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DEVELOPMENT, SYNTHESIS AND ASSESSMENT OF ANTI-INFLAMMATORY ACTIVITY OF CHROMONES DERIVATIVES

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ABSTRACT

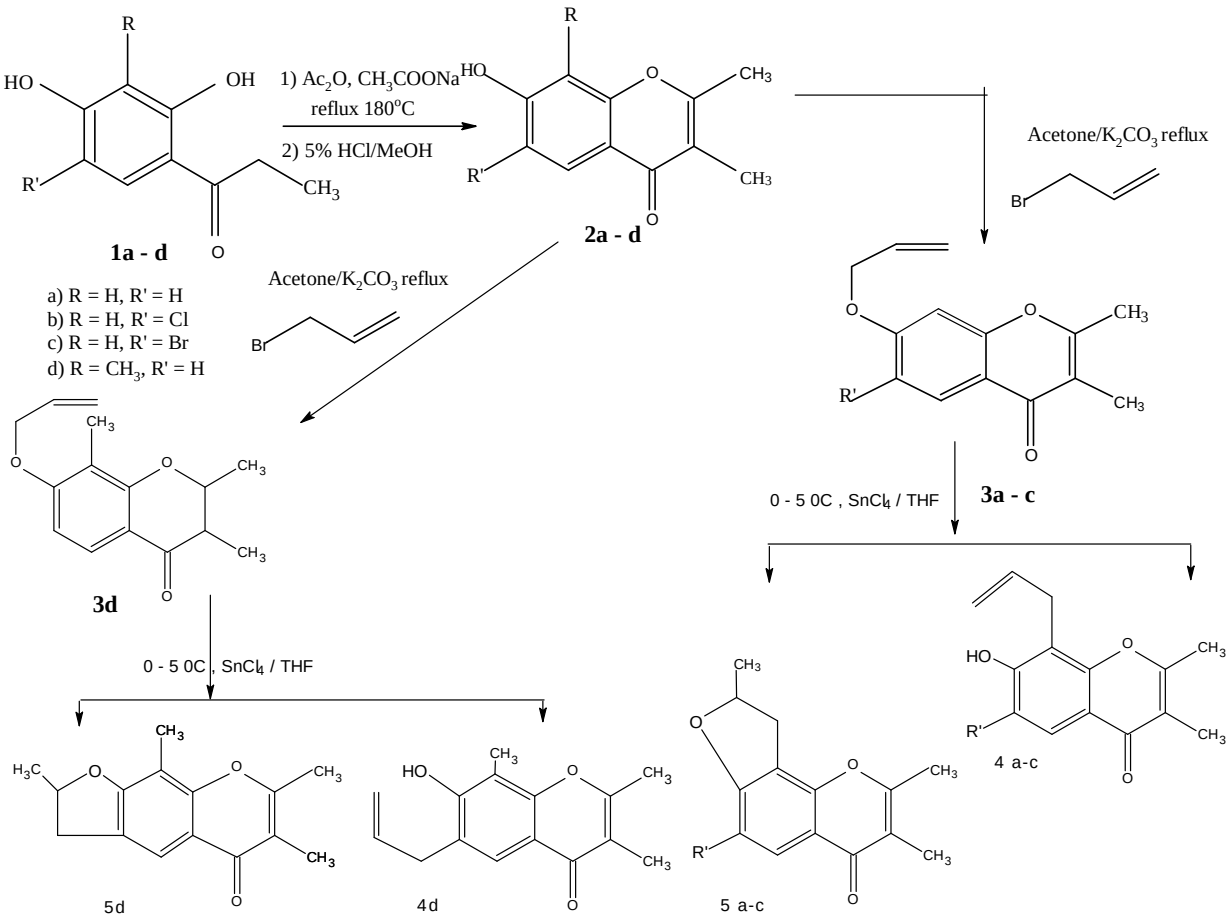
$SnCl_4$ catalyzed Claisen rearrangement of allyl aryl ethers followed by cyclization gives oxygen hetrocycles. By utilizing $SnCl_4$ as lewis acid the rearragment reaction is affected under mild condition The antiinflammatory activity of the synthesized compounds was determined by rat paw edema method. Some of the compounds were found to be potent.

Keywords: NSAID, Synthesized compounds**,** Antiinflammatory activity

INTRODUCTION

Non-steriodal antiinflammatory drugs are widely used to treat pain, fever and inflammatory condition including osteoarthritis. Several research studies exhibits the antiinflammatory properties of chromones.[1-3] Chromones are also reported as antimicrobial[4, 5], anticancer[6], antiallergic[7] and coronary vasodilator[8] . Claisen rearrangement is generally affected by prolong heating of an aryl allyl ether or by heating in vacuum at high temperature. Lewis acids are known to cause the Claisen rearrangement under mild conditions. The use of $SnCl_4$ as lewis acid act as a catalyst for Claisen rearrangement is not reported. We propose the SnCl4 catalysed Claisen rearrangement of 7-allyloxy chromones to afford 7 hydroxy 6/8 allylchromones and 2'-methyl-2', 3'-dihydrofuronochromone.

7- hydroxyl chromones(2a-d) and 7-allyloxychromones(3a-d) were synthesized as per the reported methods[9, 10].7-hydrooxy-6/8-allylchromone (4a-d) and 2'-methyl-2',3'-dihydrofurano chromones (5a-d) were synthesized by the treatment of 7-allyloxychromones(3a-d) with SnCl4 in dry THF (Scheme-1).



