A Facile Regioselective Synthesis of Tetracyclic Sulphur Heterocycles by Tandem *Thio*-Claisen Rearrangement

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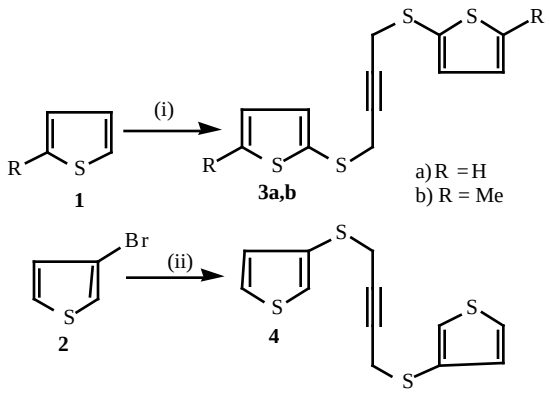
Abstract: *Thio*-Claisen rearrangement of symmetrically substituted 1,4-but-2-ynes (**3a,b** and **4**) exhibit tandem cyclization and afforded compounds **5a,b** and **6** in good yields. These sulphides **3a,b** and **4** were in turn prepared from commercially available thiophene. The key step in this transformation is tandem [3,3] sigmatropic rearrangement.

Keywords: *Thio*-Claisen rearrangement, mercaptothiophene, regioselectivity, tetracyclic sulphur compounds, tandem cyclisation.

The Claisen rearrangement [1] has been an excellent tool for the formation of carbon-carbon bonds [2-6] and synthesis of heterocyclic compounds. In continuation of our on going research on [3,3] sigmatropic rearrangement of 4-(4′-aryloxy-but-2′-ynylthio)-6-methyl pyran-2-one, [7] we have recently reported regioselective synthesis of [6,6] pyranothiopyran. [8] The synthesis of sulphur heterocycles by radical cylisation [9] is also regioselective but low yielding process due to the β-fragmentation of the intermediate radical. Here in we report the regioselective one-pot synthesis of tetracyclic sulphur heterocycles in good yield.

Some years ago Thyagrajan and co-workers reported a facile synthesis of a series of petrocarpan [10] derivatives from 1,4-bis-aryloxybut-2-ynes. We attempted to synthesize the corresponding sulphur analogues by the application of the same methodology but we failed to obtain the desired tetracyclic product. The substrates decomposed on heating even under nitrogen atmosphere and this was perhaps due to the requirement of higher activation energy for the sulphur analogues compared to its oxygen counterpart. [11, 12] We, therefore, looked for substrates devoid of aromatic ring. This was accomplished by replacing the aromatic ring by heterocyclic ring with reduced aromaticity. Thiophene is much less aromatic than benzene and we decided to exploit thiophene-2-thiol [13] and thiophene-3-thiol [14] to test the methodology for the synthesis of tetracyclic polyhetero-cycles. For the present study we have particularly chosen **3a,b** and **4** as substrates. These are symmetrical molecules and there is a possibility of two fold *thio*-Claisen rearrangement. [15] In these cases the requirement of activation energy for the rearrangement is also expected to be lower.

The starting materials for this study, 1,4-bis-(2-thienylsulfanyl)but-2-yne (**3a,b**) were prepared by the reaction of 2-mercaptothiophene with 1,4-dichlorobut-2-yne in dry ether under inert atmosphere at room temperature. 2-Mercaptothiophene was also prepared *in situ* by the reaction of thiophene, *n*-BuLi and S-powder at 0-5 ˚C. Compound **3a,b** were analytically pure and the structures were determined by the ^{1}H NMR spectroscopy. Compound **3a** showed a four proton singlet at δ 3.49 for SCH_2. The thiophene protons appeared as three doublets of doublet at δ 6.97 (*J*=3.2, 5.2 Hz), 7.20 (*J*=0.7, 5.2 Hz) and 7.37 (*J*=0.7, 5.2Hz). The ^{13}C NMR spectrum exhibited six types of carbon at δ 28.3, 80.6, 128.0, 130.9, 133.0 and 135.0.



