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Studies in Sigmatropic Rearrangement: Synthesis of a [6,6]Pyranothiopyran Ring System by Sequential Claisen Rearrangement and Pyridine Hydrotribromide Mediated Regioselective "6-Endo" Cyclization†

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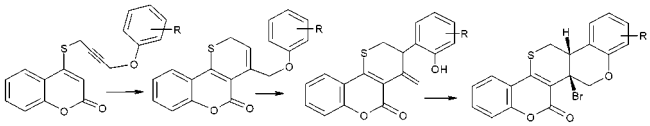
ABSTRACT



4-(4′-Aryloxybut-2′-ynylthio)[1]benzopyran-2-ones are refluxed in chlorobenzene to afford 4-aryloxymethylthiopyrano[3,2-*c*][1]benzopyran-5(2*H*)-ones which are subsequently subjected to heating in *o*-dichlorobenzene in the presence of *N*,*N*-diethylaniline and then treated with pyridine hydrotribromide to give [6,6]pyranothiopyrans in almost quantitative yield.

We have recently reported[1−5] the regioselective synthesis of pyrano- and furocoumarins and pyrido- and pyrrolocoumarins fused at the 3,4-position of the coumarin nucleus by the application of sigmatropic rearrangments. In continuation we have also successfully synthesized[6,7] thiopyrano and thieno [3,2-*c*] coumarins. In the case of studying the sigmatropic rearrangement of 4-(4′-aryloxybut-2′-ynyloxy)coumarins and 3-(4′-aryloxybut-2′-ynyloxy)coumarins, it was observed that the products of the first Claisen rearrangement contained a aryloxyallyl moiety for a further Claisen rearrangement and the second Claisen rearrangement did afford interesting results.[8,9] This has created our interest in undertaking a study on the sequential Claisen rearrangement of 4-(4′-aryloxybut-2′-ynylthio)coumarin. The substrate 4-(4′-aryloxybut-2′-ynylthio)coumarins **3a**−**d** for this purpose were synthesized in 70−80% yield by the phase transfer-catalyzed alkylation of 4-mercaptocoumarin with 1-chloro-4-aryloxybut-2-yne. Compounds **3a**−**d** are all solids and were characterized from their elemental analyses and spectral data[10] (Scheme 1).

Substrate **3a** was refluxed in chlorobenzene (132 °C) for 4 h to give a crystalline solid, **4a** (mp 186 °C), in 75% yield. This was characterized from its elemental analysis and spectral data.[11] The other substrates **3b**−**d** were also similarly treated to give products **4b**−**d**. Substrates **3a**−**d** possess two

† This paper is dedicated to Professor B. S. Thyagarajan of the University of Texas at San Antonio, Texas, on the occasion of his 75th birthday.

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(10) **Compound 3a:** mp 155 °C; yield 72%; UV (EtOH) λ_{max} 218, 273 nm; IR (KBr) ν_{max} 1700, 1590, 1230 cm^{-1}; ^{1}H NMR (300 MHz): δ 3.81 (t, 2H, J = 2 Hz), 4.78 (t, 2H, J = 2 Hz), 6.26 (s, 1H), 6.91−7.66 (m, 7H); *m*/*z* 394, 392, 390 (M^+). Anal. Calcd for $C_{19}H_{12}Cl_2O_3S$: C, 58.46; H, 3.07. Found: C, 58.59; H, 3.27.

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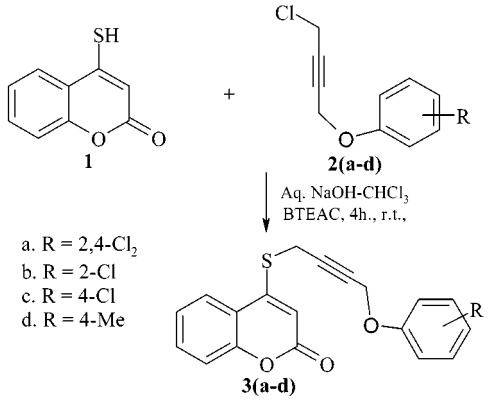
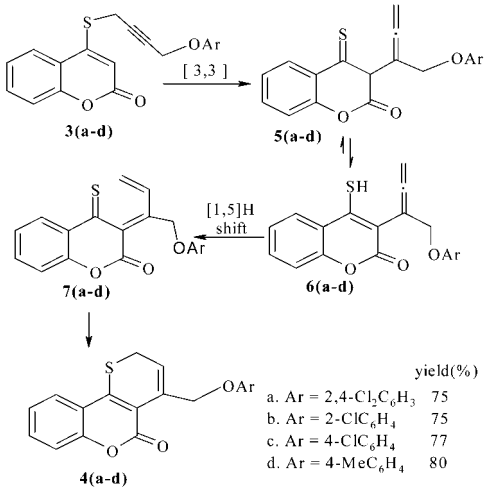
Scheme 1



