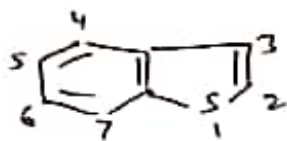




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Topic: Benzothiophene

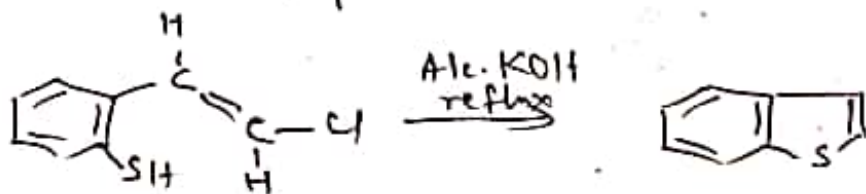
Benzothiophene

This compound and its derivatives occur in the naphthalene fraction of coal tar, crude petroleum and shark oil. It has also been called as thionaphthalene or thianaphthalene. This is also designated as benzo[b]thiophene. It is numbered as

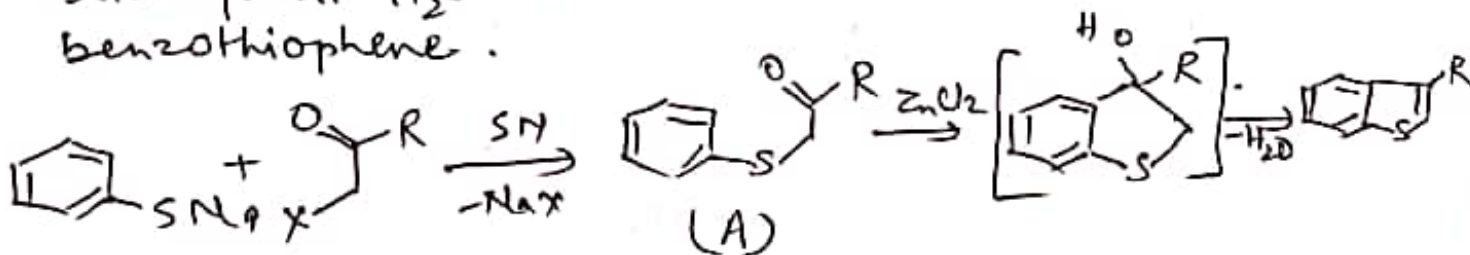


Synthesis

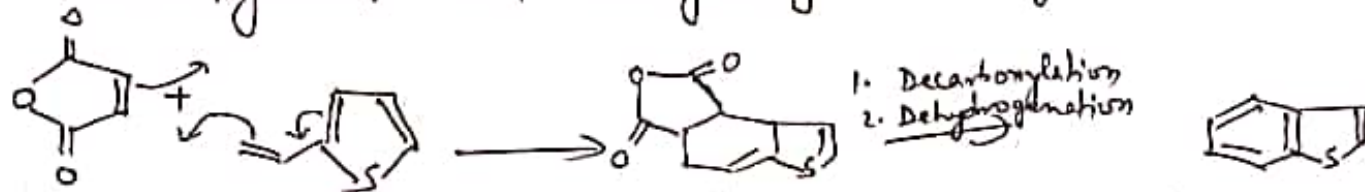
1. From o-mercapto β -chlorostyrene: This compound on refluxing with an alcoholic solution of alkali cyclizes to benzothiophene.



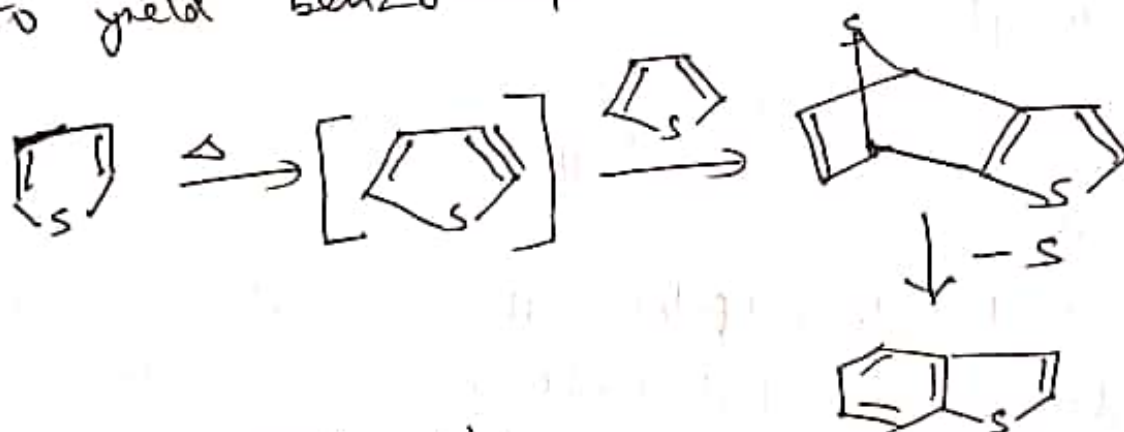
2. From Aryl keto sulfides: Thiophenolates can be S-alkylated by α -halo carbonyl compound to give (α -arylthio) carbonyl compound (A); which in the presence of $ZnCl_2$ undergoes intramolecular hydroxyalkylation and subsequent H_2O elimination to give 3-substituted benzothiophene.



