho JP., 57 (1982), 144,270; Chem. Abstr., 98 (1983) 89376.

5 F.P. Koland, IRCS Med. Sci. Libr. Compend., 9 (1981) 546; Chem. Abstr., 95 (1981), 9085.

6 R. Ganapathi and D. Grobowski, Cancer Res., 43, (1983) 3696.

7 N. Motohashi, Yakugaku, Zasshi., 103, (1983) 364.

8 L. Ai Jeng and K. Sudhaka, J. Heterocyclic Chem., 18, (1981) 759.

9 K.K. Showa Denko, Jpn., Kokai Tokyo Koho JP., 81, (1981) 166,182-84 Chem. Abstr., 96 (1982) 142871-73.

10 H.L. Yale, F. Sowinski, J. Am. Chem. Soc., 82 (1960) 2039.

11 P.N. Craig, E.A. Nodiff, J.J. Lafferty and G.E. Ullyot, J. Org. Chem., 22 (1957) 709.

12 H.L. Yale, F. Sowinski, J. Bernstein, J. Am. Chem. Soc., 79, (1957) 4375.

13 Kefales, A/S Neth. Appl, 7 407 653 (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. Burke., Monographs on Therapy., 2, (1957) 214.

16 H.L. Yale, J. Med. Pharm. Chem., 1, (1959) 121.

17 H. Budzikiewicz and C. Djerassi and D.H. Williams, Mass spectrometry of organic compounds, p. 197, Holden Day Inc. London, 1967.

18 R.L. Dannley and D.A. Zazaris, Can. J. Chem., 43 (1965) 2610.