HETEROCYCLES, Vol. 65, No. 6, 2005, pp. 1491 - 1513
Received, 22nd December, 2004, Accepted, 24th February, 2005, Published online, 3rd March, 2005

SYNTHESIS OF POLYNUCLEAR AROMATIC COMPOUNDS INCORPORATING A FUSED THIOPHENE RING

Tarun Kanti Pradhan and Asish De*

Department of Organic Chemistry; Indian Association for the Cultivation of Science

Jadavpur; Kolkata-700 032. India

e-mail - ocad@mahendra.iacs.res.in, Tel - Int + 33-2473-4971 (Ext - 120); Fax - Int + 2473-2805

Abstract - The present review gives an account of the various synthetic routes to polynuclear heteroaromatic compounds incorporating a fused thiophene ring which include analogs of several biologically active compounds. These compounds are synthesized using a suitably functionalised benzo[*b*]thiophene as the core and applying various annulation reactions. Directed metalation was extensively used both for functionalisation and in annulation reactions.

1. INTRODUCTION

Sulfur is known to mankind since the dawn of human civilization but investigation of the chemistry of sulfur heterocycles began only after the discovery of thiophene (**1**) towards the end of the nineteenth century. Availability of thiophene in large quantities during the first half of the last century and the numerous applications of thiophene derivatives provided these investigations with much needed impetus.

1

As a result, a large number of thiophene derivatives including polycondensed systems incorporating fused thiophene rings were synthesized and the interest of organic chemists in this area remains

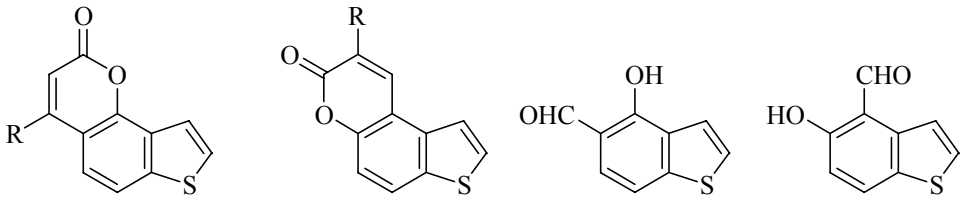
unabated till date. Synthesis of polynuclear aromatic compounds incorporating a fused benzo[*b*]thiophene core, carried out in our laboratory over the last two decades will be reviewed in this article. Important works reported by others during this period will also be reviewed.

This class of compounds were initially synthesized as sulfur analogs of biologically active natural products like indole alkaloids, furanocoumarines, furanochromones[1-4] and carcinogenic compounds.[5] Although this motive behind the synthesis of such compounds still persists, other objectives are also playing important roles in recent times.Their synthesis usually starts from an appropriately substituted benzo[*b*]thiophene core which is subjected to suitable annulation reactions. Access to the starting materials therefore involves expedient regiocontrolled functionalisation of benzo[*b*]thiophene molecule. In our work heteroatom directed *ortho*-metalation (directed metalation; DoM)[6] has played an important role in this annulation process.

2. Angular benzothienopyrans and benzothienofurans

Sulfur analogs of biologically active natural products were synthesized earlier with the hope of an improvement of biological activity. The synthetic targets were conceived through structural modification of the original compound following the principle of bioisosterism,[7] which allows replacement of a ring oxygen atom with sulfur. Sulfur analogs of biologically active linear and angular furanochromones and furanocoumarines were important synthetic target[8,9] in the sixties and seventies of the last century. Furanochromones showed anti-asthmatic properties while furanocoumarines are in use in the treatment of leukodermia and other types of vitiligo. Examples of biologically active furanochromones are khellin and visanagin and among furanocoumarines psoralen, xanthotoxin and angelicin are biologiacally important. We have reported[10,11] the synthesis of several angular tricyclic compounds which are sulfur analogs of angelicin viz 6-substituted 8-oxo-8*H*-9-oxa-3-thiacyclopenta[*a*]naphthalene (**2**) and 8-substituted 7-oxo-7*H*-6-oxa-3-thiacyclopenta[*a*]naphthalene (**3**). The key intermediates in the synthesis of **2** and **3** are 4-hydroxybenzo[*b*]thiophene-5-carboxaldehyde (**4**) and 5-hydroxybenzo[*b*]thiophene-4-carboxaldehyde (**5**). The former is best obtained from 6,7-dihydrobenzo[*b*]thiophene-4(5*H*)-one (**6**)[10,11] an easily available compound and an ubiquitous intermediate in several syntheses (*vide infra*). Conversion of the cyclic ketone into its hydroxymethylene derivative (**7**) and subsequent aromatisation with DDQ afforded **4**, both the steps proceeding in high yield. The hydroxyaldehyde (**5**) was synthesized from 5-hydroxybenzo[*b*]thiophene through Gattermann reaction as described in the literature.[12] Upon warming solution of the hydroxyaldehydes (**4** and **5**), and an active cyanomethylene compound *e.g*. malononitrile, ethyl cyanoacetate, cyanoacetamide and cyanothioacetamide, in minimum quantities of dry ethanol, in the presence of catalytic amounts of triethylamine resulted in Knoevenegal condensation and

intramolecular nucleophilic attack in one pot to afford the cyclic imines (**8** and **9**) (R = CN, CO_2Et, $CONH_2$ and $CSNH_2$) respectively. The crude imines upon heating with 2M hydrochloric acid on a boiling water bath for 30 min afforded the thienocoumarines (**2** and **3**) in yields ranging from 40 to 75%.

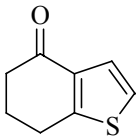


2, R = CN, CO_2Et, $CONH_2$, $CSNH_2$

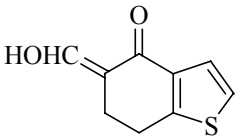
3, R = CN, CO_2Et, $CONH_2$, $CSNH_2$

4

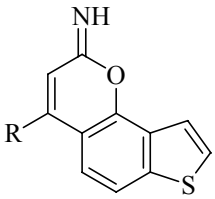
5



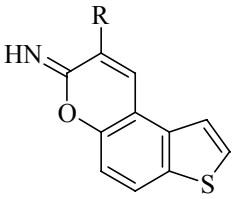
6



7



8



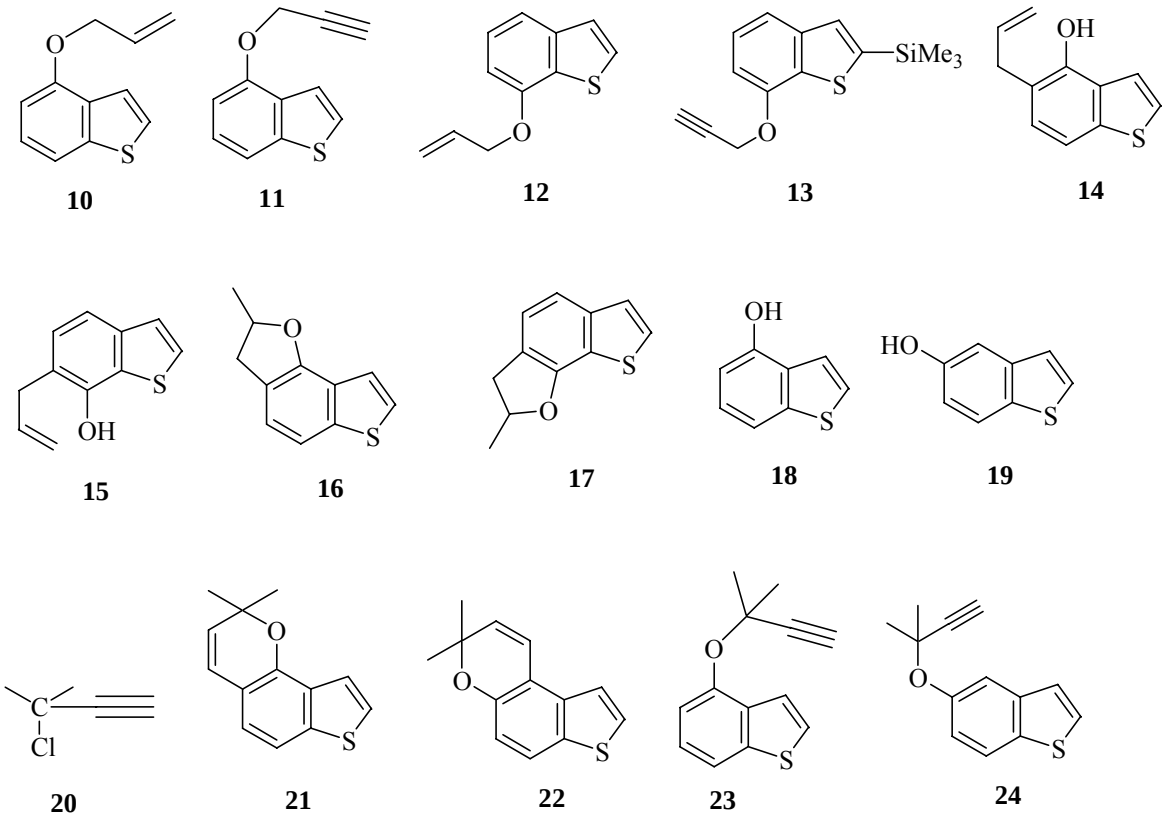
9

MS spectra[13] (EI) and ^{13}C NMR studies[14] of the tricyclic compounds (**2** and **3**) were reported. MS spectral fragmentation of these compounds under electron impact were dependent upon the nature of the substituent R in the pyrone ring. For instance the molecular ion loses carbon monoxide when R is CN or $CONH_2$. Loss of sulfhydryl radical and hydrogen atom from the molecular ion precedes the loss of carbon monoxide when the pyrone ring carries a thiocarboxamide substituent and when the pyrone ring carries an ethoxycarbonyl substituent, it is the oxocarbonium ion formed by the loss of ethoxy group which loses carbon monoxide under electron impact. Chemical shifts of all the carbon atoms in these compounds were unambiguously assigned in the ^{13}C NMR spectra of these compounds.

