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Synthesis of Some New Spiro Heterocycles from the Reaction of 2-Coumarylidenemalononitrile with Active Methylene and Bidentate Reagents

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SYNTHESIS OF SOME NEW SPIRO HETEROCYCLES FROM THE REACTION OF 2-COUMARYLIDENEMALONONITRILE WITH ACTIVE METHYLENE AND BIDENTATE REAGENTS

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Abstract: The reaction of 2-Coumarylidenemalononitriles **1a,b** with some active methylene, bidentates and ketoketene S, S or N, S acetals affords a series of new spiro heterocyclic systems.

α,β-Unsaturated nitriles are versatile reagents which have been extensively utilized in heterocyclic synthesis[1-4]. The physiological, antibacterial and antifungal properties of coumarin derivatives[5-10] prompted us to investigate the addition of active methylene, bidentates and ketoketene S,S or N,S acetals to 2-coumarylidenemalononitrile derivatives to synthesize new spiro heterocyclic systems attached to coumarin nucleus.

Compounds **1a,b** were prepared from the reaction of thiocoumarin or 6-methylthiocoumarin with malononitrile in refluxing ethanol in presence of triethylamine as a catalyst.

The active methylene compounds including ethylacetoacetate, acetyl-acetone, cyanoacetamide, 3-methyl-1-phenylpyrazol-5-one as well as the used

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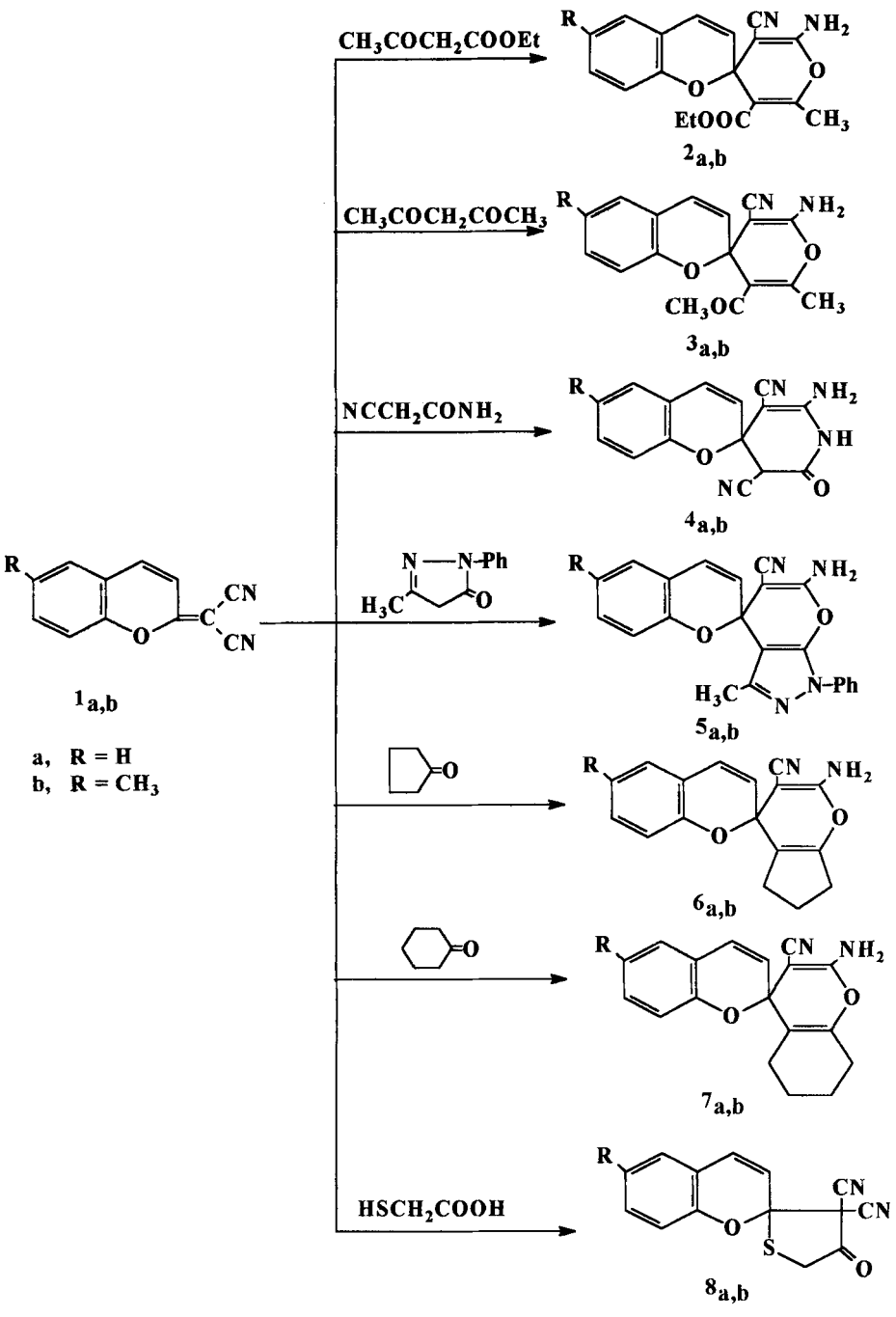
cycloalkanone (cyclopentanone or cyclohexanone) on reaction with 2-coumarylidenemalononitriles **1a,b** afforded the spiro compounds **2a,b - 7a,b** (cf Scheme 1).

