Reactions of 2-Aminobenzenethiols with 4-Hydroxycoumarin, Maleic Anhydride and *p*-Chlorobenzoylacetone: A Single Step Synthesis of Heterocycles Containing the 1,4-Thiazine Nucleus

R. R. Gupta*, R. K. Gautam and Rakesh Kumar

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

Received February 26, 1986

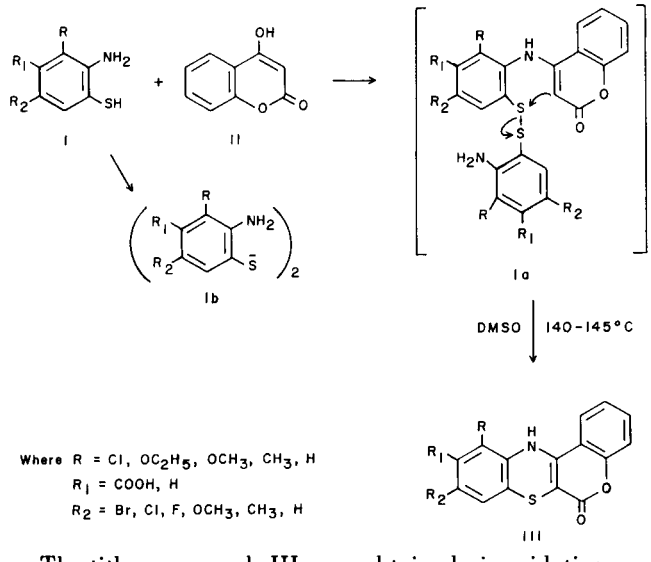
A single step and convenient synthesis of some heterocycles containing the 1,4-thiazine nucleus are reported by the condensation and cyclization of substituted 2-aminobenzenethiols with 4-hydroxycoumarin, maleic anhydride and *p*-chlorobenzoylacetone.

J. Heterocyclic Chem., **24**, 171 (1987).

Our research programs concern with the development of suitable synthetic routes for novel heterocyclic pharmaceuticals. In search of better medicinal agents we investigated the reaction of 2-aminobenzenethiols with *o*-halonitrobenzenes to synthesize variously substituted phenothiazines [1-5]. It is worthwhile to investigate the reactions of such substituted 2-aminobenzenethiols with 4-hydroxycoumarin, maleic anhydride and *p*-chlorobenzoylacetone to develop suitable methods for the synthesis of substituted 6,12-dihydro-1-benzopyrano[3,4-*b*][1,4]benzothiazin-6-ones, substituted 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-2-acetic acids and substituted 2-(*p*-chlorobenzoyl)-3-methyl-4*H*-1,4-benzothiazines.

The condensation and oxidative cyclization of substituted 2-aminobenzenethiols with 4-hydroxycoumarin in DMSO provides substituted 6,12-dihydro-1-benzopyrano-[3,4-*b*][1,4]benzothiazin-6-ones III.

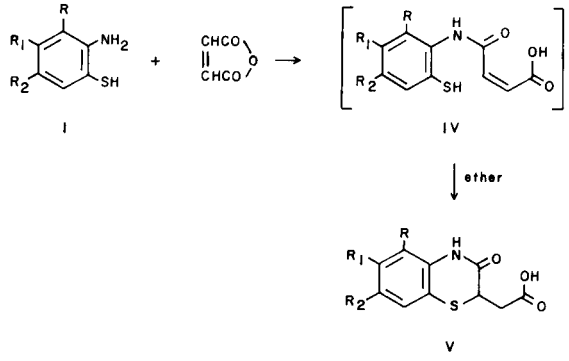
Scheme 1



The title compounds III were obtained *via* oxidative cyclization [6] by merely heating a mixture of I and II in DMSO at 140-150° for thirty to fifty minutes. Since compound I is readily oxidized to bis-(substituted 2-aminophenyl) disulfide Ib under these reaction conditions, the reaction is considered to proceed through the formation of an intermediate Ia which is readily cyclized by the scission of the sulfur-sulfur bond [7,8] upon the attack by the nucleophilic enaminone system (Scheme 1).