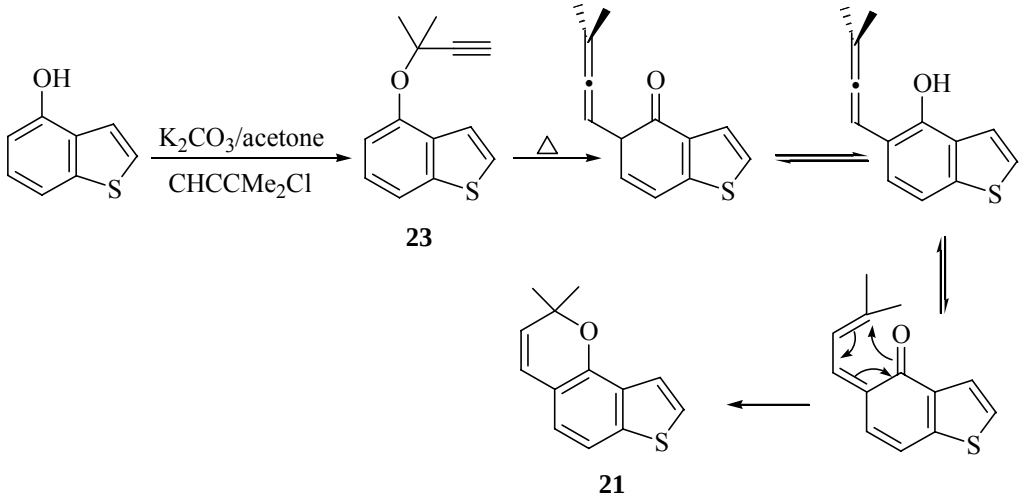
A number of tricyclic compounds consisting of five and six member oxygen heterocycles annulated to the benzo[*b*]thiophene core were obtained through cyclisation of compounds obtained *via* thermally induced Claisen rearrangement[10,15] of allyl and propargyl ethers derived from hydroxybenzo[*b*]thiophenes. Treatment of 4-hydroxybenzo[*b*]thiophene with allyl and propargyl ethers in dry acetone under reflux in the presence of anhydrous potassium carbonate afforded the ethers (**10** and **11**) respectively in very high yields.[10,16] Yields of allyl and propergyl ethers (**12** and **13**) obtained from 7-hydroxybenzo[*b*]thiophene and 2-trimethylsilyl-7-hydroxybenzo[*b*]thiophene were also excellent. Upon heating under reflux in *N*,*N*-dimethylaniline for 5 h both **10** and **12** underwent both 4-hydroxy-5-allyl-(**14**) and 7-hydroxy-6-allylbenzo[*b*]thiophene (**15**) in 78% and 75% yields

respectively. The reaarranged products were cyclised with polyphosphoric acid in hot chlorobenzene affording 2-methyl-2,3-dihydro-1-oxa-6-thia-*as*-indacene (**16**) and 2-methyl-2,3-dihydro-1-oxa-8-thia-*as*-indacene (**17**) in 68% and 82% yields.[16]

Upon heating 4-hydroxy-(**18**) and 5-hydroxybenzo[*b*]thiophene (**19**) with 3-chloro-3-methyl-1-butyne (**20**) under reflux for 4 h in dry methyl ethyl ketone in the presence of anhydrous potassium carbonate 8,8-dimethyl-8*H*-9-oxa-3-thiacyclopenta[*a*]naphthalene (**21**) and 7,7-dimethyl-7*H*-6-oxa-3-thiacyclopenta[*a*]naphthalene (**22**) were formed in 58% and 49% yields respectively. Initially formed ethers viz. 4-(1,1-dimethylprop-2-ynyloxy)benzo[*b*]thiophene (**23**) and 5-(1,1-dimethylprop-2-ynyloxy)benzo[*b*]thiophene (**24**) were cyclised in situ to afford the tricyclic compound.

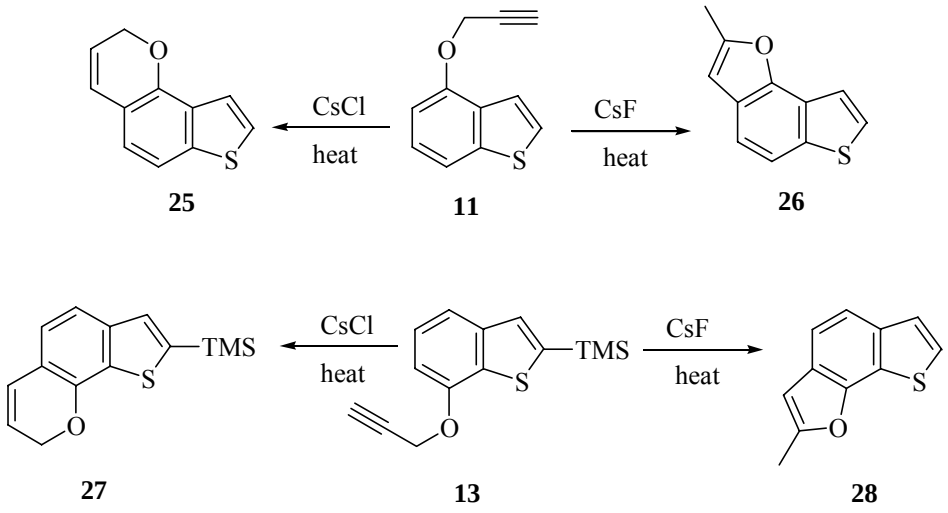


The mechanism (**Scheme 1**) involves a rate determining [3,3]-sigmatropic shift followed by[15] sigmatropic rearrangement of the product. The keto tautomer of the resulting allene subsequently undergoes electrocyclisation. Upon heating the propargyl ethers 4-(prop-2-ynyloxy)benzo[*b*]thiophene (**11**) and trimethyl(7-prop-2-ynyloxybenzo[*b*]thiphene-2-yl)silane (**13**)[16] under reflux in *N*,*N*-dimethylaniline in the presence of cesium chloride and cesium fluoride undergoes Claisen rearrangement and cyclisation in tandem affording the tricyclic compounds (**26**-**28**) in excellent yields (**Scheme 2**).



Scheme 1

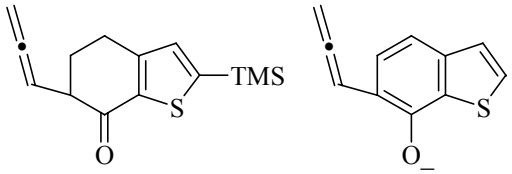
The use of additives in Claisen rearrangement of primary ethers have been reported[17] and the size of the oxygenated ring angularly annulated to the benzo[*b*]thiophene core depends on the type of additive used. In the presence of cesium chloride a pyran ring is annulated while the use of cesium fluoride results in the annulation of a furan ring. The results can be explained in terms of the mechanism of rearrangement–cyclisation, which is similar to the one shown in **Scheme 1**.



Scheme 2

The α-allenyl ketone (**29**) formed during the [3,3]-sigmatropic rearrangement undergoes enolisation in the usual manner followed by hydrogen shift prior to ring closure, leading to the annulation of a six member ring. Cesium fluoride, on the other hand, abstracts the α-hydrogen atom from the allenyl

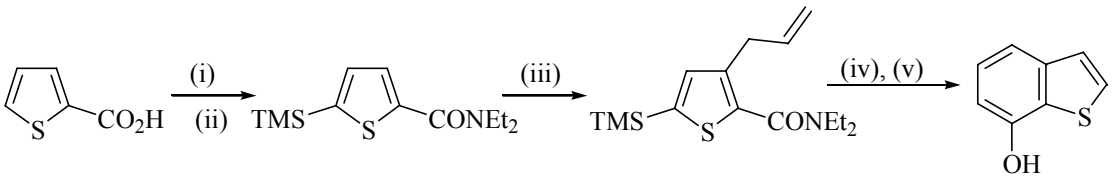
ketone (with simultaneous desilylation in the case of **13**) leading to the intermediate (**30**), which then undergoes ring closure resulting in the annulation of a furan ring.



29 **30**

3. Linear tricyclic compounds, including sulfur analogs of semivioxanthin

A number of tricyclic compounds incorporating a fused thiophene ring were reported from our laboratory during the period under review. Similar to the angularly fused tricyclic compounds described above, these compounds were also synthesized from suitably functionalised benzo[*b*]thipohenes *via* appropriate annulation reactions. Extensive use was made of heteroatom directed *ortho*-metalation (directed metalation; DoM)[6] both for expedient synthesis of intermediates as well as for ring annulation. In our application was made of directed metalating group (DMG) mediated regiocontrolled *ortho*-deprotonation as well as other ramifications of DoM *viz*. lateral deprotonation of side chains present in the same position and anionic rearrangements which take place during directed metalation.[18-24]

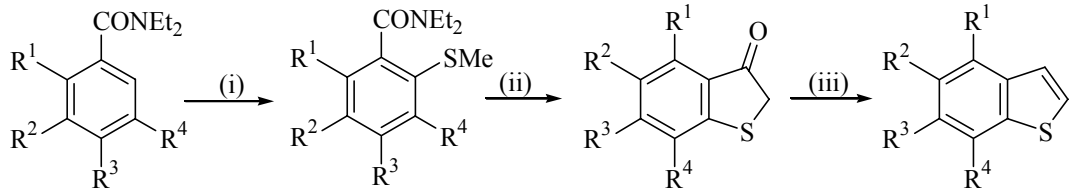


Reagents: (i) $SOCl_2$ / Et_2NH / C_6H_6/reflux; (ii) *s*-BuLi / TMEDA / THF / -78°C / TMSCl; (iii) *s*-BuLi / TMEDA / THF / -78°C /CuBr-Me_2S / allyl bromide; (iv) LDA/THF; (v) Bu_4NF.

