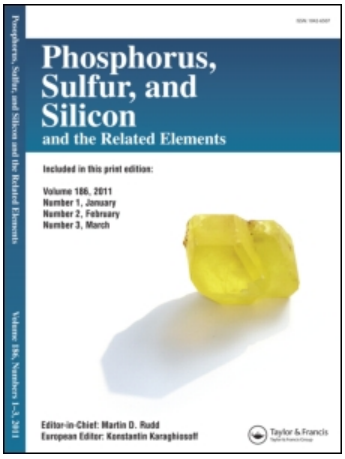

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3-acetyl coumarins on condensation with various aromatic aldehydes in the presence of piperidine gave corresponding chalcones in a solid state under solvent free conditions. These chalcones are isolated and characterized. The in-situ-formed chalcones (1) are also converted into corresponding 2-aryl-4-[2H-2-oxo[1]benzopyran-3-yl]-2,3-dihydro (3) and 2,5-dihydro-1,5-benzothiazepines (4) in one step by interacting with orthoamino thiophenol. Both the 2,3-dihydro (3) and 2,5-dihydrobenzothiazepines (4) have been converted into same tetrahydrobenzothiazepine (5). Finally, the tetrahydrobenzo thiazepine (5) is converted into its acetyl derivative (11). The structures of the title compounds have been confirmed on the basis of their microanalytical, IR, ^{1}H NMR, and mass spectral data.

Keywords 3-acetylcoumarin; chalcone; benzothiazepine

INTRODUCTION

Immensechemotherapeutic applications of 1,5-benzothiazepine derivatives such as diltiazem,[1a,b] clentiazem (TA-3090),[2] anticoagulant,[3] antiarteriosclerotic,[4] antiischemic,[5] antiatherosclerotic,[6] antihypertensive,[7] and antidepressant[8] etc. activity and their comparative study with diazepams,[9] and clobazam[10] etc. interested us to synthesize a series of new 1,5-benzothazepines having substituents at the 2 and 4 positions.

The progress in the field of solid state organic reactions (SSOR) is gaining significance both from the mechanistic and synthetic point of view.[11–14] There are a number of reports on the synthesis of chalcones

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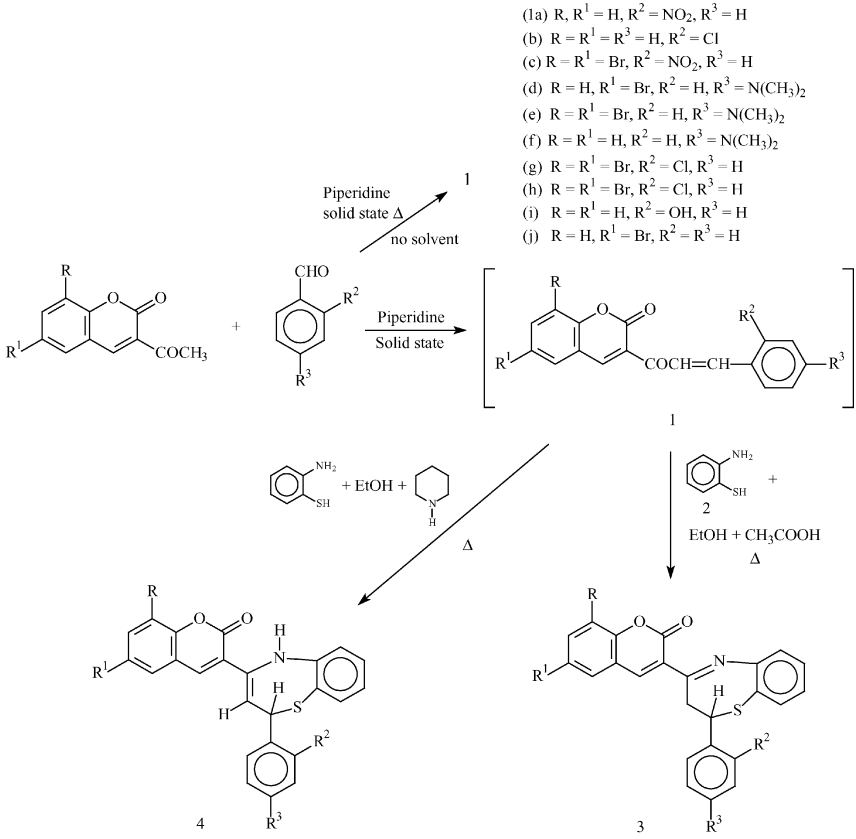
derived from 3-acetyl coumarins.[15–19] These procedures involve the reaction of 3-acetyl coumarins with aromatic aldehydes in ethanol using a catalytic amount of piperidine by refluxing for several hours. Often these procedures were tedious because of the low solubility of the 3-acetyl coumarins in ethanol and long reaction times. In view of these



