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Note

Synthesis of 3-(1-aryl-2-mercapto-imidazolyl)-2*H*-1-benzopyran-2-one derivatives

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Reaction of 3-(2-bromoacetyl) coumarins with various substituted aromatic primary amines resulted in the formation of 3-(2-anilino acetyl) coumarins **1** which on subsequent reaction with potassium thiocyanate furnishes corresponding 3-(1-aryl-2-mercapto-imidazolyl)-2*H*-1-benzopyran-2-ones **2**. The latter on treatment with alkyl halides/phenacyl halides/acyl halides in the presence of anhydrous ethanol and DMF gave the corresponding thioethers and thioesters **3**.

A large number of imidazole derivatives, particularly those derived from 2-mercapto imidazoles have been reported to possess antiinflammatory properties.[1] In continuation of our earlier work on the synthesis of heterocyclic systems derived from coumarins[2-6] we herein report the synthesis of heterocyclic system, 3-[1-aryl-2-mercapto-4-imidazolyl]-2*H*-1-benzopyran-2-ones and their thioethers and thioesters respectively.

A common method for the synthesis of imidazoles is due to Markwald.[7] Its chief limitation, however, is the involvement of α-aminoketones which are not generally stable. 3-(2-Bromoacetyl) coumarins on treatment with appropriate anilines in boiling ethanol gave the corresponding 3-(2-anilino acetyl) coumarin **1**. The α-amino ketones in the present case were fairly stable and could be purified by crystallization. These were converted to 2-mercapto-imidazoles **2** by treatment with KSCN in acetic acid and obtained as crystalline solids at the end of the reaction in 60 – 80% yield. The mercapto imidazoles **2** were converted into the corresponding thioethers and thioesters **3** by condensing with various alkyl, phenacyl and acid halides (**Scheme I**).

Experimental Section

All melting points reported are uncorrected. IR spectra (ν_{max} in cm^{-1}) were recorded on Perkin Elmer 283 spectrometer using KBr, PMR spectra on 200 MHz spectrometer (chemical shifts in δ, ppm) using TMS as internal standard and mass spectra on JEOL-JMS D-300 (Japan) mass spectrometer at 70eV.

3-(2-Anilino acetyl) coumarins were synthesized by treating 3-(2-bromoacetyl) coumarin and anilines according to the procedure described in the literature.[8,9]

Spectra of 1c : IR (KBr, ν max cm^{-1}): 1599.13 (C=C), 1685 (-NH-C=O) 1726 (lactone C=O) and 3375 (-NH-). PMR ($CDCl_3$, δ ppm) : 4.0 (s, 3H, OCH_3), 4.70 (s, 2H, -CO $-CH_2$), 6.7 – 7.3 (m, 8H, Ar-H), 8.6 (s, 1H, C_4 of coumarin) and 13.0 (s, 1H, -NH-CO, D_2O exchangeable).

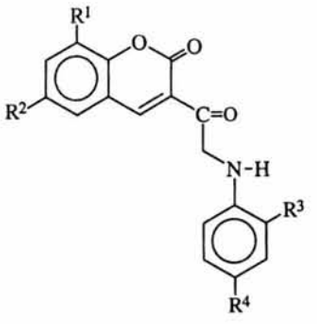
Reaction of 3-(2-anilino acetyl) coumarin 1 with potassium thiocyanate 2. A mixture of 3-(2-anilino acetyl) coumarin (0.01 mole) and potassium thiocyanate (0.01 mole) was refluxed for 2 hr in glacial acetic acid (20 mL). The reaction mixture was cooled, the separated solid was filtered dried and recrystallized from benzene to isolate **3**.