potential sites for [3,3] sigmatropic rearrangement: an aryl propargyl ether moiety and a vinyl propargyl sulfide moiety. All the substrates underwent [3,3] sigmatropic rearrangement at the vinyl propargyl sulfide moiety to give thiopyrano-[3,2-*c*][1]benzopyran-5(2*H*)-ones. The formation of products **4a**−**d** from substrates **3a**−**d** may be easily explained by the [3,3] sigmatropic rearrangement of **3a**−**d** and rapid enolization to form the intermediate allenylene-thiols **6a**−**d** followed by [1,5] hydrogen shift and 6π-electrocyclic ring closure to give the products **4a**−**d** (Scheme 2).

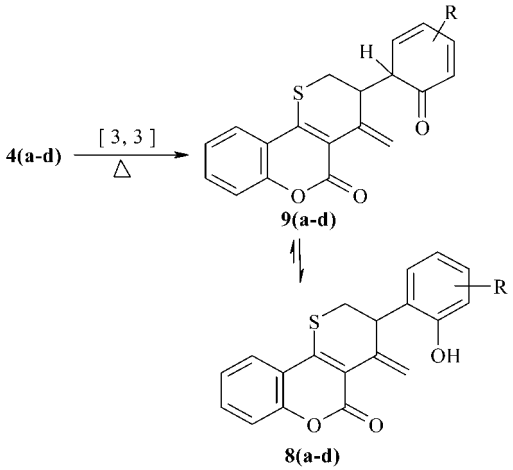
Scheme 2



Substrates **3a**−**d** on thermal rearrangement by heating in chlorobenzene (132 °C) could have yielded other types of products, e.g. 3-aryloxymethyl-2-methylthieno[3,2-*c*]coumarin[12] or 4′-aryloxybut-2′-ynyl-4-mercaptocoumarin[13] (by 1,3-radical shift) as a consequence of the usual course of rearrangement. It is remarkable to note that all the substrates **3a**−**d** studied in this instance regioselectively afforded exclusively products **4a**−**d**.

As products **4a**−**d** possess the aryl allyl ether moiety, these were subjected to heating in refluxing 1,2-dichlorobenzene in the presence of *N*,*N*-diethylaniline for 12−14 h to give phenolic products **8a**−**d**. These were characterized from their elemental analyses and spectral data.[14] Here again the isolation of phenolic product is quite unusual. In all other previous instances either the formation of cyclic products or the rearranged endo cyclic phenolic products were reported.[9,15] The formation of products **8a**−**d** from **4a**−**d** is easily explained by a [3,3] sigmatropic rearrangement followed by enolization (Scheme 3).

Scheme 3



Our target was to synthesize polyheterocyclic compounds. We had earlier used pyridine hydrotribromide[16] and hexamethylenetetramine hydrotribromide[17] for regioseletive cyclization of *o*-cyclohex-2-enyl phenols. We therefore treated products **8a**−**d** with 1 equiv of pyridine hydrotribromide in chloroform at 0−5 °C for 0.5 h to afford [6,6]pyranothiopyrans[18] **10a**−**d** in almost quantitative yield. The formation of products **10a**−**d** from **8a**−**d** is easily explained by the formation of a cyclic bromonium ion **11a**−**d** followed by a "6-endo" cyclization (Scheme 4).

