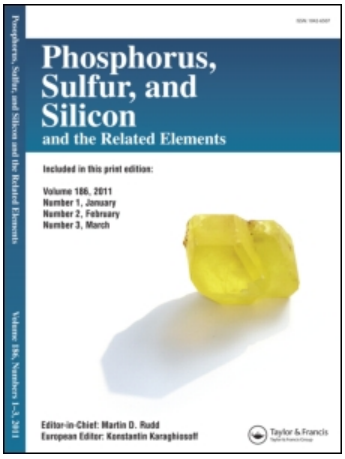

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Gupta, Vandana , Gautam, R. K. , Jain, S. K. and Gupta, R. R.(1990) 'SINGLE STEP SYNTHESIS OF SULFONATED 4H-1,4-BENZOTHIAZINES', Phosphorus, Sulfur, and Silicon and the Related Elements, 47: 1, 225 — 228
To link to this Article: DOI: 10.1080/10426509008046864
URL: http://dx.doi.org/10.1080/10426509008046864

Phosphorus, Sulfur, and Silicon, 1990, Vol. 47, pp. 225–228
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Printed in the United Kingdom

SINGLE STEP SYNTHESIS OF SULFONATED 4H-1,4-BENZOTHIAZINES

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(Received May 22, 1989; in final form May 26, 1989)

Single step and convenient synthesis for 6-sulfonated 4H-1,4-benzothiazines is reported by the condensation and oxidative cyclization of 2-aminobenzenethiol-4-sulphonic acid with β-diketones/β-ketoesters. 2-Aminobenzenethiol-4-sulphonic acid has been synthesized directly by the reaction of sulfuric acid with 2-aminobenzenethiol. The structure of synthesized compounds was confirmed by analytical and spectral data.

Key words: 4H-1,4-Benzothiazines; single step synthesis; 2-aminobenzenethiol-4-sulfonic acid; β-diketones; β-ketoesters.

INTRODUCTION

Phenothiazines possess a wide spectrum of pharmacological activities[1] and its some derivatives are in clinical use.[1] One of the structural specificity considered responsible for such a wide spectrum of biological activities in phenothiazines is a fold along nitrogen-sulfur axis. Such a structural specificity is also present in 4H-1,4-benzothiazines and they are also anticipated to possess significant biological activities, but due to their non-availability not much work has been done. Therefore we have considered worthwhile to synthesize title compounds to make available them for screening their biological activities.

DISCUSSION

In the present communication we report a single step and convenient synthesis of 6-sulfonated 4H-1,4-benzothiazines which involves the condensation and oxidative cyclization of 2-aminobenzenethiol-4-sulfonic acid with β-diketones/β-ketoesters in dimethyl sulfoxide. Although a number of methods have been developed for the synthesis of substituted 2-aminobenzenethiols, none of them has been found convenient for the synthesis of 2-aminobenzenethiol-4-sulfonic acid. Substituted 2-aminobenzenethiols are generally prepared by alkaline hydrolysis of Herz compound,[7] but this reaction cannot be used to obtain 2-aminobenzenethiol-4-sulfonic acid because chlorination takes place at both 3- and 5-positions during Herz reaction. Another widely used method[8] is by the hydrolytic fission of 2-aminobenzothiazole which in turn are prepared by the

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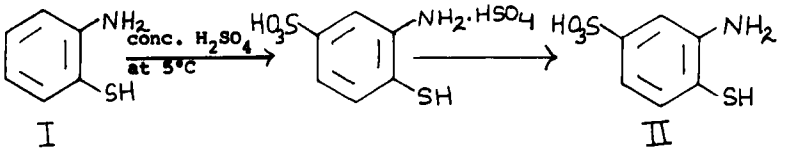


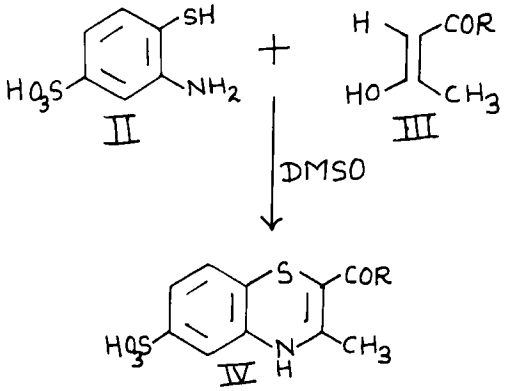
SCHEME 1

thiocyanation of aryl amines. The process also does not provide 2-amino-benzenethiol-4-sulfonic acid, since thiocyanation occurs at both ortho and para positions. Most reported methods[9–11] used for the preparation of substituted 2-aminobenzenethiol involved the formation of zinc thiolate as intermediate in which purification of zinc salt was found unsatisfactory and difficult.

In the present work 2-aminobenzenethiol-4-sulfonic acid(II) has been synthesized[12] directly from 2-aminobenzenethiol(I) by the reaction of sulfuric acid at 5°C in quantitative yield (Scheme 1). Since thiol group is o,p-orienting and protonated amino group being electron withdrawing is meta orienting, the formation of para product would be most favoured. The formation of ortho or ortho and para disulfonic acid product is less likely due to steric hinderance of bulky sulfonic acid group. 6-Sulfonated 4H-1,4-benzothiazines(IV) have been synthesized by the condensation and oxidative cyclisation of 2-aminobenzenethiol 4-sulfonic acid(II) with β-diketones/β-ketoesters(III) in DMSO (Scheme 2).

