Monatshefte für Chemie 135, 581–587 (2004)
DOI 10.1007/s00706-003-0109-y

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

Synthesis of Sulfur Heterocycles by Thio-*Claisen* Rearrangement

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Received August 14, 2003; accepted August 14, 2003
Published online April 14, 2004

Summary. 7-Chloro-4-hydroxydithiocoumarin was alkylated with allylic halides under phase transfer catalysis condition in the presence of *TBAB* or *BTEAC* in chloroform-aqueous NaOH (1%) at room temperature. 2,3-Dichloroprop-2-ene on similar treatment with 7-chloro-4-hydroxydithiocoumarin afforded 2-methylthieno[2,3-*b*]thiochromen-4-one in 65% yield. The S-alkylated thiochromen-4-ones were then refluxed in quinoline to give 7-chloro-2,3-dihydrothieno[2,3-*b*]thiochromen-4-ones or 7-chloro-2,3,4-trihydrothiopyrano[2,3-*b*]thiochromen-5-ones or 7-chloro-2,3-dihydro-3-vinylthieno[2,3-*b*]thiochromen-4-one.

Keywords. Allylic halides; 7-Chloro-4-hydroxydithiocoumarin; Phase transfer catalysed alkylation; [3,3] Sigmatropic rearrangement; Thio-*Claisen* rearrangement.

Introduction

The thieno[2,3-*b*]thiochromen-4-one moiety is present in a series of drugs [1] used for the treatment of psychotic disturbances. Patent reports give a long route [2] for the synthesis of this important intermediate. In continuation of our work on the [3,3] sigmatropic rearrangement [3] we studied the thio-*Claisen* rearrangement [4] because the latter [5] and aza-*Claisen* rearrangements [6] are much less studied compared to their oxygen [7] counterpart. We have recently reported the synthesis of a number of sulfur heterocycles [8] using 4-hydroxydithiocoumarin as the starting material. This has motivated us to undertake a study on the *thio-Claisen* rearrangement of 4-allylmercaptothiochromen-4-one derivatives. The results are reported here.

Results and Discussion

The substrates for this investigation, 2-allylthio-7-chlorothiochromen-4-ones (**3a**–**3d**) were prepared in 85% yield by phase transfer catalysed alkylation [9] of

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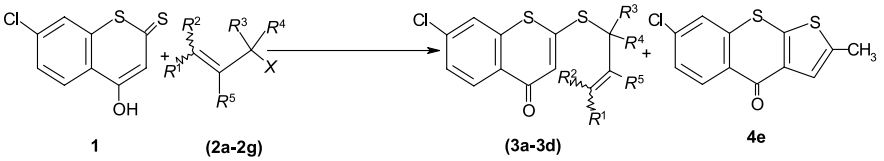


2	R^1	R^2	R^3	R^4	R^5	X
a	CH_3	H	H	H	H	Br
b	*Ph*	H	H	H	H	Br
c	CH_3	CH_3	H	H	H	Br
d	CH_2Cl	H	H	H	H	Cl
e	H	H	CH_3	CH_3	H	Br
f	H	H	CH_3	H	H	Br
g	H	H	H	H	Cl	Cl

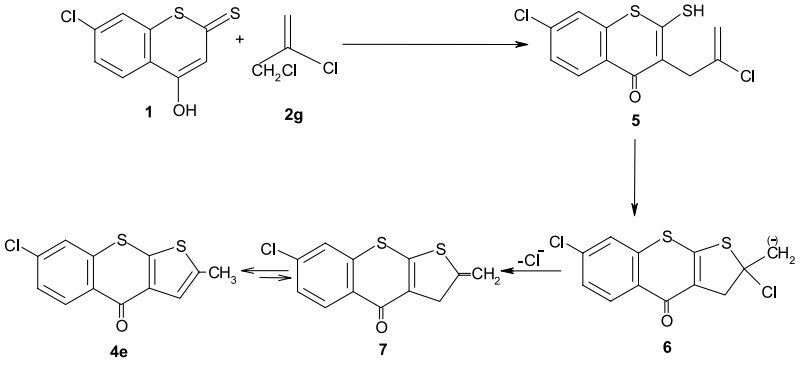
3	R^1	R^2	R^3	R^4	R^5
a	CH_3	H	H	H	H
b	*Ph*	H	H	H	H
c	CH_3	CH_3	H	H	H
d	CH_2Cl	H	H	H	H

Scheme 1

7-chloro-4-hydroxydithiocoumarin (**1**) with different allyl halides **2a**–**2f** in the presence of a catalytic amount of tetrabutylammonium bromide (*TBAB*) or benzyltriethylammonium chloride (*BTEAC*) in chloroform – aqueous sodium hydroxide (1%) at room temperature for 5 h. In the case of 2,3-dichloropropene (**2g**) the cyclized product 2-methylthieno[2,3-*b*]-4*H*-thiochromen-4-one (**4e**) was obtained in 65% yield. Halides **2a** and **2f** gave the same sulfide **3a** by S_N2 and S_N2' mechanisms. Similarly **2c** and **2e** gave the same sulfide **3c** (Scheme 1).

