SYNTHESIS OF SOME NEW 3-(2-OXO-2H-CHROMEN-3-YL)-5H-[1,3]THIAZOLO[3,2-a] PYRIMIDINE-5-ONES

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Abstract: Condensation of 3-(2-amino-4-thiazolyl)coumarins (I) with α-acetyl-γ-butyrolactone in a mixture of polyphosphoric acid and $POCl_3$ affords 6-(2-chloromethyl)-7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]-thiazolo[3,2-a] pyrimidine-5-one (IIa-f), while condensation of I with β-ketoesters gives 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo [3,2-a]pyrimidine-5-ones (IIIa-g). Reaction between I and diethyl methoxy methylene malonate under solvent free conditions gives 3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-one-6-carboxylic acid ethyl ester (IV). The structures of newly synthesized compounds have been established by elemental analysis and spectral data.

Introduction

Benzopyran-2-ones exhibit significant biological activities. Coumarins bearing heterocyclic moiety at 3rd position are spasmolytic[1], uricosuric[2] and CNS active agents.[3] Further thiazole[4] and also coumarin derivatives with heterocyclic system at the 3rd position exhibit promising biological activities[5]. In view of this and in continuation of our earlier work on the synthesis of heterocyclic systems from coumarin derivatives[6-9], we report here the synthesis of some new heterocyclic thiazolo pyrimidine-5-ones of coumarins by making use of 3-(2-amino-4-thiazolyl)coumarins.

Experimental

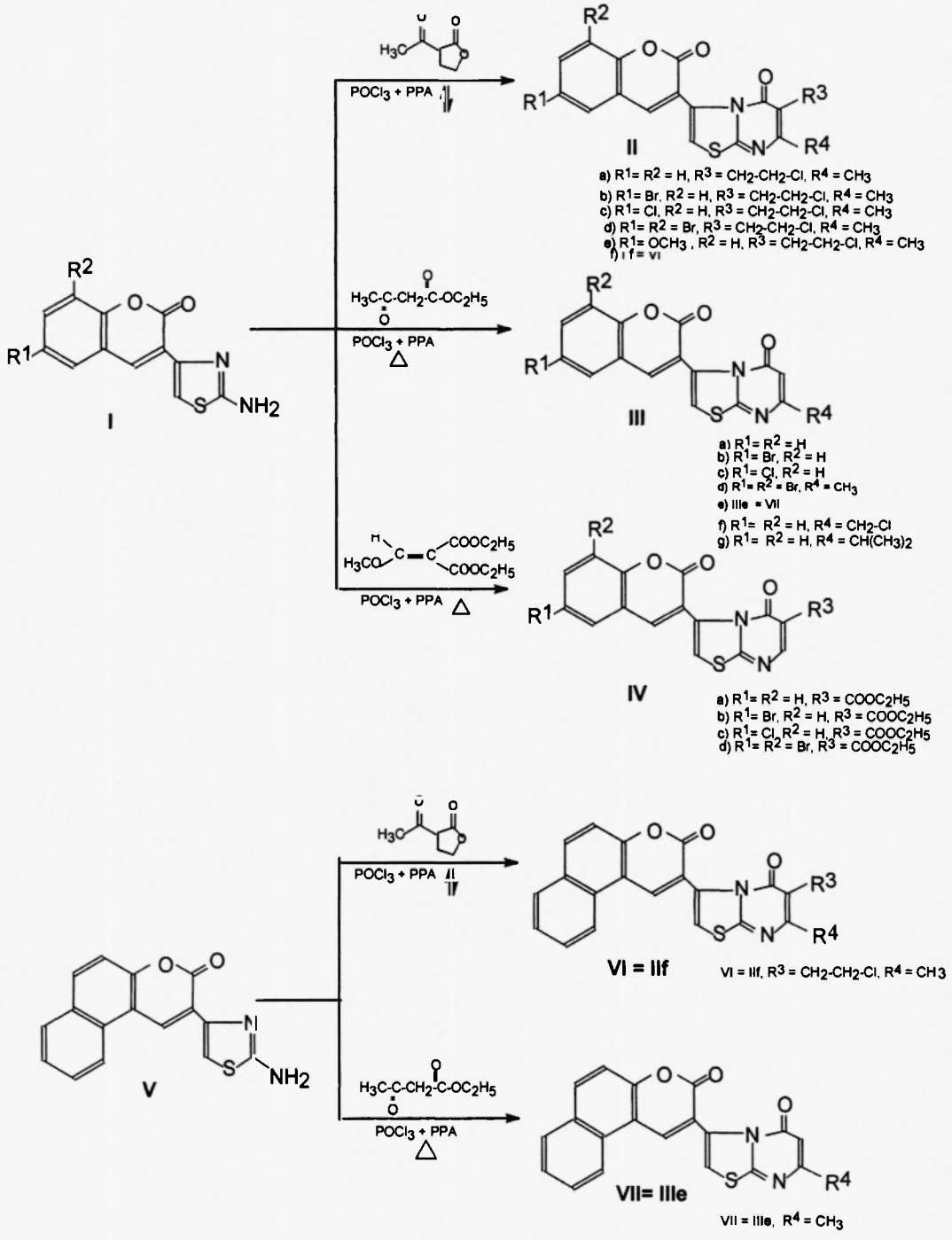
All meting points were determined by POLMAN-MP apparatus (model no. MP-96), IR spectra (ν_{max} cm^{-1}) were recorded on Perkin-Elmer spectrophotometer. The ^1H NMR was recorded on Bruker-Avance 300 MHz instrument and the chemical shifts were recorded δ ppm using TMS as an internal standard. The mass spectra were scanned on Perkin-Elmer SCIEX API-2000 instrument (Scheme-1).

