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RESEARCH ARTICLE

Synthesis of New Condensed Coumarin 4- Acetic Acid Derivatives

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ABSTRACT

Synthesis of a series of 2-(2,5-dihydro-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid. **(4a-g)** was achieved from different substituted 4-hydroxycoumarin, anhydrous citric acid and using H_2SO_4 added and 10°C with string. The structures of the products were supported by FTIR, PMR and mass spectral data.

KEYWORDS

2-(2,5-dihydro-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid, Different substituted 4-hydroxycoumarin, Anhydrous citric acid, H_2SO_4 only 10°C string

INTRODUCTION

Coumarins are a group of naturally occurring lactones with wide ranging biological activities[1]. Varieties of 4-substituted coumarins possessing hydroxyl[2], ami-noalkyl[3] arylaminomethyl[4], sulphonamido[5] and aryloxymethyl[6] groups have exhibited anti coagulant, anti microbial and anti inflammatory activities. Coumarin 4-acetic acids have been found to exhibit good inflammation inhibiting activity in animal models[7]. They have been employed as key intermediates in the design and synthesis of polycyclic coumarins related to Protober-berine alkaloids[8]. The reactivity of C4-methylene group has been employed for the construction of many 4-substituted bi-heterocyclic coumarins. Solid state con-formational studies on coumarin 4-acetic acid[9], ester[10,11] and dithionate[12] have been reported recently. It needs to be emphasized that the crystallographic study on esters is of considerable biological interest[13].

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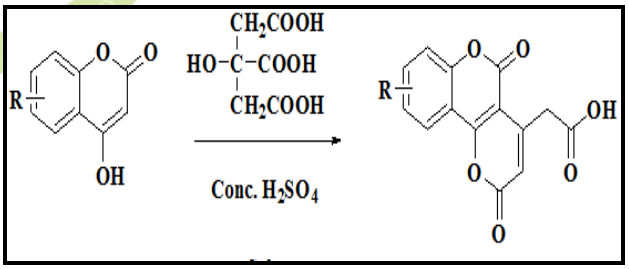
To evade these problems, we have developed a new etiquette for the synthesis of novel 4-hydroxy-6-methyl-3-(substituted methyl)-2H-chromen-2-one ***(4a-g)*** with the advantage of good yield and environmentally friendliness (**Scheme-a**).



EXPERIMENTAL

Typical Experimental Procedure for the Synthesis of Pyrano Coumarin 4-Acetic Acid

A mixture of anhydrous citric acid (0.1M) and 28 ml of concentrated sulphuric acid was stirred at room temperature for one hour, and then slowly heated up to 70°C on oil bath. After half an hour at this temperature, with stirring throughout, the evolution of carbon monoxide

had slackened and the clear yellow colored solution was rapidly cooled to 0°C. To this stirred solution, phenol (4-Hydroxy coumarin) (0.08 M) was added and 11.2 ml of concentrated sulphuric acid, each in three equal portions, at a rate that the temperature does not exceed 10°C. The resulting reaction mixture was stored at 0°C for sixteen hours, poured into ice and the resulting precipitates were filtered off and washed thoroughly with water. It was then treated with 10% sodium bicarbonate solution and then filtered. The filtrate, on acidification gave coumarin-4-acetic acids. The bicarbonate insoluble portion is 4-methyl Coumarin. The purity of the compound is checked by TLC (Methanol: Chloroform = 1:9).

2-(2,5-dihydro-8-hydroxy-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid 4a. Yield: 55%; MP 186-188ºC; MS: m/z M+1 273 and M-1 271; IR (cm^{-1}): 3350 to 2877 (Broad) (O-H stretching of COOH), 3034 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH_2 group), 2887 (C-H symmetrical stretching of CH_2 group), 1699, 1608 (C=O stretching of coumarin), 1565, 1502 and 1458 (C=C stretching of aromatic ring), 1309 (C-H asymmetrical deformation of CH_2 group), 1276 (C-H symmetrical deformation of CH_2 group), 1195, 1103, 833 (C-O-C stretching); ^{1}H NMR (DMSO-d6) δ ppm: 3.35 (s, 2H), 5.60 (s, 1H), 7.33-7.38 (multi, 2H), 7.63-7.67 (d of t, 1H), 7.82-7.84 (d of d, 1H), 12.52 (s, 1H (COOH); Anal. Calcd. $C_{14}H_8O_6$: C, 61.77; H, 2.96; Found: C, 62.01; H, 2.73%.