3-(1-Aryl-2-mercapto-4-imidazolyl)-2*H*-1-benzopyran-2-one 2a. It was recrystallised from benzene m.p. 152-54°C; yield 80%; IR (KBr) : 1150 (C = S),[10] 1590 (C = N), 1710.5 (lactone carbonyl) and 2841 cm^{-1} (weak, -SH); ^1H NMR (DMSO-d_6) : δ 7.38 – 7.80 (m, 10H including 1H of imidazole), 8.57 (s, 1H, coumarin C_4) and 13.05 (s, 1H, 5H, D_2O exchangeable); MS (Int %); m/z 320 (M^+, 100), 318 (49), 292 (10.6), 290 (10.9), 288 (13.8), 281 (9.4), 269 (18.0), 264 (17.8), 263 (19.1), 262 (12.3), 260 (10.3), 257 (17.3), 236 (10.3), 235 (17.6) and 238 (12.3).

3-(1-Aryl-2-alkyl/phenacyl/acyl mercapto-4-imidazolyl)-2*H*-1-benzopyran-2-one 3. A mixture of 2 (0.01 mol) and appropriate alkyl/phenacyl/acyl halide (0.01 mol) in a mixture of equal volumes (10 ml each) of anhydrous ethanol and DMF was refluxed for 6 hr. The reaction mixture was then cooled. The solid separated was filtered, dried and recrystallized from suitable solvents (**Table I**).

3b : IR (KBr) : 1600 (-C=N), 1687 (-C=O) and 1732 cm^{-1} (lactone C=O), ^1H NMR ($CDCl_3$, δ ppm); δ 4.7 (s, 2H, -S-CH_2-), aromatic protons of coumarin, phenyl and phenacyl moieties appeared as multiplet at 7.20 – 7.70 (14H). The imidazole proton appeared as singlet at 8.1 and the coumarin C_4-H appeared as singlet in down field at 8.2; MS: (m/z) 438 (M^+ 42.8) 333 (59.0), 320 (13.9), 319 (4.9) and 105 (100).

3-(1-Aryl-2-methyl-mercapto-4-imidazolyl-2*H*-1-benzopyran-2-one 3a. m.p. 220-22°C, yield 80%,



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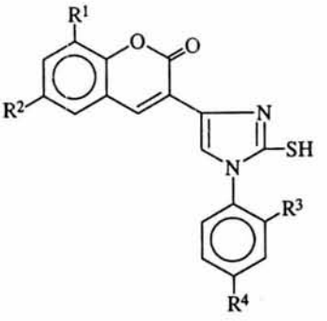

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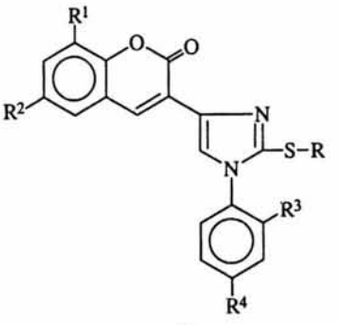

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Scheme I

Table I — Characterisation data of various compounds prepared (**1**, **2** and **3**)

