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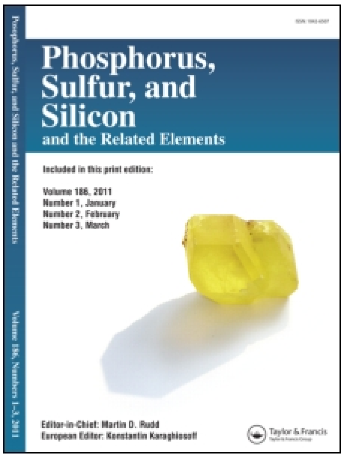

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A CONVENIENT SYNTHESIS 2-AMINO-5-METHYL-3-NITROBENZENETHIOL AND ITS CONVERSION INTO PHENOTHIAZINES VIA A SMILES REARRANGEMENT

K. G. Ojha[a]; Priyanka Mathur[a]; Neera Jaisinghani[a]; Purnima Adwani[a]
[a] Department of Applied Chemistry, M.D.S. University, Ajmer, INDIA

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A CONVENIENT SYNTHESIS OF 2-AMINO-5-METHYL-3-NITROBENZENETHIOL AND ITS CONVERSION INTO PHENOTHIAZINES VIA A SMILES REARRANGEMENT

K.G. OJHA*, PRIYANKA MATHUR, NEERA JAISINGHANI and PURNIMA ADWANI

Department of Applied Chemistry, M.D.S.University AJMER 305 001, INDIA†

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The synthesis of some substituted 3-methyl-1-nitro phenothiazines via a Smiles rearrangement is reported. 2-Amino-5-methyl 3-nitrobenzenethiol was prepared by alkaline hydrolysis of 2-amino-6-methyl-4-nitrobenzothiazole and condensed with o-halonitrobenzenes to obtain diaryl sulphides. They were converted by formic acid into formyl derivatives which by a Smiles rearrangement give the corresponding phenothiazines.

Keywords: phenothiazines; Smiles rearrangement; Antitumor; Alkaline hydrolysis

Phenothiazines[1] occupy an important place in medicinal chemistry as they find a number of uses as anticancer drugs, tranquilizers, antiinflammatory agents. In addition they exhibit antitumor activity, tuberculostatic activity, and in industry phenothiazene are used as heat stabilizers, antioxidants and analytical reagents.

In connection with our work on phenothiazines we required a reliable and rapid method for the synthesis of substituted 2-aminobenzenethiols. A literature survery showed that in earlier studies reduction of o-nitrophenyl disulphides obtained from o-chloronitrobenzenes and sodium polysulphide was used as a comman route to 2-aminobenzenethiols. However this method can not be used to prepare aminonitrothiophenols because of concomitant reduction of the nitro group.

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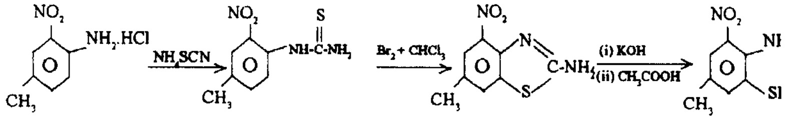
* Correspondence Author.

† Address for correspondence B-6 Mayur Colony Alwar gate, Ajmer 305 008 [INDIA]

The Herz reaction has been studied for the synthesis of 2-aminobezenethiols from aromatic amines but it gives only very low yields[2].

2-Amino-5-methyl-3-nitrobenzenethiol (IV) required in the synthesis of phenothiazines described in this paper was prepared by hydrolytic cleavage of 2-amino-6-methyl-4-nitrobenzothiazole (III) with 50% aqueous KOH solution. Benzothiazole was obtained by thiocyanogenation of 4-methyl-2-nitroaniline hydrochloride (I) following a process reported earlier[3]. (SCHEME 1).



SCHEME 1

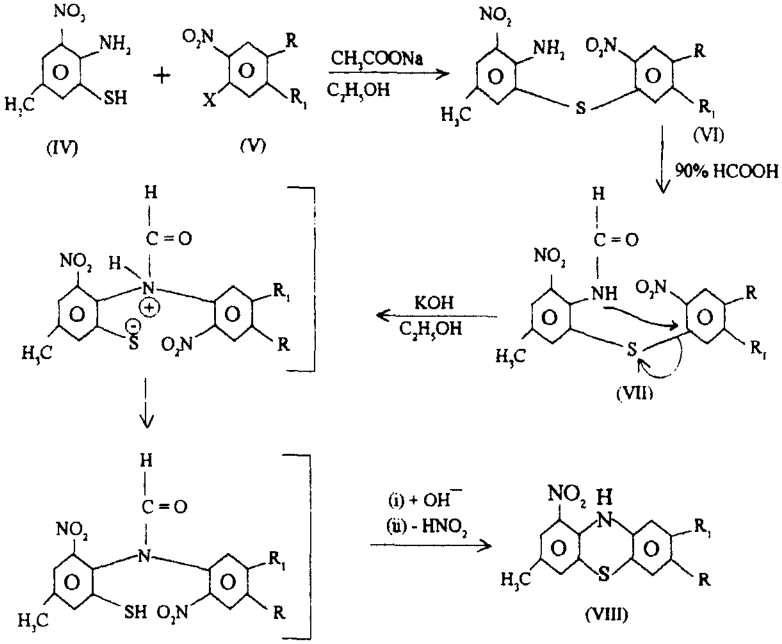
3-Methyl-1-nitrophenothiazines (VIII) were prepared by a Smiles rearragement of 5-methyl-2-formamido-2,3-dinitrodiphenyl sulphides (VII) with alcoholic KOH. Diphenyl sulphides (VII) were obtained by the formylation of 2-amino-5-methyl-2′,3-dinitrodiphenyl sulphides (VI) which are the condensation products of 2-amino-5-methyl-3-nitrobenzenethiol (IV) and substituted o-halonitrobenzenes (V) (SCHEME 2)