6-(2-Chloromethyl)-7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-one (II)

A mixture of 3-(2-amino-4-thiazolyl)-2H-chromen-2-one (0.01 mol) and phosphorus oxychloride (0.05 mol) were heated to 80°C added α-acetyl-γ-butyrolactone (0.02 mol) and polyphosphoric acid (0.025 mol) and maintained for 2 hrs at 80-85°C to complete the cyclisation. The mass was cooled to 25°C, diluted with 20 ml water; the solid was filtered, washed with 5% sodium bicarbonate solution. Recrystallised from methanol.

7-Methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-one (III)

A mixture of 3-(2-amino-4-thiazolyl)-2H-1-benzopyran-2-one (0.01 mol) and ethyl acetoacetate (0.01 mol) was suspended in phosphorous oxychloride (0.03 mol) at 25°C added freshly prepared polyphosphoric acid (0.003 mol), raised the temp. to 90°C and maintained for 1 hr till the HCl evolution subsides. Reaction mass was cooled to 25°C and 25 ml of water was added. Filtered the solid, washed with 5% sodium bicarbonate solution and recrystallized from methanol.



Scheme 1

3-(2-Oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-one-6-carboxylic acid ethyl ester (IV)

A mixture of 3-(2-amino-4-thiazolyl)-2H-chromen-2-one (0.01 mol) and methoxy methylene diethyl malonate (0.02 mol) was heated to 140°C for 4 hrs. The reaction mixture was cooled to 50 °C. The mixture was treated with phosphorous oxychloride (0.03 mol) and polyphosphoric acid (0.003 mol).

The reaction mixture was further heated for 1 hr at 100 °C. The reaction mixture was cooled, the oily residue obtained was treated with ethanol and washed with 5% sodium bicarbonate solution. The solid obtained was recrystallised from methanol to get pure pyrimidine derivative in 40% yield. Analytical data of synthesized compounds is included in Table-1.