Comp*		R	m.p. °C	Recrystallization solvent	Mol. formula (M.Wt.)	Found (Calcd.) % N	S
1a	$R^1=R^2=R^3=H$; $R^4=COOH$	—	256-58	aq. DMF	$C_{18}H_{13}NO_5$ [323]	4.31 [4.33]	—
1b	$R^1=R^2=R^4=H$; $R^3=NO_2$	—	196-98	C_6H_6/hexane	$C_{17}H_{12}N_2O_5$ [324]	8.61 [8.64]	—
1c	$R^1=OCH_3$ $R^2=R^3=R^4=H$	—	162-64	aq. DMF	$C_{18}H_{15}NO_4$ [325]	4.28 [4.30]	—
1d	$R^1=R^2=R^3=H$; $R^4=COOH_3$	—	212-14	aq. CH_3OH	$C_{18}H_{15}NO_4$ [309]	4.50 [4.53]	—
2a	$R^1=R^2=R^3=R^4=H$	—	152-54	CH_3OH	$C_{18}H_{12}N_2O_2S$ [320]	8.72 [8.75]	9.98 [10.00]
3a	$R^1=R^2=R^3=R^4=H$	CH_3	320-22	CH_3OH	$C_{19}H_{14}N_2O_2S$ [334]	8.35 [8.38]	9.55 [9.58]
3b	$R^1=R^2=R^3=R^4=H$	$-CH_2COC_6H_5$	145-47	CH_3OH	$C_{26}H_{18}N_2O_3S$ [438]	6.36 [6.39]	7.28 [7.30]
3c	$R^1=R^2=R^3=R^4=H$	$-CH_2COCH_3$	118-20	DMF/H_2O	$C_{21}H_{16}N_2O_3S$ [376]	7.41 [7.44]	8.54 [8.57]
3d	$R^1=R^2=R^3=R^4=H$	$-CH_2COOH$	162-64	CH_3COOH	$C_{20}H_{14}N_3O_4S$ [378]	7.36 [7.40]	8.43 [8.46]
3e	$R^1=R^2=R^3=R^4=H$	*p*-chloro-phenacyl	172-74	C_6H_6	$C_{26}H_{17}N_2ClO_3S$ [472.5]	5.90 [5.92]	6.75 [6.77]

—contd

Table I — Characterisation data of various compounds prepared (**1, 2** and **3**) (— *contd*)

