SYNTHESIS OF 3-[2-(SUBSTITUTED SULFONYL)-1H-IMIDAZOL-YL] CHROMEN-2-ONE DERIVATIVES

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Absract: Reaction of 3-(2-Mercapto-1H-imidazol-4-yl)chromen-2-one (**1**) with various alkyl/aryl/phenacyl halides in a mixture of anhydrous ethanol and dimethyl formamide gave the corresponding 3-(2-substituted sulfanyl-1H-imidazol-4-yl)chromen-2-ones (**2**).These on further reaction with hydrogen peroxide in acetic acid resulted in the formation of corresponding sulfones(**3**) in good yields.the structure of the synthesized compounds were established from evidences like IR,NMR and mass spectral data.

Introduction

Substituted imidazoles are a class of pharmaceutically important heterocyclic compounds due to the presence of N-C-N grouping [1, 2]. They are well known as antiinflammatory agents[3],antimicrobials[4], CNS depressants [5] , fungicides, and herbicides[7].The sulfonyl moiety has received much attention as a potential pharmacophore in medicinal chemistry due to their antibacterial,antimalarial antifungal and anti tubercular properties [8-14].

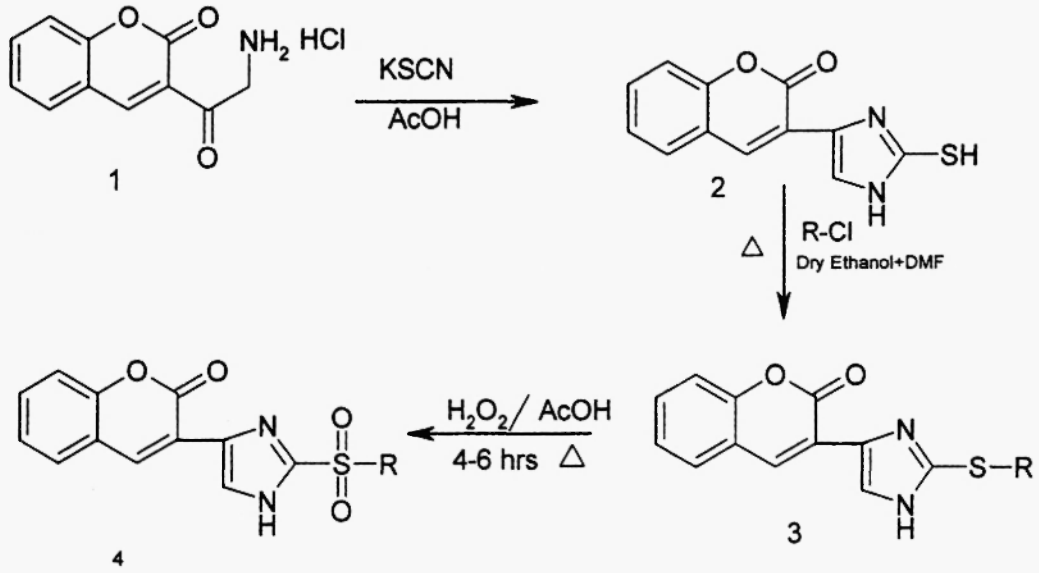
Coumarin derivatives are well known for their anticoagulant,antifungal,diuretic,firinocytic and antitubercular activates [15]. Among the various heterocyclic system linked to the third position of the coumarin ring, pyridyl-coumarins have been reported as CNS depressants[16] and antimicrobial agents[17]. In continuation of our earlier work, on the synthesis of heterocyclic systems derived from coumarin, we report here in a synthesis 3-(2-substituted sulfonyl –1H-imidazol-4-yl) chromen-2-ones.