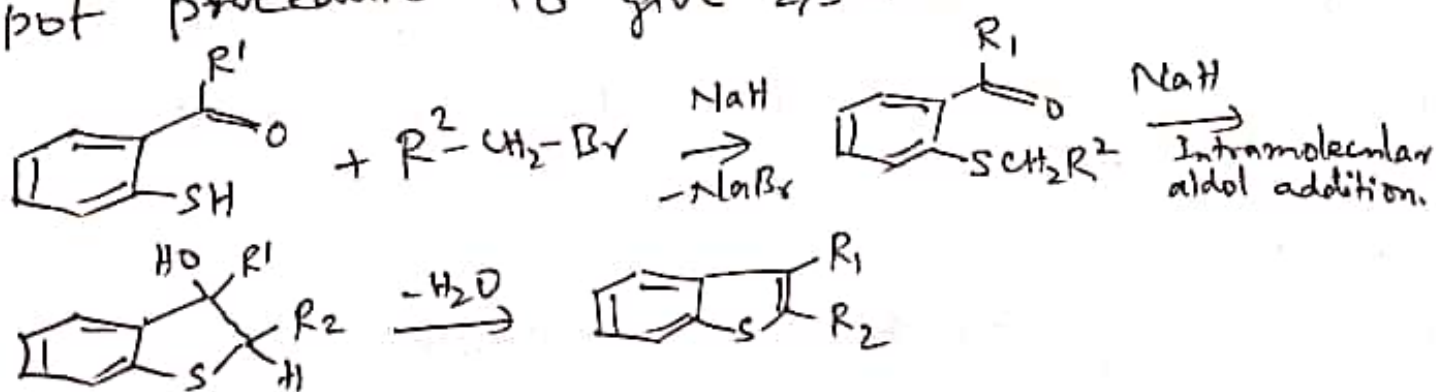
3. From Diels Alder reaction. The adduct obtained from maleic anhydride and 2-vinylthiophene on decarboxylation and dehydrogenation yields benzothiophene.



4. Benzothiophene can be synthesized by the direct pyrolysis of thiophene via the thiopyne intermediate. This intermediate undergoes [4+2] cycloaddition with another molecule of thiophene followed by chelotropic elimination of sulfur to yield benzothiophene.