Scheme 3

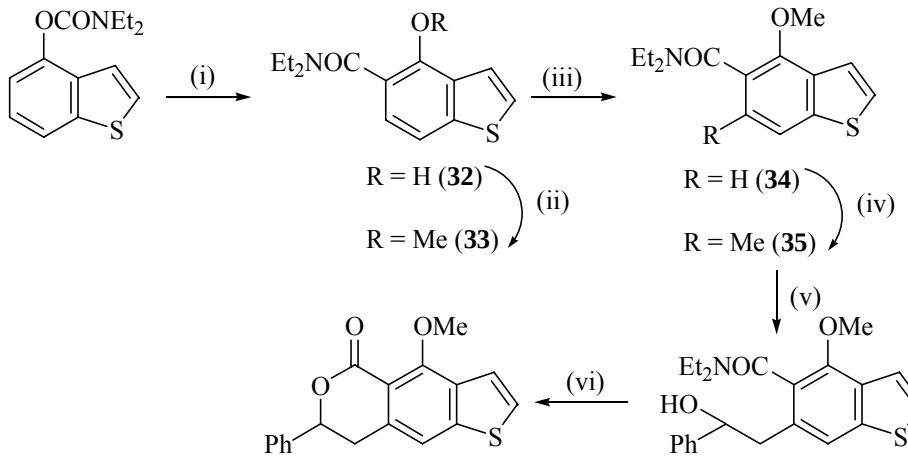
Benzo[*b*]thiophenes carrying various DMGs, which served as intermediates in these syntheses were prepared from hydroxybenzo[*b*]thiophenes, now available in better overall yields and in fewer number of steps in comparison to methods reported earlier in literature.[25-27] An example in hand is the synthesis[28] of 7-hydroxybenzo[*b*]thiophene (**Scheme 3**) from commercially available thiphene-2-carboxylic acid. The method which is a vast improvement over earlier lengthy synthesis of this compound consists of conversion of the carboxylic acid into its diethyl amide and after the free α-position was silyl protected, allyl group was introduced in the β-position of the amide DMG *via*

directed lithiation-transmetalation (with copper) protocol[29] followed by LDA mediated cyclisation and desilylation. Subsequently, a more general method of synthesis of diversely substituted benzo[*b*]thiophene[30,31] was developed in our laboratory (**Scheme 4**). In this method methyl sulfanyl function was introduced *ortho*-position to the amide function in *N*,*N*-diethylarylamides by usual DoM protocol. After lateral deprotonation of the methylsulfanyl side chain with LDA, the deprotonated species witnesses instantaneous intramolecular nucleophilic attack on the amide DMG by the SCH_2^- anion affording a thioindoxyl which can be reduced to the different substituted benzo[*b*]thiophene.



Reagents : (i) *s*-BuLi/TMEDA/THF/-78 °C/Me_2SSMe_2; (ii) LDA/THF; (iii) $NaBH_4$/NaOH/MeOH.

Scheme 4



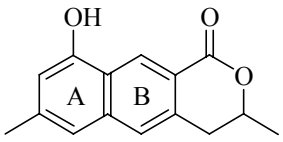
36

Reagents : (i) *s*-BuLi / THF / TMEDA/ -78°C to rt /12 h; (ii) K_2CO_3 /acetone / MeI / heat; (iii) *s*-BuLi / THF /TMEDA / TBDMSCl / -78°C; (iv) *s*-BuLi / THF / TMEDA / - 78°C/MeI; (v) LDA / PhCHO; (vi) NaOH.

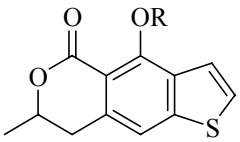
Scheme 5

The reaction tolerates the presence of different substituents in the aromatic ring of the starting aryl-amides and thus benzo[*b*]thiophenes carrying methoxy functions in 4-, 5-, 6-, and 7- positions were synthesized by this method. Smooth demethylation with 48% HBr afforded the corresponding hydroxybenzo[*b*]thiophenes in good overall yields. The hydroxy function of the

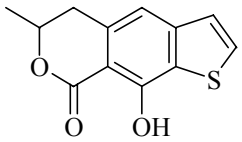
hydroxybenzo[*b*]thiophenes were converted into methoxy, *O*-carbamate and OMOM groups of which the *O*-carbamate, as expected, was endowed with the most powerful directing power. Regiocontrolled introduction of electrophiles in the *ortho*-position to these DMGs in benzo[*b*]thiophene requires silyl protection of the α-position of the thiophene moiety[32,33] reflecting the high acidity of the thiophene α-proton. Necessity of similar silyl protection was earlier reported by Snieckus[34] in DoM experiment with thiophene. Anionic *ortho*-Fries rearrangement[18] of the *O*-carbamate (**31**) does not require silyl protection and the salicylamide (**32**) was the starting material in the synthesis of the tricyclic compound (**36**) *via* chain extension-ring annulation protocol (**Scheme 5**).[32,33] Introduction of the methyl group in the 6-position of the silyl protected methoxy compound (**34**) *via* DoM protocol was followed by lateral deprotonation and chain extension by treating the deprotonated species with benzaldehyde. Cyclisation of the resulting carbinol was accomplished with hot alkali to afford 4-methoxy-7-phenyl-7,8-dihydro-6-oxa-1-thiacyclopenta[*b*]naphthalen-5-one (**36**).



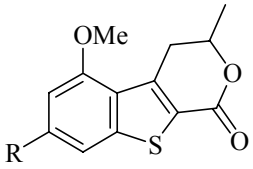
37



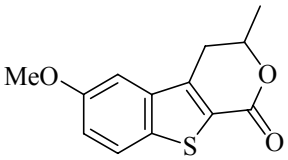
38, R = H
39, R = OMe



40



41, R = H
42, R = Me

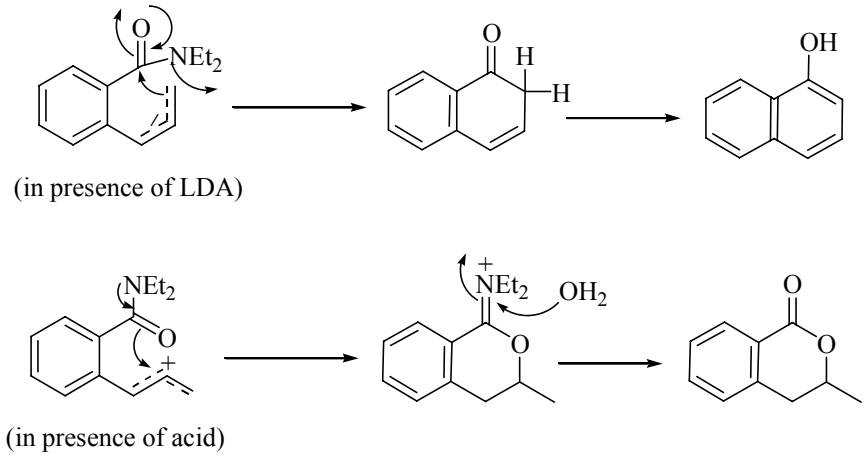


43

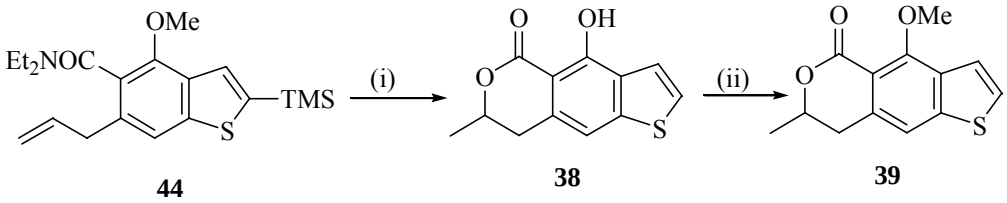
Synthesis[35,36] of sulfur analogs (**38-43**) of the biologically active linear naphthopyrone semivioxanthin (**37**)[37] provides an example of the usefulness of the DoM methodology. The analogs were designed following the principle of bioisosterism.[7] Thus the linear tricyclic system incorporating the fused pyrone ring containing the methyl substituent was kept intact. The two benzene rings A and B were replaced in turn with thiophene and the positions of the oxygenated substituents were varied. Annulation of the pyrone ring carrying a methyl substituent was based on the methodology of cyclisation of *ortho*-allyl benzamides,[6] based on what Snieckus has termed as the "chameleon" type character of the allyl function in such a molecular set up. Introduction of the allyl function *ortho*- to the tertiary amide was carried out (*vide supra*) by usual metalation-transmetalation[29] protocol. The two modes of cyclisation (**Scheme 6**) in the presence of LDA or strong mineral acid leads to the formation of phenol or pyranone respectively. We have utilised the former mode in the synthesis of 7-

hydroxybenzo[*b*]thiophene (*vide supra*) and the latter mode in the synthesis of analogs of semivioxanthin. Starting from the compound (**44**), the analogs (**38** and **39**) were synthesized in three and four steps respectively. Allyl function was introduced in the 6-position using metalation-trasnsmetalation protocol.

During cyclisation with hot mineral acid simultaneous demethylation and desilylation afforded the hydroxy compound (**38**) which showed signs of deterioration upon prolonged exposure to air and was converted to its more stable methyl ether (**39**) with methyl iodide in dry acetone (**Scheme 7**).



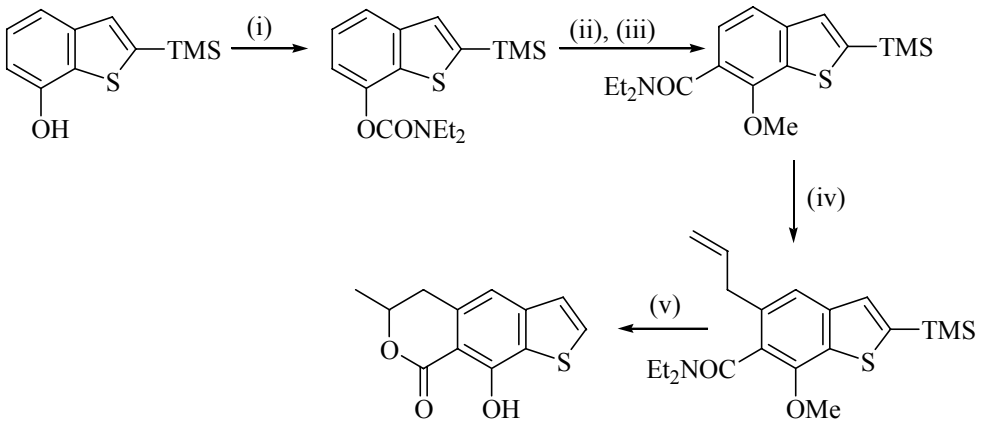
Scheme 6



Reagents: (i) HCl/heat; (ii) K_2CO_3/ MeI/ acetone.

Scheme 7

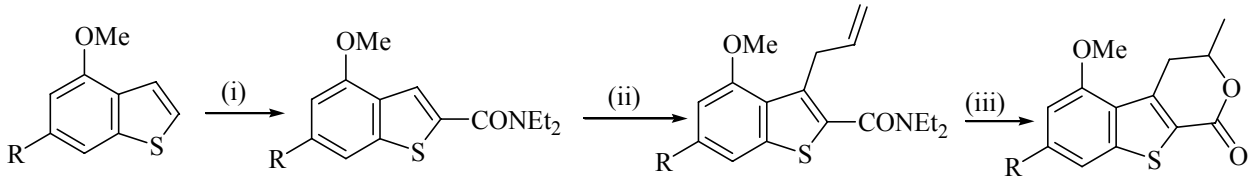
Another analog (**40**) of semivioxanthin in which the ring A of the natural product was replaced with thiophene was synthesized in high overall yield from 2-trimethylsilyl-7-hydroxybenzo[*b*]thiophene (*vide* **Scheme 3**), using the same protocol (**Scheme 8**). Yields of all the steps were between 68% to 72%. Both demethylation and desilylation took place during cyclisation affording the phenolic compound (**40**) which was stable in air.