The reaction pathway was assumed to follow the preliminary formation of carbanion of the active methylene compound or the cycloalkanone reagent followed by neucleophilic addition at the ethylenic bond and cyclization to give the desired spiro heterocycles.

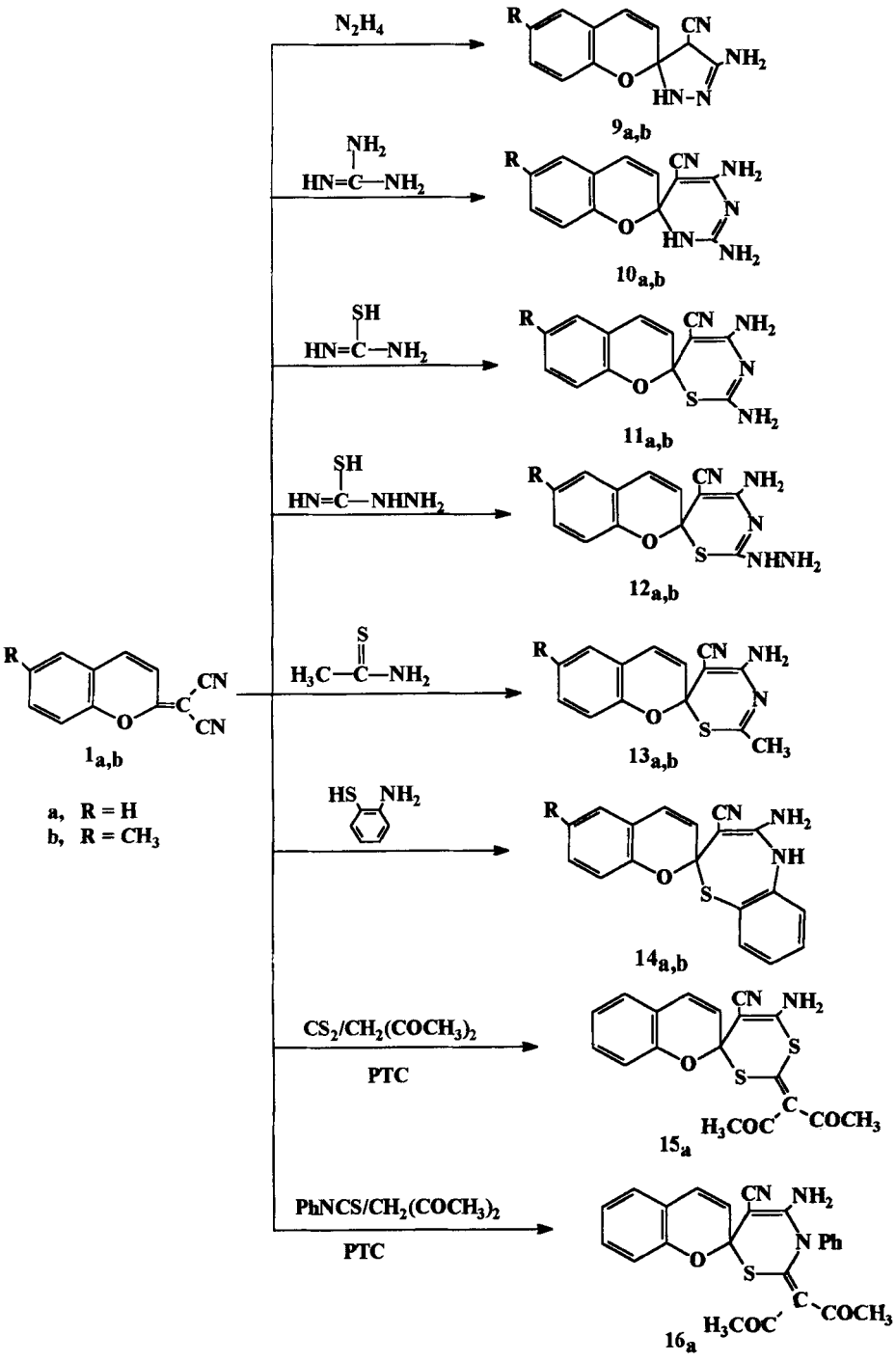
The reaction of compounds **1a,b** with mercaptoacetic acid[11,12] in refluxing pyridine gave the corresponding spiro thiophen-3-one derivatives **8a,b**. The postulated mechanism involves addition of the mercapto group on the ethylenic bond followed by cyclization via elimination of water molecule to afford the spiro compounds, (cf Scheme 1).