The reaction of substituted 2-aminobenzenethiols with maleic anhydride in ether at room temperature yielded ring substituted 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-2-acetic acids V. This is an exothermic reaction and directly yields the cyclized 1,4-benzothiazines at room temperature.

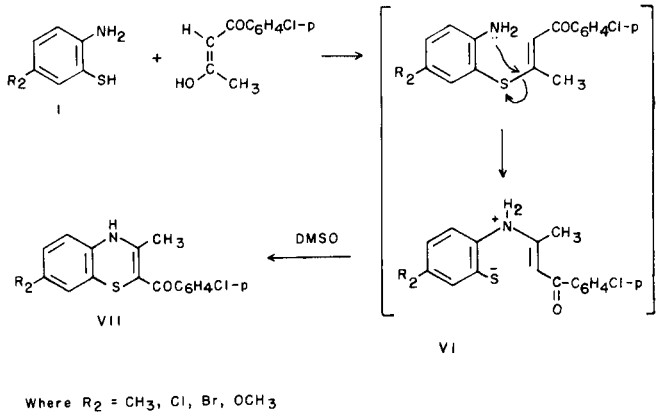
Scheme 2



The reaction is believed to proceed through the formation of the *o*-mercapto meleanilic acid intermediate IV formed from the initial nucleophilic anhydride ring opening with the amino nitrogen, cyclizes *in situ* and provides substituted 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-2-acetic acids (Scheme 2).

However, the condensation of substituted 2-aminobenzenethiols with *p*-chlorobenzoylacetone in DMSO provided substituted 2-(*p*-chlorobenzoyl)-3-methyl-4*H*-1,4-benzothiazines.

Scheme 3

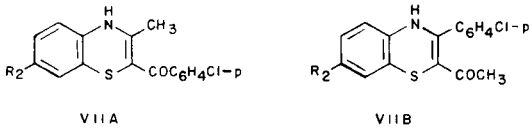


Where R_2 = CH_3, Cl, Br, OCH_3

In the formatin of 4*H*-1,4-benzothiazine the reaction is believed to proceed through the formation of an intermediate enaminoketone.

Because of the high nucleophilic reactivity of the α-position of the enaminoketone system [9,10], the formation of 2-(*p*-chlorobenzoyl)-3-methyl-4*H*-1,4-benzothiazines may be considered to be an intramolecular nucleophilic attack on the intermediate enaminoketone followed by oxidative cyclization (Scheme 3).

The two isomeric products of substituted 2-(*p*-chlorobenzoyl)-3-methyl-4*H*-1,4-benzothiazines may be formed theoretically, but compound VIIA predominates over the compound VIIB (identified by mass spectral studies).



The combined effect of conjugation and positive inductive effect of the CH_3 group facilitate the enolisation of ketonic group attached to the methyl group. Enolisation of the ketonic group attached to the benzene ring is retarded because of the electronegative nature of the ring instead of enhancement and explains the formation of product VIIA instead of VIIB.

Infrared Spectra.

The infrared spectra of all these compounds showed an NH absorption in the region 3100-3440 cm^{-1} and carbonyl absorption in the region 1570-1715 cm^{-1} respectively. The bands in the region 1240-1260 cm^{-1} and 1045-1080 cm^{-1} can probably be assignable to the C-O-C bonding in compounds having an ethoxy linkage. A sharp band at 1610-1690 cm^{-1} observed in compounds having a COOH group may be assigned to the carbonyl stretching vibrations of COOH group. The benzothiazines V exhibit -OH stretching vibrations in the region 3200-3440 cm^{-1} while corresponding stretching vibrations in cyclic carbonyl compounds appear in the region 3500-3560 cm^{-1} [11]. This large shift to a lower frequency region may be due to the proximicity of a cyclic carbonyl group at position-3 to the carboxylic moiety, which suggests the formation of a seven membered chelate of high stability through a strong C=O.....H-O, intramolecular hydrogen bonding (Figure 1).

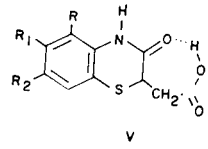


Figure 1

Nuclear Magnetic Resonance Spectra.