Scheme 1. *Reagents and condtions:* i) [a] *n*-BuLi, Et_2O; [b] S-powder, 0-5˚C; [c] 1,4-Dichlorobut-2-yne, r.t, Et_2O; ii) [a] *n*-BuLi, Et_2O, -70˚C; [b] S-powder, -70˚C; [c] 1,4-Dichlorobut-2-yne, r.t, Et_2O.

Compounds **3a,b** contain 2-allylpropargyl sulphide moiety and are very prone to undergo tandem Claisen rearrangement. Different solvents have been tried in this rearrangement and the best result was obtained by the use of DMF. Therefore, compound **3a** was refluxed in DMF and the progress of the reaction was monitored by TLC. Complete conversion was achieved in 1h. After work up and purification of the viscous liquid by silica-gel (60-120 mesh) column chromatography compound **5a** was obtained in 70% yield. Encouraged by the initial success, substrate **3b** was similarly treated and the corresponding product **5b** were obtained in 75% yield. The structures were determined from ^{1}H NMR spectroscopy.

The proton NMR spectrum of compound **5a** showed a three proton singlet at δ 1.9 due to the presence of an angular methyl group. Two $SC\mathbf{H}_2$ protons appeared as two doublets of a doublet, one at δ 2.8 (*J* = 3, 12.8 Hz) and the

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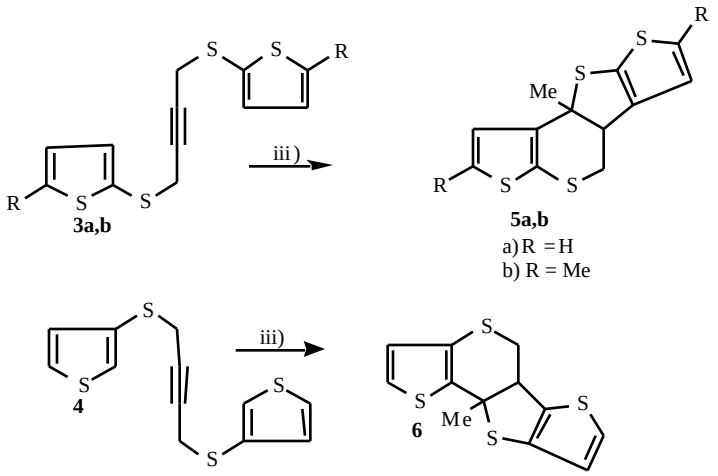


Scheme 2. *Reagents and conditions:* iii) DMF, reflux, 1h.

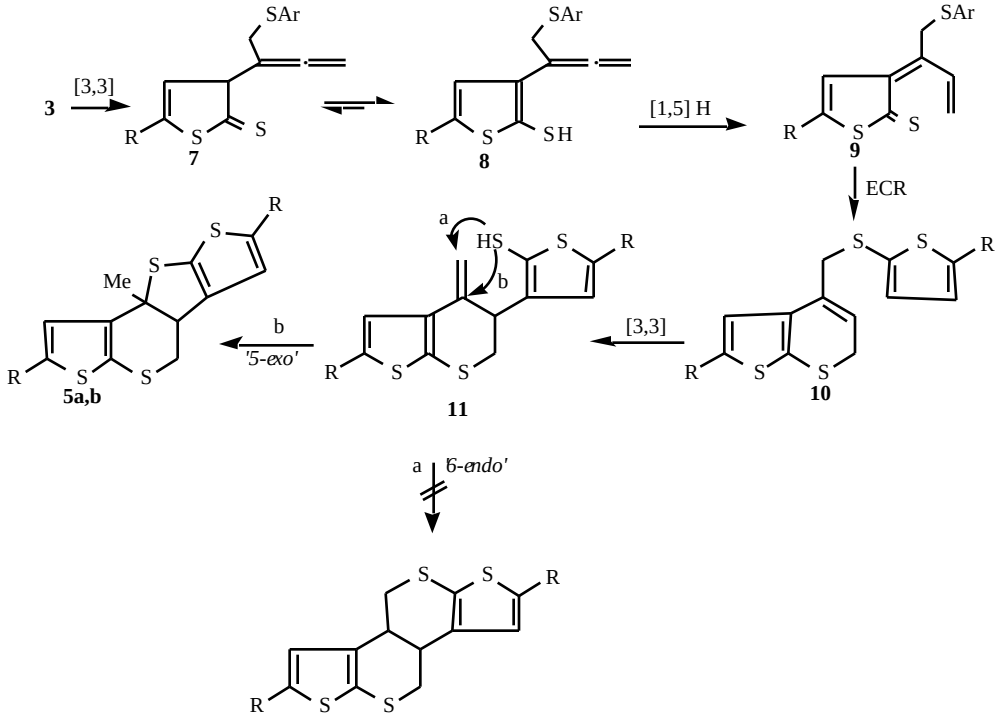
other at δ 3.14 (*J* = 11, 12.8 Hz), the ring junction proton appeared as one proton doublet of a doublet at δ 3.30 (*J* = 3, 11 Hz), and four thiophene protons appeared as two, one proton doublets at δ 6.91 (*J* = 5 Hz) and 6.99 (*J* = 5.3 Hz), and a two proton multiplet at δ 7.08-7.11.