(1a) R, R^1 = H, R^2 = NO_2, R^3 = H
(b) R = R^1 = R^3 = H, R^2 = Cl
(c) R = R^1 = Br, R^2 = NO_2, R^3 = H
(d) R = H, R^1 = Br, R^2 = H, R^3 = $N(CH_3)_2$
(e) R = R^1 = Br, R^2 = H, R^3 = $N(CH_3)_2$
(f) R = R^1 = H, R^2 = H, R^3 = $N(CH_3)_2$
(g) R = R^1 = Br, R^2 = Cl, R^3 = H
(h) R = R^1 = Br, R^2 = Cl, R^3 = H
(i) R = R^1 = H, R^2 = OH, R^3 = H
(j) R = H, R^1 = Br, R^2 = R^3 = H

(4a) R^1 = R = R^3 = H, R^2 = Cl
(b) R^2 = NO_2, R = R^1 = R^3 = H
(c) R = R^1 = R^3 = H, R^2 = OH
(d) R^1 = Br, R = R^2 = H, R^3 = $N(CH_3)_2$
(e) R = R^3 = H, R^1 = Br, R^2 = Cl
(f) R^1 = R = R^2 = H, R^3 = $N(CH_3)_2$
(g) R = R^2 = R^3 = H, R^1 = Br

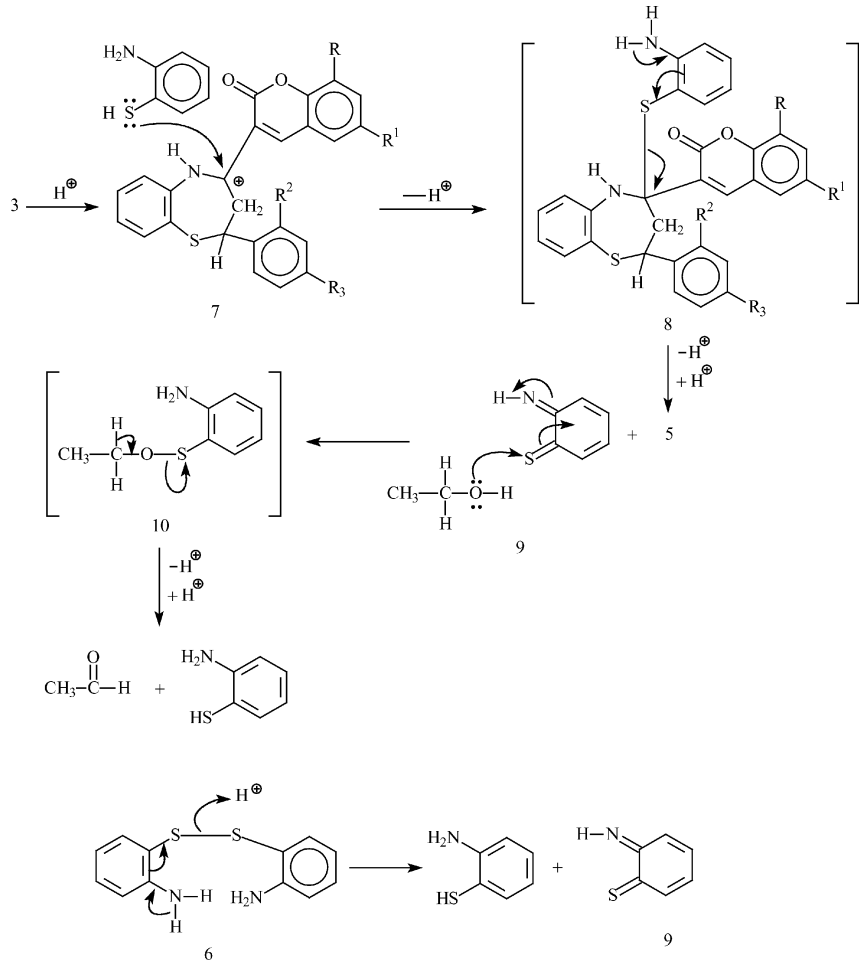
(3a) R = R^1 = R^2 = H, R^3 = $N(CH_3)_2$
(b) R = R^1 = R^3 = H, R^2 = Cl
(c) R = R^1 = R^3 = H, R^2 = NO_2
(d) R = R^1 = Br, R^2 = H, R^3 = $N(CH_3)_2$
(e) R = R^1 = R^3 = H, R^2 = OH
(f) R^1 = Br, R = R^2 = H, R^3 = $N(CH_3)_2$
(g) R = R^3 = H, R^1 = Br, R^2 = Cl
(h) R = R^1 = Br, R^2 = Cl, R^3 = H
(i) R = H, R^1 = Br, R^2 = NO_2, R^3 = H
(j) R = H, R^1 = Br, R^2 = R^3 = H