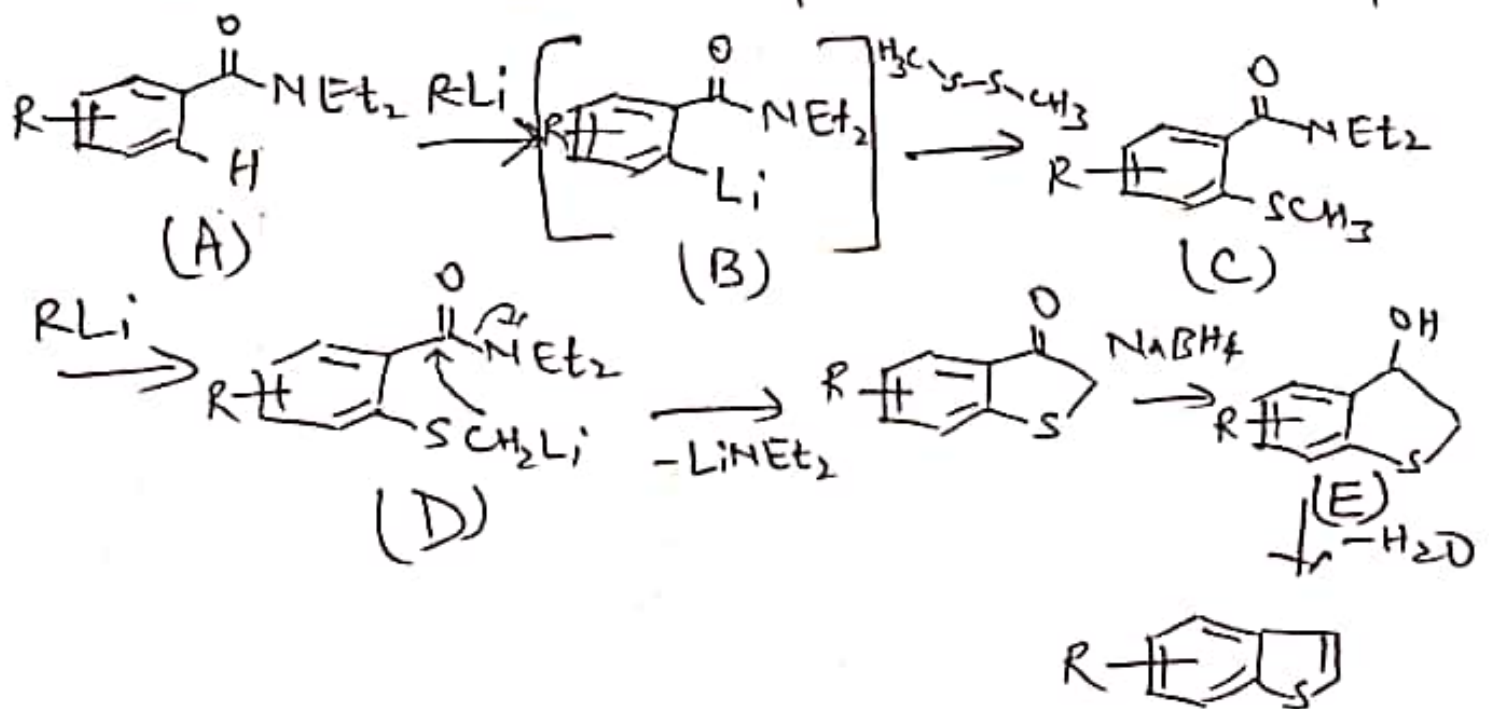


5. (2-mercaptophenyl) ketone react with bromoacetates, bromoacetonitrile or phenacylbromide in the presence of 2 equiv. of NaH in THF in one pot procedure to give 2,3-disubstituted benzothiophene

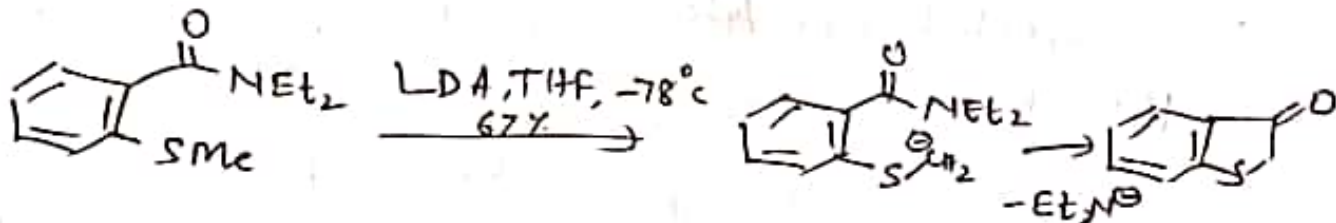


Here $R_2 = -COOR, -CN, -COPh$

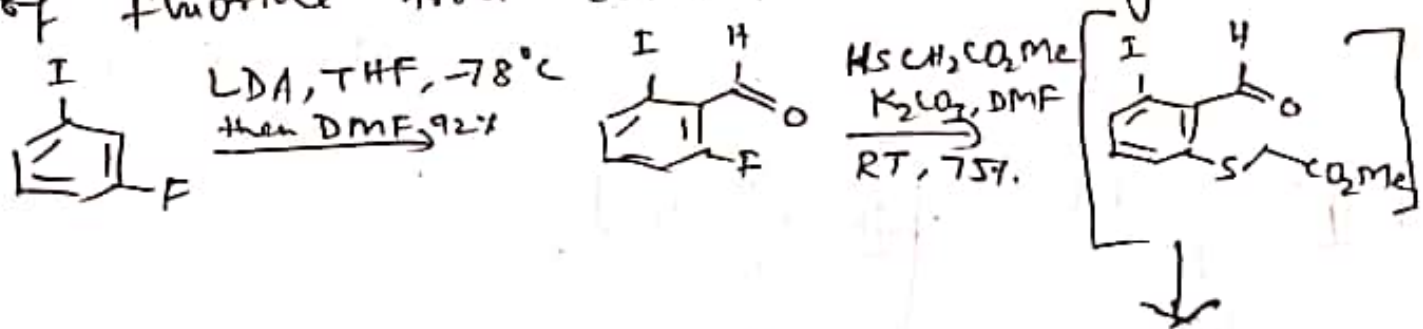
6. Benzosubstituted and in the heteroring unsubstituted benzothiophenes can be prepared in a flexible synthesis starting from *N,N*-diethylbenzamide (A). The directed ~~metalation~~ metalation of A to *o*-lithioderivative B allows the introduction of a sulfur function by reaction of B with $\text{CH}_3\text{-S-S-CH}_3$ regioselectively to give C. The SCH_3 group in C is subjected to a second metalation D, which leads to an intramolecular acylation of the generated thiomethyl-Li compound by the adjacent amide function. The thioindoxyl D thus obtained is reduced with NaBH_4 to carbinol E, which spontaneously eliminates H_2O to provide a benzothiophene.