Comp*		R	m.p. °C	Recrystallization solvent	Mol. formula (M.Wt.)	Found (Calcd.) % N	S
3f	$R^1=R^2=R^3=R^4=H$	Allyl	132-34	CH_3OH	$C_{21}H_{16}N_2O_2S$ [360]	7.76 [7.77]	8.86 [8.88]
3g	$R^1=R^2=R^3=R^4=H$	Allyl	123-25	CH_3OH	$C_{22}H_{20}N_2O_2S$ [376]	7.46 [7.49]	8.50 [8.51]
3h	$R^1=R^2=R^3=R^4=H$	Allyl	158-60	C_6H_6/CH_3OH	$C_{25}H_{18}N_2O_5S$ [410]	6.81 [6.82]	7.79 [7.80]
3I	$R^1=R^2=R^3=R^4=H$	Allyl	128-30	C_6H_6/CH_3OH	$C_{20}H_{13}N_2ClO_3S$ [396.5]	7.00 [7.06]	8.00 [8.01]
2b	$R^1=R^2=R^3=H$ $R^4=OCH_3$	Allyl	157-59	CH_3COOH	$C_{19}H_{14}N_2O_3S$ [350]	7.89 [8.00]	13.70 [13.71]
3j	$R^1=R^2=R^3=H$ $R^4=OCH_3$	$-CH_2COC_6H_5$	128-30	DMF/H_2O	$C_{27}H_{20}N_2O_4S$ [324]	5.97 [5.98]	6.81 [6.83]
3k	$R^1=R^2=R^3=H$ $R^4=OCH_3$	$-CH_2COCH_3$	212-14	CH_3COOH	$C_{22}H_{18}N_2O_4S$ [406]	6.88 [6.89]	7.86 [7.88]
3l	$R^1=R^2=R^3=H$ $R^4=OCH_3$	$-CH_2COOH$	148-50	CH_3COOH	$C_{21}H_{16}N_2O_5S$ [408]	6.85 [6.86]	7.83 [7.84]
3m	$R^1=R^2=R^3=H$ $R^4=OCH_3$	Allyl	188-90	CH_3COOH	$C_{22}H_{18}N_2O_3S$ [390]	7.18 [7.19]	8.17 [8.20]
3n	$R^1=R^2=R^3=H$ $R^4=OCH_3$	Benzyl	160-62	aq. CH_3OH	$C_{26}H_{20}N_2O_3S$ [440]	6.34 [6.36]	7.26 [7.27]
3o	$R^1=R^2=R^3=H$ $R^4=OCH_3$	Benzoyl	272-74	aq. DMF	$C_{26}H_{18}N_2O_4S$ [454]	6.13 [6.16]	7.00 [7.04]
3p	$R^1=R^2=R^3=H$ $R^4=OCH_3$	*p*-Chloro-phenacyl	132-34	aq. CH_3OH	$C_{27}H_{14}N_2ClO_4S$ [503.5]	5.53 [5.56]	6.32 [6.35]
2c	$R^1=R^2=R^3=H$ $R^4=COOH_3$	—	232-34	aq. DMF	$C_{19}H_{12}N_2O_4S$ [364]	7.66 [7.69]	8.76 [8.79]
3q	$R^1=R^2=R^3=H$ $R^4=COOH_3$	phenacyl	212-14	$CHCl_3$	$C_{27}H_{18}N_2O_5S$ [482]	5.77 [5.80]	6.62 [6.63]
3r	$R^1=R^2=R^3=H$ $R^4=COOH_3$	$-CH_2COCH_3$	190-92	aq. DMF	$C_{22}H_{16}N_2O_5S$ [420]	6.64 [6.66]	7.60 [7.61]
3s	$R^1=R^2=R^3=H$ $R^4=COOH_3$	$-CH_2COOH$	226-28	$CHCl_3$	$C_{21}H_{14}N_2O_6S$ [422]	3.29 [3.31]	7.54 [7.58]
3t	$R^1=R^2=R^3=H$ $R^4=COOH_3$	Allyl	268-70	CH_3OH	$C_{22}H_{16}N_2O_4S$ [404]	6.90 [6.93]	7.90 [7.91]
3u	$R^1=R^2=R^3=H$ $R^4=COOH_3$	Benzyl	185-87	Aq. DMF	$C_{26}H_{18}N_2O_4S$ [454]	6.14 [6.16]	7.00 [7.04]
3v	$R^1=R^2=R^3=H$ $R^4=COOH_3$	Benzoyl	185-87	aq. DMF	$C_{26}H_{16}N_2O_5S$ [468]	5.94 [5.98]	6.80 [6.83]
3w	$R^1=R^2=R^3=H$ $R^4=COOH_3$	$-COCH_2Cl$	200-02	CH_3OH	$C_{21}H_{13}N_2ClO_5S$ [440.5]	6.32 [6.35]	7.23 [7.26]
2d	$R^1=R^2=R^3=H$ $R^4=Cl$	—	232-34	CH_3OH	$C_{18}H_{11}N_2ClO_2S$ [354.5]	7.87 [7.89]	9.00 [9.02]
3x	$R^1=R^2=R^3=H$ $R^4=Cl$	Phenacyl	244-46	aq. DMF	$C_{26}H_{17}N_2ClO_3S$ [472.5]	5.94 [5.92]	6.74 [6.77]

—contd

Table I — Characterisation data of various compounds prepared (**1, 2** and **3**) (— *contd*)