40

Reagents: (i) NaH/THF/$ClCONEt_2$/rt; (ii) *sec*-BuLi(2.5 equiv.)/TMEDA/THF/-78 ^oC-rt; (iii) K_2CO_3 (1.2 equiv.)/acetone/MeI; (iv) *sec*-BuLi (2.5 equiv.)/CuBr-Me_2S/allyl bromide (3 equiv.) /THF; (v) 6 N HCl/reflux/ 51 h.

Scheme 8



45, R = H
46, R = OMe

47, R = H
48, R = OMe

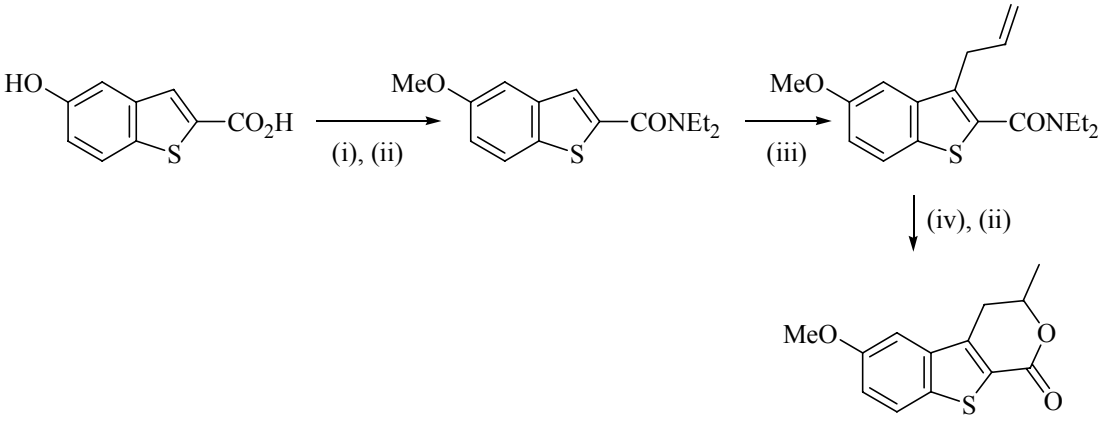
49, R = H
50, R = OMe

41, R = H
42, R = OMe

Reagents: (i) *s*-Bu*Li* / TMEDA / THF / - 78 ^oC /$ClCONEt_2$; (ii) *s*-BuLi / TMEDA / THF / -78 ^oC / CuBr-Me_2S/allyl bromide; (iii) 6 N HCl / reflux / 56 h.

Scheme 9

In the three other analogs (**41**-**43**) of semivioxanthin, the ring B of the natural product was replaced with thiophene. The starting materials for the target molecules (**41** and **42**) were 4-methoxy-(**45**) and 4,6-dimethoxybenzo[*b*]thiophene (**46**) respectively, which are now available[30,31] *via* short and expedient route. Synthesis of the target molecules, as shown in **Scheme 9** consisted of introduction of $CONEt_2$ group in the 2-position of the starting benzo[*b*]thiophenes. Subsequent *ortho*-allylation and acid induced cyclisation was accompanied by demethylation of the benzylic methoxy groups in both the cases. The air-sensitive phenolic compounds were immediately *O*-methylated to afford (**41** and **42**) which were stable in air.



43

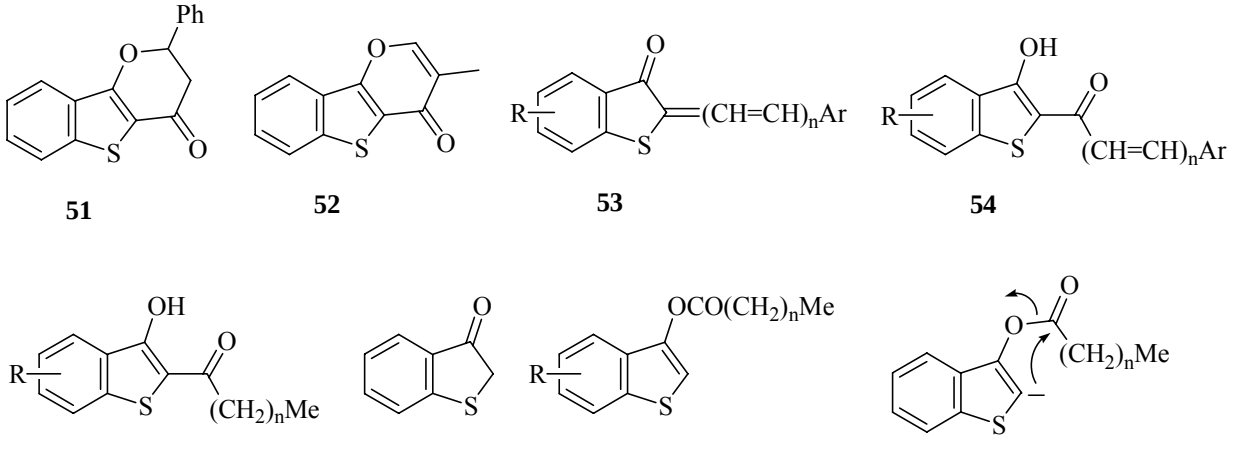
Reagents: (i) $SOCl_2$/benzene/diethylamine; (ii) K_2CO_3/MeI/acetone; (iii) *s*-BuLi/ THF/-78 ^oC/CuBr-Me_2S/allyl bromide; (iv) 6 N HCl/reflux.

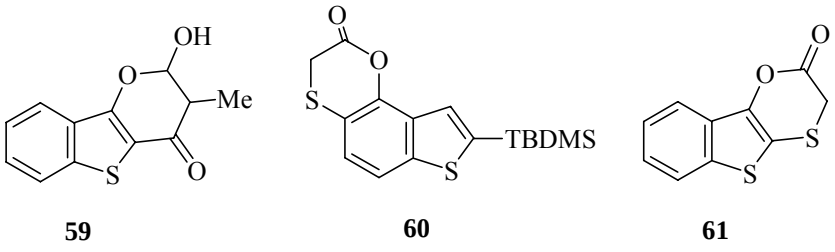
Scheme 10

Last of the sulfur analog (**43**) of semivioxanthin was synthesized from 5-hydroxybenzo[*b*]thiophene-2-carboxylic acid.[26] As shown in **Scheme 10**, conversion of the carboxylic acid group into *N*,*N*-diethylamide and the hydroxyl function into methoxy respectively is followed by introduction of allyl group in the position *ortho*- to the amide and acid induced cyclisation. Very recently we have synthesized[38] two tricyclic compounds (**51** and **52**) in which dihydropyrone and pyrone rings are linearly fused to the benzo[*b*]thiophene core. *N*,*N*-Diethyl-*ortho*-methylsulfanylbenzamides, with or without substituents in the benzene ring, when treatment with LDA, followed by aryl aldehydes afford two types of products depending upon the experimental conditions. Acidic work up after keeping the reaction mixture at 0 °C for 1 h leads to the formation of thioaurones (**53**), while allowing the reaction mixture to attain room temperature and stirring at that temperature for 4 to 5 h before acidic work up 3-hydroxybenzo[*b*]thienyl aryl ketone (**54**) is formed. By careful control of the reaction conditions it is possible to achieve exclusive formation of either of the two products. Presence of hydroxyl and aryloxo functions in (**54**) and similar compounds makes them suitable substrates for annulation of a dihydropyrone ring carrying an aryl substituent. Thus, bubbling dry HCl gas in an ethanolic (anhydrous) solution of (**54**) affords the tricyclic compound (**51**) after usual work up. The tricyclic compound (**52**) is obtained from 1-(3-hydroxybenzo[*b*]thiophene-2-yl)propan-1-one (**55**, n = 1) which was obtained by a hitherto unreported anionic rearrangement. Aninic *ortho*-Fries rearrangement[18] reported by Snieckus consists of conversion of an *ortho*-lithio aryl-*O*-carbamate into corrsponding salicylamide through intramolecular anionic rearrangement. We showed for the first time that similar rearrangement is possible with *ortho*-lithio *O*-acetates or propionates affording *ortho*-hydroxyaryl

ketones. Thus the parent thioindoxyl (**56**)[30,31] was converted to its acetoxy (**57**, n = 0) or propionyloxy (**57**, n = 1) by treating with acetyl chloride and propionyl chloride respectively in the presence of sodium hydride. Deprotonation of **57** in the 2-position with LDA at 0 °C and stirring the lithio derivative at room temperature for 8 to 12 h results in intramolecular anionic rearrangement (**58**) affording the *ortho*-hydroxy ketones (**55**, n = 0,1). Formylation of **55** with ethyl formate in the presence of sodium hydride followed by in situ cyclisation with affords the hydroxy compound (**59**) which was dehydrated with *p*-toluenesulfonic acid to affords **52** in good yield. Compounds (**51** and **52**) are representative members of classes of compounds which have potential for showing biological activity.[39] Work is in progress for synthesizing other members of the two series.

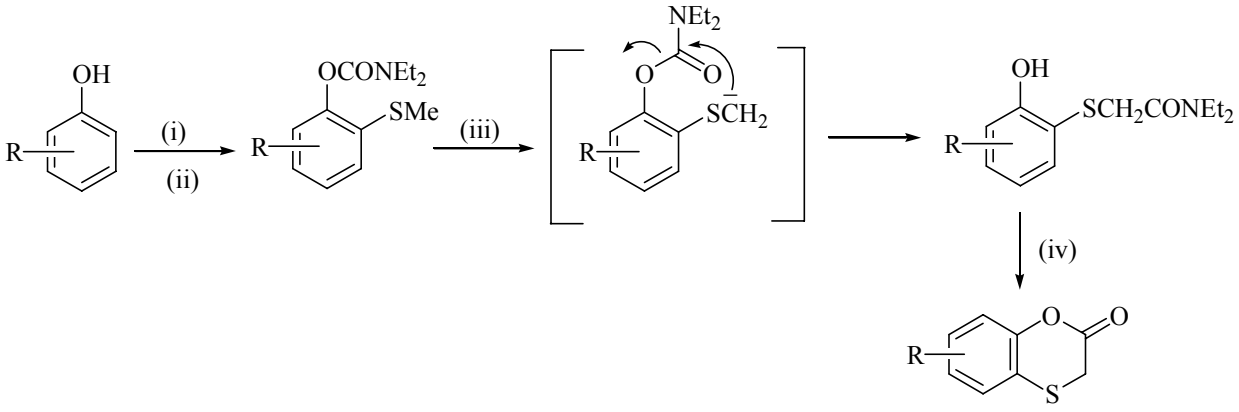
We have also reported[40,41] another class of condensed heterocycles in which a [1,4]oxathiin ring is fused to an aromatic core. As shown in **Scheme 11**, the synthesis consists of lateral metalation and intramolecular rearrangement in tandem and is yet another example of the versatility of directed metalation. Introduction of methylsulfanyl group *ortho*-to the *O*-carbamate function is followed by lateral metalation of the introduced functionality and in situ anionic rearrangement.