SCHEME 1

limitations and in continuation of our interest on solvent free organic reactions,[20] herein we report a mild and highly efficient procedure for the synthesis of chalcones derived from 3-acetyl coumarins using a catalytic amount of piperidine under solvent free conditions in the solid state. This procedure can be extended to other substituted heterocyclic chalcones. No solvent is needed as in the classical preparation of chalcones. The method is convenient, more economic, and environmentally benign. The mild reaction conditions, operational similarity, short reaction time, and excellent yields make the process more versatile.

RESULTS AND DISCUSSION

The chalcones derived from 3-acetyl coumarins, i.e., 3-[1-oxo-3-(substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones (1), have been reacted with 2-amino benzene thiol (2) in a mild acidic medium using weakly acidified ethanol in an attempt primarily to obtain the intermediates, but here attempts failed and the final products 2-aryl-4-(2H-2-oxo-[1]-benzopyran-3-yl]-2,3-dihydro-1,5-benzothiaze-pines (3) have been formed. When the chalcones (1) are refluxed in ethanol containing 2-amino benzene thiol and piperidine gave the corresponding 2-aryl-4-[2H-2-oxo-[1]benzopyran-2-one-3-yl]-2,5-dihydro-1,5-benzothiazepines (4). Further, the sodium borohydride reduction of the dihydrobenzothiazepine (3) provided the tetrahydrobenzothiazepine (5). The compound 5 is also formed by the reduction of 3 with o-ATP (catalytic amount) in ethanol containing an acid. However, it is well known that o-ATP is contaminated with a little amount of Di O-Aminophenyl Disulphide (DAPDS) (VI) due to its aerial oxidation. Hence, the involvement of DAPDS in the reduction of 3 could not be ruled out. Keeping this in view, 3 was also treated with DAPDS as well as o-ATP in refluxing ethanol in the presence of an acid (HCl or HBr). In all these cases compound 5 was obtained in good yields. The reduction of 3 to 5 has been outlined in Scheme 2. Because reduction is catalyzed by both o-ATP as well as DAPDS it may be suggested that in the reduction of 3 with o-ATP/$H^{\oplus}$ in ethanol, the effective catalyst is o-ATP. The nucleophilic addition of o-ATP to the initially formed carbocation 7 may result in the formation of 8, which may cleave to 5 and 1,2-benzothioquinone imine 9. The addition of ethanol to 9 may give rise to another intermediate 10, which may in turn regenerate o-ATP with a concomitant elimination of the corresponding carbonyl compound. The compound 9 may now reenter the reductive cycle, which may continue until 3 is completely reduced to 5. However, when DAPDS is used in place of o-ATP, it may first undergo acid-catalyzed disproportionation

