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Note

A facile one step synthesis of some 3-trifluoromethyl-7*H*-6(6/8, 6,8-disubstituted-3-coumarino)-*s*-triazolo[3,4-*b*][1,3,4]-thiadiazines and 3-(2-phenyl hydrazino thiazolyl) coumarins

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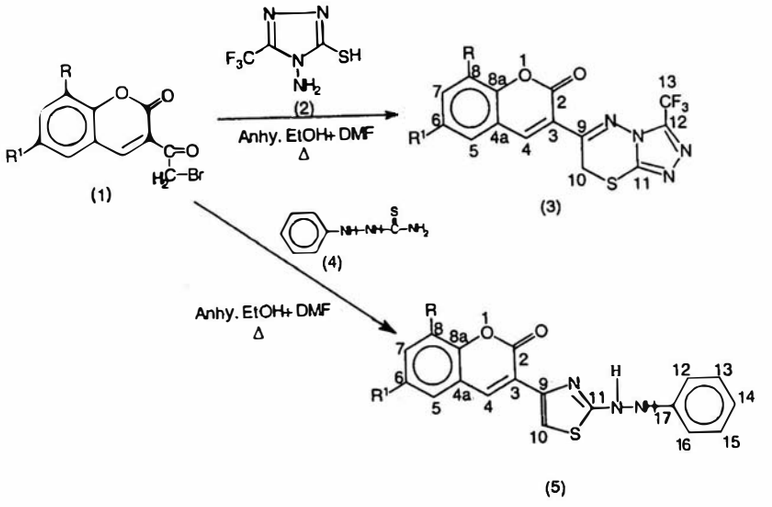
3-Trifluoromethyl-7*H*-6(6 or 8, or 6,8-disubstituted-3-coumarino)-*s*-triazolo [3,4-*b*][1,3,4] thiadiazines **3** have been prepared from simple condensation of appropriate 3-trifluoromethyl-4-amino-5-mercapto-1,2,4-triazole **2** with various 3(2-bromoacetyl)coumarins in anhyd. ethanol and dimethyl formamide. Some 3-(2-phenyl hydrazino-4-thiazolyl) courmarins **5** have also been prepared by the condensation of 3-(2-bromoacetyl) coumarins **1** and N^4-phenyl thiosemicarbazide **4** in anhyd. ethanol and dimethyl formamide.

Courmarin nucleus is found in a variety of natural products exhibiting various pharmacological effects. Derivatives of coumarin also form component of important drugs having varied properties. There are excellent monographs and review articles[1-5] describing the structure, synthetic reactions and properties of coumarins. Numerous reports have appeared in the literature describing antimicrobial[6,7], antiradiation[8,9] and antiparasitic[10] properties of thiazole ring. Various 1,2,4-triazoles and *N*-bridged heterocycles derived from them are found to be associated with diverse pharmacological activity[11-16]. The 1,2,4-triazole nucleus has been recently incorporated into wide variety of therapeutically interesting drugs including H_1/H_2 histamine receptor blockers, cholinesterase active agents, CNS stimulants, antianxiety agents and sedatives[17]. Prompted by the above observations and in continuation of our search for biologically active[18-20] nitrogen and sulphur heterocycles it was contemplated to synthesize these heterocyclic coumarins. The 3-trifluoro methyl 7*H*-6-(6 or 8 or 6,8 disubstituted 3-coumarino-s-triazolo [3,4-*b*] [1,3,4] thiadiazines **3a-i** were synthesized by condensing 3-trifluoromethyl-4-amino-5-mercapto-1,2,4-triazole **2** with 3-(2-bromo-acetyl)coumarins **1** in equal volumes of anhyd. ethanol and dimethyl formamide (**Scheme I**). All the compounds displayed strong absorption bands due to –C=N- and lactone carbonyl of coumarin absorptions at 1606 and 1716 cm^{-1} respectively. The ^{1}H-NMR ($CDCl_3$, δ ppm) spectrum of **3a** showed the singlet for two protons at 4.21, corresponds to those of -S-CH_2- of the thiadiazine ring. Apart from this peak, other characteristic signals at 7.39 to 7.44 (m, 2H, H_6 and H_8), 7.69 to 7.74 (m, 2H, H_5 and H_7) and 8.44 (s, 1H, coumarin C_4) is also in accordance with the proposed



Scheme I

Table I—^{13}C-NMR spectral data of **3a**

Carbon No.	Chemical shift value (δ ppm)	Carbon No.	Chemical shift value **5a** (δ ppm)
2	159.07	2	165.05
3	118.78	3	115.66
4	122.70	4	142.35
4a	126.01	4a	118.84
5	121.00	5	127.91
6	125.86	6	127.61
7	130.78	7	131.03
8	116.96	8	127.80
8a	154.68	8a	153.02
9	134.88	9	147.05
10	24.92	10	115.66
11	156.46	11	173.00
12	145.84	12	114.03
13	110.00	13	128.66
		14	124.04
		15	128.60
		16	114.03
		17	158.48

structure. The ^{13}C-NMR (DMSO-d_6) of **3a**, recorded on a Varian dpx 200 NMR spectrometer, displayed 14 signals. The signal assignments are based on the values for model compounds. The signals at downfield 159.07, 156.46, 154.68 and 145.84 corresponds to C_2, C_{11}, 8a and C_{12} respectively. The signals at different values of coumarin nucleus are in good agreement with literature values[23]. **Table I** indicates the detailed assignment of ^{13}C signals.