Treatment of compounds **1a,b** with bidentates namely hydrazine hydrate, guanidine hydrochloride, thiourea, thiosemicarbazide, thioacetamide or o-aminothiophenol gave the corresponding spiro pyrazole, pyrimidine, 1,3-thiazine or 1,5-benzothiazepine derivatives **9a,b - 14a,b** respectively, (cf Scheme 2).

The suggested reaction mechanism involves addition of the amino or mercapto groups at the ethylenic double bond followed by cyclization through nucleophilic attack of the amino or imino group at the cyano group to give the cyclized spiro products.



Scheme I



Scheme II

The reaction of compound **1a** with ketoketene S,S or N,S acetals, from the reaction of acetylacetone with CS_2 or phenylisothiocyanate under solid-liquid phase transfer catalysis (PTC) conditions [K_2CO_3/dioxan/tetrabutylammonium bromide (TBAB) catalyst], afforded the corresponding spiro dithiolane or 1,3-thiazine derivatives **15a** and **16a** respectively (cf Scheme 2).

All the new synthesized products are proved by their analytical (CHN) and spectral (IR, ^{1}H-NMR) data.

EXPERIMENTAL

Synthesis of 2-coumarylidenemalononitrile and 6-methylcoumarylidene-malononitrile 1a,b.

General procedure

To a solution of malononitrile (0.01 mol) in ethanol (50 ml) was added an equimolar amount of thiocoumarin or 6-methylthiocoumarin and few drops of triethyamine. The reaction mixture was refluxed for 5 h and concentrated. The separated solid was collected by filteration and recrystalized from ethanol (cf. Table I).

Synthesis of compounds 2a,b-7a,b.

General procedure

0.01 Mol of 2-coumarylidenemalononitrile **1** was added to a stirred mixture of the active methylene compounds or cycloalkanones and a catalytic amount of piperidine in 50 ml of ethanol. The reaction mixture was refluxed for 4 h then

Table I: Analytical and spectral data of the prepared compounds.