Acid induced cyclisation of the rearranged product completes the annulation process. The tricyclic compounds include those in which [1,4]oxathiin rings are angularly **60** or linearly **61** fused to a benzo[*b*]thiophene core. Synthesis of **60** starts from silylprotected 4-hydroxybenzo[*b*]thiophene[32] and

61 is synthesized from **56** which is *O*-alkylated with *N,N*-diethylcarbamyl chloride before introduction of methylsulfanyl group in the 2-position.



Reagents: (i) NaH/THF/$ClCONEt_2$; (ii) *s*-BuLi/TMEDA/THF/Me_2S_2/ -78 ^oC; (iii) *s*-BuLi /TMEDA/ THF/ -78 ^oC to rt; (iv) AcOH/reflux.

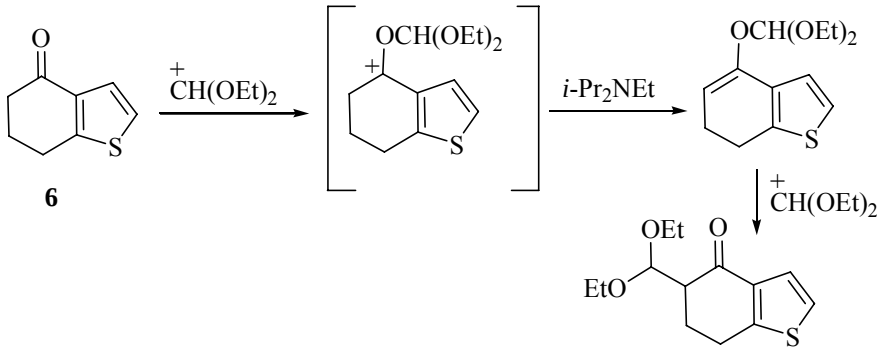
Scheme 11

4. Tricyclic compounds obtained by annulation of nitrogen heterocycles on to a benzo[*b*]thiophene core.

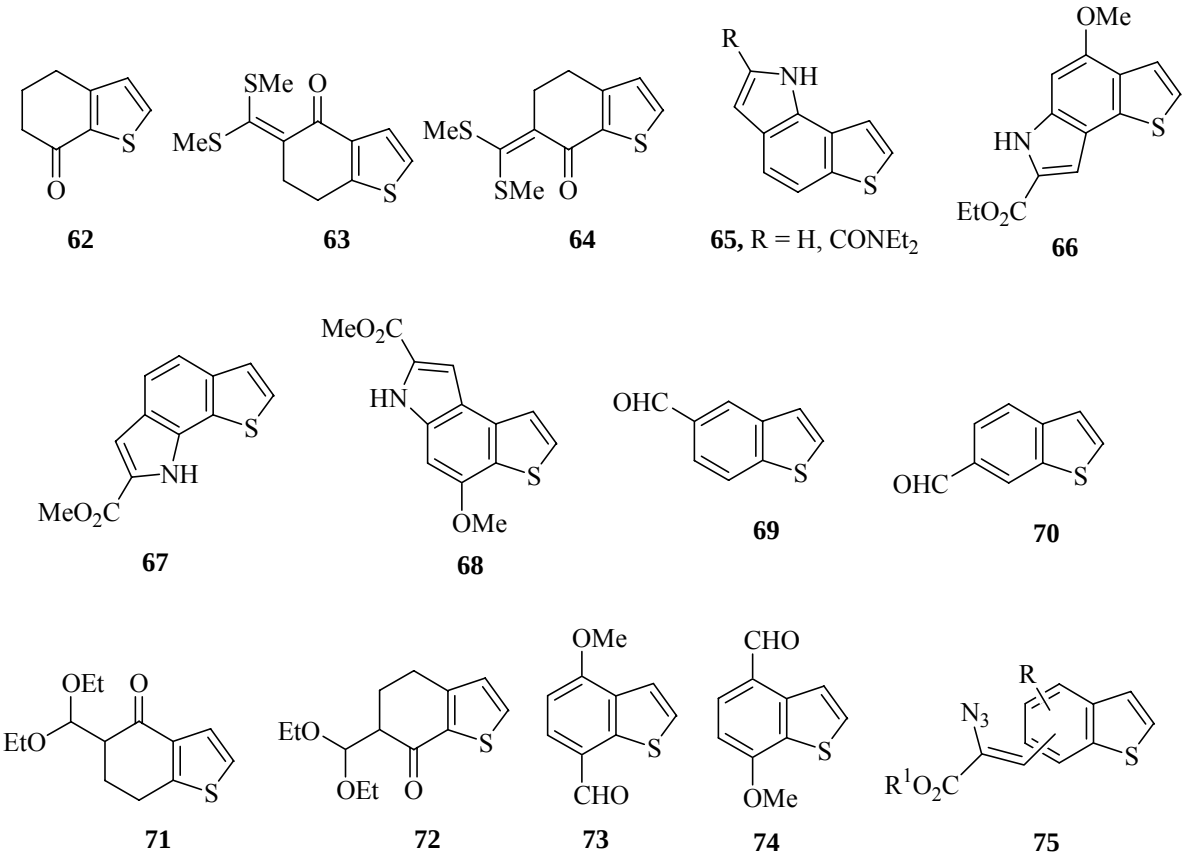
During the period under review a number of such compounds were synthesized utilizing the ketone (**6**), its isomer 5,6-dihydrobenzo[*b*]thiophen-7-(4*H*)-one (**62**) and the oxoketone dithioacetals (**63** and **64**) derived from these compounds. The five member nitrogen heterocycles which have been annulated to a benzo[*b*]thiophene core include pyrole, pyrazole, pyrazolone, isoxazole and six member pyrimidine ring was also annulated.

The four thioenoindoles (**65-68**) were synthesized[42-44] from the appropriate benzo[*b*]thiophene-carboxaldehydes *via* corresponding azidocinamates. Benzo[*b*]thiophene-5-carboxaldehyde (**69**)[44] and benzo[*b*]thiophene-6-carboxaldehyde (**70**)[45] were prepared from cyclic ketones (**6** and **62**) respectively *via* the keto acetals (**71** and **72**)[46] which are in reality masked keto aldehydes. The pathway through which the keto acetal (**71**) is formed from **6** is shown in **Scheme 12**. The cyclic ketone (**6**) is treated with triethyl orthoformate in the presence of boron trifluoride etherate followed by diisopropylethylamine. Diethyloxonium fluoroborate, the resulting species, is similar to Vilsmeier reagent. Electrophillic addition of the diethoxycarbonium ion to the double bond of the enol ether and simultaneous expulsion of the $CH(OEt)_2$ species gives the keto acetal (**71**) which is immediately subjected to borohydride reduction. During acidic work up the resulting carbinol is dehydrated in situ to afford 6,7-dihydrobenzo[*b*]thiophene-5-carboxaldehyde in 82% yield. Aromatization with *N*-

bromosuccinamide gives the aldehyde (**69**) in 70% yield. The aldehyde (**70**) is similarly prepared from the keto acetal (**72**) also in 70% yield. Both 4-methoxybenzo[*b*]thiophene-7-carboxaldehyde (**73**) and 7-methoxybenzo[*b*]thiophene-4-carboxaldehyde (**74**) are prepared from 4-methoxy and 7-methoxybenzo[*b*]thiophene by Vilsmeier-Haack formylation.

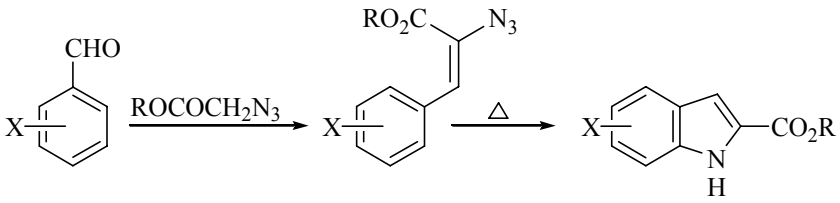


Scheme 12



The four benzo[*b*]thiophenecarboxaldehyde upon subjecting to Knoevengal condensation with methyl or ethyl azidoacetate at –15 °C in the presence of appropriate sodium alcoholate affords the corresponding azidocinnamates in around 60% yield. Heating the resulting azidocinnamates in an

appropriate solvent *e.g.* tolune or xylene for 3 to 4 h results in the annulation of the pyrrole ring *via* nitrene insertion (**Scheme-13**).[47]

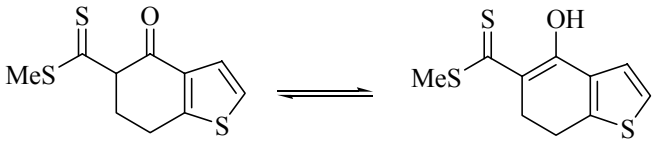


Scheme 13

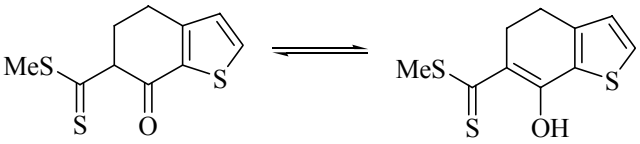
The most attractive feature of the reaction is that no protection against moisture or oxygen is necessary. Thermal decomposition of the azidocinnamates under reaction condition affords azirines which are in equilibrium with vinylnitrenes. The cyclisation involves electrocyclization of the latter followed by a rapid [1,5] hydrogen shift resulting in aromatization. Removal of the ester function in those tricyclic compounds proved to be difficult. Hydrolysis and decarboxylation of **65** (R=CO_2Et) gave the parent compound (**65**) (R=H) in 81% yield but required prolonged boiling with ethanolic potassium hydroxide. Attempts of removal of the ester function in **66-68** resulted in the decomposition of those compounds. Tricyclic compounds (**76** and **77**) (R=H) and **80, 81** consisting of isoxazole and pyrazole rings annulated to partially hydrogenated benzo[*b*]thiophene core have shown interesting biological activities. These compounds are obtained from the hydroxymethylene compounds with hydroxylamine and hydrazine hydrate. Shaking the alcoholic solution of the reactants[11,15] rather than refluxing in acetic acid[48] afforded the products in improved yield and also shortened the reaction time. We have reported[11,15] other members of the series **76** (R=Me, Br) and **77** (R= Me, Br) and also aromatized the dihydro compounds with DDQ.

