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Facile Regioselective Synthesis of Benzofuran-Annulated Six-Membered Sulfur Heterocycles and the Occurrence of Thermal [1,3] Sigmatropic Rearrangement

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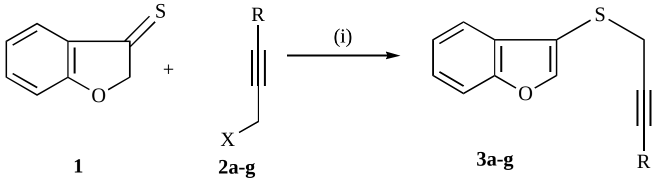
Abstract: Thio-Claisen rearrangement of a number of 3-(4-aryloxybut-2–ynlthio)benzofurans has been achieved under very mild conditions to give 2*H*-benzo[*b*]thiopyrano[2,3-*d*]furans. Attempts at further thio-claisen rearrangement resulted in the occurrence of thermal [1s, 3a] sigmatropic shift.

Keywords: Thio-Claisen rearrangement, [3,3] sigmatropic rearrangement, sulfur heterocycles, regioselective cyclization, [1,3] hydrogen shift.

The Claisen rearrangement since its discovery in 1912 [1] has become a powerful method for carbon–carbon bond formation. Much of its current popularity is due to the subsequent development of a series of new variants as well as versatile application in the synthesis of various heterocycles using oxy-, [2] aza-, [3] and thia- [4] Claisen rearrangement. We have recently reported the regioselective synthesis [5, 6] of thiopyrano and thieno[3,2-*c*]coumarins by the application of the sigmatropic rearrangement. In continuation of our ongoing research on [3,3] sigmatropic rearrangement of 4-(4' aryloxy-but-2'-ynylthio)-6-methyl pyran-2-one, [7] we have recently reported the regioselective synthesis of [6,6] pyranothiopyran [8]. The synthesis of sulfur heterocycles by radical cyclization [9] is also a regioselective but low yielding process due to *β*-fragmentation of the intermediate radical. Here we apply this simple methodology to different substrates for the formation of hitherto unreported sulfur heterocycles, 2*H*-benzo[b]thiopyrano[2,3-*d*]furan and its derivatives .

The starting materials 3-(4-aryloxybut-2-ynlthio)benzofuran **(3a-f)** and 3-propargylthio benzofuran (**3g**) were synthesized in 80-90 % yields by the phase transfer catalyzed alkylation of 3-(2*H*)-benzofuranthione (**1**), with 1-aryloxy-4-chlorobut-2-yne (**2a-f**) and propargyl bromide (**2g**), respectively, in dichloromethane and 1% aq. NaOH in the presence of benzyltriethylammonium chloride (BTEAC) at room temperature for 20 min. (Scheme **1**).

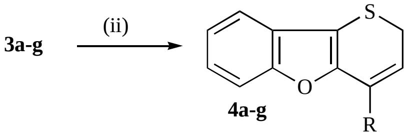
However the compounds **3a-g** are found to be very unstable and undergo [3,3] sigmatropic rearrangement at room temperature. As a result compounds **3a-g** could not be isolated in their pure state. For complete conversion the substrate **3a** was refluxed in dichloromethane (bp 39 ^{o}C) and the reaction was monitored by TLC. Complete conversion was achieved in 2 h. to afford the cyclic product **4a** [10] (85% yield) (Scheme **2**).



1 **2a-g** **3a-g**

a, R = 2,3-$Me_2C_6H_3OCH_2$, X = Cl
b, R = 4-$MeC_6H_4OCH_2$, X = Cl
c, R = 4-$MeOC_6H_4OCH_2$, X = Cl
d, R = 2,4-$Me_2C_6H_3OCH_2$, X = Cl
e, R = 2-$ClC_6H_4OCH_2$, X = Cl
f, R = 3,5-$Me_2C_6H_3OCH_2$, X = Cl
g, R = H, X = Br

Scheme 1. Reagents and conditions (i) BTEAC, 1% NaOH (aq), CH_2Cl_2, rt, 20 min.



4a-g

Scheme 2. Reagents and conditions (ii) CH_2Cl_2, reflux, 2h.