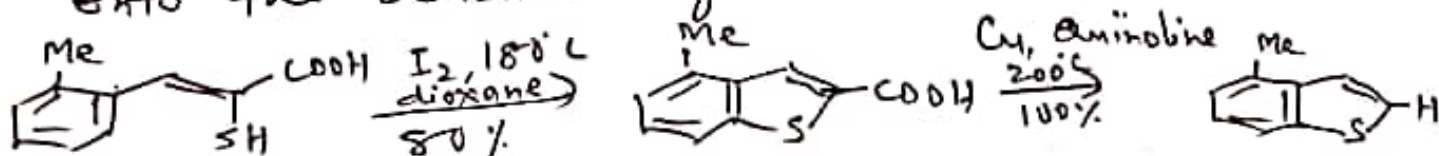
7. S-methyl groups of ortho-methylthio-arylcaboxamides can be deprotonated leading by cyclisation to benzothiophene-3-ones.



8. Intramolecular Aldol/Perkin type condensation of ~~ortho-formylacetic acids and benz~~ of arylthioacetic ester produces benzothiophene-2-esters. The synthesis can be performed in one pot for benzothiophenes, the ring closure substrates can be obtained via methyl thioacetate displacement of fluoride from ortho-fluoro-arylaldehydes.

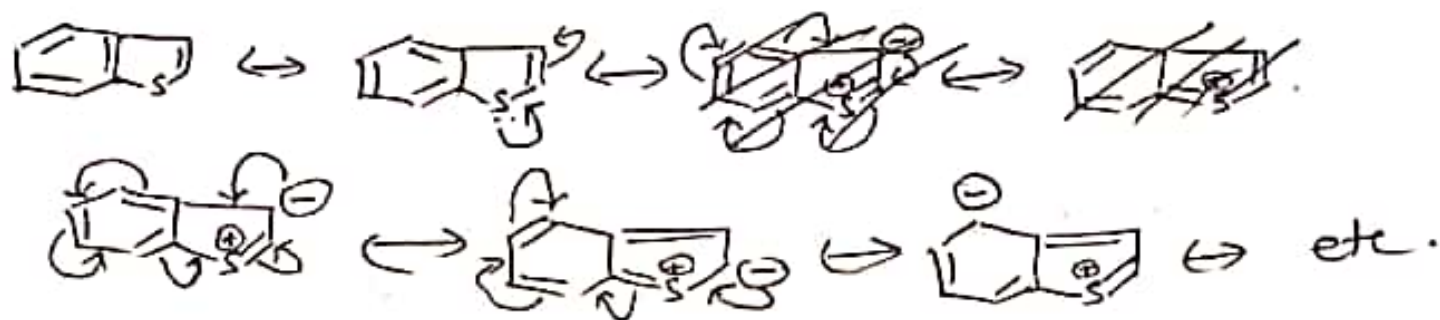


9. By ring closure of 2-mercapto-3-arylprop-2-enoic acids with iodine and heating, best applied using microwaves. This process probably involves S-iodination and then electrophilic cyclisation onto the benzene ring.



Properties

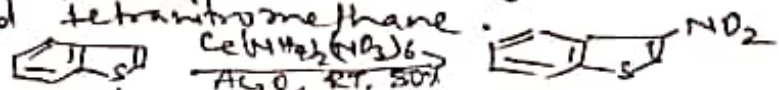
Benzo[*b*]thiophene is a colourless solid, M.Pt. 32°C and is stored in amber coloured bottle. It can be expressed as a resonance hybrid of the following resonating forms.



It possesses a dipole moment of 6.2 D. The electrophilic substitution of these system is much less regioselective than that of indole, for which there is effectively complete selectivity of attack at C-3, even to the extent that the hetero ring positions are only a little more reactive than some of the benzene ring positions.

Nitration: Nitric acid nitration gives a mixture in which the main product is 3-nitro derivative with lesser quantities of 2-nitro, 4-nitro, 6-nitro and 7-nitrobenzo[*b*]thiophenes. However ceric ammonium nitrate in acetic anhydride at room temperature produces a high yield of 3-nitrobenzo[*b*]thiophene, 2-nitrobenzo[*b*]thiophene can be obtained in good yield by the ~~pot~~ photo promoted reaction

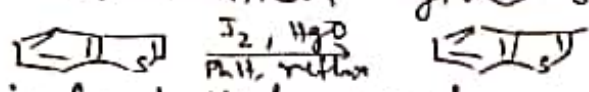
of corresponding 2-trimethylstannyl heterocycles with N_2O_4 and tetranitromethane.



Friedel Crafts Reaction - Friedel Crafts acetylation of benzothiophene gives a mixture of 3- and 2-acetyl derivative in a ratio of 7:3.