Results and Discussion

The derivatives of 2-aminothiazole[11] and pyrimidine[12] are of current interest in view of their broad spectrum biological activity. Reaction of 3-(2-amino-4-thiazolyl)coumarins with α-acetyl-γ-butyrolactone, β-ketoesters and diethylmethoxy methylene malonate leads to ring closure reaction (Scheme-1). When the above reactions were carried out with the versatile cyclocondensing agents like polyphosphoric acid or phosphorous oxychloride separately in the synthesis of nitrogen bridged ring systems have failed. Hence, in the present investigation an attempt has been made to use the mixture of phosphorus oxychloride and polyphosphoric acid as useful cyclizing agent for the synthesis nitrogen bridged ring systems. The reaction of α-acetyl-γ-butyrolactone with 3-(2-amino-4-thiazolyl)coumarins in a mixture of phosphorus oxychloride and polyphosphoric acid afforded the expected 6-(2-chloromethyl)-7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a] pyrimidine-5-one (II) in good yields. The IR spectra of II with bands in the region of 1595-1609 (-C=N-), 1656-1660 (-CO-O-, pyrimidine ring) and 1717 – 1728 (lactone – C=O-). The structures of II were supported by their ^{1}H NMR spectra. The ^{1}H-NMR spectrum of IIa exhibited a characteristic triplet for $-CH_2$ at δ 2.86 – 2.91 and another triplet for $-CH_2$-Cl at δ 3.62 – 3.66 of side chain. The coumarin C_4 proton appeared as characteristic singlet at δ 8.15 – 8.51. The remaining protons were observed in the usual region.

The synthesis of 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-ones (III) accomplished in good yields by condensing substituted 3-(2-amino-4-thiazolyl)coumarin (I) with β-ketoesters. The 3-(2-amino-4-thiazolyl)coumarins (I) in turn were prepared from the corresponding 3-(2-bromoacetyl)coumarins following the literature procedure[9]. All the 7-methyl-3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-ones (III) displayed strong absorption bands due to –C=N-, cyclic amide, and lactone –C=O at 1590-1606, 1677-1684 and 1720-1748 cm^{-1}. The structures of III were supported by their ^{1}H-NMR spectra. The ^{1}H-NMR spectrum of IIIa exhibited a characteristic singlet for vinylic proton at δ 6.07. The C_4 proton of coumarin appeared as characteristic singlet at 8.58. The remaining protons were observed in the usual region. 3-(2-aminothiazolyl)coumarins (I) on treatmentwith diethylmethoxy methylene malonate under solvent free conditions using a mixture of phosphorous oxychloride and polyphosphoric acid resulted in the formation of cycloproduct 3-(2-oxo-2H-chromen-3-yl)-5H-[1,3]thiazolo[3,2-a]pyrimidine-5-one-6-carboxylic acid ethylester (IV). IVa exhibited absorption bands at 1680, 1723, 1704 due to the pyrimidine ring >C=O, ester >C=O and lactone >C=O respectively. The PMR spectrum of IVa did not reveal any exchangeable proton and exhibited only a downfield multiplet (δ 7.35 – 7.86) due to aromatic and vinylic protons. Spectral data is presented in Table-2.