The structure of the compound **4a** was readily elucidated by ^{1}H NMR spectroscopy, which exhibited two proton doublets at δ_H = 3.65 (J = 5.3 Hz) and another two proton singlet at δ_H = 4.93 for S-C**H₂** and O-C**H₂** protons respectively and a one proton triplet at δ_H = 5.93 (J = 5.3 Hz, =C**H**). The ^{13}C-NMR spectrum of **4a** also supported the proposed structure. The mass spectrum of the compound **4a** showed the molecular ion peak at m/z: 322. Similar results were also obtained from other substrates **4b-g.**

The formation of the products **4a-g** may be rationalized by a [3,3] sigmatropic rearrangement of the propynyl vinyl sulfides to give allenyl intermediates **5**, which may undergo enolization to form allenyl-ene thiols **6**. Allenyl-ene thiols **6** through [1,5] hydrogen shift may give intermediate **7**, which

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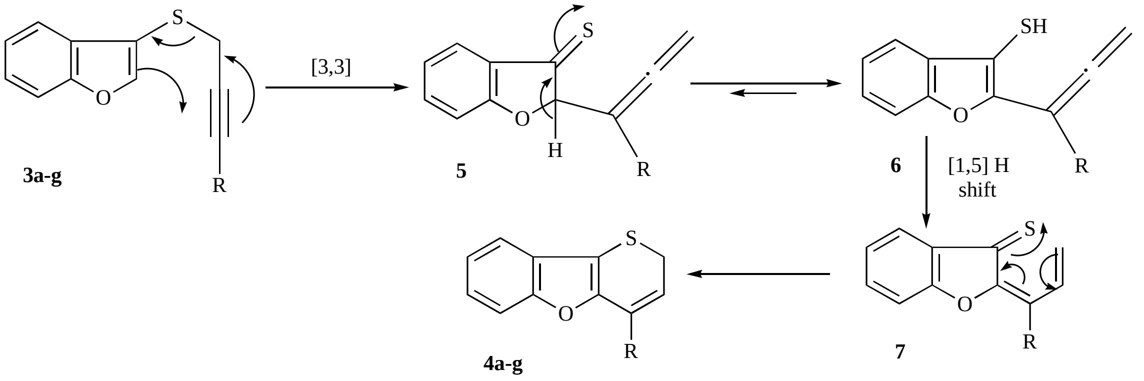
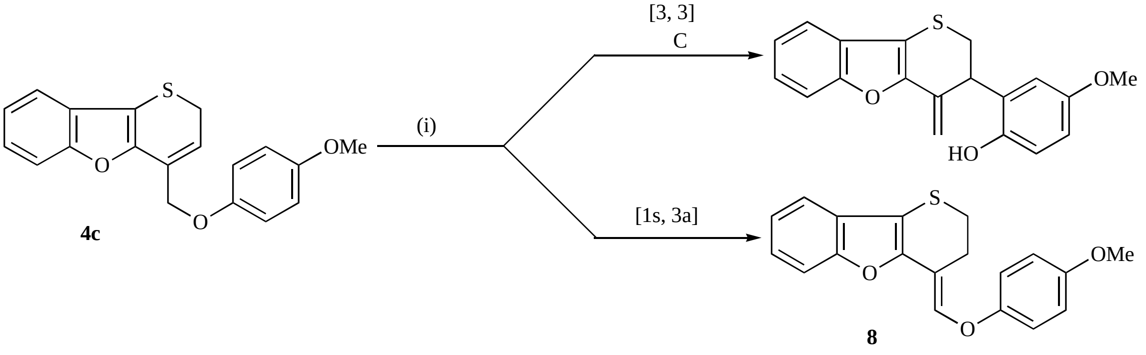


Scheme 3.



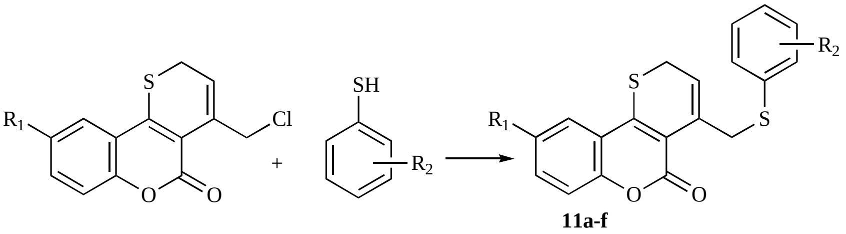
Scheme 4. Reagents and conditions, (i) 1,2-Dichlorobenzene, reflux, 3h.

may undergo an electrocyclic ring closure to provide the products **4a-g** (Scheme **3**).