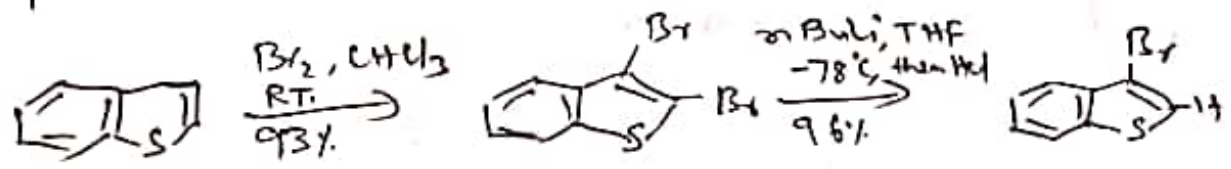
~~For~~

Iodination: Iodination gives only 3-iodo product



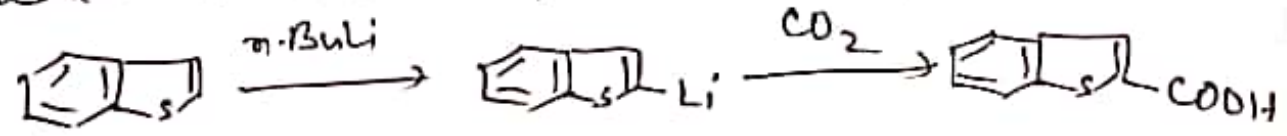
Bromination: Controlled reaction of benzothiophene

with Br_2 produces 3-bromobenzothiophene in moderate yield. However this product is better prepared by room temperature by getting high yield of 2,3-dibromination then regioselective metallation at C-2 and protonation.



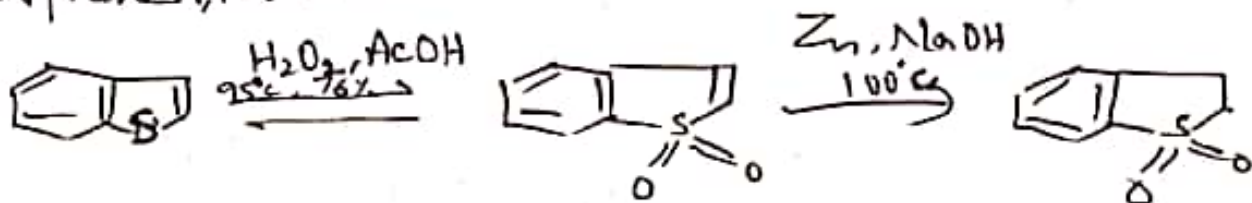
Vilsmeier Reaction - Benzothiophene does not undergo formylation under Vilsmeier conditions which occurs readily with thiophene.

Metallation: Direct metallation of benzothiophene with n-butyl Lithium or sodium takes place at the 2-position and subsequent carbonation leads to benzothiophene-2-carboxylic acid

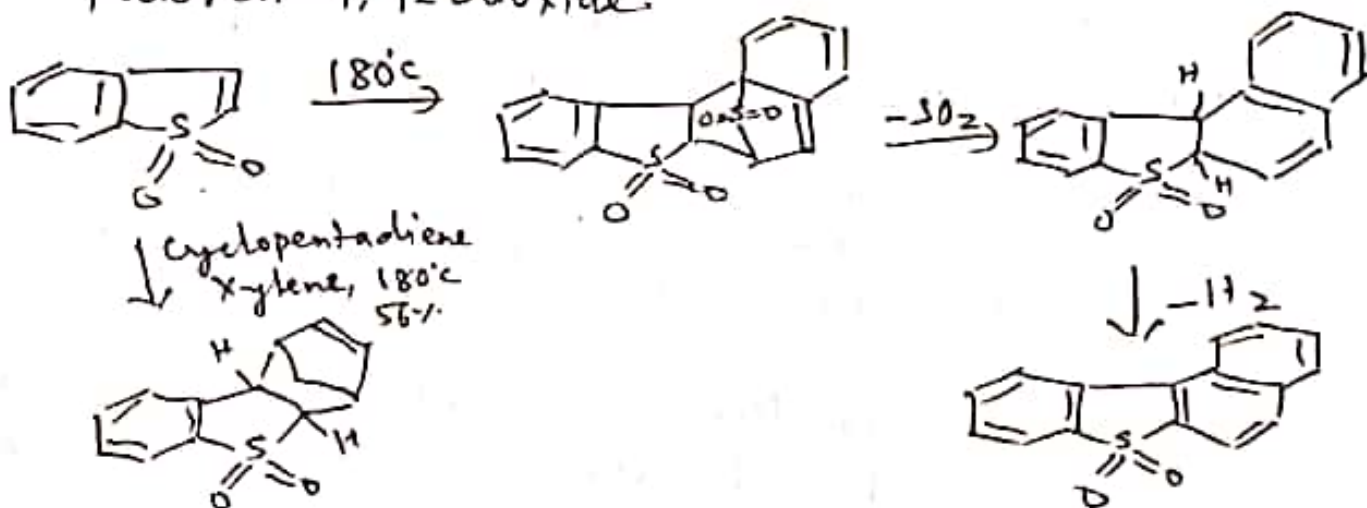


Reaction with oxidising agent: Benzothiophene

on refluxing with 30% H_2O_2 in acetic acid yields benzothiophen-1,1-dioxide or benzothiophene sulfone which is much more stable than thiophene-1,1-dioxide.