(11) **Compound 4a:** mp 186 °C; yield 75%; UV (EtOH) λ_{max} 220, 360 nm; IR (KBr) ν_{max} 1690, 1580, 1240 cm^{-1}; ^{1}H NMR (300MHz) δ 3.47 (d, 2H, J = 6Hz), 5.18 (d, 2H, J = 1.0 Hz), 6.26 (tt, 1H, J = 1, 6 Hz), 6.91−7.85 (m, 7H); *m*/*z* 394, 392, 390 (M$^+$). Anal. Calcd for $C_{19}H_{12}Cl_2O_3S$: C, 58.46; H, 3.07. Found: C, 58.31; H, 3.17.

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(14) **Compound 8a:** mp 198 °C.; yield 75%; UV (EtOH) λ_{max} 220, 274, 334 nm; IR (KBr) ν_{max} 3390, 2910, 1670, 1600, 1210 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.33 (dd, J = 3.3, 12.6 Hz, 1H, SC*H*$_2$), 3.62 (dd, J = 7.1, 12.6 Hz, 1H, SC*H*$_2$), 4.40 (dd, J = 3.3, 7.1 Hz, 1H), 5.38 (s, 1H, =C*H*$_2$), 5.79 (s, 1H, =C*H*$_2$), 6.75−6.86 (m , 2H, Ar*H*) 7.28−7.33 (m, 2H, Ar*H*), 7.50−7.55 (m, 1H, Ar*H*), 7.72−7.75 (m, 1H, Ar*H*); MS *m*/*z* 394, 392, 390 (M$^+$). Anal. Calcd for $C_{19}H_{12}Cl_2O_3S$: C, 58.46; H, 3.07. Found: C, 58.32; H, 3.19.

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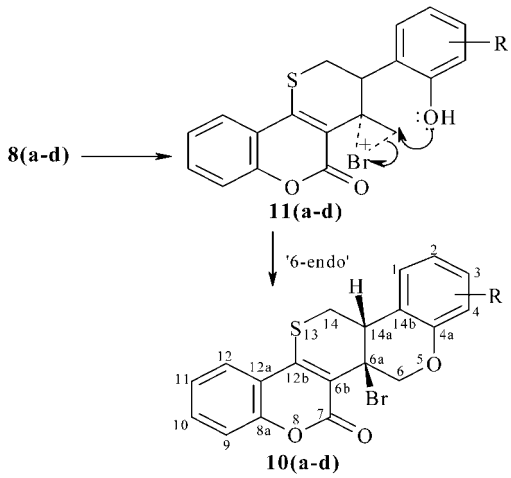
Scheme 4



The stereochemistry of the ring fusion of the cyclic system can only be surmised from molecular models (Dreiding Model) which show a strain free *cis*-arrangement.

In conclusion, all four substrates gave single products in each of the three steps used for the regioselective synthesis of the [6,6]pyranothiopyrans.This presents a simple synthesis of this type of ring system.

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Supporting Information Available: Experimental results for **3b-d**, **4b-d**, **8b-d**, and **10b-d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **Compound 10a:** mp 168 °C; yield 93%; UV (EtOH) λ_{max} 219, 280 nm; IR (KBr) ν_{max} 2910, 1700, 1190 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.87 (dd, J = 11.5,13.1 Hz,1H, SCH_2), 3.27 (dd, J = 4.2, 13.1 Hz, 1H, SCH_2), 3.65 (d, J = 9.9 Hz, 1H, −OCH_2), 4.12 (dd, J = 4.2, 11.5 Hz, 1H), 4.80 (d, J = 9.9 Hz, 1H, −OCH_2), 7.12−7.36 (m, 4H, Ar*H*), 7.58−7.81 (m, 2H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 29.05 (C_{14}), 34.78 (C_6), 48.15 (C_{14a}), 88.06 (C_{6a}), 116.18 (C_{14b}), 117.33 (C_9), 117.74 (C_{6b}), 118.08 (C_{12a}), 123.46 (C_{12}), 124.69 (C_{11}), 125.38 (C_1), 127.23 (C_4), 130.23 (C_3), 130.64 (C_2), 133.38 (C_{10}), 151.79 (C_{12b}), 152.56 (C_{8a}), 156.04 (C_{4a}), 157.22 (C_7); MS *m*/*z* 468, 470, 472, 474 (M^+). Anal. Calcd for $C_{19}H_{11}BrCl_2O_3S$: C, 48.71; H, 2.35. Found: C, 48.52; H, 2.29.