In the mass spectrum the molecular ion has been recorded at m/z 352 and is accompanied by the characteristic M+2 peak. This indicates the presence of one sulphur atom. In the fragmentation, the molecular ion gives the characteristic fragment of protonated 3-cyano coumarin (A) at m/z 172. Fragment 'A' loses carbon monoxide to give B at m/z 143. Fragment 'A'loses hydrogen to give ion radical 'C' at m/z 171. The fragment 'C' by loss of hydrogen radical gives a fragment 'D' at m/z 170. The detailed fragmentation pattern of the spectrum is given in the mass spectrum **Chart 1**.

The 3-(2-phenyl hydrazino-4-thiazolyl) coumarins **5a-g** were synthesized by condensing 3-(2-bromo-acetyl)coumarins **1** with N^4-phenyl thiosemicarbazide **4** in anhyd. ethanol and dimethyl formamide.

Compound **5a** exhibited in its IR (KBr) spectrum bands at 1404 to 1608 (thiazole)[24], 1718 (lactone carbonyl) and 3310 cm^{-1} (-NH-streching vibration). ^{1}H NMR ($CDCl_3$) : δ 7.00 – 8.00 (m, 9H, Ar-H), 8.35 (s, 1H, C_4 of coumarin) and 10.2 (s, 2H, -NH-NH-, D_2O exchangeable). The ^{13}C NMR spectrum of **5a**

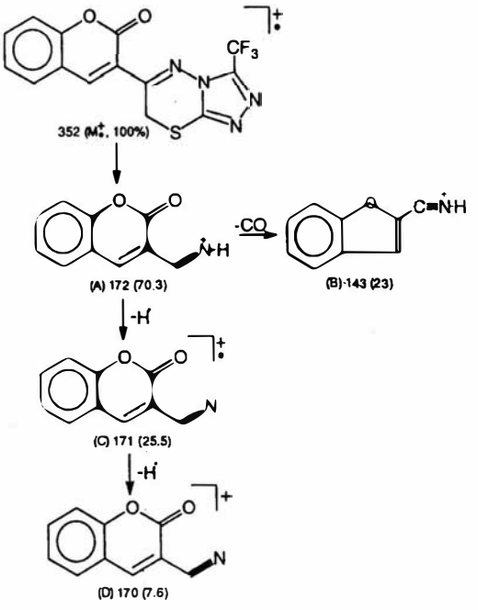


Chart 1

recorded on a Brucker 200 MHz instrument, displayed 18 signals. The most downfield signal of spectrum was observed at 173 of C_2 of thiazole. The peak at 165.05 in the spectrum may be assignable to the lactone carbonyl. The signals at 147.05, 115.66 and 173.00 are in good agreement with the values recorded for C_9, C_{10} and C_{11} of thiazole nucleus. The signals at different values for the coumarin nucleus are in good agreement with literature values. **Table I** indicates the detailed assignment of ^{13}C signals.

In the mass spectrum, the molecular ion of 3-(2-phenyl hydrazino-4-thiazolyl) coumarin was recorded at m/z 335. The molecular ion splits up to give a fragment (A) at m/z 224. Molecular ion gives ion radical (B) at m/z 146. This loses hydrogen radical to give an ion (C) at m/z 145. Molecular ion decomposes to give ion (E) at m/z 43. This ion forms the base peak of the spectrum (**Chart 2**).

Experimental Section

All melting points were determined in open capillary tubes using sulphuric acid bath and are uncorrected. IR spectra (ν_{max}, cm^{-1}) were recorded on Perkin Elmer-282 instrument and ^{1}H NMR spectra on a Varian 200 MHz spectrometer using tetramethyl silane as internal standard (chemical shift values are expressed in δ, ppm). Mass spectra were scanned on a Jeol-JMS-300 spectrometer at 70 eV. The purity of compounds was monitored by TLC performed on