2-(9-methyl-2,5-dioxo-2,5-dihydropyrano[3,2-c]chromen-4-yl)acetic acid 4b. Yield: 58%; MP 174-176 ºC; MS: m/z 286; IR (cm^{-1}): 3350 to 2874 (Broad) (O-H stretching of COOH), 3014 (C-H stretching of aromatic ring), 2937 (C-H asymmetrical stretching of Alkyl group), 2874 (C-H symmetrical stretching of Alkyl group), 1737, 1610 (C=O stretching of coumarin), 1597, 1548 and 1443 (C=C stretching of aromatic ring), 1427 (C-H asymmetrical deformation of CH_2 group), 1217 (C-H symmetrical deformation of CH_2 group), 1203, 1168, 1022 (C-O-C stretching); ^{1}H NMR (DMSO-d6) δ ppm: 2.37 (s, 3H), 3.81 (s, 2H), 6.63 (s, 1H), 7.29 and 7.38 (Two d, 2H), 7.77 (s, 1H), 12.08 (s, 1H (COOH); Anal. Calcd. $C_{15}H_{10}O_6$: C, 62.94; H, 3.52; O, 33.54; Found: C, 62.87; H, 3.46; O, 33.44%.

2-(2,5-dihydro-8-methoxy-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid 4c. Yield: 52%; MP 184-186 ºC; MS: m/z 302; IR (cm^{-1}): 3340 to 2867 (Broad) (O-H stretching of COOH), 3030 (C-H stretching of aromatic ring), 2980 (C-H asymmetrical stretching of CH_2 group), 2927 (C-H asymmetrical stretching of Alkyl group), 2870 (C-H symmetrical stretching of Alkyl group), 2877 (C-H symmetrical stretching of CH_2 group), 1690, 1600 (C=O stretching of coumarin), 1561, 1501 and 1450 (C=C stretching of aromatic ring), 1301 (C-H asymmetrical deformation of CH_2 group), 1274 (C-H symmetrical deformation of CH_2 group), 1195, 1103, 833 (C-O-C stretching); ^{1}H NMR (DMSO-d6) δ ppm: 3.30 (s, 3H), 3.80 (s, 2H), 6.43 (s, 1H), 7.22and 7.33(Two d, 2H), 7.73 (s, 1H), 12.03 (s, 1H (COOH); Anal. Calcd. $C_{15}H_{10}O_7$: C, 59.61; H, 3.33; O, 37.06; Found: C, 59.60; H, 3.31; O, 37.00%.

2-(2,5-dihydro-9-nitro-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid 4d. Yield: 50%; MP 180-183 ºC; MS: m/z 317; IR (cm^{-1}): 3353 to 2857 (Broad) (O-H stretching of COOH), 3054 (C-H stretching of aromatic ring), 2975 (C-H asymmetrical stretching of CH_2 group), 2887 (C-H symmetrical stretching of CH_2 group), 1689, 1605 (C=O stretching of coumarin), 1544 (N-O stretching of NO_2), 1504 and 1454 (C=C stretching of aromatic ring), 1309 (C-H asymmetrical deformation of CH_2 group), 1271 (C-H symmetrical deformation of CH_2 group), 1195, 1103, 833 (C-O-C stretching); ^{1}H NMR (DMSO-d6) δ ppm: 3.32 (s, 2H), 5.65(s, 1H), 7.30-7.35(multi, 1H), 7.60-7.64 (d of t, 1H), 7.72-7.74 (d of d, 1H), 12.50 (s, 1H (COOH); Anal. Calcd. $C_{14}H_7NO_8$: C, 53.01; H, 2.22; N, 4.42; O, 40.35; Found: C, 53.00; H, 2.22; N, 4.40; O, 40.30%.

2-(2,5-dihydro-9-methoxy-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid 4e. Yield: 55%; MP 184-185 ºC; MS: m/z 302;

IR (cm^{-1}): 3340 to 2865 (Broad) (O-H stretching of COOH), 3030 (C-H stretching of aromatic ring), 2980 (C-H asymmetrical stretching of CH_2 group), 2947 (C-H asymmetrical stretching of Alkyl group), 2870 (C-H symmetrical stretching of Alkyl group), 2877 (C-H symmetrical stretching of CH_2 group), 1690, 1604 (C=O stretching of coumarin), 1561, 1502 and 1450 (C=C stretching of aromatic ring), 1307 (C-H asymmetrical deformation of CH_2 group), 1272 (C-H symmetrical deformation of CH_2 group), 1185, 1104, 830 (C-O-C stretching);); ^{1}H NMR (DMSO-d6) δ ppm: 3.32 (s, 3H), 3.82 (s, 2H), 6.40 (s, 1H), 7.20 and 7.33(Two d, 2H), 7.73 (s, 1H), 12.03 (s, 1H (COOH); Anal. Calcd. $C_{15}H_{10}O_7$: C, 59.61; H, 3.33; O, 37.06; Found: C, 59.55; H, 3.21; O, 36.92%.

