Pergamon

Tetrahedron Letters 43 (2002) 2115–2117

TETRAHEDRON LETTERS

Studies of bioactive heterocycles: facile thio-Claisen rearrangement of propargylthio[1]benzopyran-2-ones

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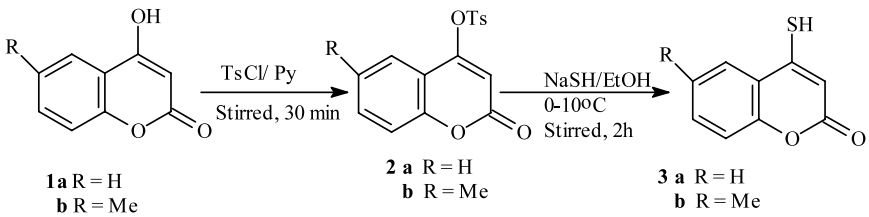
Received 3 October 2001; revised 3 January 2002; accepted 24 January 2002

Abstract—Hitherto unreported 2*H*-thiopyrano[3,2-*c*][1]benzopyran-5-ones **6a**–**f** are synthesized regioselectively in 79–85% yields by the thio-Claisen rearrangement of 4-propargylthio[1]benzopyran-2-ones **5a**–**f**. The substrates **5a**–**f** are synthesized by alkylation of hitherto unreported 4-mercaptocoumarins.

Coumarin and coumarin derivatives are reported to possess various physiological activities.[1–3] 3-Alkyl and 4-alkyl coumarins are well known[4] for their antithelmintic, hypnotic, insecticidal and antifungal activities and for their anticoagulant effect on blood and diuretic properties. Extensive work has been done on the synthesis[5] of these classes of compounds. Synthesis of pyrano[3,2-*c*][1]benzopyran-5(2*H*)-one derivatives and furo[3,2-*c*][1]-benzopyran-4-one derivatives have been reported[6–8] involving the Claisen rearrangement of propargyl ethers, 4-aryloxybut-2-ynyl ethers and allyl ethers of 4-hydroxycoumarin. Similarly pyrano[2,3-*c*][1]benzopyran-5(3*H*)-one derivatives and furo[2,3-*c*][1]benzopyran-4-one derivatives have been synthesized[6,9–12] from 3-propargyloxycoumarin, 3-[4-aryloxybut-2-ynyloxy][1]benzopyran-2-ones and 3-allyloxycoumarin by application of the Claisen rearrangement. Recently the amino-Claisen rearrangement of 4-[*N*-(4-aryloxybut-2-ynyl)-*N*-methylamino][1]-benzopyran-2-one has been reported.[13] Although the Claisen rearrangement has been studied in detail, the thio Claisen rearrangement at the 4-position of the coumarin nucleus has not been studied so far. This prompted us to undertake a study of the thio-Claisen rearrangement of 4-mercaptocoumarin analogues.

The tosyl derivatives **2a**,**b** of 4-hydroxycoumarin **1a** and 6-methyl-4-hydroxycoumarin **1b** were prepared by dissolving the corresponding 4-hydroxycoumarin in pyridine followed by addition of toluene-4-sulfonyl chloride with constant stirring at room temperature. These tosyl derivatives, on treatment with NaSH in ethanol at 0–10°C with vigorous stirring furnished the corresponding 4-mercaptocoumarins **3a**,**b** (Scheme 1).

When a two-phase mixture of (**3a**,**b**), propargyl halides **4a**–**d**, chloroform and 1% aqueous sodium hydroxide was stirred at room temperature in the presence of benzyltriethylammonium chloride (BTEAC) or tetrabutylammonium bromide (TBAB) the thiol **3a**,**b** disappeared within 4 h giving a single product (TLC monitoring) **5a**–**f** in 75–85% yields (Scheme 2).



Scheme 1.

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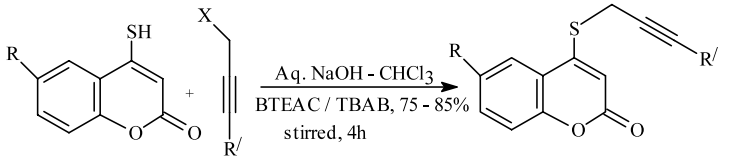


	X	R/
a	Br	H
b	Cl	CH_2Cl
c	Cl	CH_2OH
d	Cl	CH_2OAc

	R	R/	yield (%)
a	H	H	75
b	Me	H	78
c	H	CH_2Cl	82
d	Me	CH_2Cl	77
e	H	CH_2OH	75
f	H	CH_2OAc	85

Scheme 2.