Results and discussion

Condensation of 3-(2-bromo acetyl) coumarin with hexamethyleneteraamine resulted in the formation of 3-(2-amino acetyl) coumarin[18]. This on further reaction with potassium thiocynate in acetic acid gave 3-(2-mercapto-1H-imidazol-4-yl) chromen-2-one (**1**). condensation of 3-(2-mercapto-1H-imidazol-4-yl) chromen-2-one (**1**) with various alkyl/aryl/phenacyl halides in a mixture of anhydrous ethanol and dimethyl formamide provides 3-(2-Substituted sulfanyl-1H-imidazol-4-yl)chromen-2-ones (2) .These on oxidation with hydrogen peroxide in acetic acid afforded the 3[2-(substituted sulfonyl)-1H-imidazol-yl]chromen-2-one derivatives (4). The newly synthesized compounds have been characterized from their analytical and spectral data.

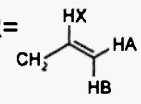
The compounds (**2**) displayed characteristic absorption bands in IR spectrum due to 2560 cm^{-1} (SH), 1726 cm^{-1} (lactone –C=O), and 3407cm^{-1} (NH) groups. The ^1H NMR spectrum of (**2**) exhibited a characteristic peaks for –SH, -NH and imidazole and C_4

proton of coumarin, at δ12.6, δ12.3, δ 7.3 and δ 8.3 respectively .The remaining protons of coumarin were observed in the usual regions. In mass spectrum of (**2**) the molecular ion was recorded at m/z 244. Reaction of (**2**) with various alkyl / aryl / phenacyl halides in a mixture of anhydrous ethanol and dimethyl formamide (equal volumes) afforded a series of 3-(2-substituted sulfanyl-1H-imidazol-4-yl) chromen-2-ones (**3**).In the alkylation process the more nucleophilic sulphur of thiol group displaces the halogen atom of alkylhalide to yield thioether(**3**).The alkylation is regioselctive and no mixture of product is formed. This is evidenced from TLC and spectra. These compounds (**3**) displayed characteristic absorption bands in the IR spectrum at 1228 cm^{-1} are due to C-N-C linkage .The lactone carbonyl absorption were found in the region of 1720 cm^{-1} and 3200-3230 cm^{-1} (-NH) . In the ^1H NMR spectra (**3**) exhibited a characteristic peaks for NH and C_4 proton of coumarin at δ 9.5 and δ 8.2 respectively. In the IR spectrum the compound 4 showed two characteristic peaks at 1301-1328 and 1148-180 cm^{-1} SO asymmetric stretching and SO asymmetric stretching. The lactone -C=O 1729-1744 cm^{-1} while NH stretiching vibration are observed at 3350-3438 cm^{-1}



a) R= CH_3

b) R= Et

c) R= 

d) R= $PhCOCH_2$

e) R=PhCO

f) R= $COCH_2Cl$

g) R= $PhCH_2$

h) R= NO_2-$PhCH_2$

i) R= Ph-$PhCOCH_2$

Scheme-1

EXPERIMENTAL

All melting points were determined in open capillaries with a "cintex" melting point apparatus Mumbai, India and were uncorrected. . CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyzer. The purity of the compounds was checked by TLC plates (E.Merek,Mumbai, India) IR spectra (KBr)were recorded on a BrukerWM-4(X)spectrometer (577model).^{1}H NMR spectra were recorded on a Bruker WM-300spectrometer in δ ppm using TMS as internal standard. Mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5eV. The 3-(2-amino acetyl) coumarin [18], 3(2-bromo acetyl) coumarin [19,20] were prepared according to the literature procedure.

3-(2-Mercapto-1H-imidazol-4-yl) chromen-2-one (1)

A mixture of 3-(2-amino acetyl) coumarin (0.01 mole) and potassiumthiocyanate (0.01 mole) in acetic acid was refluxed for four hours. The reaction mixture was cooled to room temperature, the solid separated was filtered, washed with water and recrystallised from methanol.