Table 1: Antimicrobial activity of compounds 3a-g

Compound	Antibacterial activity				Antifungal activity	
	Gram +ve		Gram -ve			
	S. aureus	S. pyrogenes	E. Cali	P. aeruginosa	C. albicans	A. clavatus
3a	24	450	450	450	250	550
3b	450	550	550	550	<550	<550
3b	100	100	250	200	550	450
3c	550	450	550	550	550	450
3d	200	100	100	200	250	550
3e	550	550	450	450	250	550
3f	450	450	250	250	250	550
3g	450	450	250	250	250	550
Gentamycin	0.25	0.5	0.05	1	-	-
Ampicillin	250	100	100	100	-	-
Chloramphenicol	50	50	50	50	-	-
Iprofloxacin	50	50	25	25	-	-
Norfloxacin	10	10	10	10	-	-
Nystatin	-	-	-	-	100	100
Greseofulvin	-	-	-	-	500	100

2-(9-chloro-2,5-dihydro-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid 4f. Yield: 60%; MP 175-180 ºC; MS: m/z 306; IR (cm^{-1}): 3353 to 2857 (Broad) (O-H stretching of COOH), 3050 (C-H stretching of aromatic ring), 2975 (C-H asymmetrical stretching of CH_2 group), 2887 (C-H symmetrical stretching of CH_2 group), 1680, 1605 (C=O stretching of coumarin), 1504 and 1453 (C=C stretching of aromatic ring), 1302 (C-H asymmetrical deformation of CH_2 group), 1274 (C-H symmetrical deformation of CH_2 group), 1195, 1103, 833 (C-O-C stretching); 851 (C-Cl stretching);); ^{1}H NMR (DMSO-d6) δ ppm: 3.30 (s, 2H), 5.60(s, 1H), 7.24-7.30(multi, 1H), 7.54-7.60 (d of t, 1H), 7.67-7.71 (d of d, 1H), 12.51 (s, 1H (COOH); Anal. Calcd. $C_{14}H_7ClO_6$: C, 54.83; H, 2.30; Cl, 11.56; O, 31.30; Found: C, 54.73; H, 2.20; Cl, 11.26; O, 31.20%.

2-(2,5-dihydro-7-nitro-2,5-dioxopyrano[3,2-c]chromen-4-yl)acetic acid 4g. Yield: 51%; MP 180-184 ºC; MS: m/z 317; IR (cm^{-1}): 3355 to 2858 (Broad) (O-H stretching of COOH), 3057 (C-H stretching of aromatic ring), 2985 (C-H asymmetrical stretching of CH_2 group), 2877 (C-H symmetrical stretching of CH_2 group), 1679, 1615 (C=O stretching of coumarin), 1541 (N-O stretching of NO_2) 1511 and 1451 (C=C stretching of aromatic ring), 1319 (C-H asymmetrical deformation of CH_2 group), 1270 (C-H symmetrical deformation of CH_2 group), 1195, 1100, 830 (C-O-C stretching);); ^{1}H NMR (DMSO-d6) δ ppm: 3.24 (s, 2H), 5.65(s, 1H), 7.30-7.24(multi, 1H), 7.45-7.54 (d of t, 1H), 7.65-7.70 (d of d, 1H), 12.44 (s, 1H (COOH); Anal. Calcd. $C_{14}H_7NO_8$: C, 53.01; H, 2.22; N, 4.42; O, 40.35; Found: C, 52.89; H, 2.21; N, 4.37; O, 40.28%.

CONCLUSION

Various Coumarin 4- acetic acids like derivatives were prepared by reaction of different 4-Hydroxy Coumarin as a phenolic compound with the citric acid the compounds prepared in this chapter possess chromene nucleus and has as fused core structure at C3 and C4 position. And this compound is good yield with biological activity.

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