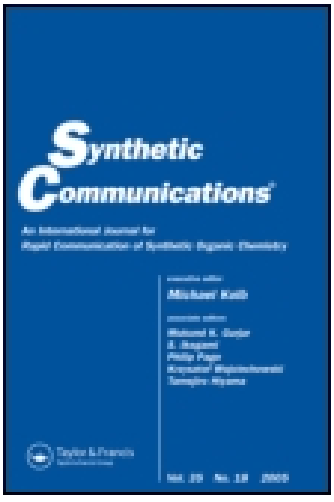

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Studies on Amine Oxide Rearrangement: Synthesis of Pyrrolo[3,2-c][1]benzothiopyran-4-one

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Studies on Amine Oxide Rearrangement: Synthesis of Pyrrolo[3,2-*c*][1]benzothiopyran-4-one

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Abstract: A methodology, based on tandem [2,3] and [3,3] sigmatropic rearrangement, has been described for the synthesis of hitherto unreported, potentially bioactive pyrrolo[3,2-*c*][1]benzothiopyran-4-ones (**6a**–**g**) derivatives.

Keywords: *m*-chloroperoxybenzoic acid, pyrrolo[3,2-*c*][1]benzothiopyran-4-ones, [2,3] and [3,3] sigmatropic rearrangement

INTRODUCTION

Synthesis of different coumarin derivatives fused with other heterocycles has been a subject of interest as a result of their interesting biological activity and photodynamic properties.[1] Literature reports a flurry of research work[2] depicting different methodologies for the synthesis of these classes of compounds as some members showed useful levels of biological activities.[3] We have recently reported a facile and high-yielding simple methodology for the construction of and pyrano- and furo-coumarins by the applications of the thermal [3,3] sigmatropic rearrangement.[4] Application of this methodology to other substrates[5] resulted in the formation of pyran and furan rings in a regioselective manner. Literature reports very little work on the synthesis of

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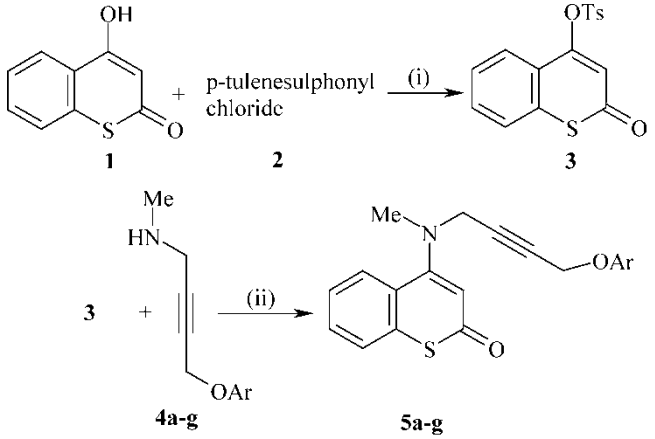
pyrrolo- and pyridino-analog of these heterocycles. This has encouraged us to undertake a study on the synthesis of pyrrolo[3,2-*c*][1]benzothiopyran-4-one derivatives from suitably substituted amines.

RESULTS AND DISCUSSION

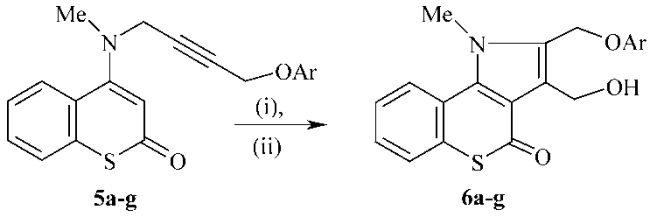
The starting material for the present investigation, 4-*N*-(4′-aryloxybut-2′-ynyl)-*N*-methylbenzothiopyran-2-ones (**4a**–**g**), were prepared in 75–90% yield by the reaction of 4-tosyloxybenzothiopyran-2-one (**3**) with (4-aryloxybut-2-ynyl)-*N*-rnethylamine (**4a**–**g**) in refluxing ethanol for 6 h (Scheme 1). 4-Tosyloxybenzothiopyran-2-one (**3**) was in turn prepared in 90% yield from the reaction of 4-hydroxybenzothiopyran-2-one (**1**) with *p*-toluenesulfonyl chloride (**2**) in the presence of pyridine (Scheme 1). Compounds **4a**–**g** were characterized from their elemental analysis and spectral data.