Annulation of isoxazole and pyrazole rings on the benzo[*b*]thiophene core was carried out using α-oxoketene dithioacetals (**63** and **64**) as key intermediates. Use of α-oxoketene dithioacetals in organic synthesis is well documented.[49] These compounds are in reality masked β-keto esters. The relative positions of the carbonyl and the bis(alkylthio) groups also make them three carbon equivalents with electrophilicity in the 1,3-position. The 1,3-electrophilic centres present in the molecule are capable of undergoing smooth reaction with stable bifunctional nucleophiles to annulate a five or six-member nitrogen heterocycle. Conversion of the ketones (**6** and **62**) to the α-oxoketene dithioacetals is carried out in two steps. In the first step the ketones are converted into β-oxodithioesters (**78** and **79**) by reacting with dimethyl trithiocarbonate in the presence of potassium *t*-butoxide in DMF. Methylation

of **78** and **79** with methyl iodide in dry acetone in the presence of anhydrous potassium carbonate affords **63** and **64** in good yields. Ethanolic solution of **63** and **64** upon heating under reflux with molar equivalent of hydrazine hydrate results[45] in the annulation of pyrazole ring on the dihydrobenzo[*b*]thiophene core with simultaneous expulsion of methanethiol to afford the tricyclic compounds.



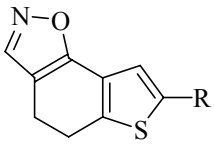
78a **78b**



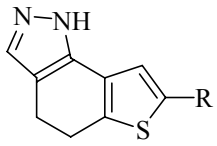
79a **79b**

Two pairs of regioisomeric condensed isooxazoles (**82-85**) are obtained[45,46] when each of the α-oxoketene dithioacetals (**63** and **64**) is treated with hydroxylamine, an asymmetric bifunctional nucleophile. The nature of the regioisomer depends on the pH of the reaction medium. Thus 8-methylsulfanyl-6,7-dihydrothieno[2,3-*g*]-2,1-benzisoxazole (**82**) and 7-methylsulfanyl-5,6-dihydrothieno[3,2-*g*]-2,1-benzisoxazole (**84**) are formed in 59% and 70% yields from **63** and **64** respectively, when the α-oxoketene dithioacetals are reacted with hydroxylamine in the presence of methanolic sodium methoxide. On the other hand, when the reaction is carried out at an acidic pH by the use of sodium acetate and acetic acid, regioisomeric 3-methylsulfanyl-4,5-dihydrothieno[2,3-*g*]-1,2 benzisoxazole (**83**) and 3-methylsulfanyl-4,5-dihydrothieno[3,2-*g*]-1,2-benzisoxazole (**85**) are obtained in 70% yields from **63** and **64** respectively. Under basic conditions, in the presence of methanolic sodium methoxide, the initially derived oximes from **63** and **64** cyclise to give the condensed isoxazoles (**82** and **84**) with the expulsion of methanethiol. Initial protonation of the α-oxoketene dithioacetals take place when the reaction conditions are acidic, the protonated species (**86**) being stabilized by charge delocalisations. Subsequent nucleophilic attack by hydroxylamine at the positive charge centre in **86b** and concomitant expulsion of methanethiol gives the intermediate (**87**) which finally cyclises to the regioisomeric condensed isoxazoles (**83** and **85**). In the presence of refluxing methanolic sodium methoxide, guanidine liberated from its hydrochloride reacts with **63** and **64** to afford 4-methoxy-5,6-dihydrothieno[2,3-*h*]qunazolin-2-ylamine (**88**) and 4-methoxy-5,6-dihydrothieno[3,2-*h*]qunazolin-2-ylamine (**89**) in 54% and 70% yields respectively. Sodium methoxide,

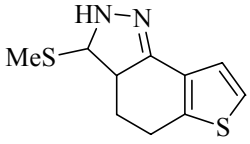
apart from releasing free guanidine from its salt, acts as the cyclising agent and also converts the methyl sulfanyl group present in the condensed diazine ring into methoxy after cyclisation.



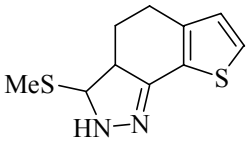
76



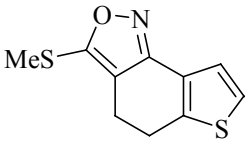
77



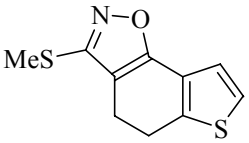
80



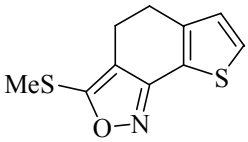
81



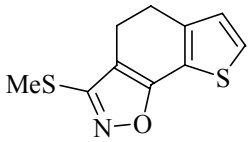
82



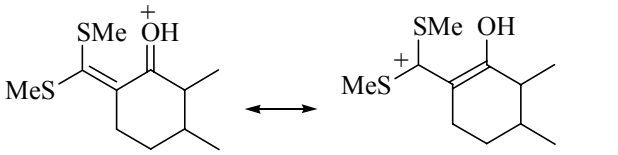
83



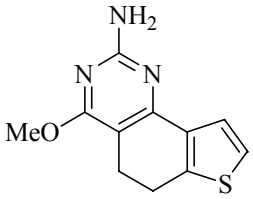
84



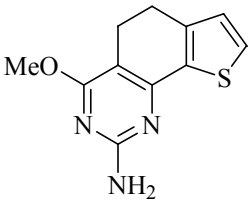
85



86a **86b** **87**



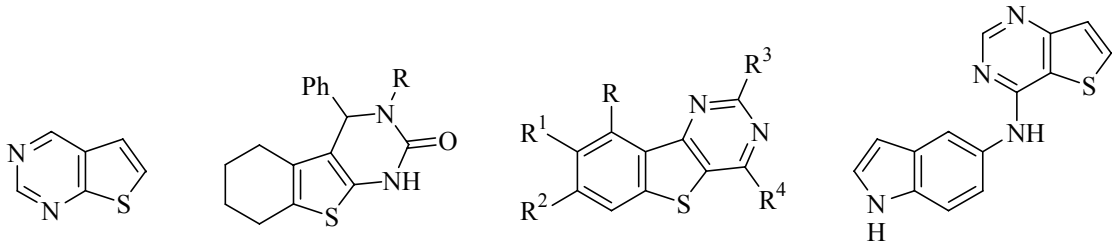
88



89

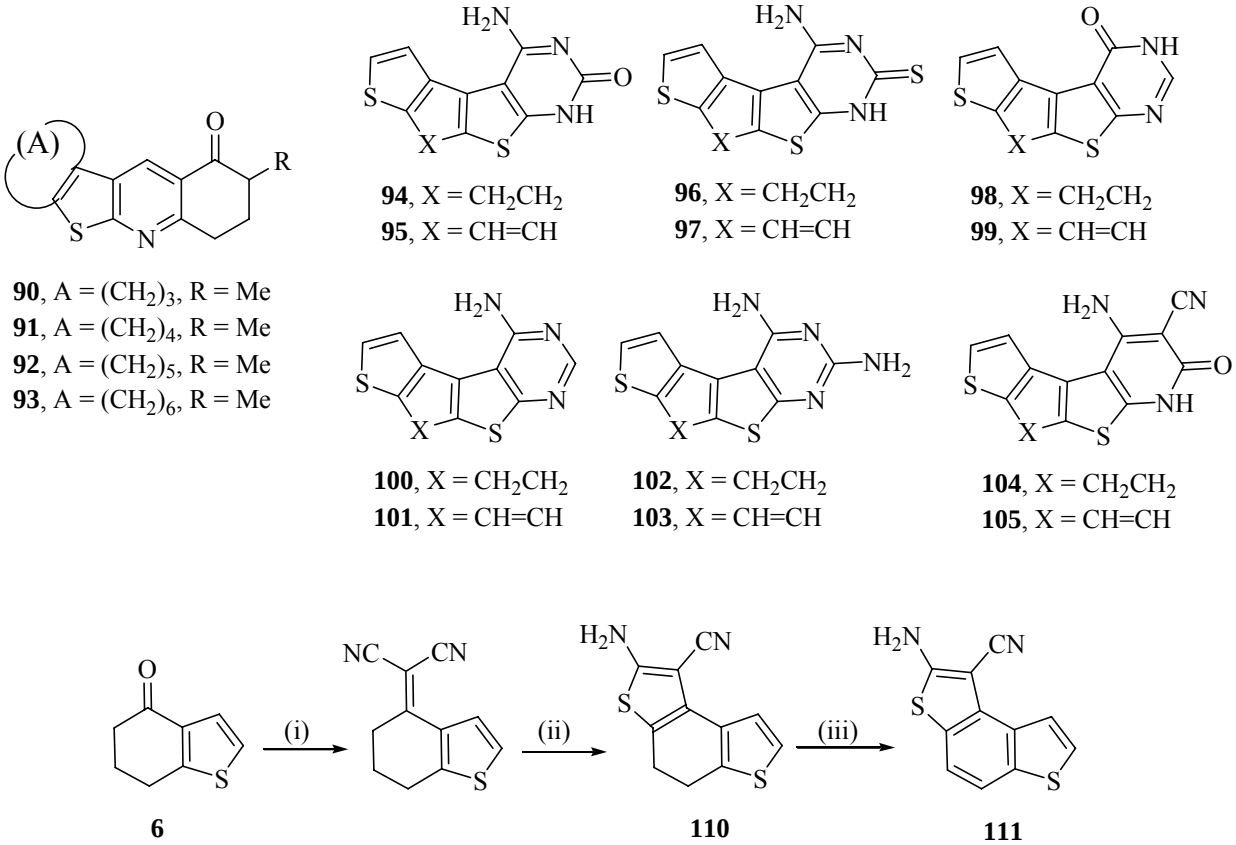
5. Tetracyclic compounds incorporating a fused thiophene ring.