3-(2-Substituted sulfanyl-1H-imidazol-4-yl) chromen-2-ones (2): General procedure

A mixture of **1** (0.001 mole) and appropriate alkyl/aryl/ phenacyl halide (0.001 mole) was refluxed in a mixture of equal volumes of anhydrous ethanol and dimethyl formamide for 6-8 hours. The reaction mixture was cooled to room temperature, the solid separated was filtered, washed with water and recrystallised (**Table-I**) from suitable solvents.

3[2-(Substitute sulfonyl)-1H-imidazol-yl] chromen-2-one derivatives (3): - General procedure

Compound **2** (0.01mole) was suspended in 15 ml glacial acetic acid. To above suspension 5 ml of 30% hydrogen peroxide was added and heated on a water bath for 2-3 hours. The contents were cooled and poured on to crushed ice and the solid separated was collected dried and recrystallised from ethyl acetate.

Conclusions :

In summary ,we have prepared 3-(2-mercapto-1H-imidazol-4-yl) chromen-2-one (**2**) in single step starting from 3-(2-amino acetyl) coumarin(1) in high yield .this compound was subsequently converted in to their basic ethers (3).the compounds (3) were oxidized into corresponding sulfones with hydrogen peroxide in acetic acid .The compounds prepared have been subjected for their anticancer activity. None of the compounds have shown anticancer activity.

Table 1: Analytical data of compounds 2, 3a-I and 4a-i

Comp*	R	Yield (%)	m p (°C)	Mol.formula(Mol.wt)	Found (calcd) %			
					C	H	N	S
2	-	90	>300	$C_{12}H_{10}N_2O_2S$ (244)	58.95 (59.00)	3.26 (3.30)	11.43 (11.47	13.10 (13.13)
3a	CH_3-	93	130-132	$C_{13}H_{10}N_2O_2S$ (258)	60.41 (60.45)	3 87 (3 90)	10 81 (10.85)	12.36 (12.40)
3b	Et-	95	140-142	$C_{14}H_{12}N_2O_2S$ (272)	61.78 (61.75)	4 40 (4 44)	10 25 (10 29)	11.67 (11.7)
3c	CH_2=CH-CH_2-	82	200-202	$C_{15}H_{12}N_2O_2S$ (284)	66 24 (63.36)	4 21 (4 25)	9.88 (9.85)	11.21 (11.20)
3d	$PhCOCH_2$-	85	226-228	$C_{20}H_{14}N_2O_3S$ (362)	66 24 (66 28)	3 85 (3 89)	7.70 (7.73)	8.81 (8.85
3e	PhCO-	68	140-144	$C_{19}H_{12}N_2O_3S$ (348)	65.50 (65.51)	3 43 (3 47)	8.00 (8.04)	9.17 (9.20)
3f	$COCH_2Cl$-	90	212 214	$C_{14}H_{13}C\ N_2O_3S$ (320)	52.42 (52.45)	2 83 (2 81)	8.73 (8.70)	10.00 (10.05)
3g	$PhCH_2$-	83	260-262	$C_{19}H_{14}N_2O_2S$ (334)	68.21 (68.25)	4 20 (4 22)	8.38 (8.38)	9.54 (9.59)
3h	O_2N-$PhCH_2$-	88	212-213	$C_{19}H_{13}N_2O_2S$ (379)	60.10 (60.15)	3 41 (3 45)	11.00 (11.08)	8.1 (8.4)
3i	Ph-$PhCOCH_2$-	87	230-232	$C_{26}H_{18}N_2O_3S$ (438)	71.20 (71.22)	4 10 (4 14)	6.34 (6.39)	7.28 (7.31)
4a	CH_3-	60	80-82	$C_{13}H_{16}N_2O_4S$ (290)	53.91 (53.97)	3 41 (3.47)	9 60 (9.65)	11.00 (11.05)
4b	Et-	55	88-90	$C_{14}H_{12}N_2O_4S$ (304)	55.20 (55.26)	3 90 (3.97)	9 18 (9 21)	10.44 (10 50)
Comp*	R	Yield (%)	m p (°C)	Mol.formula(M	Found (calcd) %			