EXPERIMENTAL

All the melting points are uncorrected. The purity of synthesized compounds has been tested by thin layer chromatography. Infrared spectra of all the compounds have been scanned in KBr on Perkin-Elmer spectrophotometer model 577. All the NMR spectra have been recorded at 90 MHz on Jeol FX 90Q FT NMR using TMS as an internal standard in (DMSO-d_6 + $CDCl_3$)/Polysol. IR and



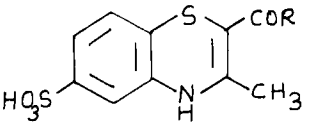
R = OCH_3, C_6H_4-CH_3(p), C_6H_4-OCH_3(m), C_6H_4-OCH_3(p),

C_6H_3(OCH$_3$(o), OCH$_3$(p)), C_6H_3(OCH$_3$(m), OCH$_3$(p))

SCHEME 2

TABLE I

6-sulfonated 4H-1,4-benzothiazines (**IVa–f**)



Compound No.	R	Melting point	Colour	Molecular formula	Found (%) C	H	N	Calcd (%) C	H	N
a	OCH_3	130°	Yellow	$C_{11}H_{11}NO_5S_2$	43.68	3.62	4.63	43.85	3.65	4.65
b	C_6H_4—CH_3(p)	123°	Red	$C_{17}H_{15}NO_4S_2$	56.16	4.13	3.85	56.50	4.15	3.87
c	C_6H_4—OCH_3(m)	183°	Red	$C_{17}H_{15}NO_5S_2$	54.37	3.95	3.70	54.11	3.97	3.71
d	C_6H_4—OCH_3(p)	150°	Red	$C_{17}H_{15}NO_5S_2$	53.89	3.44	3.69	54.11	3.97	3.71
e	C_6H_3 <(o)OCH_3 <(p)OCH_3	172°	Red	$C_{18}H_{17}NO_6S_2$	52.79	4.15	3.41	53.07	4.17	3.43
f	C_6H_3 <(m)OCH_3 <(p)OCH_3	128°	Red	$C_{18}H_{17}NO_6S_2$	53.38	4.14	3.40	53.07	4.17	3.43

NMR data are: IR cm^{-1}: 3280–3320 (NH), 1595–1625 (CO), 1335–1470 (C–H deformation vibrations of CH_3 group), 1285–1305 (SO_3H), 1240–1260 and 1030–1040 (C–O–C, asym and sym vibrations except in compound b). ^{1}HNMR δ: 1.83–2.56 (s, C=C—CH_3), 8.40–9.09 (s, NH), 6.43–7.76 (m, aromatic), 7.60–7.92 (s, SO_3H), 3.96 (s, $COOCH_3$ at C_2, compound a), 3.83 (s, OCH_3 at meta position of benzoyl side chain at C_2, compound c), 3.93 (s, OCH_3 at para position of benzoyl side chain at C_2, compound d), 3.89 and 3.80 (2s, OCH_3 at ortho and para positions of benzoyl side chain at C_2, compound e), 3.89 and 3.87 (2s, OCH_3 at meta and para positions of benzoyl side chain at C_2, compound f).

Synthesis of 2-aminobenzenethiol-4-sulphonic acid (II). To the distilled 2-aminobenzenethiol (I, 50 ml) was added sulfuric acid (sp. gr. 1.84) (100 ml) dropwise. The yellowish white mass obtained was dissolved immediately by mechanical stirring. The stirring was continued for 30 to 60 min till all the yellowish mass was converted into white mass which was then poured into a beaker containing crushed ice and stirred continuously till the effervescence ceased. The precipitate was filtered, washed with ice cold water and recrystallized from water and dried over calcium chloride. The colourless shining crystals were obtained (m.p. 190°C, Calc: C, 35.12, H, 3.41, N, 6.82, S, 31.21 & found: C, 35.20, H, 3.44, N, 6.87, S, 31.24%).

Synthesis of 6-sulfonated 4H-1,4-Benzothiazines (IVa–f). β-Diketone/β-ketoester (III: 0.01 mol) (methylacetoacetate, p-methylbenzoylacetone, m-methoxybenzoylacetone, p-methoxybenzoylacetone, o-, p-dimethoxybenzoylacetone and m-, p-dimethoxybenzoylacetone) was added to the stirred suspension of 2-aminobenzenethiol-4-sulfonic acid (II; 0.01 mol) in DMSO (5 ml) and heated for 15 min at 80°C. The reaction mixture was cooled down to room temperature and solid substance separated out was filtered and crystallized from methanol. The physical data are summarized in Table I.

ACKNOWLEDGEMENTS

Financial support in the form of a research project from University Grants Commission, New Delhi is duly acknowledged. Thanks are due to RSIC, Lucknow for providing IR spectra.

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