Comp. No.	Yield (%)	M.P. (°C)[a] Cryst. Solv.	M. Formula (M. Wt)	Analysis[b] Calc./Found			
				C	H	N	%
1_a	83	129	$C_{12}H_6N_2O$	74.22	3.11	14.43	
		(EtOH)	(194.18)	73.92	3.01	14.21	
1_b	86	121	$C_{13}H_8N_2O$	74.99	3.87	13.45	
		(EtOH)	(208.21)	74.63	3.65	13.23	
2_a	69	103	$C_{18}H_{16}N_2O_4$	66.67	4.97	8.64	
		(Benzene)	(324.32)	66.72	4.75	8.43	
2_b	83	129	$C_{19}H_{18}N_2O_4$	67.44	5.36	8.28	
		(Benzene)	(338.35)	67.22	5.16	8.11	
3_a	73	136	$C_{17}H_{14}N_2O_3$	69.37	4.80	9.52	
		(EtOH)	(294.30)	69.02	4.61	9.33	
3_b	77	143	$C_{18}H_{16}N_2O_3$	70.12	5.23	9.09	
		(EtOH)	(308.32)	69.90	5.11	9.16	
4_a	76	129	$C_{15}H_{10}N_4O_2$	64.74	3.62	20.14	
		(EtOH)	(278.26)	64.42	3.41	19.92	
4_b	79	133	$C_{16}H_{12}N_4O_2$	65.75	4.14	19.17	
		(EtOH)	(292.28)	65.42	4.01	19.03	
5_a	81	198	$C_{22}H_{16}N_4O_2$	71.72	4.38	15.21	
		(Dioxan)	(368.38)	71.54	4.17	14.99	
5_b	83	221	$C_{23}H_{18}N_4O_2$	72.24	4.74	14.65	
		(Dioxan)	(382.40)	71.98	4.51	14.43	
6_a	75	142	$C_{17}H_{14}N_2O_2$	73.36	5.07	10.07	
		(Benzene)	(278.30)	73.22	5.00	10.01	
6_b	77	143	$C_{18}H_{16}N_2O_2$	73.95	5.52	9.58	
		(Benzene)	(292.32)	73.59	5.31	9.74	
7_a	68	151	$C_{18}H_{16}N_2O_2$	73.95	5.52	9.58	
		(Benzene)	(292.32)	73.59	5.29	9.37	
7_b	70	162	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.14	
		(Benzene)	(306.35)	74.68	5.72	8.93	
8_a	68	176	$C_{14}H_8N_2O_2S$	62.67	3.01	10.44	
		(EtOH)	(268.28)	62.31	2.91	10.22	
8_b	68	196	$C_{15}H_{10}N_2O_2S$	63.81	3.57	9.92	
		(EtOH)	(282.31)	63.57	3.34	9.71	
9_a	63	156	$C_{12}H_{10}N_4O$	63.71	4.46	24.77	
		(EtOH)	(226.23)	63.57	4.27	24.55	
9_b	65	169	$C_{13}H_{12}N_4O$	64.99	5.03	23.32	
		(EtOH)	(240.25)	64.75	4.83	23.11	
10_a	71	190	$C_{13}H_{11}N_5O$	61.65	4.38	27.65	
		(EtOH)	(253.25)	61.37	4.22	27.43	
10_b	73	206	$C_{14}H_{13}N_5O$	62.91	4.90	26.20	
		(EtOH)	(267.28)	62.66	4.67	26.01	
11_a	68	154	$C_{13}H_{10}N_4OS$	57.76	3.73	20.73	
		(EtOH)	(270.30)	57.53	3.57	20.52	

(continued)