The products **4a-f** are allyl-aryl ethers and therefore suitable substrates for the occurrence of a second Claisen rearrangement. However, this would require higher temperature than the first [3,3] sigmatropic rearrangement of compounds **3a-f**, as during this rearrangement the aromatic sextet of the aryl part will be disturbed. At higher temperature in refluxing 1,2-dichlorobenzene, (b.p. 180 °C) **4c** underwent [1,3] hydrogen shift and the endocyclic double bond of compound **4c** was transformed to an exocyclic double bond, giving product **8**. The expected [3,3] sigmatropic rearrangement was not observed (Scheme **4**).

Thermal sigmatropic [1,3] shifts are reported to be rare in the literature [11]. However, there are recent reports of thermal [1,3] sigmatropic rearrangement in the case of 2-crotylthiophene, [12] 1,3-dimethyl-5-(crotylthio)uracil, [13] 4-(prop-2-ynyloxy)quinolin-2[1*H*]-thiones, [14] and also in the rearrangement of 3-benzyloxymethylcoumarin to give hydroxylated-3-benzylcoumarins [15].

Similarly, a [1,3] hydrogen shift is also observed in the case of 4-(phenylthiomethyl)thiopyrano[3,2-*c*]chromen-

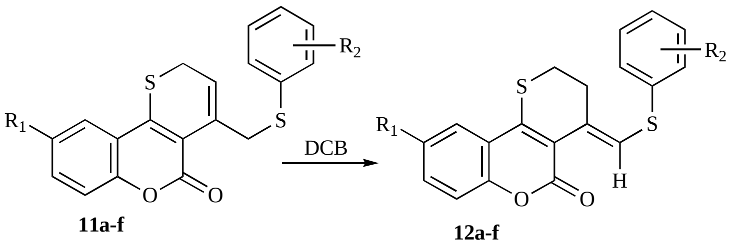


9a, $R_1 = CH_3$
9b, $R_1 = H$

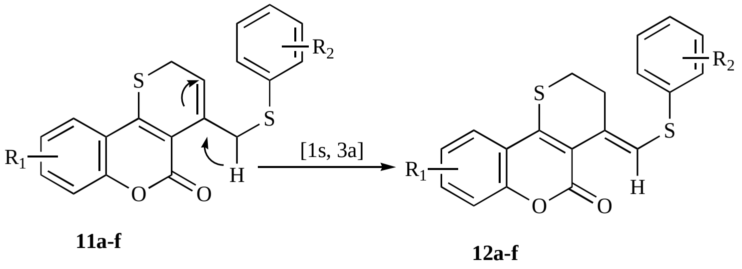
10a, R_2 = 2 - Br
10b, R_2 = 4 - CH_3
10c, R_3 = H

11	R_1	R_2
a	CH_3	2 - Br
b	CH_3	4 - CH_3
c	CH_3	H
d	H	2 - Br
e	H	4 - CH_3
f	H	H

Scheme 5. Reagents and conditions, (i) dry acetone, K_2CO_3, NaI, reflux, 1-1.5 h.



Scheme 6.



Scheme 7.

5(2*H*)-one derivatives (**11a-f**). 4-(phenylthiomethyl)thiopyrano [3,2-*c*]chromen-5(2*H*)-ones were in turn synthesized by the classical alkylation of 4-(chloromethyl)thiopyrano [3,2-*c*]chromen-5(2*H*)-ones (**9a,b**) with thiophenols (**10a-c**) in refluxing dry acetone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide (Finkelstein conditions [16]) for 1-1.5h (Scheme **5**). The substrates (**9a, b**) were in turn prepared according to the earlier published procedure [6].

Compound (**11a**) on refluxing in 1,2-dichlorobenzene (DCB) (b. p 180°C) for about 4-5 h underwent [1,3] hydrogen shift to produce 4-(phenylthiomethylene)-3,4-dihydrothiopyrano[3,2-*c*]chromen-5(2*H*)-one (**12a)** (Scheme **6**).

The structure of the compound **12a** was determined from its elemental analysis and spectroscopic data. Other substrates **11(b-f)** were similarly treated to give the products **12(b-f)** in overall excellent yields (80-96%).

The formation of the products **12(a-f)** from **11(a-f)** may be rationalized by the occurrence of a [1,3]-hydrogen shift to afford the products **12(a-f)** (Scheme **7**).

In conclusion, we have successfully performed a thio-Claisen rearrangement of the prop-2-ynyl vinyl sulfides using a very mild conditions to afford the tricyclic sulfur heterocycles. This methodology displays appreciable regioselectivity. The mildness of the reaction conditions and high degree of chemoselectivity of the methodology is notable. This methodology is a general one and is attractive by its simplicity.

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SUPPLEMENTARY MATERIAL

Supplementary material is available on the publishers Web site along with the published article.