EXPERIMENTAL

Melting points were taken in open capillaries and are uncorrected. IR spectra have been scanned in KBr. The purity of compounds was checked by TLC on plates coated with silica gel (0.25 mm) using various nonaqueous solvent system. All the compounds gave satisfactory C, H & N analyses.

Prepration of 2-amino-5-methyl-3 nitrobenzenethiol (IV)

2-Amino-6-methyl-4-nitrobenzothiazole (III) was prepared by a method reported earlier (m.p 147°C; N% Found 20.07, Calcd 20.09; yield 70%). It was refluxed with aqueous KOH (five times by the weight of benzothia-



a : R = Cl, R_1 = H, X = Cl
b : R = H, R_1 = Br, X = Br
c : R = CH_3, R_1 = H, X = Cl

SCHEME 2

zole) and water (ten times by the weight of benzothiazole) till evolution of ammonia gas ceased (24 hrs). Contents were diluted with water and filtered, the clear solution was neutralised by acetic acid to get (IV). (M.P. 127°C, yield 32%, N% Found 15.19 Calced. 15.21).

Preparation of Diarly Sulphide (VIa-c)

A solution of anhydrous sodium acetate (0.01 mol) in ethanol (5 ml) was added to a hot solution of (IV) (0.012 mol). An alcoholic solution of halonitrobenzene (V, 0.01 mol) was then slowly added with stirring. The solution was refluxed for 4 hrs, concentrated and cooled in ice over night.

After filtration the solid was washed with water until the filterate was colourless. Recrystallisation from methanol afforded the desired product (VI). The physical data are summarized in Table I.

TABLE I

Compound	*Yield %*	*Molecular Formula*	*M.P.°C*	*N%*	
				Found	*Calcd.*
VI_a	70	$C_{13}H_{10}N_3ClS$	193	12.35	12.37
VI_b	65	$C_{13}H_{10}N_3BrS$	201	10.92	10.93
VI_c	70	$C_{14}H_{13}N_3O_4S$	233	13.15	13.16
VII_a	65	$C_{14}H_{10}N_3O_5ClS$	203	11.43	11.42
VII_b	72	$C_{14}H_{10}N_3O_5BrS$	212	10.18	10.19
VII_c	68	$C_{15}H_{13}N_3O_5S$	257	12.11	12.10
$VIII_a$	60	$C_{13}H_9N_2O_2ClS$	207	9.56	9.57
$VIII_b$	65	$C_{13}H_9N_2O_2BrS$	219	8.31	8.30
$VIII_c$	58	$C_{14}H_{12}N_2O_2S$	280	10.28	10.29

Prepration of 2-formamidodiarly sulphide (VIIa-c)

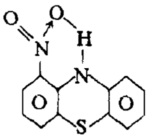
The diarylsulphides (VI a-c, 0.01 mol) were dissoolved in 90% formic acid (20–25 ml) and heated under reflux for 6 hrs and poured on to crushed ice. The solid so obtained was collected, washed and mixed with crushed ice. After collecting the solid was washed with cold water until the filterate was neutral and recrystallized from benzene (Table I).

Prepration of 1-Nitrophenothiazines (VIIIa-c)

An alcoholic solution of KOH (0.2 gm in 5 ml ethanol) was added to the refluxing solution of the formly derivatives (VII a-c, 0.01 mol) dissolved in acetone (15 ml). The colour of the reaction mixture darkened immediately. After refluxing for half an hour. The second lot of ethanolic solution of KOH (ethanol 5 ml, KOH 0.2 gm) was added and refluxing was continued for 2 hrs. The contents were poured into a beaker containing crushed ice. The precipitate was filtred off, washed with cold water and finally with 30% ethanol then it was recrystallised from benzene to get the desired compounds (VIII a-c).

I R Spectra

In all of the compounds (VIa-c, VIIa-c, VIIIa-c) two peaks were observed in the region 1560–1530 {cm^{-1}} for asymmetric and symmetric valance vibrations of the nitro group. Phenothiazines have been reported to exhibit a single sharp peak at 3450 {cm^{-1}} due to the NH stretching vibration. But 1- nitrophenothiazines exhibit this characteristic peak in the region 3325–3320 {cm^{-1}}. This shift to a lower frequency suggests the possibility of a six membered chelate ring of high stability through a strong -NH ----- O = N – intramolecular hydrogen bond which could arise[4–7]due to the proximity of the NH proton to one of the – NO_2 group at position – 1.



A sharp peak at 745–730 {cm^{-1}} exhibited by (VIa, VIIa, and VIIIa) could be attributed to C-Cl stretching vibrations. All the sulphides (VIa-c) exhibit two peaks in the region of 3380–3360 {cm-1} and 3480–3445 {cm^{-1}} which probably is due to symmetric and asymmetric vibrations of the primary amino group.

Acknowledgements

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