The tertiary amine **5a** was treated with *m*-chloroperoxybenzoic acid in dichloromethane at 0°C. The generated amine oxide intermediate, when allowed to stirr at room temperature for 12 h gave the pyrrolo[3,2-*c*][1]benzothiopyran-4-one derivative (**6a**) in 65% yield (Scheme 2). Compound **6a** was characterized from its elemental analysis and spectroscopic data. The ^{1}H NMR spectrum of **6a** displayed two two-proton singlets at δ 4.02 and



a. Ar = 4-BrC_6H_4 d. Ar = 4-$Me_3C_6H_4$
b. Ar = 4-$OMeC_6H_4$ e. Ar = 3,5-Me_2-4-ClC_6H_2
c. Ar = 3- MeC_6H_4 f. Ar = 2,4-$Me_2C_6H_4$
g. Ar = 2-BrC_6H_4

Scheme 1. Reagent and conditions: (i) dry pyridine, rt, stirring, 1 h; (ii) EtOH, reflux, 6 h.



5a-g **6a-g**

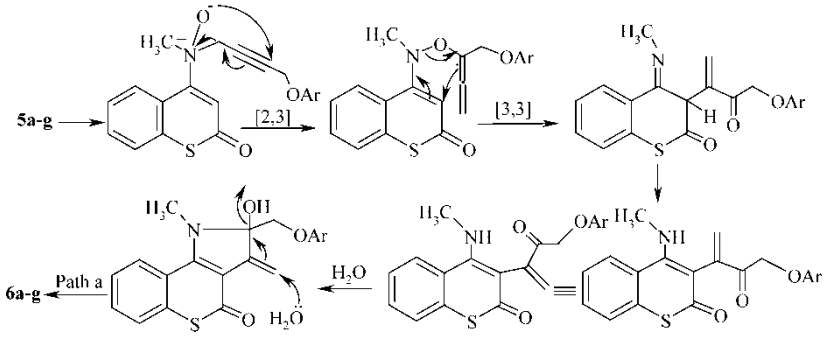
a. Ar = 4-BrC_6H_4 d. Ar = 4-$Me_3C_6H_4$
b. Ar = 4-$OMeC_6H_4$ e. Ar = 3,5-Me_2-4-ClC_6H_2
c. Ar = 3- MeC_6H_4 f. Ar = 2,4-$Me_2C_6H_4$
g. Ar = 2-BrC_6H_4

Scheme 2. Reagent and conditions: (i) *m*-CPBA, CH_2CI_2, 0 °C, 1 h; (ii) rt, stirring, 12 h.

4.65, indicating the presence of two methylene protons. The -*N*CH_3 protons appeared as a three-proton singlet at δ 2.94. Mass spectrum of **6a** showed a molecular ion peak at $m/z = 429$, 431 (M^+). The other substrates (**5b**–**g**) similarly afforded the pyrrolo [3,2-*c*][1]benzothiopyran-4-ones derivatives (**6b**–**g**) in 55–70% yield (Scheme 2).

The mechanism for the formation of **6a**–**g** from the corresponding tertiary amine **5a**–**g** can be explained by assuming a tandem [2,3] and [3,3] sigmatropic rearrangement sequence as described in, Scheme 3.

In conclusion we have demonstrated a broadly useful one-pot tandem rearrangement approach for the synthesis of pyrrole moiety fused at the 3,4-position of thiocoumarin moiety. To our knowledge this is the first report of the synthesis of fused pyrrolo[3,2-*c*][1]benzothiopyran-4-one (**6a**–**g**) heterocycles. The mildness of the reaction conditions makes this an attractive route for the synthesis of potentially bioactive pyrrolo[3,2-*c*][1]benzothiopyran-4-ones heterocycles.



Scheme 3.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer L 120-000A spectrometer (γ_{max} in centimeters^{-1}) using samples as neat liquids, solid samples were recorded in KBr disks, and UV absorption spectra were recorded in EtOH on a Shimadzu UV-2401PC spectrophotometer (λ_{max} in nm). ^{1}H NMR (300 MHz, 500 MHz) spectra were recorded on a Bruker DPX-300 and Bruker DRX-500 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Elemental analyses and mass spectra were recorded on a Jeol JMS600 instrument. Silica gel [(60–120 mesh), Spectrochem, India] was used far chromatographic separation. Silica gel G [E-Merck (India)] was used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80°C.