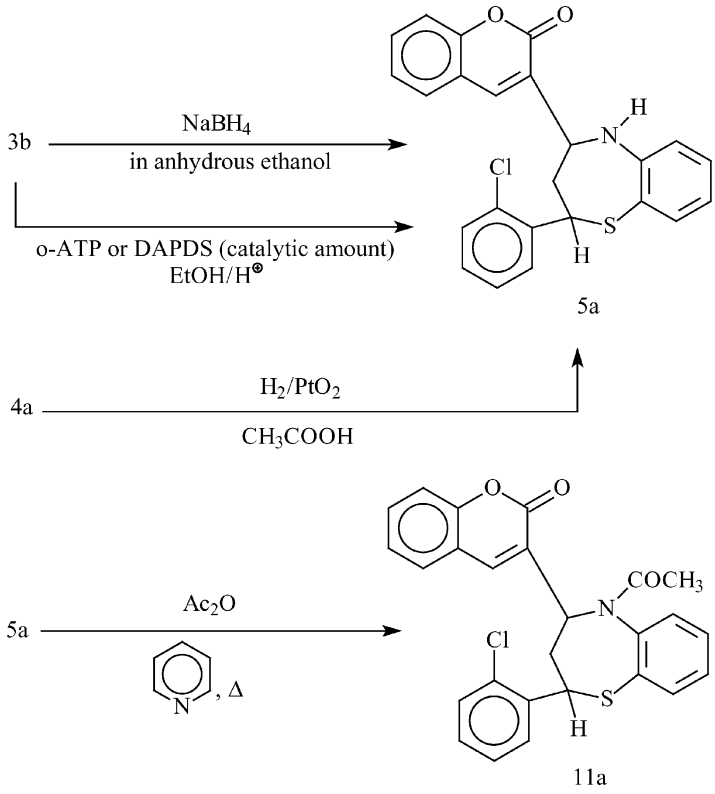


SCHEME 2

to give 9 and o-ATP, which may catalyze the reduction as previously described.

In conclusion it is worth mentioning that the present reductive one-step conversion of 3 into 5 by using o-ATP or DAPDS in acidic ethanol is quite significant as it constitutes a convenient access to tetrahydro benzothiazepine derivatives (5). Also this procedure is cheaper than the reduction of 3 to 5 by using $NaBH_4$ as a reducing agent.

The reduction of 4 with H_2 using Pt resulted in the formation of tetrahydro benzothiazepine derivative 5. The reduction product (5)



SCHEME 3

obtained by this method was found indentical to the product that was obtained by the reduction of 3 with either $NaBH_4$, o-ATP, or DPDS in ethanol containing an acid. This was further confirmed by Co-TLC, m.p., and mixed m.p.s of these compounds.

The formation of 5 was further confirmed by the conversion into the corresponding acetyl derivatives 11 using Ac_2O and pyridine (Scheme 3).

The structures of newly synthesized compounds were confirmed on the basis of spectral and analytical data.

All the chalcones (1) displayed characteristic absorption bands in the IR due to 1678 (α, β-unsaturated ketone) and 1740 $\pm$ 5 (lactone —C=O). The ^1H NMR spectrum of Ia exhibited a characteristic multiplet for three aromatic and two —CH=CH— protons at 7.25–7.40. Another multiplet was observed for four aromatic protons at 7.60–7.70. The C_4 proton of coumarin appeared as singlet at 8.5. All the cyclized compounds

(3) displayed characteristic absorption bands due to —C=N— and lactone carbonyl at 1606 and 1705 cm^{-1}, respectively. The absence of an absorption band at 1678 cm^{-1} in compound 3 confirms that it was cyclized. The ^1H NMR spectra of 3a exhibited a characteristic triplet for the —CH—S— proton at 2.90 and a doublet for —CH_2— at 4.40. The remaining protons were observed in the usual regions. The cyclized compound 4 exhibited -NH- absorptions in the region 3293 and lactone carbonyl at 1710 cm^{-1}, respectively. The PMR spectrum of 4f displayed two characteristic doublets at 3.6 due to C_2-H and another at 6.75 due to C_3-H. The C_4 proton of coumarin appeared as a singlet at 8.35. The remaining protons were observed in the usual regions.

EXPERIMENTAL

All melting points were determined in open capillary tubes using a sulphuric acid bath and were uncorrected. IR spectra (ν_{max}, cm^{-1}) were recorded on a Perkin-Elmer spectrophotometer. The ^1H NMR spectra were recorded on a Varian 200 MHz, and the chemical shifts were recorded in δ (ppm) using TMS as an internal standard. The mass spectra were scanned on a Jeol-JMS 300 spectrometer at 70 eV.