Table-1 : Analytical data of compounds II, III, IV, VI and VII

Compd.*	R^1	R^2	R^3	R^4	mp (°C)	Formula (m.w.)	Calc. (Found) %	
							N	S
IIa	H	H	CH_2CH_2Cl	CH_3	233-235	$C_{18}H_{13}ClN_2O_3S$ (372.5)	7.46 (7.54)	8.59 (8.60)
IIb	Br	H	CH_2CH_2Cl	CH_3	254-256	$C_{18}H_{12}BrClN_2O_3S$ (451.5)	6.12 (6.19)	7.08 (7.11)
IIc	Cl	H	CH_2CH_2Cl	CH_3	238-240	$C_{18}H_{12}Cl_2N_2O_3S$ (407)	6.87 (6.89)	7.80 (7.87)
IId	Br	Br	CH_2CH_2Cl	CH_3	230-232	$C_{18}H_{11}Br_2ClN_2O_3S$ (530.5)	5.20 (5.28)	6.03 (6.06)
IIe	OCH_3	H	CH_2CH_2Cl	CH_3	236-238	$C_{19}H_{15}ClN_2O_4S$ (403.5)	6.93 (6.91)	7.96 (7.90)
IIf=VI	--	--	CH_2CH_2Cl	CH_3	278-280	$C_{22}H_{15}ClN_2O_3S$ (422.5)	6.62 (6.65)	7.57 (7.60)
IIIa	H	H	--	CH_3	230-232	$C_{16}H_{10}ClN_2O_3S$ (310)	9.00 (9.08)	10.35 (10.30)
IIIb	Br	H	--	CH_3	264-266	$C_{16}H_9BrN_2O_3S$ (389)	7.15 (7.21)	8.22 (8.19)
IIIc	Cl	H	--	CH_3	>300	$C_{16}H_9ClN_2O_3S$ (344.5)	8.12 (8.15)	9.28 (9.30)
IIId	Br	Br	--	CH_3	>300	$C_{16}H_8Br_2N_2O_3S$ (468)	5.98 (6.00)	6.83 (6.86)
IIIe=VII	--	--	--	CH_3	198-200	$C_{20}H_{12}N_2O_3S$ (360)	7.77 (7.70)	8.80 (8.78)
IIIf	H	H	--	CH_2Cl	169-172	$C_{16}H_9ClN_2O_3S$ (344.5)	8.12 (8.15)	9.28 (9.31)
IIIg	H	H	--	$CH(CH_3)_2$	198-200	$C_{18}H_{14}N_2O_3S$ (338)	8.28 (8.30)	9.46 (9.50)
IVa	H	H	$COOC_2H_5$	--	278-280	$C_{18}H_{12}N_2O_5S$ (368)	7.60 (7.56)	8.69 (8.71)
IVb	Br	H	$COOC_2H_5$	--	208-210	$C_{18}H_{11}BrN_2O_5S$ (447)	6.26 (6.30)	7.15 (7.19)
IVc	Cl	H	$COOC_2H_5$	--	218-220	$C_{18}H_{11}ClN_2O_5S$ (392.5)	7.13 (7.16)	8.15 (8.12)
IVd	Br	Br	$COOC_2H_5$	--	270-272	$C_{18}H_{10}Br_2N_2O_5S$ (526)	5.32 (5.35)	6.08 (6.10)

*All the compounds were recrystallized from methanol.

* Compounds IIa – IIf were obtained in 70 – 80% yield. While IIIa – IIIg 70 – 85%. The remaining compounds IVa – IVd in 30 – 40% yield

Table- 2 : Spectra data.