The 1-aryloxy-4-chlorobut-2-ynes were prepared according to the published procedure.[6]

General Procedure for the Preparation of 4-Tosyloxybenzothiopyran-2-one (3)

To a solution of 4-hydroxybenzothiopyran-2-one (**1**) (2 g, 11.23 mmol) in pyridine (5 mL), p-toluene sulphonyl chloride (**2**) (2.5 g, 13.15 mmol) was added, stirred for 1 h, and poured into ice. The reaction mixture was extracted with dichloromethane (3 × 10 mL), washed with water (2 × 10 mL) and brine (10 mL), and dried (Na_2SO_4). Removal of solvent gave the crude mass, which was column chromatographed on silica gel and eluted with 5% ethyl acetate in petroleum ether to afford the desired compound 4-tosyloxybenzothiopyran-2-one (**3**) (90%) as a white solid. Mp: 127°C. UV (EtOH): $\lambda_{max} = 222$, 234, 263, 291 nm. IR (KBr): $\nu_{max} = 818$, 1045, 1176, 1359, 1638, 3060 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.47$ (s, 3H, ArC**H**$_3$), 6.38 (s, 1H,=CH), 7.26–7.97 (m, 8H, Ar**H**). MS: $m/z = 332$ (M^+). Anal. calcd. for $C_{16}H_{12}O_4S_2$: C, 57.83; H, 3.61%. Found: C, 57.97; H, 3.97%.

General Procedure for the Synthesis of 4-*N*-(4′-Aryloxybut-2′-ynyl),*N*-methylthiopyran-2-ones (5a–g)

4-Tosyloxybenzothiopyran-2-one (**3**) (1 g, 3.01 mmol) and 1-aryloxy-4-*N*-methylaminobut-2-yne (**4a–g**) (5 mmol) in EtOH was heated under reflux on a water bath for 6 h and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), washed with brine (3 × 10 mL), dried (Na_2SO_4), and evaporated. The crude product was purified on silica gel by eluting with 10% ethyl acetate in petroleum ether to give compounds **5a–g**.

Compound 5a: Yield: 90%; viscous liquid. UV (EtOH): $\lambda_{max} =$ 204, 235, 264, 330 nm. IR (KBr): $\nu_{max} = 818, 1221, 1486, 1622, 2921, 3047\,cm^{-1}$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.92$ (s, 3H, *N*C**H**$_3$), 4.00 (s, 2H, *N*C**H**$_2$), 4.72 (s, 2H, OC**H**$_2$), 6.21 (s, 1H, =C**H**), 6.83–7.90 (m, 8H, Ar**H**). MS: m/z=413, 415 (M^+). Anal. calcd. for $C_{20}H_{16}NO_2SBr$: C, 77.29; H, 3.86, N, 3.38%. Found: C, 77.5; H, 4.05; N, 3.62%.

Compound 5b: Yield: 84% viscous liquid. UV (EtOH): $\lambda_{max} = 205, 235, 265, 330$ nm. IR (KBr): $\nu_{max} = 1038, 1211, 1506; 1615, 2906, 3061\,cm^2$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.92$ (s, 3H, *N*C**H**$_3$), 3.77 (s, 3H, OC**H**$_3$), 4.00 (s, 2H, *N*C**H**$_2$), 4.69 (s, 1H, OC**H**$_2$), 6.20 (s, 1H, =C**H**), 6.83–7.91 (m, 8H, Ar**H**). MS: m/z=365 (M^+). Anal. calcd. for $C_{21}H_{19}NO_3S$: C, 69.04; H, 5.20; N, 3.83%. Found: C, 69.22; H, 5.42; N, 3.99%.

Compound 5c: Yield: 75%; viscous liquid. UV (EtOH): $\lambda_{max} = 204, 238, 263, 328$ nm. IR (KBr): $\nu_{max} = 1153, 1214, 1488, 1615, 2918, 3055\,cm^{-1}$ ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.33$ (s, 3H, ArC**H**$_3$), 2.93. (s, 3H, *N*C**H**$_3$), 4.00 (s, 2H, *N*C**H**$_2$), 4.73 (s, 1H, OC**H**$_2$), 6.20 (s, 1H,=C**H**), 6.76–7.91 (m, 8H, Ar**H**). MS: $m/z = 349$ (M^+). Anal. calcd. for $C_{21}H_{19}NO_2S$: C, 72.20; H, 5.44; N, 4.01%. Found: C, 72.45; H, 5.61; N, 4.24%.

Compound 5d: Yield: 75% viscous liquid. UV (EtOH): $\lambda_{max} = 206, 238, 265, 330$ nm. IR (KBr): $\nu_{max} = 1221, 1512, 1622, 2904, 3060\,cm^{-1}$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.29$ [s, 9H, ArC(C**H**$_3$)$_3$], 2.92 (s, 3H, *N*C**H**$_3$), 4.00 (s, 2H, *N*C**H**$_2$), 4.73 (s, 1H, OC**H**$_2$), 6.21 (s, 1H, =C**H**), 6.86–7.91 (m, 8H, Ar**H**). MS: m/z=391 (M^+). Anal. calcd. for $C_{24}H_{25}NO_2S$: C, 73.65; H, 6.39; N, 3.58%. Found: C, 73.81; H, 6.60; N, 3.82%.