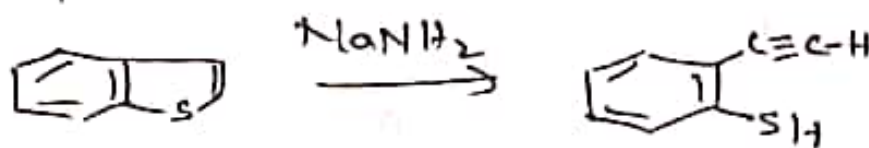


Benzothiophene-1,1-dioxide undergoes self Diels Alder reaction at $180^\circ C$ and the adduct formed loses SO_2 to give 9-thia-3,4-benzofluoren-9,9-dioxide.

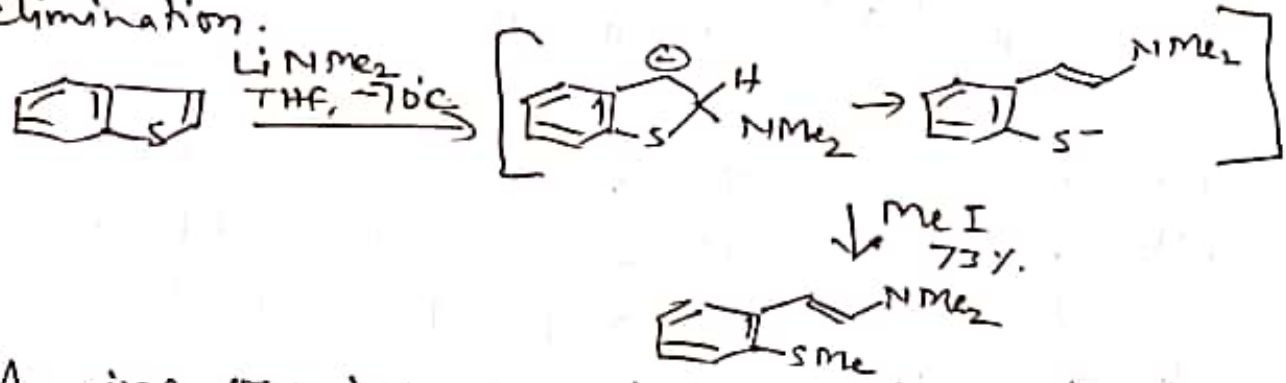


Here Benzothiophene-1,1-dioxide acts as dienophile during reaction with cyclopentadiene.

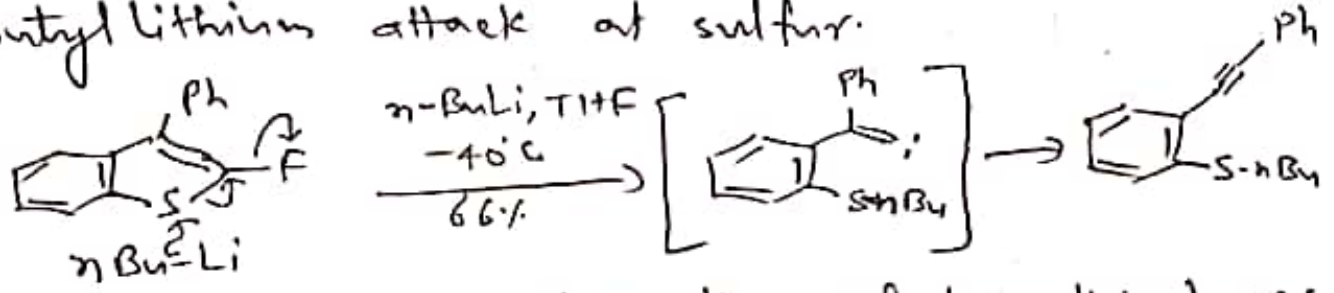
Ring opening: Sodium amide causes ring cleavage of benzothiophene to produce 2-ethynylphenylthiol



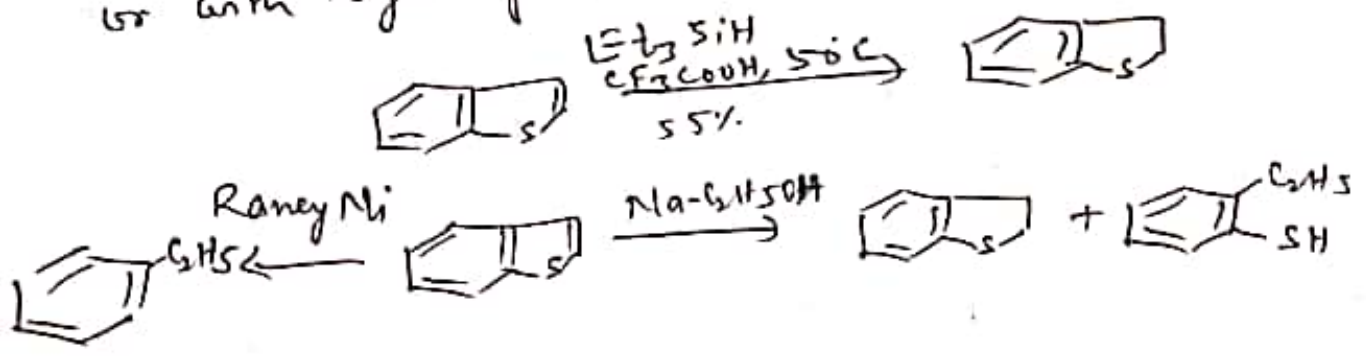
Ring opening in a rather different manner results from exposure of the heterocycle to lithium dimethylamide, followed by trapping with iodomethane, producing an enammine which must result from initial addition at C-2, perhaps by a minor pathway, but one which then leads to irreversible ring opening elimination.