The 3-acetyl coumarins[21] were prepared according to the literature procedure.

3-[1-Oxo-3-(substituted phenyl)-2-propenyl]-2H-1-benzopyran-2-ones (1)

A mixture 3-acetyl coumarin (0.01 mol) and appropriate aromatic aldehyde (0.01 mol) and 1 mL of piperidine was intimately ground for about 20 min while heating on a water bath at 45–50°C. The grinding was continued for 10 more min, on completion of reaction as indicated by TLC, the reaction mixture was treated with methanol. The resultant product was filtered. The solids were recrystallized from suitable solvents (80–93%); products were characterized by comparison with authenitic samples (Table I).

2-Phenyl-4-(2H-2-Oxo-[1]-Benzopyran-3-Yl]-2,3-dihydro-1,5-benzothiazepines (3)

General Procedure (One-Step Process)

A mixture of 3-acetyl coumarin (0.01 mol), appropriate aromatic aldehyde (0.01 mol) and 1 mL of piperidine was taken in a round-bottom

TABLE I Physical Data of Compounds (1a–j)

Compound*	RR^1	R^2R^3	M.P.°C	Yield			
				Reported	Time	Found	Reported
1a	H	NO_2	142–144	—	20	86	—
	H	H					
1b	H	Cl	212–214	—	25	93	—
	Br	H					
1c	Br	NO_2	228–230	—	30	88	—
	Br	H					
1d	H	H	204–206	—	25	92	—
	Br	$N(CH_3)_2$					
1e	Br	H	252–254	—	22	93	—
	Br	$N(CH_3)_2$					
1f	H	H	281–282	>280	30	91	75
	H	$N(CH_3)_2$					
1g	H	Cl	188–190	190	25	94	70
	H	H					
1h	Br	CI	252–254	—	24	90	—
	Br	H					
1i	H	OH	281–283	>280	22	80	50
	H	H					
1j	H	H	242–244	—	20	86	—
	Br	H					

*All compounds were recrystallized from methanol.

flask and intimately ground with glass rod for about 20 min while heating on a water bath at 45–50°C. The grinding was continued for 10 more min; on completion of reaction as indicated by TLC, the reaction mixture was treated with methanol or ethanol (20 mL) followed by the addition of 1 mL of glacial acetic acid. The resultant reaction mixture was treated with an equimolar quantity of 2-aminothiophenol (0.01 mol) and refluxed for 5 h. The reaction mixture was cooled the yellow solid formed was collected by filtration and recrystallized from methanol (Table II).

2-Phenyl-4-[2H-2-oxo-[1]-benzopyran-3-Yl]-2,5-dihydro-1,5-benzothiazepines (4)

General Procedure (One-Step Process)

A mixture of 3-acetyl coumarin (0.01 mol), an appropriate aromatic aldehyde (0.01 mol), and 1 mL of piperidine was taken in a round-bottom flask and intimately ground with glass rod for about 20 min while heating on a water bath at 40–45°C. The grinding

TABLE II Physical Data of Compounds (3a–j)

Compound*	RR^1	R^2R^3	M.P. °C	Yield (%)	Mol. formula (Mol. wt.)	Found (calc.) % C	H	N	S
	H	H			$C_{26}H_{22}N_2O_2S$	73.18	5.12	6.54	7.50
3a	H	$-N(CH_3)_2$	164–166	90	(426)	(73.21)	(5.16)	(6.57)	(7.52)
3b	H	Cl	166–168	84	$C_{24}H_{16}NClO_2S$	68.95	3.83	3.31	7.64
	H	H			(417)	(68.98)	(3.86)	(3.34)	(7.67)
3c	H	NO_2	87–89	79	$C_{24}H_{16}N_2O_4S$	67.24	3.73	6.52	7.45
	H	H			(428)	(67.28)	(3.76)	(6.54)	(7.58)
3d	Br	H	90–92	82	$C_{26}H_{20}N_2Br_2O_2S$	53.41	3.42	4.75	5.46
	Br	$N(CH_3)_2$			(584)	(53.44)	(3.45)	(4.79)	(5.49)
3e	H	OH	95–97	75	$C_{24}H_{17}NO_3S$	(72.16)	4.26	3.48	8.00
	H	H			(399)	72.12	(4.29)	(3.51)	(8.03)
3f	H	H	110–112	83	$C_{26}H_{21}N_2BrO_2S$	61.75	4.12	5.51	6.30
	Br	$N(CH_3)_2$			(505)	(61.79)	(4.15)	(5.54)	(6.33)
3g	H	Cl	170–172	80	$C_{24}H_{15}NBrClO_2$	49.96	3.00	2.80	6.42
	Br	H			S (496)	(50.00)	(3.04)	(2.82)	(6.45)
3h	Br	Cl	87–89	88	$C_{24}H_{14}NBr_2ClO_2S$	49.87	2.42	2.42	5.52
	Br	H			(577.5)	(50.04)	(2.43)	(2.43)	(5.57)
3i	H	NO_2	209–211	88	$C_{24}H_{15}N_2BrO_4S$	56.80	2.94	5.51	6.28
	Br	H			(507)	(56.80)	(2.95)	(5.52)	(6.31)
3j	H	H	220–222	86	$C_{24}H_{16}NO_2SBr$	62.30	3.44	3.00	6.88
	Br	H			(462)	(62.33)	(3.46)	(3.02)	(6.92)