Compd.	IR (ν_{max} cm^{-1})			^{1}H-NMR (δ ppm) solvent DMSO-d_6	Mass spectrum
	-C=N-	-C=O Pyrimidone	-COO- Lactone		
IIa	1604	1656	1717	2.39 (s, 1H, -CH_3), 2.86-2.91 (t, 2H, CH_2), 3.62-3.664 (t, 2H, CH_2Cl), 7.41-7.79(m, 5H, ArH), 8.15 (s, 1H, C_4-H of coumarin)	372(100), 374(45), 336(50), 394(42, Na adduct)
IIb	1602	1658	1724	2.39 (s, 3H, CH_3), 2.86-2.91 (t, 2H, CH_2), 3.62-3.67 (m, 2H, CH_2Cl), 7.46-7.49 (d, 1H, ArH), 7.63 (s, 1H, thiazole), 7.82-7.85(d, 1H, ArH), 8.05-8.09 (m, 2H, ArH)	----
IIc	1604	1660	1726	2.39 (s,3H, CH_3), 2.86-2.91 (t, 2H, CH_2), 3.61-3.66 (t, 2H, CH_2), 7.5-7.55 (d, 1H, ArH), 7.64 (s, 1H, thiazole), 7.70-7.74 (d, 1H, ArH), 7.79-7.92 (d, 1H, ArH), 8.1 (s, 1H, C_4-H of coumarin)	407 (100), 409 (70), 473 (20), 371 (50), 279 (80), 429 (30)
IId	1595	1660	1728	2.39 (s, 3H, CH_3), 2.87-2.92 (t, 2H, CH_2), 3.62-3.67 (t, 2H, CH_2Cl), 7.63 (s, 1H, thiazole), 8.07-8.09 (m, 2H, ArH)	---
IIe	---	---	---	2.38 (s, 3H, CH_3), 2.87-2.92 (t, 2H, -CH_2-), 3.62-3.67 (t, 2H, -CH_2Cl), 3.89(s, 2H, -OCH_3), 6.96-6.98 (d, 1H, ArH), 7.05 (d, 1H, ArH), 7.58 (s, 1H, thiazole), 7.68-7.7 (d, 1H, ArH), 8.07 (s, 1H, C_4-H of coumarin)	---
IIIa	1600	1684	1720	2.28 (s, 3H, CH_3), 6.07 (s, 1H, pyrimidone), 7.31 – 7.79 (m, 5H, ArH), 8.13 (s, 1H, C_4-H of coumarin)	---
IIIb	1600	1677	1726.5	---	---
IIIc	1603	1676	1724.4	2.28 (s, 3H, CH_3), 6.08 (s, 1H, pyrimidone), 7.52-7.55 (d, 1H, ArH), 7.62 (s, 1H, thiazole), 7.69-7.73(d, 1H, ArH), 7.92-7.97(d, 1H, ArH), 8.52(s, 1H, C_4-H of coumarin)	344 (82, 346 (27), 278 (92), 280(45), 242 (100), 366 (Na adduct)
IIIf	1594	1683	1713.4	3.87 (s, 2H, CH_2Cl), 6.36 (s, 1H, pyrimidone), 7.37-8.15 (m, 5H, 4Ar-H and 1H of thiazole), 8.56 (s, 1H, C_4-H of coumarin)	---
IIIg	---	---	---	1.06-1.09 (d, 6H, -$CH(CH_3)_2$), 2.70-2.79 (m, 1H, -CH, isopropyl), 5.44 (s, 1H, pyrimidone), 7.38-7.68 (m, 3H, Ar-H), 7.83-7.68 (d, 1H, Ar-H), 8.02 (s, 1H, thiazole), 8.59 (s, 1H, C_4-H of coumarin)	---

Table- 2 continued : Spectra data.

Compd.	IR (ν_{max} cm $^{-1}$)			^{1}H-NMR (δ ppm) solvent DMSO-d_6	Mass spectrum
	-C=N-	-C=O Pyrimidone	-COO- Lactone		
IVa	1608	1680	1704 1723 (ester)	1.23 (t, 3H, ethyl,J = 7Hz), 4.18 (q, 2H, J = 7.3 Hz), 7.37-7.86 (m, 5H, Ar-H), 8.00 (s, 1H, thiazole) 8.55 (s, 1H, C_4-H of coumarin)	368 (42), 322 (30), 299 (100), 296 (20), 268 (10)
IVb	---	---	---	1.29 (t, 3H, CH_3 ethyl, J = 7 Hz), 4.24 (q, 2H, CH_2, J = 8 Hz, ethyl), 7.5 – 8.08 (m, 5H, Ar-H), 8.54 (s, 1H, C_4-H of coumarin)	---
IVc	---	---	---	1.36-1.41 (t, 3H, CH_3 ethyl, J = 7 Hz), 4.33-4.40 (q, 2H, CH_2 ethyl, J=8 Hz), 6.77 (s, 1H, pyrimidine), 746-8.11 (m, 3H, Ar-H), 8.34 (s, 1H, thiazole), 8.66 (s, 1H, C_4-H of coumarin).	402 (40), 388 (20), 356 (35), 424 (100% Na adduct).
IIf = VI	1595	1653	1727	2.32 (s, 3H, CH_3), 2.87-2.92 (t, 2H, CH_2), 3.62-3.67 (t, 2H, CH_2Cl), 7.58-7.79 (m, 4H, Ar-H and 1H of thiazole), 8.09-8.12 (d, 1H, Ar-H), 8.25-8.28 (d, 1H, ArH), 8.59-8.61 (d, 1H, ArH), 9.02 (s, 1H, C_4-H of coumarin)	---
IIIf	1594	1683	1713.4	3.87 (s, 2H, CH_2Cl), 6.36 (s, 1H, pyrimidone), 7.37-8.15 (m, 5H, 4Ar-H and 1H of thiazole), 8.56 (s, 1H, C_4-H of coumarin)	---