The formation of **4e** from **1** and **2g** may be explained by C-alkylation of **1** to give intermediate **5**, which in the presence of a base cyclizes to **6**. The intermediate **6** may instantaneously eliminate a chloride ion to give **7** and subsequent tautomerization (1,3 H-shift) provides 2-methylthieno[2,3-*b*]-4*H*-thiochromen-4-one (**4e**) (Scheme 2).

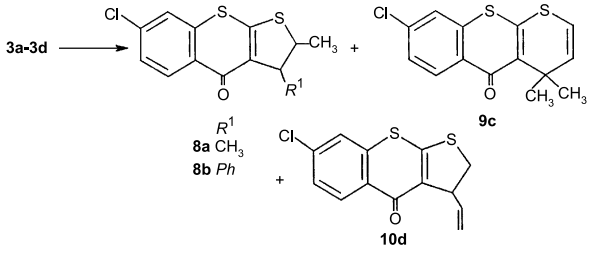
Recently we have reported the thio-*Claisen* rearrangement of 4-propargylthiocoumarin [10] and 4-propargylthioquinolone derivatives [11] in chlorobenzene. We have also reported [5] the thio-*Claisen* rearrangement of 5-allylthiouracil derivatives in *N,N*-diethylaniline. The thio-*Claisen* rearrangement of 2-(aryloxybut-2-ynylthio)-4*H*-thiochromen-4-ones was also successfully achieved [8d] in chlorobenzene.



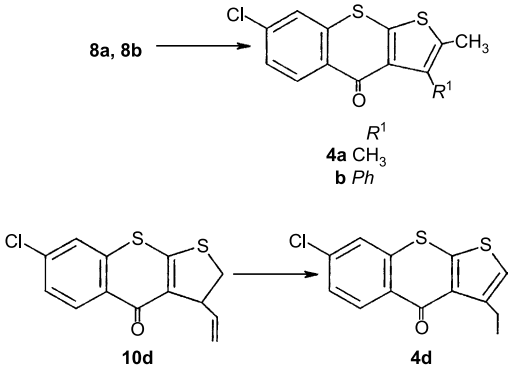
Scheme 2

Substrate **3a** was therefore refluxed in chlorobenzene. The reaction was monitored by TLC. No change was observed. This was then refluxed in 1,2-dichlorobenzene (179°C) and also in *N,N*-diethylaniline (216°C). No appreciable change was observed. So, it was heated in quinoline (238°C) for 1 h. A white crystalline solid of mp 85°C was obtained in 80% yield. This was characterized as 7-chloro-2,3-dihydro-2,3-dimethylthieno[2,3-*b*]-4*H*-thiochromen-4-one (**8a**) from its elemental analysis and spectral data. Substrate **3b** on similar treatment afforded **8b** in 70% yield. However, when **3c** was similarly heated in quinoline a product different from the anticipated one was obtained in 70% yield. This was characterized as 7-chloro-2,3,4-trihydrothiopyrano[2,3-*b*]-4*H*-thiochromen-5-one (**9c**) from its elemental analysis and spectral data. Another new product, 7-chloro-2,3-dihydro-3-vinylthieno[2,3-*b*]thiochromen-4-one (**10d**) was obtained in 70% yield when **3d** was treated similarly in quinoline for 1 h (Scheme 3). This compound was also characterized from its elemental analysis and spectral data. Products **8a** and **8b** were dehydrogenated with palladised charcoal (10%) in boiling diphenyl ether for 2–3 h to give thieno[2,3-*b*]-4*H*-thiochromen-4-ones **4a** and **4b** in 70% and 80% yield. However, an attempt to dehydrogenate product **10d** under similar conditions resulted mostly in decomposition giving a low yield of **4d** (Scheme 4).