11_b	70	143 (EtOH)	$C_{14}H_{12}N_4OS$ (284.33)	59.14 58.86	4.25 4.05	19.71 19.53
12_a	59	149 (EtOH)	$C_{13}H_{11}N_5OS$ (285.32)	54.72 54.46	3.89 3.96	24.55 24.33
12_b	66	170 (EtOH)	$C_{14}H_{13}N_5OS$ (299.34)	56.17 55.90	4.38 4.28	23.40 23.18
13_a	72	110 (EtOH)	$C_{14}H_{11}N_3OS$ (269.31)	62.43 62.11	4.12 3.92	15.60 15.41
13_b	72	141 (EtOH)	$C_{15}H_{13}N_3OS$ (283.34)	63.58 63.36	4.62 4.39	14.83 14.61
14_a	57	203 (Dioxan)	$C_{18}H_{13}N_3OS$ (319.37)	67.69 67.33	4.10 3.90	13.16 13.01
14_b	66	223 (Dioxan)	$C_{19}H_{15}N_3OS$ (333.40)	68.44 68.16	4.54 4.69	12.60 12.41
15_a	55	181 (Benzene)	$C_{18}H_{14}N_2O_3S_2$ (370.43)	58.36 58.02	3.81 3.63	7.56 7.34
16_a	58	193 (Dioxan)	$C_{24}H_{19}N_3O_3S$ (429.48)	67.11 66.81	4.46 4.23	9.78 9.56

[a])Uncorrected [b]) Satisfactory microanalysis obtained C; ± 0.36 & H; ± 0.23 & N; ± 0.22

Table I: (Continued)

Comp. No.	IR (Kbr)[c] ν cm^{-1}	^{1}H-NMR[d] δ (ppm)
1_a	3079(CH,arom.);2193(2C≡N);1576 (C=C).	8.1-7.1(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin).
1_b	3061(CH,arom.);2911(CH,aliph.); 2197(2C≡N);1551(C=C).	8.0-6.8(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);2.3(s,3H,CH_3).
2_a	3333,3281(NH_2);3092(CH,arom.); 2943,2896(CH,aliph.);2198(C≡N); 1713(C=O);1605(C=C).	8.1-7.1(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);6.0-5.8(br,2H,NH_2);4.3-4.0(q,2H, CH_2);2.2(s,3H,CH_3);1.2-0.9(t,3H,CH_3 ester).
2_b	3306,3256(NH_2);3089(CH,arom.); 2951,2891(CH,aliph.);2201(C≡N); 1701(C=O);1609(C=C).	8.1-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.9-5.7(br,2H,NH_2);4.3-4.0(q,2H, CH_2);2.3(s,3H,Ar-CH_3); 2.2(s,3H,CH_3);1.2-0.9(t,3H, CH_3 ester).
3_a	3354,3299(NH_2);3071(CH,arom.); 2956,2889(CH,aliph.);2188(C≡N); 1656(C=O);1599(C=C).	8.0-7.0(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.8-5.6(br,2H,NH_2);2.2(s,3H, $COCH_3$);2.1(s,3H,CH_3).
3_b	3337,3286(NH_2);3090(CH,arom.); 2965,2898(CH,aliph.);2191(C≡N); 1661(C=O);1001(C=C).	7.9-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.9-5.7(br,2H,NH_2);2.3(s,3H, Ar-CH_3);2.2(s,3H,$COCH_3$);2.1(s,3H,CH_3).
4_a	3369,3296,3221(NH_2+NH);3069(CH, arom.);2961(CH,aliph.);2191(C≡N); 2212(C≡N);1681(C=O);1598(C=C).	10.9-10.7(br,1H,NH);8.1-7.0(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);4.9-4.7(br,2H, NH_2);3.1(s,1H,CH).