Comp*		R	m.p. °C	Recrystallization solvent	Mol. formula (M.Wt.)	Found (Calcd.) % N	S
3y	$R^1=R^2=R^3=H$ $R^4=Cl$	CH_2COCH_3	172-74	aq.DMF	$C_{21}H_{15}N_2ClO_3S$ [410.5]	6.81 [6.82]	7.75 [7.79]
3z	$R^1=R^2=R^3=H$ $R^4=Cl$	$-COCH_2Cl$	191-93	aq. CH_3OH	$C_{20}H_{12}N_2Cl_2O_3S$ [431]	6.43 [6.49]	7.40 [7.42]
3a`	$R^1=R^2=R^3=H$ $R^4=Cl$	Benzyl	274-76	aq. DMF	$C_{25}H_{17}N_2ClO_2S$ [445.5]	6.26 [6.29]	7.16 [7.19]
3b`	$R^1=R^2=R^3=H$ $R^4=Cl$	Benzoyl	244-46	aq. DMF	$C_{26}H_{17}N_2ClO_3S$ [472.5]	5.90 [5.92]	6.74 [6.77]
3c`	$R^1=R^2=R^3=H$ $R^4=Cl$	$-CH_2COOH$	208-10	DMF/CH_3OH	$C_{20}H_{13}N_2ClO_4S$ [412.5]	6.74 [6.78]	7.72 [7.75]
2e	$R^1=R^2=R^4=H$ $R^3=NO_2$	—	142-44	$CHCl_3/CH_3OH$	$C_{18}H_{11}N_3O_4S$ [365]	11.48 [11.50]	8.72 [7.86]
3d`	$R^1=R^2=R^4=H$ $R^3=NO_2$	Phenacyl	184-86	aq. DMF	$C_{26}H_{17}N_3O_5S$ [483]	8.65 [8.69]	6.60 [6.62]
3e`	$R^1=R^2=R^4=H$ $R^3=NO_2$	$-CH_2COCH_3$	168-70	aq. DMF	$C_{21}H_{15}N_3O_5S$ [421]	9.94 [9.97]	7.57 [7.60]
3f`	$R^1=R^2=R^4=H$ $R^3=NO_2$	$-CH_2COOH$	160-62	DMF/CH_3OH	$C_{20}H_{13}N_3O_6S$ [423]	9.20 [9.23]	7.00 [7.03]
3g`	$R^1=R^2=R^4=H$ $R^3=NO_2$	Allyl	156-58	aq. DMF	$C_{21}H_{15}N_3O_4S$ [405]	10.34 [10.37]	7.88 [7.90
3h`	$R^1=R^2=R^4=H$ $R^3=NO_2$	Benzyl	>300	DMF/CH_3OH	$C_{25}H_{17}N_3O_4S$ [455]	9.20 [9.23]	7.00 [7.03]

*1a - 1d 70-80%, while 2a to 2d were in 60-70% yield. The remaining compounds were obtained in 70-85 yields

^{1}H-NMR (DMSO-d_6) : δ 2.67 (s, 3H, S CH_3), 7.2 – 7.8 (m, 9H, Ar-H), 8.1 (s, 1H, imidazole) and 8.58 (s, 1H, coumarin C_4).

3-(1-Aryl-2-allyl-mercapto-4-imidazolyl)-2*H*-1-benzopyran-2-ones 3f. m.p. 132-134°C, yield 85%; ^{1}H-NMR (DMSO-d_6 δ ppm). It showed a doublet at 3.84, accounting for two protons assignable to the methylene group flanked by the sulphur atom and the terminal doublet bond. In the spectrum another doublet accounting for one (H_A) of double bond was observed at δ 5.1 ($-CH_x = C(H_A)$ (H_B), J = 10 Hz). Another doublet accounting for one proton (H_B) is observed at 5.2 (($-CH_x = C(H_A)$ (H_B), J = 16.8 Hz). A multiplet is observed at 5.8 to 6.00 accounting for one proton is assignable to H_x of allyl group. Another multiplet is observed at 7.35 to 7.60 accounting for 9H of aromatic protons. The imidazole proton is observed at 8.0 as singlet. The most down field signal observed at 8.64 as singlet is due to C_4 of coumarin. MS : m/z 360 (29.1), 359 (100), 358 (21.7), 345 (13.4), 344 (71.5), 333 (18.4), 332 (9.4), 326 (30.7), 319 (13.4), 318 (32.5) and 260 (19.2).

3-(1-Phenyl-2-mercapto-chloroacetyl-4-imidazolyl)-2*H*-1-benzopyran-2-one (3i). ^{1}H NMR ($CDCl_3$) : δ 4.0 (s, 2H, $-S-COCH_2Cl$), 7.25 – 7.65 (m, 9H, Ar-H), 8.1 (s, 1H, imidazole) and 8.5 (s, 1H, C_4 of coumarin).

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