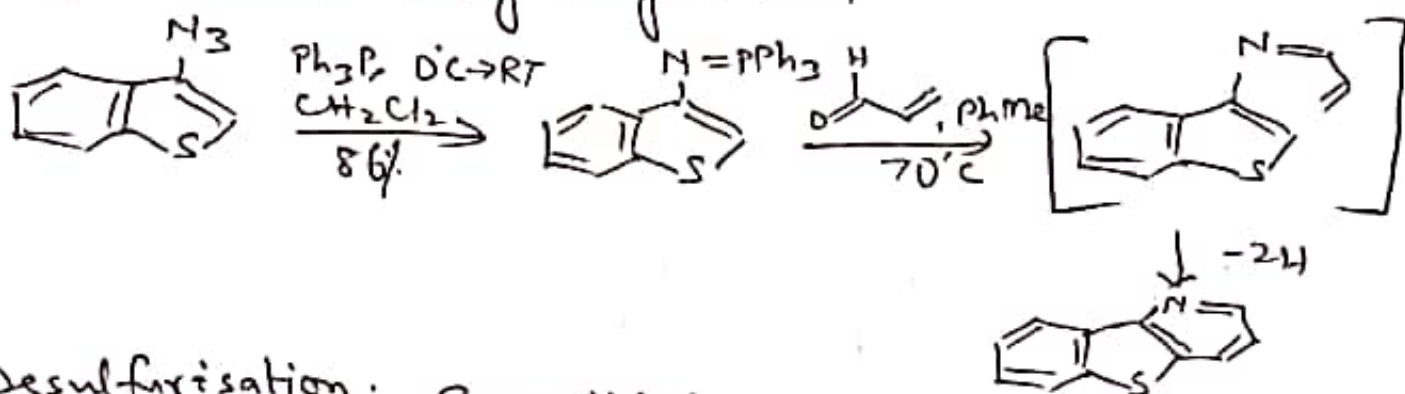
A ring opening can also be observed via n-butyl lithium attack at sulfur.



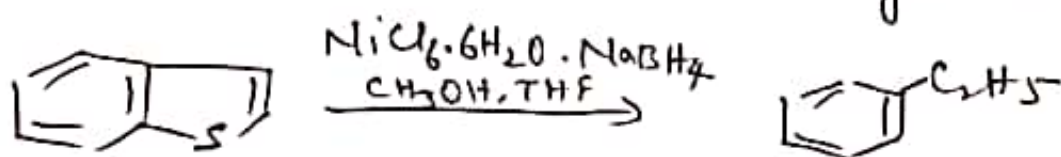
Reduction: Hydrodesulfurisation of benzothiophenes is conveniently achieved using Raney Ni. Reduction of the hetero rings of benzothiophene gives 2,3-dihydro derivatives, notably with retention of the sulphur using triethylsilane in acidic solution or with hydrogen over colloidal rhodium.



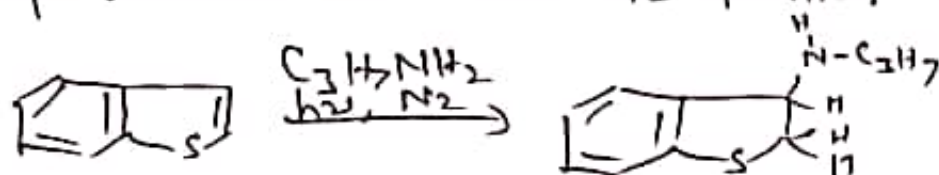
Electrocyclic Reaction: The fusion of a pyridine ring onto benzothiophene can be achieved via a Staudinger reaction using either 2 or 3-azides to give phosphinimines, which undergo aza-Wittig condensation with unsaturated aldehyde, the ensuing electrocyclicisation being followed by spontaneous dehydrogenation.



Desulfurisation: Benzothiophene are desulfurised by the action of nickel borohydride prepared from nickel chloride and sodium borohydride.