Compound 5e: Yield: 85%; viscous liquid. UV (EtOH): $\lambda_{max} = 205, 235, 261, 330$ nm. IR (KBr): $\nu_{max} = 769, 1161, 1214, 1471, 1615, 2921\,cm^{-1}$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.33$ [s, 6H, Ar(C**H**$_3$)$_2$], 2.93 (s, 3H, *N*C**H**$_3$), 4.00 (s, 2H, *N*C**H**$_2$), 4.70 (s, 2H, OC**H**$_2$), 6.20 (s, 1H, =C**H**), 6.62–7.91 (m, 6H, Ar**H**). MS: m/z=397, 399 (M^+). Anal. calcd. for $C_{22}H_{21}NO_2SCI$: C, 66.33; H, 5.20; N, 3.51%. Found: C, 66.51; H, 5.44; N, 3.78%.

Compound 5f: Yield: 87% viscous liquid. UV (EtOH): $\lambda_{max} = 204, 238, 265, 331$ nm. IR (KBr): $\nu_{max} = 769, 1214, 1503, 1624, 2920\,cm^{-1}$. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.2$ (s, 3H, C**H**$_3$), 2.26 (s, 3H, *N*C**H**$_3$), 2.92 (s, 3H, *N*C**H**$_3$), 3.99 (s, 2H, –*N*C**H**$_2$), 4.73 (s, 2H, OC**H**$_2$), 6.20 (s, 1H, =C**H**), 6.81–7.92 (m, 7H, Ar**H**). MS: m/z=363 (M^+). Anal. calcd. for $C_{22}H_{21}O_2SN$: C, 72.72; H, 5.78; N, 3.85%. Found: C, 72.97; H, 5.97; N, 4.04%.

Compound 5g: Yield: 87%; viscous liquid. UV (EtOH): $\lambda_{max} = 769, 109, 206, 238, 264, 330$ nm. IR (KBr): $\nu_{max} = 1221, 1476, 1614, 2924, 3064\,cm^{-1}$. ^1H NMR ($CDC1_3$, 300 MHz): $\delta_H = 2.92$ (s, 3H, *N***CH**$_3$), 4.00

(s, 2H, *N*C**H**$_2$), 4.83 (s, 2H, OC**H**$_2$), 6.20 (s, 1H, =C**H**), 6.81–7.92 (m, 7H, Ar**H**). MS: m/z: 413, 415 (M^+). Anal. calcd. for $C_{20}H_{16}NO_2SBr$: C, 77.29; H, 3.86; N, 3.38%. Found: C, 77.47; H, 4.11; N, 3.59%.

General Procedure for the Preparation of Pyrrolo[3,2-*c*][1]benzothiopyran-4-ones (6a–g)

To a stirred solution of **5a–g** (0.24 mmol) in dichloroethane (25 mL) at 0–5°C, *m*-chloroperoxybenzoic acid (50%, 125 mg, 0.72 mmol) in dichloromethane (25 mL) was added over a period of 1 h. After 12 h the reaction mixture was washed with a saturated solution of sodium carbonate (3 × 20 mL) and brine (20 mL) and dried (Na_2SO_4). Solvent was evaporated and chromatographed over silica gel using 15% ethyl acetate in petroleum ether as eluant to give **6a–g**.

Compound 6a: Yield: 72%; viscous liquid. UV (EtOH): $\lambda_{max} = 227$, 272, 290, 323 nm. IR (KBr): $\nu_{max} = 755$, 1235, 1487, 1587, 2926, 3232 cm^{-1}. ^{1}H NMR ($CDCl_3$, 360 MHz): $\delta_H = 2.94$ (s, 3H, –*N*C**H**$_3$), 4.02 (s, 2H, –OC**H**$_2$), 4.65 (s, 2H, –OC**H**$_2$), 6.58–8.39 (m, 8H, Ar**H**). MS: $m/z = 429$, 431 (M^+). Anal. calcd. for $C_{20}H_{16}NO_3SBr$: C, 55.81; H, 3.72; N, 3.24%. Found, C, 56.02; H, 3.8; N, 3.42%.