				ol.wt)	C	H	N	S
4c	CH_2=CH.CH_2-	50	92-94	$C_{15}H_{12}N_2O_4S$ (316)	56.91 (56.95)	3.80 (3.82)	8 83 (8.86)	10.17 (10 2)
4d	$PhCOCH_2$-	80	120-124	$C_{20}H_{14}N_2O_5S$ (394)	60.88 (60.91)	3.50 (3.58)	7 08 (7.10)	8.1((8.13)
4e	PhCO-	77	110-112	$C_{19}H_{12}N_2O_5$ (380)	59.97 (60.00)	3.14 (3.18)	7.32 (7.36)	8.40 (8.43)
4f	$COCH_2Cl$-	90	96-98	$C_{14}H_{13}ClN_2O_4S$ (352)	59.49 (59.59)	4 64 (4.67)	9 21 (9 27)	10.54 (10.60)
4g	$PhCH_2$-	85	118-120	$C_{19}H_{14}N_2O_4S$ (366)	62 24 (62.29)	3.81 (3.85)	7.61 (7 65)	8.70 (8.79)
4h	O N-$PhCH_2$-	88	155-156	$C_{19}H_{13}N_2O_6S$ (411)	55.44 (55.47)	3 15 (3.19)	10 2 (10 21)	7.65 (7.7)
4i	Ph-$PhCOCH_2$-	85	160-162	$C_{26}H_{18}N_2O_5S$ (470)	66.31 (66 37)	3.80 (3.85)	5.91 (5 97)	6 75 (6 81)

Compound 2 was recrystallised from methanol. Compounds 3a,,c,d,f were recrystallised from methanol. 3d,e,g,h,i were recrystallised aqueous acetone. 4(a-i) was recrystallised from ethyl acetate.

Table : 2 Spectroscopic data of compounds 2,3(a-i) and 4(a-i)

compd	IR (ν_{max} cm^{-1})						^{1}H NMR (δ ppm	Mass spectra (m/Z) 100%
	-C=N-	>C=O(lactone)	NH	-C=O	SO_2(sym.)	SO_2(asym.)		
2	1609	1726	3407	---	---	---	7.3-7.6 (m,4H,Ar-H), 8.0(s,1H,imidazole),8.45(s,1H C$_4$ of coumarin)12.3(s,1H NH)&12.6(s,1H,SH)	244
3a	1611	1709	3436	---	---	---	2.68 (s, 3H, -CH$_3$), 7.3-7.60 (m,4H Ar-H), 8.5 (s,1H,C4 of coumarin) and 9.3 (b,NH)	272
3b	1606	1706	3621	---	---	---	1.38(t,3H,-CH$_3$), 3.12(q,2H,-CH$_2$) 7.35-7.6(m,4H,Ar-H), 7.99(1H,imidazole), 8.5 (s,1H,C$_4$ of coumarin) 9.4 (b, NH)	284
3c	1636	1706	3420	---	---	---	3.6(d,2H, J=6HzS-CH$_2$),5.1(d,1H,H$_A$,J=12Hz),5.20(d,H$_B$,H$_X$ H$_B$,J=18Hz),6.0(m 1H H$_x$)7.30-7.60 (4H,Ar-H), 8.54 (s,1H, C4 of coumarin), 7.95 (s,1H,imidazole), 9.5 (s,1H,NH)	362
3d	1607	1715	3399	1690	---	----	4.8(s,2H,S-CH$_2$),7.1-7.6(m,9H,Ar-H) 8.05(s,1H NH), 8.15(s,1H,imidazole),8.18(s,1H, C4 of coumarin),	---
3e	1610	1720	3437	1750	---	---	7.43-7.54 (m, 11H, Ar-H) and 8.25 (s,1H C$_4$ of coumarin)	---
3f	1615	1730	3420	--	---	---	4.5(s 2H,-CH$_2$-),7.3-7.6(m,4H,Ar-H),8.10 (s,1H,imidazole),8.20(s,1H,C$_4$ of coumarin) and 8.58 (s,1H,NH)	----
3g	1606	1720	3060	---	---	---	4.26 (s,2H,-CH$_2$),7.3-7.62 (m,9H,Ar-H)7.59 (1H,imidazole),7.89 (C$_4$ of Coumarin),8.53 (s,1H,NH)	---
3h	1602	1719	3436	---	---	---	4.37 (s,2H,CH$_2$), 5.42 (s,1H,NH),7.33-7.46 (m,8H,Ar-H), 8.55 (s,1H,imidazole) and 8.66 (s,1H,C$_4$ of coumarin)	379
3i	1600	1721	3621	1662	---	---	4.65 (s,2H,-SCH$_2$), 5.6 (s,1H,NH),7.46-7.70 (m,14H,Ar-H),8.02 (s,1H,imidazole) and 8.24 (s,1H,C4 of Coumarin)	437