References

1. K. Kumar and S.S. Joshi, Indian J. Appl. Chem., **26**, 149 (1963); R.S. Thakur, Experientia, **34**, 158 (1978); N.T. Pryanshikova, I.V. Chermynkova, L.I. Misailova, V.L. Saveies and O S. Arlamomova Khim, Farmaza, 58 (1978); Weifenabach, H. Teschem drof and H. Inergen, Ger. Pat. 3834861/1990; L. Fontain, M. Grand, D. Molno and F. Boscelli, Med. Pharmacol. Exp., **17**, 497 (1967); M. Bhalla, P.K. Naithani, Kumar, T.N. Bhalla and K. Shankar, Indian J. Chem. Sec. B, **31**, 183 (1992); D.P. Chakravorty, A. Das Gupta and D.K. Bose, Ann. Biochem. Expl. Med., **17**, 59 (1957); A. Paoletti and L.S. Orrientino, Rivist siero leerp it al, **33**, 3848 (1958); N.C. Brown, D.T. Hollinshed, P.A. Kingsbery and J.C. Malone, Nature, **194**, 379 (1962). D.P. Chakraborthy, M. Sen and P.K. Bose, Trans Bose. Res. Inst., **24**, 31 (1961).
2. W. Baker and C.S. Howese, J. Chem. Soc., 119 (1953).
3. T. Nakabayashi, H. Miyazaki and T. Tokaroyama, J. Pharm. Soc., Japan, **13**, 565 (1953); Chem. Abstr., **48**, 5187e (1954).
4. M.D. Friedmann, P.L. Stoller, T.H. Porter and K. Folkers, J. Med. Chem., **16**, 1314 (1973).
5. S.N. Sawhney, S.P. Singh and S.K. Arora, Indian J. Chem., **15B**, 729 (1977).
6. V. Rajeswar Rao, M.S. Rao and T.V. Padmanabha Rao, Coll. Czech. Chem. Commun., **51**, 2214 (1986).
7. P. Ravinder, V. Rajeswar Rao and T.V. Padmanabha Rao, Coll. Czech. Chem. Commun., **53**, 326 (1988).
8. V. Rajeswar Rao, V. Aditya Vardhan, Indian J. Chem., **36B**, 1085 (1997).
9. V. Rajeswar Rao, G. Mohan Rao, V. Ravi Kumar and V. Aditya Vardhan, Phos. Sulf. And Silicon, **113**, 47 (1996).
10. T. Surya Kumari and T.V. Padmanabha Rao, Phosphorous Sulfur and Silicon, **107**, 197 (1995).
11. V. Ravi Kumar and V. Rajeswar Rao, Phosphorous, Sulfur and Silicon, **130**, 185 (1997).
12. (a) S.N. Dehuri, P.C. Pradhan and A. Nayak, Indian J. Chem., **23B**, 815 (1983); (b) J.K. Sahu, S.N. Dehuri, S.K. Naik and A. Nayak, Indian J. Chem., **23B**, 117 (1984).

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