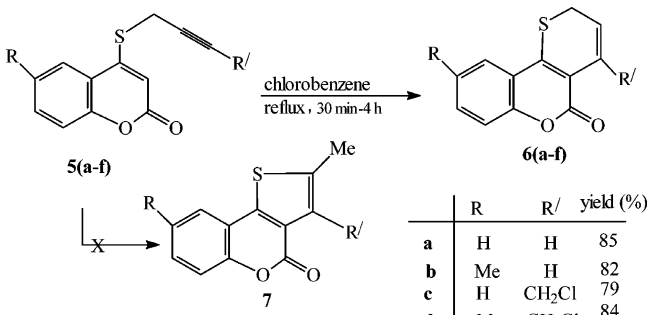
The use of BTEAC seems to give better yields of alkylated products than TBAB. The alkylation of **3a**,**b** under classical conditions using K_2CO_3 and acetone was also investigated for the preparation of **5a** and **5b** but the yield of products **5a** and **5b** was found to be lower (50–60%). Phase-transfer catalyzed alkylation is advantageous over classical alkylation as the reaction time is shorter and the yield of the *S*-alkylated product is higher.

Phase-transfer catalyzed alkylation of **3a**,**b** leads only to *S*-alkylated products **5a**–**f** unlike the case of anthrone,[14] 3-hydroxy-[1]-benzopyran-2(*H*)-one,[15] 4-hydroxy-[1]-benzopyran-2(*H*)-one[16,17] and 4-hydroxyquinolin-2(1*H*)-one.[18,19]

Compounds **5a**–**f** were characterized from their elemental analyses and spectroscopic data. The ^{1}H NMR spectrum of **5a** revealed a one proton triplet at δ 2.35 ($J=2$ Hz) due to the acetylenic proton, a two proton doublet at δ 3.82 ($J=2$ Hz) due to the -SC**H**$_2$-, a one proton singlet at δ 6.35 and a four proton multiplet at δ 7.15–7.70. The mass spectrum of compound **5a** showed a molecular ion peak at m/z 216 (M^+).

Substrate **5a** was refluxed in chlorobenzene for 30 min to give a crystalline solid **6a** in 85% yield. This was characterized from its elemental analysis and spectroscopic data. The ^{1}H NMR spectrum of **6a** revealed a two proton double doublet at δ 3.55 ($J=1$, 6 Hz) for the -SC**H**$_2$-, a one proton double triplet at δ 5.78 ($J=6$, 9 Hz) and a one proton double triplet at δ 6.80 ($J=1$, 9 Hz) due to the two protons of the thiopyran ring and a four proton multiplet at δ 7.19–7.75. The mass spectrum of **6a** showed a molecular ion peak at m/z 216 (M^+) (Scheme 3).

To test the generality of the reaction, the thermal rearrangement of five other sulfides **5b**–**f** were studied. Similar treatment of **5b**–**f** gave crystalline products **6b**–**f** in 79–85% yields. However, longer reaction times (4 h) were required for substrates **5c**–**f**. The products **6a**,**b** were obtained in 82–85% yield when the sulfides **5a**,**b** were refluxed in pyridine for 30 min. Similar results were also obtained when the substrates **5a**,**b** were refluxed in chlorobenzene in the presence of toluene-4-sulfonic acid. Substrate **5** on thermal rearrangement could have yielded



	R	R/	yield (%)
a	H	H	85
b	Me	H	82
c	H	CH_2Cl	79
d	Me	CH_2Cl	84
e	H	CH_2OH	85
f	H	CH_2OAc	83

Scheme 3.

either products **6** or **7** as a consequence of the usual course of the rearrangement. However, none of the substrates **5a**–**f** gave products of the type **7** (Scheme 3). The thermal thio-Claisen rearrangement is also known to be accompanied by 1,3-radical shifts.[20,21] The formation of **6a**–**f** from **5a**–**f** may be explained by the mechanism given in the preceding paper.[22]

It is interesting to note that the thermal rearrangement of the six sulfides studied so far exhibited regioselective ring closure in all the cases. Therefore, this is a general regioselective method for the synthesis of 2*H*-thiopyrano[3,2-*c*][1]benzopyran-5(2*H*)-one derivatives **6a**–**f**, in excellent yields.

Acknowledgements

We are thankful to CSIR (New Delhi) for financial assistance. One of us (S.K.G) is grateful to CSIR for a fellowship.

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