*All compounds were recrystallized from methanol.

was continued for 10 minutes; on completion of the reaction as indicated by TLC, the reaction mixture was treated with methanol or ethanol (20 mL) followed by addition of 1 mL of piperidine. The resultant mixture was treated with an equimolar quantity of ortho aminothiophenol (0.01 mole) and refluxed for 9 h. The reaction mixture was cooled, the excess a solvent was removed, and the residue was poured onto crushed ice to give a pale yellow solid. The product was filtered, washed with water, and recrystallized from methanol (Table IV).

3-[2-(2-Chlorophenyl)-2,3,4,5-tetrahydro-benzo[b][1,4]thiazepin-4-Yl]-chromen-2-One (5a) from 3b

(i) Using o-ATP or DAPDS

A solution of 3b (0.001 mol) and o-ATP or DAPDS (0.0015 mol) in ethanol (10 mL) and hydrochloric acid or hydrobromic acid (4–5 drops) was refluxed for 10–12 h. The reaction mixture was then cooled to r. t. and poured into aqueous $NaHCO_3$ and extracted with

TABLE III Physical Data of Compounds (4a–f)

Compound*	RR^1	R^2R^3	M.P. °C	Yield (%)	Mol. formula (Mol. wt.)	Found (calc.) % C	H	N	S
4a	H	Cl	206–208	75	$C_{24}H_{16}NClO_2S$	68.94	3.82	3.30	7.62
	H	H			(417)	(68.98)	(3.86)	(3.35)	(7.66)
4b	H	NO_2	118–120	68	$C_{24}H_{16}N_2O_4S$	67.25	3.72	6.50	7.45
	H	H			(428)	(67.28)	(3.76)	(6.54)	(7.48)
4c	H	OH	177–179	76	$C_{24}H_{17}NO_3S$	72.12	4.24	3.48	8.00
	H	H			(399)	(72.16)	(4.29)	(3.51)	(8.03)
4d	H	H	160–162	76	$C_{26}H_{21}N_2BrO_2S$	61.75	4.12	5.50	6.60
	Br	$N(CH_3)_2$			(505)	(61.79)	(4.15)	(5.54)	(6.33)
4e	H	Cl	210–212	74	$C_{24}H_{15}NBrClO_2S$	57.96	3.00	2.79	6.40
	Br	H			(496)	(58.02)	(3.04)	(2.82)	(6.45)
4f	H	H	150–152	78	$C_{26}H_{22}N_2O_2S$	73.16	5.13	6.52	7.49
	H	$N(CH_3)_2$			(426)	(73.21)	(5.16)	(6.57)	(7.52)
5a	H	Cl	95–96	75	$C_{24}H_{18}NClO_2S$	68.62	4.30	3.30	7.61
	H	H			(419)	(68.65)	(4.32)	(3.34)	(7.64)
11a	H	Cl	132–134	90	$C_{26}H_{20}NClO_3S$	67.57	4.33	3.00	6.91
	H	H				(67.60)	(4.36)	(3.03)	(6.94)

*All compounds were recrystallized from methanol.