4_b	3390,3339,3261(NH_2+NH);3060(CH, arom.);2956,2889(CH,aliph.);2190 (C≡N);2206(C≡N);1676(C=O); 1591(C=C).	11.2-11.0(br,1H,NH);8.2-7.0(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.0-4.8(br,2H, NH_2);3.1(s,1H,CH);2.3(s,3H,CH_3).
5_a	3422,3381(NH_2);3061(CH,arom.); 2963,2879(CH,aliph.);2203(C≡N); 1593(C=C).	8.2-6.9(m,10H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.8-5.6(br,2H,NH_2);2.1(s,3H,CH_3).
5_b	3396,3326(NH_2);3019(CH,arom.); 2936,2879(CH,aliph.);2199(C≡N); 1601(C=C).	8.1-6.8(m,9H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.8-5.6(br,2H,NH_2);2.3(s,3H, Ar-CH_3);2.1(s,3H,CH_3).
6_a	3330,3286(NH_2);3063(CH,arom.); 2961,2887(CH,aliph.);2191(C≡N); 1606(C=C).	8.2-7.1(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.9-5.7(br,2H,NH_2);1.8-1.2(m,6H, cyclic CH_2).
6_b	3336,3289(NH_2);3072(CH,arom.); 2973,2896(CH,aliph.);2199(C≡N); 1601(C=C).	8.1-7.1(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);6.0-5.8(br,2H,NH_2);2.3(s,3H,CH_3); 1.8-1.3(m,6H, cyclic CH_2).
7_a	3398,3339(NH_2);3060(CH,arom.); 2970,2896(CH,aliph.);2199(C≡N); 1607(C=C).	8.2-7.0(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);6.1-5.8(br,2H,NH_2);1.8-1.2(m,8H, cyclic CH_2).
7_b	3326,3289(NH_2);3082(CH,arom.); 2936,2859(CH,aliph.);2201(C≡N); 1599(C=C).	8.0-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);6.0-5.8(br,2H,NH_2);2.3(s,3H,CH_3); 1.8-1.2(m,8H, cyclic CH_2).
8_a	3091(CH,arom.);2920(CH,aliph.) 2199(2C≡N);1709(C=O);1611(C=C)	8.1-6.9(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);3.9(s,2H,CH_2).
8_b	3072(CH,arom.);2930,2879(CH, aliph.)2203(2C≡N);1698(C=O);1601 (C=C).	8.0-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);3.9(s,2H,CH_2);2.3(s,3H,CH_3).
9_a	3389,3319,3208(NH_2+NH);3091(CH, arom.);2990(CH,aliph.);2201(C≡N); 1628(C=N);1603(C=C).	10.6-10.4(br,1H,NH);8.2-7.0(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);6.1-5.9(br,2H, NH_2).
9_b	3362,3281,3213(NH_2+NH);3039(CH, arom.);2969(CH,aliph.);2205(C≡N); 1630(C=N);1609(C=C).	10.8-10.6(br,1H,NH);8.1-7.0(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);6.1-5.9(br,2H, NH_2);2.3(s,3H,CH_3).
10_a	3399,3356,3281,3211(2NH_2+NH); 3056(CH,arom.);2200(C≡N);1622 (C=N);1591(C=C).	11.0-10.8(br,1H,NH);8.2-6.9(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.7-5.0(br,4H, 2NH_2).
10_b	3411,3376,3322,3290(2NH_2+NH); 3019(CH,arom.);2970(CH,aliph.) 2203(C≡N);1632(C=N)1602(C=C).	11.8-10.8(br,1H,NH);8.1-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.7-5.0(br,4H, 2NH_2);2.3(s,3H,CH_3).
11_a	3402,3381,3332,3286(2NH_2);3090 (CHarom.);2199(C≡N);1636(C=N); 1589(C=C).	8.2-7.0(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.9-5.0(br,4H,2NH_2).
11_b	3411,3376,3322,3290(2NH_2);3063 (CHarom.);2911,2880(CH,aliph.); 2207 (C≡N);1640(C=N)1600(C=C).	8.1-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.9-5.1(br,4H,2NH_2);2.3(s,3H,CH_3).
12_a	3442,3388,3329,3296,3226(2NH_2+ NH);3030(CH,arom.)2202(C≡N); 1619(C=N);1589(C=C).	12.1-11.8(br,1H,NH);8.2-6.9(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.4-4.7(br,4H, 2NH_2).