REFERENCES AND NOTES

[1] Claisen, L. Über Umlagerung von Phenol-allyläthern in *C*-Allyl-phenole. *Chem. Ber.*, **1912**, *45*, 3157-3166.

[2] (a) Majumdar, K. C.; De, R. N, Khan, A. T.; Chattopadhyay, S. K.; Dey, K.; Patra. A. Studies of [3,3] sigmatropic rearrangements: Rearrangement of 3-(4-*p*-tolyoxybut-2-ynyloxy)[1]benzopyran-2-ones. *J. Chem. Soc. Chem. Comm.*, **1988**, 777-779. (b) Subramanian, R. S.; Balasubramanian, K. K. A novel synthesis of spirochromenes. *Tetrahedron Lett.*, **1989**, *30*, 2297-2300. (c) Majumdar, K. C.; Ghosh, S. K. Sequential [3,3] sigmatropic rearrangement of 7-(4-aryloxybut-2'-ynyloxy)[1]benzopyran-2-ones. *J. Chem. Res. (S)*, **1994**, 462-463; *(M)*, **1994**, 2601-2618. (d) Otter, B .A.; Suluja, S. S.; Fox, J. J. Pyrimidine XII. A propargyl Claisen rearrangement in the pyrimidine series. Synthesis of furo-and pyrano[3,2-*d*]pyrimidines. *J. Org. Chem.*, **1972**, *37*, 2858-2864.

[3] (a) Kurth, J.; Decker, O. H. W. Enantioselective preparation of 3-substituted 4-pentenoic acids *via* the Claisen rearrangement. *J. Org. Chem.*, **1985**, *50*, 5769-5775. (b) Majumdar, K. C.; Bhattacharrya, T. Synthesis of bioactive heterocycles: Sigmatropic rearrangement of 6-*N*-(4'-aryloxybut-2'-ynyl), *N*-methylamino-1,3-dimethylpyrimidine-2,4-dione. *Synthesis*, **2001**, 1568-1572. (c) Majumdar, K. C.; Bhattacharrya, T. Studies of bioactive heterocycles: Amino-Claisen rearrangement of 4-*N*-(4-aryloxybut-2-ynyl)*N*-methyl-aminoicoumarins. *Tetrahedron Lett.*, **2001**, *42*, 4231-4233. (d) Majumdar, K. C.; Ghosh, S. Studies of sigmatropic rearrangement: Synthesis of 4-aryloxy-methynlene-1,7-dimethyl-1,2,3-trihydropyrimidino[3,2-*c*]pyran-5-ones. *Tetrahedron*, **2001**, *57*, 1589-1592. (e) Danishefsky, S. J.; Phillips, G. B. A rapid route to ergot precursors *via* aza-Claisen rearrangement. *Tetrahedron Lett.*, **1984**, *25*, 3159-3162.

[4] (a) Majumdar, K. C.; Bandyopadhyay, A.; Biswas, A. Regioselective synthesis of pentacyclic heterocycles by sequential [3,3] sigmatropic rearrangement of 2-(4'-aryloxybut-2'-ynl-mercapto)thiochromen-4-ones. *Tetrahedron*, **2003**, *59*, 5289-5293. (b) Majumdar, K. C.; Jana, G. H. Synthesis of linear heterocycles: Thermal sigmatropic rearrangement of 4-(4-aryloxybut-2-ynyloxy[1]benzopyran-2-thiones. *Synthesis*, **2001**, 924-928. (c) Ellwood, A. R.; Mortimer, A. J. P.; Tocher, D. A.; Porter, M. J. Diastereoselective thia-Claisen rearrangement of pyrrolidinone-derived ketene *N*, *S*-acetals. *Synlett.*, **2008**, 2199-2209.

[5] Majumdar, K. C.; Ghosh, S. K. Studies of bioactive heterocycles: Facile thio-Claisen rearrangement of propargylthio[1]benzopyran-2-ones. *Tetrahedron Lett.*, **2002**, *43*, 2115-2117.

[6] Majumdar, K. C.; Ghosh, S. K. Studies in sulfoxide rearrangement: Regioselective synthesis of 3-(aryloxyacetal)-2,3-dihydrothieno[3,2-*c*][1]benzopyran-2-ones. *Tetrahedron Lett.*, **2002**, *43*, 2123-2125.

[7] Majumdar, K. C.; Kundu, U. K.; Ghosh, S. Regioselective synthesis of heterocycles by sigmatropic rearrangement: Passage to benzofuro[3,2-*c*]-6a,11a-dihydro-3,11a-dimethylthiopyranopyran-1-one. *J. Chem. Soc. Perkin Trans 1*., **2002**, 2139-2140.