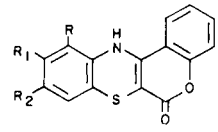
The ^1H nmr spectrum of all the synthesized compounds exhibit a broad signal in the region δ 8.3-10.70 due to N-H proton. A singlet in the region δ 1.9-2.8 is observed in compounds have a methyl group. A singlet in the region δ 3.45-4.22 arising in methoxy derivatives was also observed due to the methoxyl protons. The quartet in the region δ 1.47-1.85 and the triplet in the region δ 3.95-4.95 in compounds III-2, V-2 having ethoxy linkage at postion-1 and -5 are observed due to methyl and methylene protons of the ethyl groups respectively. In benzothiazines III-5 and V,1-10, a singlet observed at extremely low field δ 9.0-10.90 can be assigned to proton of carboxyl group. The multiplets in the region δ 6.20-8.71 are due to aromatic ring protons.

Mass Spectra.

The mass spectrum of all the substituted 1,4-thiazines showed a molecular ion peak in accordance with their molecular weights. The molecular ion peak is the base peak in compounds III and V while in compound VII the base peak was obtained by the fission of the C-C bond at position 2. All the compounds display a comparatively intense doubly charged molecular ion peak which indicates the overall stability of the benzothiazine ring system to electron impact. All *p*-chlorobenzoyl-4*H*-1,4-benzothiazines showed peaks at m/e = M^+-139 (with high intensity), 139 ($C^+OC_6H_4Cl$-*p*, base peak), but did not show any peak corresponding to the M^+-$COCH_3$ or $COCH_3^+$ moiety, proving the structure of these benzothiazines to be VIIA. All the 6,12-dihydro-1-benzopyrano[3,4-*b*][1,4]benzothiazin-6-ones gave a peak at m/z = M^+-CO which is parallel to the mass fragmentation pattern reported for the alkyl-aryl-ether [12,13]. The peak m/z = M^+-43 is present in methoxy derivatives of 6,12-dihydro-1-benzopyrano[3,4-*b*][1,4]ben-

Table 1

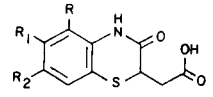
Physical Data of Substituted 6,12-Dihydro-1-benzopyrano[3,4-*b*][1,4]benzothiazin-6-ones III **1-10**



Compound No.	R	Compound R_1	Compound R_2	MP °C	Colour	Yield %	Molecular Formula	% C, H, N Found			% C, H, N Calcd.		
1	Cl	H	H	224-225	Dirty Yellow	55	$C_{15}H_8ClNSO_2$	59.56	2.66	4.61	59.70	2.65	4.64
2	OC_2H_5	H	H	221-222	Orange	47.5	$C_{17}H_{13}NSO_3$	65.48	4.20	4.53	65.59	4.18	4.50
3	OCH_3	H	H	226-228	Dark brown	50	$C_{16}H_{11}NSO_3$	64.48	3.68	4.67	64.64	3.70	4.71
4	CH_3	H	H	266	Red	52	$C_{16}H_{11}NSO_2$	68.18	3.93	4.95	68.32	3.91	4.98
5	H	COOH	H	342 dec	Orange	43.5	$C_{16}H_9NSO_4$	61.60	2.90	4.47	61.73	2.89	4.50
6	H	H	Br	310	Orange	60	$C_{15}H_8BrNSO_2$	51.90	2.29	4.08	52.02	2.31	4.04
7	H	H	Cl	328	Red	70	$C_{15}H_8ClNSO_2$	59.62	2.64	4.66	59.70	2.65	4.64
8	H	H	F	322	Red	65	$C_{15}H_8FNSO_2$	63.06	2.82	4.88	63.15	2.80	4.91
9	H	H	OCH_3	297-298	Dark red	63	$C_{16}H_{11}NSO_3$	64.52	3.72	4.75	64.64	3.70	4.71
10	H	H	CH_3	334 dec	Red	67.5	$C_{16}H_{11}NSO_2$	68.24	3.89	5.02	68.32	3.91	4.98