The stereochemistry of the thienothiopyran (**5a,b**) can be surmised from molecular model (Dreiding Model) of the molecule which shows a strain free *cis* arrangement (Scheme **3**).

1,4-bis-(3-thienylsulfanyl)but-2-yne (**4**) was prepared by the reaction between 1,4-dichlorobut-2-yne and 3-mercapto thiophene anion, which in turn was prepared from the reaction of 3-bromothiophene (**2**), *n*-butyl lithium and sulphur powder in anhydrous ether at –70ºC under inert atmosphere.

A close examination of the product **4** reveals that it also contains propargyl-thienyl sulphide moiety well situated for the Claisen rearrangement. The substrate **4** was also refluxed in DMF (151ºC) and the reaction was completed in 1h. Work up and purification by column chromatography furnished compound **6** as a viscous liquid in 72% yield.

The mechanistic rationale for the formation of compound **5a,b** from the substrate **3a,b** has been delineated in Scheme-**3**. Initial [3,3] sigmatropic rearrangement in **3** may give unstable intermediate allene derivative **7** which may immediately tautomerise to allenyl thiol **8**. [1,5] Hydrogen shift in **8** generates **9** which may then undergo a 6π-electrocyclic ring closure to give products **10**. These products **10** are unstable under the condition of the experiment. These products still possess allyl thienyl sulphide moieties and may undergo a further [3,3]



Scheme 3.

sigmatropic rearrangement and enolisation to give **11**. 5-*Exo* cyclisation of **11** may finally give products **5a,b**.

Similar rationalization also holds good for the formation of the product **6** from the substrate **4** as in case of **5(a,b)** from **3(a,b)**. It may be noted that so far to our knowledge no successful case of Claisen rearrangement of disulphide has been reported in the literature.

In conclusion, we, for the first time, have successfully performed sequential *thio*-Claisen rearrangement of the butynyl disulphide moiety of thiophene for the construction of [6,5] fused heterocycles. This methodology displayed appreciable regioselectivity and may prove useful in this type of synthesis. This methodology is attractive by its simplicity.

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SUPPORTING DATA

Experimental

IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer (ν_{max} in cm^{-1}) on KBr disks. UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^1H NMR (300 MHz, 500 MHz) and ^{13}C NMR (125.7 MHz) spectra were recorded on a Bruker DPX-300 and Bruker DPX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Mass spectra were recorded on a JEOL JMS-600 instrument. Silica gel [(60-120 mesh), Spectrochem] was used for chromatographic separation. Silica gel G [E-Merck] was used for TLC. Petroleum ether refers to the fraction boiling between 60ºC and 80ºC.