Compound 6b: Yield: 65%; viscous liquid. UV (EtOH): $\lambda_{max} = 230$, 290, 326 nm. IR (KBr): $\nu_{max} = 1034$, 1223, 1507, 1610, 2930, 3375 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.75$ (s, 3H, –*N*C**H**$_3$), 3.77 (s, 3H, –OC**H**$_3$), 4.05 (s, 2H, –OC**H**$_2$), 4.40 (s, 2H, –OCH$_2$), 6.73–7.70 (m, 8H, Ar**H**). MS: $m/z = 381'(M^+)$. Anal. calcd. for $C_{21}H_{19}NO_4S$: C, 66.14; H, 4.98; N, 3.67%. Found: C, 66.30; H, 5.20; N, 3.88%.

Compound 6c: Yield: 62%; viscous liquid. UV (EtOH): $\lambda_{max} = 225$, 270, 326 nm. IR (KBr): $\nu_{max} = 1029$, 1258, 1488, 1582, 2919, 3357 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.32$ (s, 3H, ArC**H**$_3$), 2.99 (s, 3H, –*N*C**H**$_3$), 4.03 (s, 2H, –OC**H**$_2$), 4.67 (s, 2H, –OC**H**$_2$), 6.72–8.18 (m, 8H, Ar**H**). MS: $m/z = 365$ (M^+), Anal. calcd. for $C_{21}H_{19}NO_3S$: C, 69.04; H, 5.20; N, 3.83%. Found: C, 69.19; H, 5.39; N, 3.97%.

Compound 6d: Yield: 55%; viscous liquid. UV (EtOH): $\lambda_{max} = 205$, 224, 319 nm. IR (KBr): $\nu_{max} = 1051$, 1238, 1584, 1609, 2961, 3374 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 1.30$ [s, 9H, Ar**C** (C**H**$_3$)$_3$], 2.98 (s, 3H, –*N*C**H**$_3$), 4.03 (s, 2H, –C**H**$_2$), 4.66 (s, 2H, –OC**H**$_2$), 6.85–8.18 (m, 8H, –Ar**H**). MS: $m/z = 407$ (M^+), Anal. calcd. for $C_{24}H_{25}NO_3S$: C, 70.76; H, 6.14; N, 3.43%. Found: C, 70.99; H, 6.31; N, 3.65%.

Compound 6e: Yield: 68%; viscous liquid. UV (EtOH): λ_{max} 204, 230, 340 nm. IR (KBr): $\nu_{max} = 760$, 1163, 1216, 1470, 1587, 2917, 3383 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.35$ [s, 9H, Ar(C**H**$_3$)$_2$], 2.97 (s, 3H, -NC**H**$_3$), 4.02 (s, 2H, –OC**H**$_2$), 4.65 (s, 2H, –OC**H**$_2$), 6.57–8.13 (m, 6H,

Ar**H**). MS: $m/z = 413, 415$ (M^+). Anal. calcd. for $C_{22}H_{20}NO_3SCl$: C, 63.76; H, 4.83; N, 3.38%. Found: C, 63.97; H, 5.01; N, 3.58%.

Compound 6f: Yield: 64%; viscous liquid. UV (EtOH): λ_{max}= 204, 217, 272, 337 nm. IR (KBr): $\lambda_{max} = 1027$, 1219, 1580, 2921, 3356 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.18$ (s, 3H, ArC**H**$_3$), 2.25 (s, 3H, ArC**H**$_3$), 2.97 (s, 3H, $-N$C**H**$_3$), 4.01 (s, 2H, $-$OC**H**$_2$), 4.66 (s, 2H, $-$OC**H**$_2$), 6.76–8.16 (m, 7H, Ar**H**). MS: $m/z = 379$ (M^+). Anal. calcd. for $C_{22}H_{21}NO_3S$: C, 69:65; H, 5.54; N, 3.69%. Found: C, 69.83; H, 5.78; N, 3.85%.

Compound 6g: Yield: 68%; viscous liquid. UV (EtOH): $\lambda_{max} = 206$, 305, 342, 360 nm. IR (KBr): $\nu_{max} = 769$, 1032, 1242, 1435; 1586, 2925, 3340 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): $\delta_H = 2.95$ (s, 3H, $-N$C**H**$_3$), 4.01 (s, 2H, $-$OC**H**$_2$), 4.82 (s, 2H, $-$OC**H**$_2$), 6.84–8.17 (m, 7H, Ar**H**). MS: $m/z = 429, 431(M^+)$. Anal. ca1cd. for $C_{20}H_{16}NO_3SBr$: C, 55.81; H, 3.72; N, 3.24%. Found: C, 55.99; H, 3:96; N, 3.46%.

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