Table 2

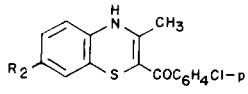
Physical Data of Substituted 3,4-Dihydro-3-oxo-2*H*-1,4-Benzothiazin-2-Acetic Acids V **1-10**



Compound No.	R	Compound R_1	Compound R_2	MP °C	Colour	Yield %	Molecular Formula	% C, H, N Found			% C, H, N Calcd.		
1	Cl	H	H	158	Yellow	78	$C_{10}H_8ClNSO_3$	46.49	3.08	5.48	46.60	3.10	5.43
2	OC_2H_5	H	H	118	Light Yellow	80	$C_{12}H_{13}NSO_4$	53.78	4.82	5.29	53.93	4.86	5.24
3	OCH_3	H	H	112	Dirty Yellow	90	$C_{11}H_{11}NSO_4$	52.32	4.31	5.49	52.17	4.34	5.53
4	CH_3	H	H	121	Light Yellow	82	$C_{11}H_{11}NSO_3$	55.48	4.67	5.92	55.69	4.64	5.90
5	H	COOH	H	218	Light Yellow	75	$C_{11}H_9NSO_5$	49.28	3.39	5.20	49.43	3.37	5.24
6	H	H	Br	192	Yellow	88.5	$C_{10}H_8BrNSO_3$	39.58	2.65	4.67	39.73	2.64	4.63
7	H	H	Cl	203	Yellow	94	$C_{10}H_8ClNSO_3$	46.44	3.13	5.38	46.60	3.10	5.43
8	H	H	F	198	Dirty Yellow	87	$C_{10}H_8FNSO_3$	49.72	3.28	5.76	49.79	3.31	5.80
9	H	H	OCH_3	181	Dirty Yellow	84	$C_{11}H_{11}NSO_4$	52.02	4.38	5.58	52.17	4.34	5.53
10	H	H	CH_3	200	Yellow	92	$C_{11}H_{11}NSO_3$	52.52	4.62	5.95	55.69	4.64	5.90

Table 3

Physical Data of 2-(*p*-Chlorobenzoyl)-3-methyl-7-substituted-4*H*-1,4-benzothiazines VII **1-4**



Compound	Compound R_2	MP °C	Yield %	Colour	Molecular Formula	% C, H, N Found			% C, H, N Calcd.		
1	CH_3	190°	65	Red	$C_{17}H_{14}ClNSO$	64.75	4.50	4.48	64.65	4.43	4.43
2	Cl	196°	55	Deep Red	$C_{16}H_{11}Cl_2NSO$	57.02	3.20	4.10	57.14	3.27	4.16
3	Br	229°	65	Red	$C_{16}H_{11}BrClNSO$	50.32	2.85	3.65	50.45	2.89	3.67
4	OCH_3	201°	66	Red	$C_{17}H_{14}ClNSO_2$	61.43	4.18	4.20	61.53	4.22	4.22

zothiazin-6-one due to the loss of the $COCH_3$ group. The 1-ethoxy-6,12-dihydro-1-benzopyrano[3,4-*b*][1,4]benzothiazin-6-one gave peaks at m/z = M^+-C_2H_4, M^+-OC_2H_5, and M^+-C_2H_5. The elimination of ethylene in the mass spectra of this compound can be explained by a McLafferty rearrangement [14] which suggests the formation of a 4 membered intermediate in the following way (Figure 2):

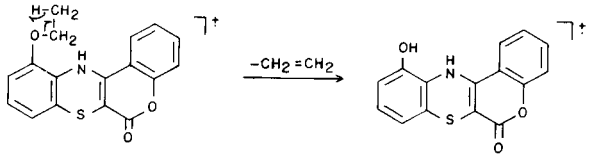


Figure 2

EXPERIMENTAL

Melting points are uncorrected. The purity of all the synthesized compounds was tested chromatographically and characterized by their elemental analyses and spectral datas. The ir spectra were recorded on a Perkin-Elmer M 577 spectrophotometer in potassium bromide. The ^1H nmr spectra were recorded with a Perkin-Elmer $R_{12}B$ spectrometer using TMS as an internal standard and solvents DMSO-d_6 and deuteriochloroform. The mass spectra were measured on JMS-D 300 at 70 eV.