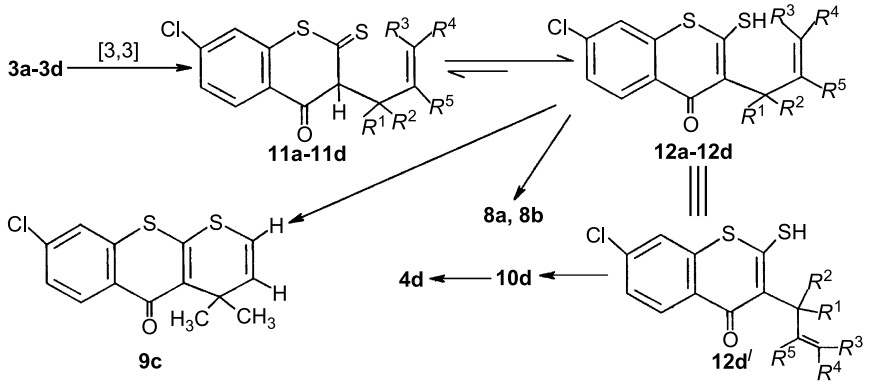
The formation of different products from the substrates **3a**–**3d** may be explained by an initial [3,3] sigmatropic rearrangement followed by rapid enolization to give allyl-ene-thiols **12a**–**12d** and subsequent base (quinoline) catalysed cyclization gives **8a**, **8b**, and **9c** from **12a**, **12b**, and **12c**, respectively. Intermediate **12d** can be rewritten as an equivalent structure **12d′** by rotating the single bond and



Scheme 3



Scheme 4



Scheme 5

base catalysed cyclization may give product **10d**. Conpound **10d** may give **4d** by two consecutive 1,3-prototropic shifts (Scheme 5).

Thermal thio-*Claisen* rearrangement is known to accompany [1,3] radical shift [4, 11, 12]. However, in the present instance, only [3,3] sigmatropic rearrangement was observed without occurrence of any such [1,3] radical migration. This reaction thus results in a simple synthesis of thieno[2,3-*b*]thiochromen-4-one derivatives.

Experimental

UV absorption spectra were recorded on a UV-VIS Spectrophotometer Shimadzu Model No. UV-2401PC (absolute ethanol). IR spectra were taken in KBr discs on a Perkin-Elmer 1330 apparatus and FTIR spectrophotometer Perkin-Elmer Model No. L120-000A. ^{1}H NMR spectra were recorded in $CDCl_3$ with *TMS* as internal standard on a Bruker AC-250 (300 MHz) and Bruker DRS-500 (600 MHz) spectrometers. Mass spectra were recorded on a JEOL D-300 (El) instrument and elemental analyses (agreeing within the error with calculated values) at RSIC(CDRI) Lucknow. Silica gel (60–120) was obtained from Spectrochem. Extracts were dried over anhydrous Na_2SO_4.

Alkylation of 7-Chloro-4-hydroxydithiocoumarin [11]

To a mixture of 1 g of **1** (6 mmol) and 12 mmol of allyl halide (*RX*, X = Br, Cl) **2a**–**2g** in 50 cm^3 of chloroform is added a solution of 0.25 mmol of *TBAB* or 0.9 mmol of *BTEAC* in 50 cm^3 of 1% aq. NaOH and the mixture was stirred at room temperature for 5 h. The mixture was then diluted with 100 cm^3 of H_2O and extracted with 3×25 cm^3 of $CHCl_3$. The organic layer was washed with 3×25 cm^3 of brine and dried (Na_2SO_4). The solvent was removed *in vacuo* and the residual crude mass was purified by chromatography over silica gel using benzene/petroleum ether (1/2) as eluent to afford the following compounds **3a**–**3d** and **4e**.

2-(But-2-enylsulfanyl)-7-chloro-4H-thiochromen-4-one (**3a**, $C_{13}H_{11}ClOS_2$)

Yield 1.05 g (85%); white solid; mp 115°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.69$–1.72 (d, $J = 6.3$ Hz, C**H**$_3$), 3.68–3.70 (d, $J = 7$ Hz, SC**H**$_2$), 5.48–5.57 (m, SCH$_2$CH=C***H***), 5.73–5.84 (m, SCH$_2$C***H***=CH), 6.94 (s, C$_3$–***H***), 7.26–7.50 (m, 2Ar**H**), 8.42 (d, $J = 8.5$ Hz,1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1630$, 1460 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 270 (3.343), 255 (3.593), 210 (3.129) nm; MS: $m/z = 284$, 282 (M$^+$).