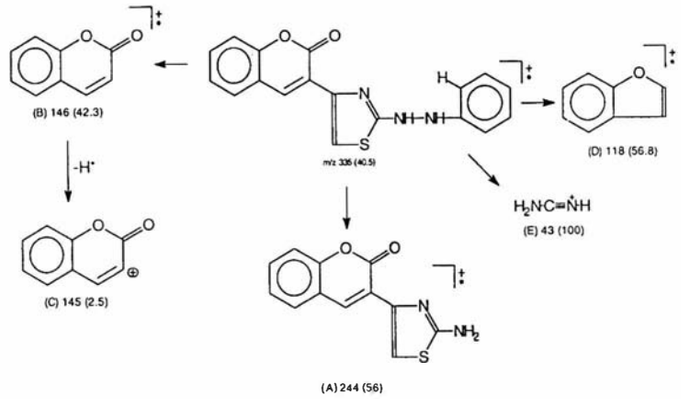


Chart 2

Table II—Analytical and physical data of compounds **3** and **5**

Compd		m.p. (°C)	Yield (%)	Recrystallized from	Mol. formula (M. wt.)	Found (Calcd)% N	S
3a	$R=R^1=H$	220-22	80	aq. DMF	$C_{14}H_7N_4F_3O_2S$ (352)	15.88 (15.90	8.99 9.09)
3b	$R=OCH_3$, $R^1=H$	230-32	78	aq. DMF	$C_{15}H_9N_4F_3O_3S$ (382)	14.63 (14.65	8.35 8.37)
3c	$R=H$, $R^1=Br$	241-42	80	aq. DMF	$C_{14}H_6N_4Br_2F_3O_2S$ (431)	12.95 (12.99	7.40 7.42)
3d	$R=R^1=Br$	228-30	82	aq. DMF	$C_{14}H_5N_4Br_2F_3O_2S$ (510)	10.95 (10.98	6.25 6.27)
3e	5,6-Benzo	222-24	82	aq. DMF	$C_{18}H_9N_4F_3O_2S$ (402)	13.90 (13.93	7.94 7.96)
3f	$R=H$, $R^1=Cl$	220-22	75	aq. DMF	$C_{14}H_6N_4ClF_3O_2S$ (368.5)	14.45 (14.48	8.25 8.27)
3g	$R=R^1=Cl$	180-82	70	aq. DMF	$C_{14}H_5N_4Cl_2F_3O_2S$ (421)	13.27 (13.30	7.58 7.60)
3h	$R=OCH_3$ $R^1=Br$	218-20	75	aq. DMF	$C_{15}H_8N_4BrF_3O_2S$ (461)	12.11 (12.14	6.92 6.94)
3i	$R=OCH_3$, $R^1=NO_2$	218-20	75	aq. DMF	$C_{15}H_8N_5F_3O_5S$ (427)	16.37 (16.39	7.47 7.49)
5a	$R=R^1=H$	258-60	70	CH_3OH	$C_{18}H_{13}N_3O_2S$ (335)	12.51 (12.53	9.50 9.55)
5b	$R=OCH_3$, $R^1=H$	128-30	75	CH_3OH	$C_{19}H_{15}N_3O_3S$ (365)	11.47 (11.50	8.72 8.76)
5c	$R=H$, $R^1=Br$	140-42	72	C_6H_6	$C_{18}H_{12}N_3BrO_2S$ (414)	10.12 (10.14	7.70 7.72)
5d	$R=R^1=Br$	147-49	73	C_6H_6	$C_{18}H_{11}N_3Br_2O_2S$ (493)	8.48 (8.51	6.47 6.49)
5e	$R=H$, $R^1=Cl$	134-36	71	CH_3OH	$C_{18}H_{12}N_3ClO_2S$ (369.5)	11.34 (11.36	8.63 8.66)
5f	$R=R^1=Cl$	110-12	76	C_6H_6	$C_{18}H_{11}N_3Cl_2O_2S$ (404)	10.36 (10.39	7.90 7.92)
5g	5,6-Benzo	132-34	72	C_6H_6	$C_{22}H_{15}N_3O_2S$ (385)	10.89 (10.90	8.30 8.31)

silica gel plates (Merck) using benzene and acetone (3:1) solvent. 3-Trifluoro-4-amino-5-mercapto-1,2,4-triazole[21] **2** and 3-(2-bromoacetyl) coumarins[22] were prepared according to the literature procedure.

Synthesis of 3-trifluoro-7*H*-6-(6 or 8 or 6,8-disubstituted-3-coumarino)-s-triazolo[3,4-*b*][1,3,4]-thiadiazines 3. An equimolar mixture of 3-trifluoro-4-amino-5-mercapto-1,2,4-triazole (0.01 mole) and 3-(2-bromoacetyl) coumarin (0.01 mole) in anhyd. ethanol and dimethyl formamide (10 mL each) was heated under reflux for 2 hr. The reaction mixture was then cooled to room temperature. The precipitated

solids were collected by filtration, washed with ethanol, dried and recrystallized viz. **Table II**.

Synthesis of 3-(2-phenyl hydrazino-4-thiazolyl)-coumarin 5. A mixture of N^4-phenyl thiosemicarbazide (0.01 mole) and 3-(2-bromoacetyl) coumarin (0.01 mole) was refluxed in either equal volumes of anhyd. ethanol and dimethyl formamide or in anhyd. ethanol and catalytical amounts of piperidine for 2 hr. The reaction mixture was cooled, the solid separated was filtered and crystallized viz. **Table II**.

Acknowledgement

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