CH_2Cl_2 (2 × 15 mL). The organic layer was washed with water (2 × 15 mL) and dried ($MgSO_4$). The mass obtained was crystallized from hexane.

(ii) Using $NaBH_4$

A solution of 0.001 mol of compound 3b and 0.001 mol of $NaBH_4$ in 30 mL of anhydrous ethanol was refluxed for 8 h. During this time the yellow color of the starting material disappeared. After decomposing the complex by adding few drops of acetic acid, the alcohol was removed in vacuum. The product (5b) was treated with H_2O and extracted with ether. The solvent was removed to leave a solid; the solid was recrystallized from n-hexane.

Synthesis of 3-[2-(2-Chlorophenyl)-2,3,4,5-tetrahydrobenzo[b][1,4] thiazepin-4-yl]-chromen-2-one (5a) by the Reduction of 4a

The compound 4a (0.001 mol) in acetic acid (10 mL) was hydrogenated at atmospheric pressure and r. t. during 24 h using a platinum catalyst (from 0.1 g of PtO_2). The reaction mixture was filtered and the

TABLE IV Spectral Data of Compounds 3 and 4

Compound	IR (ν_{max} cm^{-1}) O=C–C=C	IR (ν_{max} cm^{-1}) –C=O	–C=N C=C	–NH–	^{1}H NMR (δ ppm) (DMSO-D_6)	Mass spectra (m/z)
1a	1678	1741	— 1614	—	7.25–7.40 (m, 6H, 4Ar–H and 2H of –CH=CH–), 7.60–7.70 (m, 4Ar–H) and 8.50 (s, 1H, C_4 of coumarin)	—
1b	1674	1734	— 1606	—	7.80–8.20 (m, 7H, Ar–H) and 8.60 (s, 1H, C_4 of coumarin)	—
1j	1685	1730	— 1600	—	7.40–7.50 (m, 2H, –CH=CH–), 7.80–7.90 (m, 7H, Ar–H) and 8.60 (s, 1H, C_4 of coumarin)	
3a	—	1705	1606	—	2.50 (s, 6H, $N(CH_3)_2$), 2.90 (t, 1H, CH at C_2), 4.40 (d, 2H, CH_2 at C_3, J = 8.5 Hz), 6.10 (d, 2H, J = 9 Hz, H-3', H-5'), 6.30–7.50 (m, 10H, Ar-H) and 8.00 (s, 1H, C_4 of coumarin)	124 (30), 125 (60), 147 (70), 251 (46), 279 (100), 356 (26), and 426 (10%)
4f	—	1710	—	3293	1.5 (s, 6H, $N(CH_3)_2$), 3.60 (d, 1H, C_2–H, J = 6Hz), 6.75 (d, 1H, C_3H, J = 6Hz), 7.0–8.2 (m, 13H, 12Ar–H and –NH–) and 8.35 (s, 1H, C_4 of coumarin)	—
5a	—	1707	1606	3360	2.40–2.60 (m, 2H, C_3–CH_2–) 3.10 (1H, s, C_5–NH, exchangeable with D_2O), 3.60 (1H, dd, C_2–H, J = 5 Hz and 8 Hz), 4.70 (dd, 1H, C_4–H, J = 7Hz and 10 Hz), 6.40–7.50 (m, 12H, aromatic protons) and 8.50 (s, 1H, C_4 of coumarin)	—
11a	—	1716 1670 ($NCOCH_3$)	—	—	2.2 (s, 3H, $COCH_3$), 1.80–2.10 (m, 2H, C_3, CH_2), 4,50–4.70 (m, 1H, C_2H), 5.50–5.60 (m, 1H, C_4-H), 6.90–7.40 (m, 12H, Ar–H) and 8.60 (s, 1H, C_4 of coumarin)	—

filtrate was removed in vacuum to give 5. This was recrystallized from n-hexane.

3-[5-Acetyl-2-(2-chlorophenyl)-2,3,4,5-tetrahydrobenzo[b][1,4] thiazepin-4-yl]chromen-2-one (11a)

A solution of 5a (0.001 mol) in dry Ac_2O (3 mL) and pyridine (0.1 mL) was refluxed for 2–3 h, cooled to r.t., and kept for 24 h at r.t., and poured into ice-cold water. The solid obtained was filtered, washed with water, and crystallized from ethanol to afford 11a.

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