2-(3-Phenylprop-2-enylsulfanyl)-7-chloro-4H-thiochromen-4-one (**3b**, $C_{18}H_{13}ClOS_2$)

Yield 1.13 g (75%); white solid; mp 120°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.90$–3.92 (d, $J = 7$ Hz, SC**H**$_2$), 6.18–6.28 (m, $SCH_2C\boldsymbol{H}$=CH), 6.62–6.68 (d, $J = 15$ Hz, SCH_2CH=C***H***), 7.00–7.59 (m, 7Ar**H**), 8.36–8.39 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1630$, 1470 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 252 (3.545), 244 (3.536), 211 (3.224) nm; MS: $m/z = 346$, 344 (M^+).

2-(3-Methylbut-2-enylsulfanyl)-7-chloro-4H-thiochromen-4-one (**3c**, $C_{14}H_{13}ClOS_2$)

Yield 0.77 g (60%); white solid; mp 117°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.72$ (s, C**H**$_3$), 1.76 (s, C**H**$_3$), 3.73–3.75 (d, $J = 7$ Hz, SC**H**$_2$), 5.28–5.33 (tt, $J = 7.7$, 1.2 Hz, $SCH_2C\boldsymbol{H}$, vinylic), 6.91 (s, C_3–***H***), 7.26–7.49 (m, 2Ar**H**), 8.36–8.39 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1520, 1360, 750 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 270 (3.599), 249 (3.561), 217 (3.674) nm; MS: $m/z = 298$, 296 (M^+).

2-(4-Chlorobut-2-enylsulfanyl)-7-chloro-4H-thiochromen-4-one (**3d**, $C_{13}H_{10}ClOS_2$)

Yield 0.86 g (70%); white solid; mp 110°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.72$–3.74 (d, $J = 5$ Hz, 1H of C**H**$_2$Cl), 3.78–3.81 (d, $J = 7$ Hz, 1H of SC**H**$_2$), 4.01–4.03 (d, $J = 5$ Hz, 1H of C**H**$_2$Cl), 4.08–4.11 (d, $J = 7$ Hz, 1H of SC**H**$_2$), 5.71–5.79 (m, SCH_2CH=C***H***), 5.84–5.91 (m, $SCH_2C\boldsymbol{H}$=CH), 6.96 (s, C_3–***H***), 7.44–7.52 (m, 2Ar**H**), 8.73–8.40 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1510, 1360, 750 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 272 (3.729), 251 (3.511), 211 (3.605) nm; MS: $m/z = 283$, 281 (M^+).

7-Chloro-2-methyl-4H-thieno[2,3-b]thiochromen-4-one (**4e**, $C_{12}H_7ClOS_2$)

Yield 0.75 g (65%); white solid; mp 102°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.56$ (s, =CC**H**$_3$), 7.26–7.60 (m, 3Ar**H**), 8.57–8.59 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1520, 1360, 760 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 268 (3.692), 253 (3.664), 211 (3.783) nm; MS: $m/z = 268$, 266 (M^+).

General Procedure for Rearrangement of Compound **3a–3d**

2-Allylthiothiochromen-4-one derivatives (0.2 mg) **3a–3d** were refluxed in 5 cm^3 of quinoline for 1 h. The reaction mixture was cooled, poured into 30 cm^3 of ice-cold 6 *N* HCl and extracted with $CHCl_3$ to give a viscous liquid which was chromatographed over silica gel. Elution of the column with benzene furnished the cyclized products **8a**, **8b**, **9c**, and **10d**.

7-Chloro-2,3-dihydro-2,3-dimethyl-4H-thieno[2,3-b]thiochromen-4-one (**8a**, $C_{13}H_{11}ClOS_2$)

Yield 0.16 g (80%); white solid; mp 85°C; ^{1}H NMR($CDCl_3$, 300 MHz): $\delta = 1.15$–1.17 (d, $J = 6.72$ Hz, C**H**$_3$), 1.48–1.50 (d, $J = 6.93$ Hz, C**H**$_3$), 3.66–3.72 (m, $SCH(CH_3)C\boldsymbol{H}CH_3$), 4.34–4.43 (m, $SC\boldsymbol{H}CH_3$), 7.26–7.49 (m, 2Ar**H**), 8.41–8.44 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1520, 1380, 750 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 271 (3.728), 209 (3.513), 201 (3.137) nm; MS: $m/z = 284$, 282 (M^+).

7-Chloro-2,3-dihydro-2-methyl-3-phenyl-4H-thieno[2,3-b]thiochromen-4-one
(**8b**, $C_{18}H_{13}ClOS_2$)

Yield 0.14 g (70%); white solid; mp 90°C; ^{1}H NMR($CDCl_3$, 300 MHz): $\delta = 1.14$–1.16 (d, $J = 6.72$ Hz, C**H**$_3$), 4.64–4.77 (m, PhC**H** + SC**H**), 7.24–7.53 (m, 7Ar**H**), 8.29–8.32 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1520, 1360 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 261 (3.603), 254 (3.606), 211 (3.788) nm; MS: $m/z = 346$, 344 (M^+).