SCHEME 1`

Experimental

Antiinflammatory activity

The antiinflammatory activity of the synthesized compounds was carried out by the method of Winter et al[11]. Wistar rats weighing 150-250 g were used for the edema test. Animals were divided into six rats per group. Rats were put on fast for 18 h. prior to the experiment. The standard drug ibuprofen (100mg / kg body wt.) and the drug (100mg / kg body wt.) were given orally as a suspension in 0.1% sodium carboxy methylcellulose as vehicle. One h later 0.1 ml of carageenin solution in saline was injected in the sub plantar region of the right hind paw of each rats. After 3 h of carageenin injection the reduction in paw volume compared to control vehicle was measured using plethysmometer. (Table-1)

Table-1 Characterization and antiinflammatory activity of synthesized compounds

Compounds	M.P(ºC)	Yield (%)	Paw Volume (% protection)
Control			2.25± 0.08
Ibuprofen			0.89± 0.13(60)
4a	134	34	1.80± 0.19(20)
4b	147	36	1.73± 0.14(23)
4c	132	57	0.77± 0.18(66)
4d	176	74	1.08± 0.02(52)
5a	145	45	1.40± 0.01(38)
5b	139	51	1.64± 0.11(27)
5c	152	59	1.10± 0.13(54)
5d	182	45	1.54± 0.08(42)

The melting points were determined in open capillary tubes and are uncorrected. Elemental analysis was determined using Carlo Erba model 1108. IR Spectras were recorded on Perkin-Elmer 881 spectrophotometer in KBr($cm^{-1.}$) and ^{1}H NMR spectra on a Bruckers advanced DXP 200 spectrophotometer using TMS as internal reference.

Synthesis of 7- Hydroxyl chromones (2a-d) and 7-allyloxychromones (3a-d)

10 mmols of 1(a-d) and acetic anhydride were refluxed with 5% hydrochloric acid, methanol and sodium acetate at 180ºC for 6h. The solution was filtered and the products (2a-d) were recovered. 10mmols of 2(a-d) and 20ml of propylene bromide were refluxed with acetone and potassium carbonate for 5h to obtain compounds 3(a-d).

Synthesis of 7-hydroxy-6/8-allylchromone (4a-d) and 2'-methyl-2', 3'-dihydrofurano chromones (5a-d): 10 mmols of 3(a-d) and SnCl4 in dry THF(10ml) were stirred for 14 h under N2 atmosphere at 0-5ºC. The solution was filtered and solvent is removed under reduced pressure. The resulting mixture was chromotographed over silica gel. Elution with benzene-ethyl acetate (1:1, v/v) mixture gave two products 4 and 5. These compounds were crystallized from benzene. The compounds were subjected for NMR studies. 4a δ 1.95 (s, CH3-3), 2.35(s, CH3-2), 7.65(ar, H-5, J=10H-2), 3.52(m, H-1'), 5.05(dd, H-3', J=10, 1H-2), 9.95(dd, H-3', J=16, 1H-2), 5.90(m-H-2'), 10.20(s, 7-OH). 4b δ 1.96 (s, CH3-3), 2.38(s, CH3-2), 7.62(s, H-5), 3.59(m, H-1'), 5.91(m-H-2), 5.10(dd, H-3', J=10, 1H-2), 4.99(dd, H-3', J=16, 1H-2). 4c. δ 1.97 (s, CH3-3), 2.39(s, CH3-2), 7.64(s, H-5), 3.49(m, H-1'), 5.90(m-H-1'), 5.12(dd, H-3', J=10, 1H-2), 4.99(dd, H-3', J=16, 1H-2). 4d δ 2.10 (s, CH3-3), 2.46(s, CH3-2), 7.80(s, H-5), 2.30(s-CH3-1) 3.50(m, H-1'), 6.08(m-H-2), 5.30(dd, H-3', J=10, 1H-2), 5.09(dd, H-3', J=16, 1H-2). 5a. δ 1.50 (d, CH3-2', J=6H-2), 2.05(s, CH3-3), 2.45(s, CH3-2), 2.90(dd, H-3', J=12, 8H-2), 3.42(dd, H-3', J=16, 6H-2), 5.10(m, H-2'), 8.20(d, H-8, J=10H-2), 6.75(d, H-9, J=10 H-2). 5b δ 1.62(d-CH3-2', J=6H-2), 2.05 (s, CH3-3), 2.42(s, CH3-2), 3.02(dd, H-3', J=12, 8H-2), 3.56(dd, H-3', J-12, 6H-2), 5.25(m, H-2'), 8.12(s-H-5). 5c δ 1.62 (d, CH3-2', J=6H-2), 2.07(s, CH3-3), 2.41(s, CH3-2), 5.18(m, H-2'), 3.00(dd, H-3', J=12, 8H-2), 3.56(dd, H-3', J=12, 6H-2), 8.06(s, H-5). 5d δ 1.61(d, CH3-2', J=6H-2), 2.06 (s, CH3-3), 2.44(s, CH3-2), 2.30(s, CH3-8), 3.02(dd, H-3', J=12, 8H-2), 3.52(dd, H-3', J-12, 6H-2), 5.20(m, H-2'), 8.20(s, H-8).

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