General Procedure for the Preparation of Compounds 3a,b

1.6 M *n*-BuLi (4.5mL, 6.77mmol) was added to thiophene (6.77mmol) in anhydrous ether at room temperature under nitrogen atmosphere. The solution was refluxed for 30min. and after that sulphur powder (216mg, 6.77mmol) was added to it in four portions at 0-5ºC. The reaction mixture was allowed to attain room temperature and added drop wise to a well-stirred ethereal solution (100mL) of 1,4-dichlorobut-2-yne (0.27g, 2.25mmol) during 30min. The stirring was continued for another 2h. The resulting reaction mixture was poured into NH_4Cl solution (75mL). The organic layer separated was washed with water (50mL), brine solution (50mL) and dried (Na_2SO_4). The crude product was purified by column chromatography over silica gel. The product was eluted with EtOAc-petroleum ether mixture (1:99).

1,4-bis-(2-thienylsulfanyl)but-2-yne 3a

Yield 80%; viscous liquid; UV (CH_2Cl_2) λ_{max}: 274, 239 nm; IR (neat) ν_{max}: 3099, 2909,1401, 1216 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz): δ 3.49 (s, 4H, -SC**H**$_2$), 6.97 (dd, *J* = 3.2, 5.2Hz, 2H, thiophene **H**), 7.20 (dd, *J* = 0.7, 3.5Hz, 2H, thiophene **H),** 7.37 (dd, *J* = 0.7, 5.2Hz, 2H, thiophene **H)**; ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 28.3, 80.6, 128.0, 130.9, 133.0,135.45 ; MS *m/z* 282 (M^+); Anal Calcd. For $C_{12}H_{10}S_4$: C, 51.02; H, 3.57; Found C, 51.15; H, 3.60%.

1,4-bis-(5-methyl-2-thienylsulfanyl)but-2-yne 3b

Yield 76%; viscous liquid; UV (CH_2Cl_2) λ_{max}: 276, 242 nm; IR (neat) ν_{max}: 3090, 2915,1395, 1215 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz): δ 2.45 (s, 6H, -CH_3), 3.45 (s, 4H, -SC**H**$_2$), 6.63 (d, *J* = 3.4Hz, 2H, thiophene **H**), 7.00 (d, *J* = 3.4Hz, 2H, thiophene **H)**; MS *m/z* 310 (M^+); Anal Calcd. For $C_{14}H_{14}S_4$: C, 54.15; H, 4.54; Found C, 54.39; H, 4.48%.

Preparation of 1,4-bis-(3-thienylsulfanyl)but-2-yne 4

1.6M *n*-BuLi (3.8mL, 6.09mmol) in anhydrous ether (50mL) was added to 3-bromothiophene (1g, 6.09mmol) in anhydrous ether (50mL) at –70ºC. After stirring for 15min, sulphur powder (194mg, 6.09mmol) was added in three portions. The reaction mixture was allowed to reach room temperature. This was then added to a well-stirred solution of 1,4-dichlorobut-2-yne(0.25g, 2.03mmol) in ether (30mL) during one hour and the stirring was continued for another two hr. The reaction mixture was then poured into NH_4Cl solution (50mL) and the organic layer separated was washed with water (50mL), brine solution (50mL) and dried (Na_2SO_4). Evaporation of the solvent gave a crude product which was purified by column chromatography over silica gel. The product was eluted with EtOAc-petroleum ether mixture (1:99).

Yield 75%; viscous liquid; UV (CH_2Cl_2) IR (neat) λ_{max}: 261, 229 nm; ν_{max}: 3102, 2909, 1403, 1232 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz): δ 3.53 (s, 4H, SC**H**$_2$), 7.07 (dd, *J* = 1.2, 5.0Hz, 2H, thiophene **H**), 7.26 (dd, *J* = 1.2, 2.9Hz, 2H, thiophene **H),** 7.30 (dd, *J* = 2.9, 5.0Hz, 2H, thiophene**H)**; MS *m/z* 282 (M^+); Anal Calcd. For $C_{12}H_{10}S_4$: C, 51.02; H, 3.57; Found C, 51.26; H, 3.43%.