8-Chloro-4,4-dimethyl-4H,5H-thiopyrano[2,3-b]thiochromen-5-one (**9c**, $C_{14}H_{11}ClOS_2$)

Yield 0.12 g (60%); white solid; mp 130°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.49$ (s, $2CH_3$), 5.70–5.73 (d, $J = 10$ Hz, SCH=C***H***), 6.96–6.99 (d, $J = 10$ Hz, SC**H**), 7.42–7.46 (m, 2Ar**H**), 8.42–8.45 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1590$, 1530, 1350, 780 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 254 (3.444), 248 (3.435), 211 (3.672) nm; MS: $m/z = 296$, 294 (M^+).

7-Chloro-2,3-dihydro-3-vinyl-4H-thieno[2,3-b]thiochromen-4-one (**10d**, $C_{13}H_9ClOS_2$)

Yield 0.14 g (70%); white solid; mp 140°C; ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 3.27$–3.30 (dd, $J = 1.5$, 11 Hz, 1H of SC$\mathbf{H}_2$), 3.76–3.80 (dd, $J = 9$, 11 Hz, 1H of SC$\mathbf{H}_2$), 4.46–4.49 (t, $J = 7$ Hz, SCH_2C***H***), 5.13–5.15 (d, $J = 6$ Hz, 1H of $=CH_2$), 5.24–5.28 (d, $J = 6$ Hz, 1H of $=C\mathbf{H}_2$), 5.95–6.02 (m, –CH=), 7.36–7.50 (m, 2ArH), 8.41–8.43 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1510, 1350, 760 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 269 (3.698), 258 (3.665), 211 (3.713) nm; MS: $m/z = 282$, 280 (M^+).

General Procedure for Aromatization

The cyclized product (0.1 g) **8a**, **8b**, and **10d** was refluxed in 3 cm^3 of diphenyl ether with 0.01 g of 10% Pd-C for 1.5 h. Diphenyl ether was removed *in vacuo* and the residual mass was chromatographed over silica gel. Elution of the column with petroleumether (60–80°C) removed the residual diphenyl ether. White solids **4a**, **4b**, and **4d** were obtained by eluting the column with benzene/petroleumether (60–80°C), 1/1.

7-Chloro-2,3-dimethyl-4H-thieno[2,3-b]thiochromen-4-one (**4a**, $C_{13}H_9ClOS_2$)

Yield 0.08 g (80%); white solid; mp 107°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.41$ (s, C$\mathbf{H}_3$), 2.59 (s, C$\mathbf{H}_3$), 7.26–7.55 (m, 2Ar**H**), 8.53–8.56 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1520, 1380, 770 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 272 (3.662), 261 (3.647), 211 (3.713) nm; MS: $m/z = 282$, 280 (M^+).

7-Chloro-2-methyl-3-phenyl-4H-thieno[2,3-b]thiochromen-4-one (**4b**, $C_{18}H_{11}ClOS_2$)

Yield 0.07 g (70%); white solid; mp 105°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 2.30$ (s, C$\mathbf{H}_3$), 7.24–7.56 (m, 7Ar**H**), 8.43–8.46 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1510, 1370, 780 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 261 (3.699), 254 (3.673), 211 (3.829) nm; MS: $m/z = 344$, 342 (M^+).

7-Chloro-3-ethyl-4H-thieno[2,3-b]thiochromen-4-one (**4d**, $C_{13}H_9ClOS_2$)

Yield 0.02 g (20%); white solid; mp 122°C; ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 1.25$–1.40 (m, C$\mathbf{H}_3$), 3.15–3.23 (q, $J = 7$ Hz, $=CC\mathbf{H}_2$), 6.99 (s, $=C\mathbf{H}$), 7.44–7.57 (m, 2Ar**H**), 8.55–8.58 (d, $J = 8.5$ Hz, 1Ar**H**) ppm; IR (KBr): $\bar{\nu} = 1580$, 1510, 1350, 750 cm^{-1}; UV-Vis (*Et*OH): λ_{max} (log ε) = 270 (3.692), 261 (3.587), 211 (3.811) nm; MS: $m/z = 282$, 280 (M^+).

Acknowledgement

We thank the CSIR (New Delhi) for financial assistance.

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