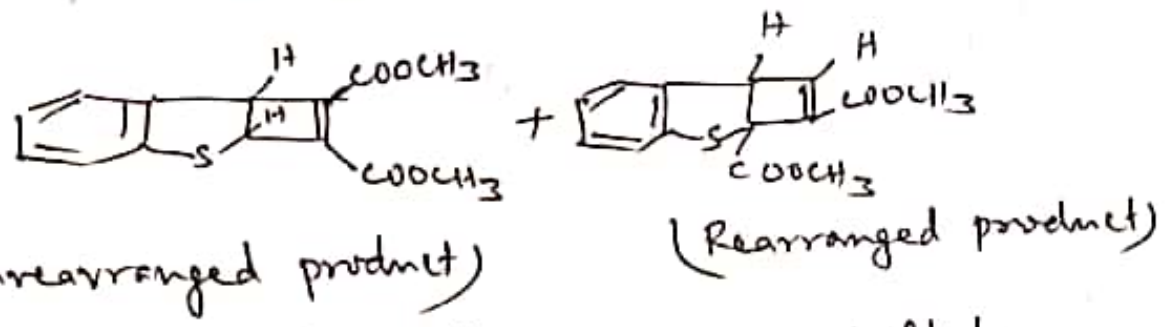
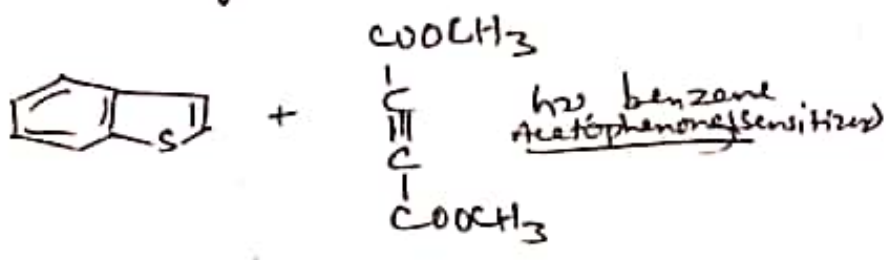


Photochemical reaction: Benzothiophene when irradiated in the presence of amine, addition of amines at the 2,3-position takes place.

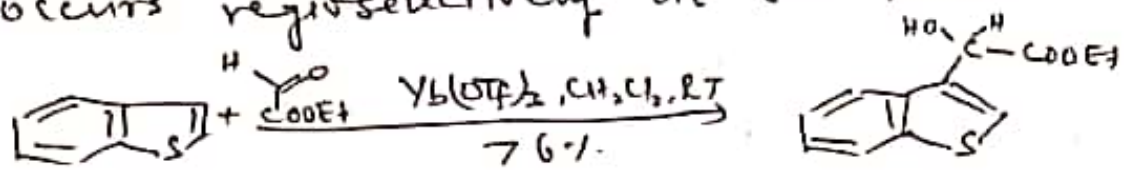


When benzothiophene is irradiated with dimethyl acetylene dicarboxylate, both unrearranged and

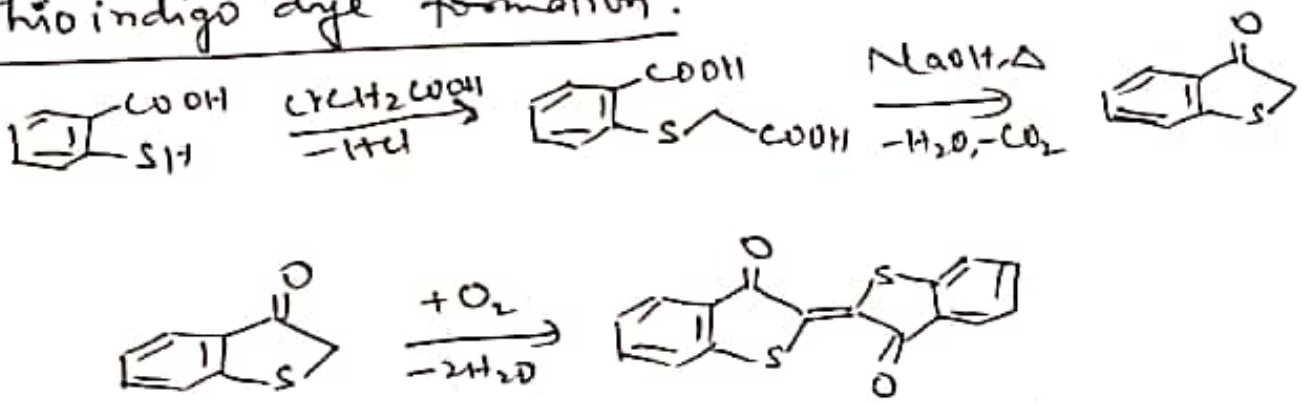
rearranged adducts are obtained.



Reaction with ethyl glyoxylate: Ytterbium-triflate catalysed hydroxyalkylation by ethyl glyoxylate occurs regioselectively at C-3 position.



Thioindigo dye formation:



(Thioindigo)

Thioindigo is a vat dye. forms red needles, and its vat is bright yellow. As a dye it has a blue-red colour.