In relatively recent times several tetracyclic compounds incorporating fused thiophene rings are reported in the literature which are synthesized with the idea of extending the π system of a potent pharmacophore and incorporating rigidity at the same time. Compounds (**90-93**) were synthesized[50,51] on the basis of this idea as sulfur analogs of potent pyridoindoles and proved to be important GABA inhibitors. We have reported[52] the synthesis of a number of tetracyclic compounds (**94-105**). It is now well established that thieno[2,3-*d*]pyrimidine (**106**) is a heterocyclic system which supports a wide spectrum of biological activity through a range of derivatives. As for example 2-substituted thieno[2,3-*d*]pyrimidin-3*H*-one has shown antiinflammatory and antihyperlipamic activities.[53,54] Partially hydrogenated [1]benzothieno[2,3-*d*]pyrimidin system (**107**)[55] has shown analgesic and antipyretic system excluding that of ibuprofen. Benzothienopyrimidines (**108**) have shown[56] antiallergic properties upto 100 times more than disodium cromoglycate and upto 10 times more that of ketotifen.



106 **107** **108** **109**

More recently[57] several thienopyrimidines developed through structural modification of the lead compound (**109**) have shown inhibition of angiogenesis and tumor growth through inhibition of VEGFR-2 kinose activity. Our idea was to examine the effect of extending the size of aromatic π-system of this potent pharmacophore (**106**) and at the same time introduce non polarity. Compounds (**94-105**), which illustrate this structural elaboration are obtained from the two key intermediate 4,5-dihydrothieno[3′,2′:4,5]benzo[*b*]thiophene (**110**) and its fully aromatised derivative (**111**) synthesized from 6,7-dihydrobenzo[*b*]thiophene-4(5*H*)-one (**6**) (**Scheme 14**). Base catalysed condensation of **6** with malononitrile is followed by subjecting the condensation product to Gewald reaction[15,58] affording **110** which was subsequently aromatised.



90, A = $(CH_2)_3$, R = Me
91, A = $(CH_2)_4$, R = Me
92, A = $(CH_2)_5$, R = Me
93, A = $(CH_2)_6$, R = Me

94, X = CH_2CH_2
95, X = CH=CH

96, X = CH_2CH_2
97, X = CH=CH

98, X = CH_2CH_2
99, X = CH=CH

100, X = CH_2CH_2
101, X = CH=CH

102, X = CH_2CH_2
103, X = CH=CH

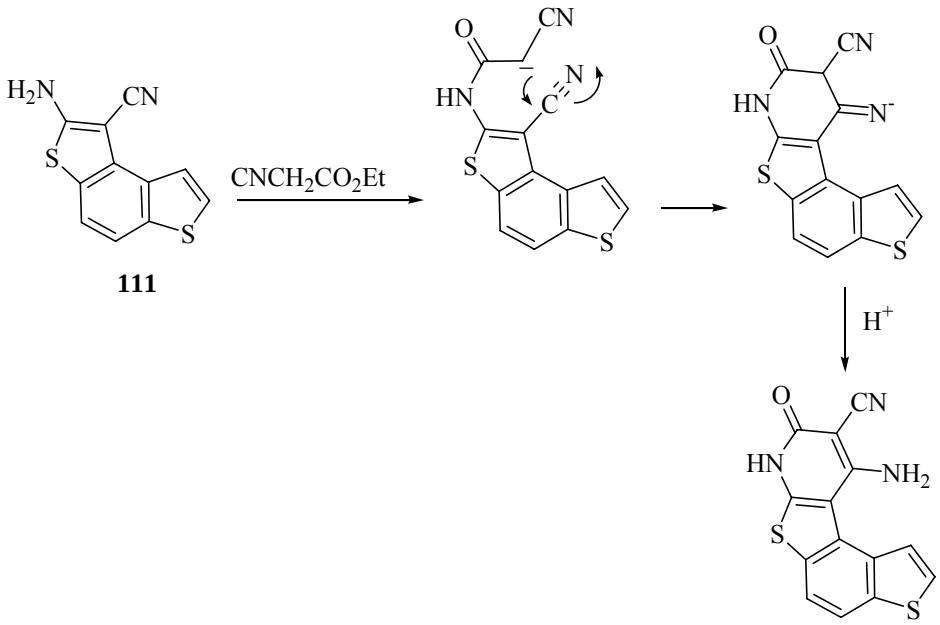
104, X = CH_2CH_2
105, X = CH=CH

6 **110** **111**

Reagents: (i) $CH_2(CN)_2/Et_3N$; (ii) sulfur/morpholine/ethanol; (iii) DDQ/benzene.

Scheme 14

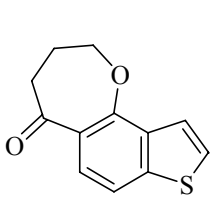
In both **110** and **111** amino and nitrile functions are appropriately located on one of the thiophene rings for further annulation of a pyrimidine ring. The tetracyclic compounds are obtained with yields usually in the range of 40-80%. The yields of the dihydroderivatives are generally higher than those of the aromatic compounds. Treatment of **110** or **111** with urea or thiourea in the presence of sodium ethoxide give **95** and **97** and the corresponding dihydro derivatives. While with formic acid in the presence of sodium formate (**98** and **99**) are obtained. Upon reacting **110** and **111** with formamide/formic acid **101** and **102** are obtained and reaction with guanidine in the presence of sodium ethoxide afforded **102** and **103**. Treatment of **110** and **111** with ethyl cyanoacetate in the presence of ammonium acetate and acetic acid with continous removal of water gives the compounds (**104** and **105**) in good yields. The most likely mechanism is shown in **Scheme 15**.



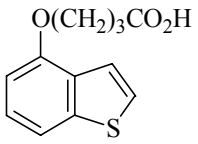
Scheme 15

Another series of tricyclic compounds reported from our laboratory during the period under review were obtained by annulating different five member heterocycles on to the tricyclic compound 3,4-dihydrothieno[2,3-*i*]benzoxapin-4-one (**112**).[59] This key intermediate was the first example of a seven member oxygen heterocycle fused to the benzene ring of benzo[*b*]thiophene. There were earlier reports[60-62] of tricyclic compounds in which a seven member oxygen heterocycle is fused to the thiophene ring of benzo[*b*]thiophene. Polyphsphoric acid cyclisation of 4-(benzo[*b*]thiophen-4-yloxy)butyric acid (**113**), available from the reaction of 4-hydroxybenzo[*b*]thiophene with γ-butyrolactone in the presence of methanolic sodium methoxide under refluxing condition, affords the

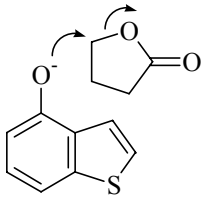
tricyclic ketone. The reaction of γ-butyrolactone with phenoxide anion involves ring opening of through a somewhat uncommon alkyl oxygen cleavage (**114**).[63] Formation of the more common acyl oxygen cleavage product was discounted from the solubility of the product in sodium bicarbonate and from the IR spectrum. Careful examination of the neutral part remaining after extraction of **113** in sodium bicarbonate solution did not show the presence of **115**, indicating that the cleavage of the γ-butyrolactone ring took place exclusively *via* alkyl oxygen cleavage.[64] Preparation of **113** in good yield require careful maintenance of experimental condition and very slow removal of excess solvent.



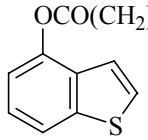
112



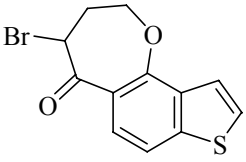
113



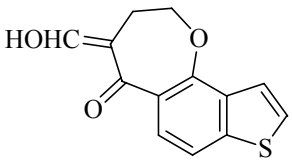
114



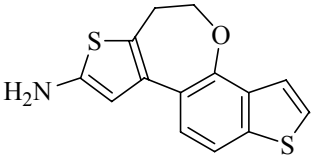
115



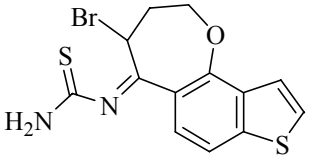
116



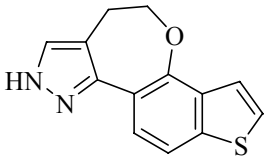
117



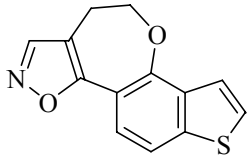
118



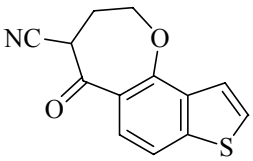
119



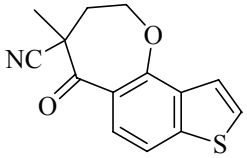
120



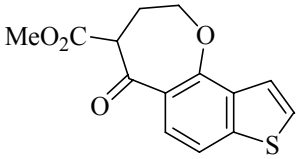
121



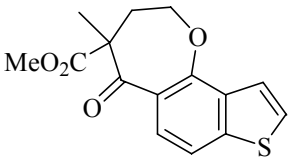
122



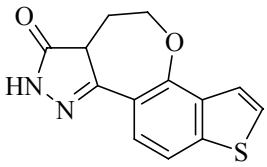
123



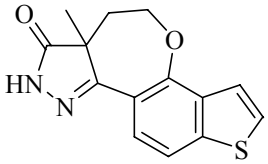
124



125



126



127

The tricyclic ketone can be brominated in ether and formylated to give the bromo ketone (**116**) and the hydroxymethylene compound (**117**) in excellent yields. The bromo ketone upon heating with thiourea under reflux in dry ethanol for 16 h affords 2-amino-10,11-dihydrothieno[2,3:8,9][1]benzoxepino[5,4-*d*]thiazole (**118**) in 91% yield, which is however susceptible to aerial oxidation on prolonged exposed to air. Initial reaction of the ketone with thiourea and cyclisation as shown in **119**, takes place in one pot. Heating a methanolic solution of the hydroxymethelene compound with hydrazine hydrate affords 5,6-dihydro-8*H*-thieno[2,3:8,9][1]benzoxepino[5,4-*c*]pyrazole (**120**) in 92% yield and reaction of the

hydroxymethelene compound with hydroxylamine in boiling ethanol affords 10,11-dihydrothieno[2′,3′:8,9][1]benzoxepino[5,4-*d*]isoxazole (**121**) in 74% yield. The isoxazole ring can be opened with sodium methoxide to the β-keto nitrile (**122**) in near quantitative yield. The β-keto nitrile can be methylated on the carbon bearing the nitrile function with methyl iodide in the presence of sodium hydride to afford **123** in 92% yield. The dry methanolic solution of the two β-keto nitriles upon saturation with dry hydrogen chloride gas affords the β-keto esters (**124** and **125**) in 63% and 94% yield respectively. The β-keto ester upon treatment with hydrazine hydrate affords the tetracyclic fused pyrazolones (**126** and **127**) in excellent yields.[65]

ACKNOWLEDGEMENT

Much of the work presented in this review was supported by financial help from the Royal Society of Chemistry (U. K.) and Council of Scientific and Industrial Research (CSIR, New Delhi). AD thanks his numerous dedicated young collaborators whose names are in the publications referred to in the review. T. K. P. thanks CSIR for Junior & Senior Research Fellowships.