[8] Majumdar, K. C.; Kundu, U. K.; Ghosh, S. K. Studies in sigmatropic rearrangement: Synthesis of [6,6] pyranothiopyran ring system by sequential Claisen rearrangement and pyridine hydrotribromide mediated regioselective “6-endo” cyclization. *Org. Lett*., **2002**, *4*, 2629-2631.

[9] Majumdar, K. C.; Biswas, A.; Mukhopadhyay, P. P. Carbon-carbon bond formation by radical cyclization: Regioselective synthesis of coumarin-annulated sulfer heterocycles. *Synthesis*, **2003**, 2385-2389.

[10] **General procedure for synthesis of 4a:** The dichloromethane solution of **3a** was refluxed for 2h. Solvent was evaporated and the reaction mixture was subjected to column chromatography over silica gel (60-120 mesh). The column was eluted with petroleum ether-ethylacetate (99:1) to afford the product **4a**.

Compound 4a: Yield: 85%, viscous liquid. IR(neat): ν_{max} = 1448, 1470, 1583 cm^{-1}. ^{1}H-NMR (CDCl$_3$, 400 MHz): δ_H = 2.20 (s, 3H, ArC$\mathbf{H_3}$), 2.30 (s, 3H, ArC$\mathbf{H_3}$), 3.65 (d, 2H, J = 5.3 Hz, -SC$\mathbf{H_2}$), 4.93 (s, 2H, -OC$\mathbf{H_2}$), 5.93 (t, 1H, J = 5.3 Hz, =C**H**), 6.84 (d, 2H, J = 7.8 Hz, Ar**H**), 7.09 (t, 1H, J = 7.8 Hz, Ar**H**), 7.25-7.33 (m, 2H, Ar**H**), 7.47 (t, 2H, J = 8.7 Hz, Ar**H**). ^{13}C-NMR (CDCl$_3$, 125 MHz): δ_C = 21.6, 25.3, 60.9, 104.7, 106.5, 109.7, 114.8, 117.8, 118.1, 118.2, 120.0, 120.7, 120.75, 120.8, 121.4, 124.0, 133.1, 144.1, 149.1, 151.4. MS: m/z = 322 (M$^+$). Anal. Calcd. for $C_{20}H_{18}O_2S$: C, 74.50; H, 5.63 %. Found: C, 74.74; H, 5.58 %.

[11] Gilchrist, T. L.; Storr, R. C.; In: *Organic Reactions and Orbital Symmetry*; Cambridge Univ. Press: Cambridge. **1979**, 257.

[12] Mortensen, J.Z.; Hedegward, B.; Lawesson, S. O. Thiophene chemistry-XVII: Thio-claisen-rearrangement of allyl thienyl sulphides. *Tetrahedron*, **1971**, *27*, 3831-3838.

[13] Majumdar, K. C.; Jana, N. K.; Bandyopadhyay, A.; Ghosh, S. K. Synthesis of purimidine-annelated heterocycles: Thermal rearrangement of 1,3-dimethyl-5-(prop-2-enyltho)pyrimidine-2,4-diones. *Synth. Commun*., **2001**, *31*, 2979-2985.

[14] Majumdar, K. C.; Ghosh, M.; Jana, M. Regioselective synthesis of thieno[2,3-*b*]quinolin-4(9*H*)-ones: Occurrence of thermal [1,3] sigmatropic rearrangement. *Synthesis*, **2002**, 669-673.

[15] Majumdar, K. C.; Saha, S.; De, R. N.; Ghosh, S. K. Sigmatropic rearrangement of 3-(aryloxymethyl)coumarins: A simple synthesis of hydroxylated-3-benzylcoumarin. *J. Chem. Soc. Perkin Trans. 1*., **1993**, 715-718.

[16] (a) Gazith, M.; Noys, R .M. Kinetics of the thermal and photochemical exchange between benzyl iodide and iodine. *J. Am. Chem. Soc*., **1955**, *77*, 6091-6098. (b) Gardner, I. J.; Noys, R. M. Effect of substitutents on the radical exchange reaction between benzyl iodide and iodine. *Ibid*., **1961**, *83*, 2409-2418.

[17] Majumdar, K. C.; Chattopadhyay, B.; Nath, S. Regioselective synthesis of benzofuran-annulated six-membered sulfer heterocycles by aryl radical cyclization. *Synth. Commun*., **2007**, *37*, 2907-2915.