(continued)

Table 1: Continued.

12_b	**3411,3366,3296,3201($2NH_2$+NH); 3051(CH,arom.);2941(CH,aliph.) 2200(C≡N);1621(C=N);1586(C=C).**	**12.2-11.9(br,1H,NH);8.1-7.0(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.3-4.7(br,4H, $2NH_2$);2.3(s,3H,CH_3).**
13_a	**3386,3333(NH_2);3071(CH,arom.); 2930,2866(CH,aliph.);2188(C≡N); 1616(C=N);1589(C=C).**	**8.1-6.9(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.1-4.8(br,2H,NH_2);2.1(s,3H,CH_3).**
13_b	**3396,3361(NH_2);3033(CH,arom.); 2919,2859(CH,aliph.);2193(C≡N); 1621(C=N);1595(C=C).**	**8.1-6.9(m,4H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.1-4.8(br,2H,NH_2);2.3(s,3H, Ar-CH_3);2.1(s,3H,CH_3).**
14_a	**3411,3366,3281(NH_2+NH);3071(CH, arom.);2199(C≡N);1600(C=C).**	**9.9-9.7(br,1H,NH);8.1-6.9(m,9H,arom.);6.6-6.4 (d,1H,proton 3 in coumarin);4.9-4.6(br,2H,NH_2**
14_b	**3413,3371,3290(NH_2+NH);3050(CH, arom.);2961,2888(CH,aliph.);2200 (C≡N);1605(C=C).**	**10.8-10.6(br,1H,NH);8.1-6.8(m,8H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);4.8-4.6(br, 2H, NH_2); 2.3(s,3H,CH_3).**
15_a	**3400,3349(NH_2);3033(CH,arom.); 2991,2860(CH,aliph.);2196(C≡N); 1681(2C=O);1601(C=C).**	**8.2-6.9(m,5H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.6-5.3(br, 2H, NH_2); 2.1(s,6H, $2CH_3$).**
16_a	**3385,3332(NH_2);3020(CH,arom.); 2966,2831(CH,aliph.);2202(C≡N); 1688(2C=O);1600(C=C).**	**8.2-6.7(m,10H,arom.);6.6-6.4(d,1H,proton 3 in coumarin);5.3-5.0(br, 2H,NH_2); 2.1(s,6H, $2CH_3$).**

[c] Measured on Nicolet 710 FT-IR Spectrophotometer.
[d] Measured with a varian EM 360 L using TMS as internal standard.

concentrated and left to cool. The desired precipitated product, was filtered off and recrystallized from the proper solvent, cf. Scheme 1, Table I.

Synthesis of compounds 8a,b.

A mixture of compound **1** (0.01 mol), mercaptoacetic acid (0.01 mol) and pyridine (20ml) was refluxed for 6 h. The reaction mixture was cooled, poured into cold water. The precipitated solid was filtered off and recrystallized from ethanol, cf. Table I.

Synthesis of compounds 9a,b-14a,b

General procedure

A solution of compound **1** (0.01 mol) in ethanol (30ml) was treated with the proper bidentate (0.01mol) and few drops of piperidine. The reaction mixture was refluxed for 3 h, concentrated, cooled and the separated solid was filtered off and recrystallized from the suitable solvent, cf. Scheme 2, Table I.

Synthesis of compounds 15a-16a

General procedure

0.01 Mole of acetylacetone along with 0.01 mole of CS_2 or 0.01 mole of phenylisothiocyanate in 50 ml dioxane was treated with 2 grams of anhydrous potassium carbonate. The formed dianionic ambident compound was then treated with 0.01 mol of compound **1** and catalytic amount of TBAB. The reaction mixture was stirred for 4 h at 60 °C whereby a noticeable change in colour was observed. The reaction mixture was filtered. The filterate was evaporated in vacuo. The residue was washed with light petroleum ether, collected by filteration and crystallized, cf. Scheme 2, Table I.

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