REFERENCES

1. B. Iddon and R. M. Scrowston, '*Advances in Heterocyclic Chemistry*,' ed. by A. R. Kartritzky and A. J. Bulton, Academic Press, London, New York, 1970, Vol. **11**, p. 177.
2. R. M. Scrowston, '*Advances in Heterocyclic Chemistry*,' ed. by A. R. Kartritzky and A. J. Bulton, Academic Press, London, New York, 1981 Vol. **29**, p. 171.
3. N. B. Chapman, C. G. Hughes, and R. M. Scrowston, *J. Chem. Soc*., *C*, 1970, 2269.
4. A. Mustafa, in '*Furopyrans and Furopyrones, The Chemistry of Heterocyclic Compounds*,' ed. by A. Weissberger, Wiley Interscience, 1967.
5. B. D. Tilak, *Tetrahedron*, 1960, **9**, 76.
6. V. Snieckus, *Chem. Rev.,* 1990, **90**, 879.
7. J. G. Canno, in '*Burger's Medicinal Chemistry and Drug Discovery*,' ed. by M. E. Wolff, John Willy, 1995, Vol. **1**, p. 783.
8. A. Mustafa, S. M. A. D. Zayed, and A. Emran, *Ann. Chem.*, 1967, **704**, 176.
9. K. Clarke, R. M. Scrowston, and T. M. Sutton, *J. Chem. Soc., Perkin Trans. 1*, 1973, 1196.
10. C. M. Asprou, J. S. A. Brunskill, H. Jeffrey, and A. De, *J. Heterocycl. Chem.*, 1980, **17**, 87.
11. H. Jeffrey, PhD Thesis, University of Wales, 1982.
12. P. M. Chakrabarti, N. B. Chapman, and K. Clarke, *J. Chem. Soc., C*, 1969, 1.
13. G. Saint Ruf, A. De, J. S. A. Brunskill, and H. Jeffrey, *J. Heterocycl. Chem*., 1980, **17**, 81.

14. N. M. D. Brown, A. De, J. S. A. Brunskill, and H. Jeffery, *Org. Magn. Reson.*, 1982, **18**, 21.
15. A. De, J. S. A. Brunskill, and H. Jeffery, *Indian J. Chem.*, 1984, **23B**, 918.
16. S. C. Ghosh and A. De, *J. Chem. Soc., Perkin Trans. 1*, 1999, 3705.
17. H. Ishii, T. Ishikawa, S. Takeda, S. Ueki, M. Suzuki, and I. Haryana, *Chem. Pharm. Bull.*, 1990, **38**, 1775.
18. M. P. Sibi and V. Snieckus, *J. Org. Chem.*,1983, **48**, 1935.
19. A. V. Kalinin, A. J. Jalil Miah, S. Chattopadhay, M. Tsukazaki, M. Wicki, T. Nguyen, A. L. Coelho, M. Kerr, and V. Snieckus, *Synlett,* 1997, **7**, 839.
20. W. Wang and V. Snieckus, *J. Org. Chem.*, 1992, **57**, 424.
21. B. A. Chauder, A. V. Kalinin, N. J. Taylor, and V. Snieckus, *Angew. Chem., Int. Ed.*, 1999, **38**, 1435.
22. P. Zhang and R. E. Gawley, *J. Org. Chem.*, 1993, **58**, 3223.
23. A. V. Kalinin, A. J. M. da Silva, C. C. Lopes, R. S. C. Lopes, and V. Snieckus, *Tetrahedron Lett.,* 1998, **39**, 4995.
24. M. A. Reed, M. T. Chang, and V. Snieckus, *Org. Lett.*, 2004, **6**, 2297.
25. S. Mukherjee, S. S. Jash, and A. De, *J. Chem. Res. (S)*, 1993, 192.
26. P. M. Chakraborti, N. B. Chapman, and K. Clarke, *Tetrahedron,* 1969, **25**, 2781.
27. (a) N. B. Chapman, K. Clarke, and A. Manolis, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1404.
(b) L. K. A. Rahman and R. M. Scrowston, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2972.
28. S. S. Samanta, S. C. Ghosh, and A. De, *J. Chem. Soc., Perkin Trans., 1*, 1997, 2683.
29. R. Casas, C. Cave, and J. d'Angelo, *Tetrahedron Lett.*, 1995, **36**, 1039.
30. C. Mukherjee and A. De, *Synlett*, 2002, 325.
31. C. Mukherjee, S. Kamila, and A. De, *Tetrahedron*, 2003, **59**, 476.
32. S. S. Mondal, S. S. Samanta, and C. Deb, A. De, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2559.
33. T. K. Pradhan, S. C. Ghosh, and A. De, *Arkivoc*, 2003, 158.
34. E. G. Doadt and V. Snieckus *Tetrahedron Lett.*, 1985, **26**, 1149.
35. S. Kamila, C. Mukherjee, and A. De, *Tetrahedron Lett*., 2001, **42**, 5955.
36. S. Kamila, C. Mukherjee, S. S. Mondal, and A. De, *Tetrahedron,* 2003, **59**, 1339.
37. A. Zeeck, P. Russ, H. Loatsch, W. Loeffler, H. Wehrde, H. Zahner, and H. Holst, *Chem. Ber.*, 1979, **112**, 957.
38. T. K. Pradhan and A. De, *Tetrahedron Lett.*, 2005, **46**, 1493.
39. J. B. Wright and H. G. Johnson, *J. Med. Chem.*, 1973, **16**, 86.
40. C. Mukherjee, S. Kamila and A. De, *Synlett*, 2003, 1474.
41. T. K. Pradhan, C. Mukherjee, S. Kamila and A. De, *Tetrahedron*, 2004, **60**, 5215.
42. S. Datta and A. De, *J. Chem. Soc., Perkin Trans. 1*, 1989, 603.

43. S. Bhattacharya, PhD thesis, Jadavpur University, (1990).
44. S. S. Samanta, S. C. Ghosh, and A. De, *J. Chem. Soc., Perkin Trans. 1*, 1997, 3673.
45. S. C. Ghosh, PhD thesis, Jadavpur University, (1999).
46. M. Suzuki, A. Yanagisawa, and R. Noyori, *Tetrahedron*, 1982, **23**, 3595.
47. L. Heun, D. M. B. Hickey, C. J. Moody, and C. W. Rees, *J. Chem. Soc., Perkin Trans. 1*, 1984, 2189.
48. W. A. Remers, G. J. Gibbs, J. F. Poletto, and M. J. Weiss, *J. Med. Chem.*, 1971, **14**, 1127.
49. H. Junjappa, H. Ila, and C. V. Asokan, *Tetrahedron*, 1987, **43**, 5367.
50. D. Bolton, I. T. Forbes, C. J. Hayward, D. C. Piper, D. R. Thomas, M. Thompson, and N. Upton, *Bio. Med. Chem. Lett.*, 1993, **3**, 1941.
51. T. P. Blockbum, D. Bolton, I. T. Forbes, C. N. Johnson, R. T. Martin, D. R. Thomas, M. Thompson, and N. Upton, *Bio. Med. Chem. Lett.*, 1994, **4**, 279.
52. S. Bhattacharya, A. De, and D. F. Ewing, *J. Chem. Soc., Perkin Trans. 1*, 1994, 689.
53. M. Perissin, M. Faure, C. L. Due, F. Huguet, G. Gaultier and G. Narcisse, *Eur. J. Med. Chem.*, 1988, 23, 453.
54. C. J. Shishoo, M. B. Devani, V. S. Bhadti, K. S. Jain, I. S. Rathod, R. K. Goyal, T. P. Gandhi, R. B. Payel, and S. R. Naik, *Arzneim Forsch*., 1990, **40**, 567.
55. S. Vega, J.Alonso, J. A. Diaz, F. Junqhera, C. Perez, V. Darias, L. Bravo, and S. Abdallah, *Eur. J. Med. Chem.*, 1991, **26**, 323.
56. J. M. Quintela, C. Peinador, C. Vega, L. Gonzalez, L. M. Botana, A. Alfonso, and R. Riguera, *Bioorg. Med. Chem.*, 1998, **6**, 1911.
57. M. J. Munchhof, J. S. Beebe, J. M. Casavant, B. A. Cooper, J. L. Doty, R. C. Higdon, S. M. Hillerman, C. L. Sodershon, E. A. Knauth, M. A. Marx, A. M. K. Rossi, S. R. Sobolov, and J. Sun, *Biorg. Med. Chem. Lett.*, 2004, **14**, 21.
58. C. Goedlicke and H. Stegmeyer, *Tetrahedron Lett.*, 1970, 937.
59. S. Mekherjee, S. S. Jash, and A. De, *J. Chem. Res. (S)*, 1993, 192.
60. E. Oshima, H. Obase, A. Karasawa, K. Kubo, I. Miki, and A. Ishii, *Eur. Pat. Appl.* EP 312051 (*Chem. Abstr*., 1989, **111**, 174009).
61. B. Chandrasekhar, D.V. Ramana, and S. R. Ramadas, *Sulfur Lett.*, 1989, **9**, 271.
62. A. Thomas, G. Singh, H. Ila, and H. Junjappa, *Tetrahedron Lett.*, 1989, **30**, 3093.
63. V. K. Tandon, J. M. Khanna, N. Anand; R. C. Srimal, C. R. Prasad, and K. Kar, *Indian. J. Chem. Soc*., 1975, **13**, 1.
64. G. H. Posner and M. Oda, *Tetrahedron Lett.*, 1981, **22**, 5003.
65. S. Mukherjee, S. S. Jash, and A. De, *J. Chem. Res.*, 1994, (*S*) 293, (*M*) 1731.