General Procedure for the Synthesis of Compounds 5a,b & 6

Compound **3a,b** and **4** (100mg) was refluxed in DMF (3mL) for one hr. The reaction mixture was cooled and poured into water (30mL). This was extracted with $CHCl_3$ (3X 30mL) and dried (Na_2SO_4). Evaporation of the solvent afforded the crude product which was purified by column chromatography over silica gel. Elution of the column with petroleum ether gave compounds **5a,b** and **6**.

9a-methyl-5a,9a-dihydro-5H-thieno[2,3-b]thieno[3',2':4,5] thieno[2,3-d]thiopyran 5a

Yield 70%; Gummy Mass; UV (CH_2Cl_2) λ_{max}: 275, 230 nm; IR (neat) ν_{max}: 3101, 2917,1415, 1039 cm^{-1}; ^1H-NMR ($CDCl_3$, 300 MHz): δ 1.9 (s, 3H, angular **Me**), 2.8 (dd, *J* = 3.0, 12.8Hz, 1H, SC**H**$_2$), 3.14 (dd, *J* = 11.0, 12.8Hz, 1H, -SC**H**$_2$)**,** 3.30 (dd, *J* = 3.0, 11.0Hz, 1H, ring junction **H**), 6.91 (d, *J* = 5.0Hz, 1H, thiophene **H),** **6**.99 (d, *J* = 5.3Hz, 1H, thiophene **H),** 7.08-7.11 (m, 2H, thiophene **H**); ^{13}C NMR ($CDCl_3$, 125.7 MHz): δ 30.3, 31.2, 51.3, 68.5, 122.9, 123.2, 126.6, 127.1, 127.4, 137.2, 142.5 MS *m/z* 282 (M^+); Anal Calcd. For $C_{12}H_{10}S_4$: C, 51.02; H, 3.57; Found C, 50.95; H, 3.52%.

2,7,9a-trimethyl-5a,9a-dihydro-5H-thieno[2,3-b]thieno[3', 2':4,5]thieno[2,3-d]thiopyran 5b

Yield 75%; Gummy Mass; UV (CH_2Cl_2) λ_{max}: 276, 235 nm; IR (neat) ν_{max}: 3106, 2915,1409, 1037 cm^{-1}; ^1H-NMR ($CDCl_3$, 400 MHz): δ 1.83 (s, 3H, angular **Me**), 2.49 (s, 3H, -C**H**$_3$), 2.54 (s, 3H, -C**H**$_3$), 2.78 (dd, *J* = 2.7, 12.5Hz, 1H, SC**H**$_2$), 3.08 (dd, *J* = 11.3, 12.5Hz, 1H, -SC**H**$_2$)**,** 3.18 (dd, *J* = 2.7, 11.3Hz, 1H, ring junction **H**), **6**.56 (s, 1H, thiophene **H),** 6.62 (s, 1H, thiophene **H**); MS *m/z* 310 (M^+); Anal Calcd. For $C_{14}H_{14}S_4$: C, 54.15; H, 4.54; Found C, 53.92; H, 4.61%.

9a-methyl-5a,9a-dihydro-5H-thieno[3,2-b]thieno[2',3':4,5] thieno[2,3-d]thiopyran 6

Yield 72%; Gummy Mass; UV (CH_2Cl_2) λ_{max}: 280, 229 nm; IR (neat) ν_{max}: 3101, 2917,1410, 1171 cm^{-1}; ^1HNMR ($CDCl_3$, 300 MHz): δ 1.99 (s, 3H, angular **Me**), 2.83 (dd, *J* = 3.0, 13.0Hz, 1H, SC**H**$_2$), 3.2 (dd, *J* = 11.0, 13.0Hz, 1H, SC**H**$_2$), 3.40 (dd, *J* = 3.0, 11.0Hz, 1H, ring junction **H**), 6.70 (d, *J* = 5.2Hz, 1H, thiophene **H),** **6**.77 (d, *J* = 5.0Hz, 1H, thiophene **H),** 7.24-7.27 (m, 2H, thiophene **H**); MS *m/z* 282 (M^+); Anal Calcd. For $C_{12}H_{10}S_4$: C, 51.02; H, 3.56; Found C, 51.10; H, 3.62%.