compd	IR (ν_{max} cm^{-1})						^{1}H NMR(δ ppm	Mass spectra (m/Z) 100%
	-C=N-	>C=O(lactone)	NH	C=O	SO_2(sym.)	SO_2(asym)		
4a	1605	1742	3390	---	1170	1303	3.1 (s, 3H, -CH_3), 7.30-7.60 (m,4H,Ar-H),),8.10 (s,1H,imidazole) 8.6 (s,1H,C4 of coumarin) and 9.3 (b NH)	244 290
4b	1628	1729	3438	---	1179	1303	1.75(t,3H,-CH_3), 3.40(q,2H,-CH_2),7.30-7.72(m,4H,Ar-H), 8.0(1H,imidazole), 8.6 (s,1H C_4 of coumarin) 9.3 (b, NH)	304
4c	1607	1735	3395	---	1176	1322	4.15(d 2H,J=5Hz SO_2-CH_2),5.3(d,1H,H_A,J=8Hz),5.4(d,H_X,H_B J=18Hz),6.12-6.30(m 1H,H_X)7.30-7.70 (4H,Ar-H), , 8.3 (s, 1H,imidazole), 8.7 (s,1H, C4 of coumarin),9.35 (s,1H,NH)	317
4d	1607	1731	3441	1689	1180	1314	5.3(s,2H,SO_2-CH_2),7.5-7.70(m 9H,Ar-H),7.95(s,1H,NH), 8.20(s,1H,imidazole),8.6(s,1H, C4 of coumarin),	394
4e	1622	1744	3400	1686	1148	1302	-----	---
4f	1619	1744	3469	1685	1150	1301	-------	---
4g	1614	1718	3365	1697	1165	1315	4.75 (s,2H,-CH_2),7.3-7.5 (m,7H,Ar-H)7.62-7.70(m 3H,2Ar-H and1H imidazole) 8.0 (C_4 of Coumarin),8.70 (s,1H,NH)	---
4h	1629	1725	3390	1680	1174	1305	--------	---
4i	1602	1729	3350	1690	1176	1328	5.6(s,2H,-SO_2-CH_2), 7.30-7.80 (m,15H,Ar-H and NH of imidazole), and 8.0 (s,1H,C_4 of Coumarin)	470

^{1}HNMR of the compounds 2,3(a,b,c,,f,g h,i) and 4 a-4 i were run in $CDCl_3$ while the compounds 3d,3e were run in $CDCl_3$+ DMSO-d_6

Acknowledgement:

The authors are thankful to Head analytical division, IICT Hyderabad for analytical and spectral data. Further the authors are very thankful to CSIR, New Delhi for the sanction of the project (No.01 (2062) 06 / EMR-II).

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Received on 10 June, 2008