Preparation of Ring-substituted 2-Aminobenzenethiols I.

The substituted 2-aminobenzenethiols have been prepared by a modified method reported by us elsewhere [1-4] by the hydrolytic fission of substituted 2-aminobenzothiazoles.

Preparation of Substituted 6,12-Dihydro-1-benzopyrano[3,4-*b*][1,4]benzothiazin-6-ones III.

4-Hydroxycoumarin (II, 0.01 mole), substituted 2-aminobenzenethiol (I, 0.01 mole) and DMSO (8 ml) were stirred and heated at 140-145° for 35-50 minutes. The product crystallized out on cooling and was filtered and recrystallized from ethanol. The physical data are given in Table 1.

Preparation of 3,4-Dihydro-3-oxo-2*H*-1,4-benzothiazin-2-acetic Acids V.

To a solution of maleic anhydride (0.05 mole) in ether (20 ml), a solution of substituted 2-aminobenzenethiol (I, 0.05 mole) in ether (20 ml) was added at room temperature with stirring. The warm reaction mixture on cooling gave a light yellow coloured solid. The product was filtered, dried and crystallized from ethanol.

A semi-solid obtained in the case of 5-substituted 3,4-dihydro-3-oxo-2*H*-1,4-benzothiazin-2-acetic acids was dissolved in alcohol and poured into a beaker containing ice cold water. The product was filtered, washed well with water and crystallized from ethanol. The physical data of these compounds are summarized in Table 2.

Preparation of 2-(*p*-Chlorobenzoyl)-3-methyl-7-substituted 4*H*-1,4-benzothiazines VII.

Substituted 2-aminobenzenthiol (I, 0.01 mole) was added to a stirred suspension of *p*-chlorobenzoylacetone (0.01 mole) in DMSO (5 ml) and the solution was refluxed for one hour, concentrated and cooled to room temperature. The contents were filtered and washed with small amount of methanol. It was recrystallized from methanol. The physical data of the synthesized compounds are given in Table 3.

Acknowledgement.

Council of Scientific and Industrial Research and University Grants Commission, New Delhi are thanked for award of fellowships to Mr. Rakesh Kumar and Mr. R. K. Gautam.

REFERENCES AND NOTES

[1] R. R. Gupta and Rakesh Kumar, *Heterocycles*, **22**, 87 (1984).

[2] R. R. Gupta, G. S. Kalwania and M. Kumar, *J. Heterocyclic Chem.*, **21**, 893 (1984).

[3] R. R. Gupta, G. S. Kalwania and M. Kumar, *Heterocycles*, **16**, 2527 (1981).

[4] R. R. Gupta, K. G. Ojha and S. K. Jain, *Synth. Commun.*, **9**, 457 (1979).

[5] R. R. Gupta, K. G. Ojha and M. Kumar, *J. Heterocyclic Chem.*, **17**, 1325 (1980).

[6] C. N. Yiannios and J. V. Kerabinos, *J. Org. Chem.*, **28**, 3246 (1963).

[7] F. M. Moracci, M. Cardilini, F. Liberatore, P. Marchini, G. Liso and U. Gulini, *Int. J. Sulphur Chem.*, **8**, 341 (1973).

[8] T. Fujiwara, K. Hata and T. Kojima, *Chem. Letters*, 287 (1973).

[9] Y. Yoshimoto, N. Nishida, T. Hiraoka, *Tetrahedron Letters*, 39 (1973) and references therein.

[10] H. J. Teuber, E. Warbs and D. Cornelius, *Chem. Ber.*, **101**, 3918 (1960).

[11] L. J. Bellamy, "The Infrared Spectra of Complex Molecules", 2nd Ed, John Wiley & Sons, Inc., New York, 1958, p 162.

[12] F. Meyer and A. G. Hamson, *Can. J. Chem.*, **42**, 2008 (1964).

[13] Z. Pelah, J. M. Willson, M. Ohashi, H. Budrikiewicz, and C. Djerassi, *Tetrahedron.*, **19**, 2233 (1963).

[14] F. W. McLafferty, *Anal. Chem.*, **31**, 2072 (1959).