SYNTHESIS OF 7-(CHROMON-3-YL)-6*a*,7-DIHYDRO-6*H*[1]-BENZOPYRANO[3,4-*c*][1,5]BENZOTHIAZEPINES AND 2-ARYL-4-(CHROMON-3-YL)BENZOPYRANO[4,3-*b*]PYRIDINES

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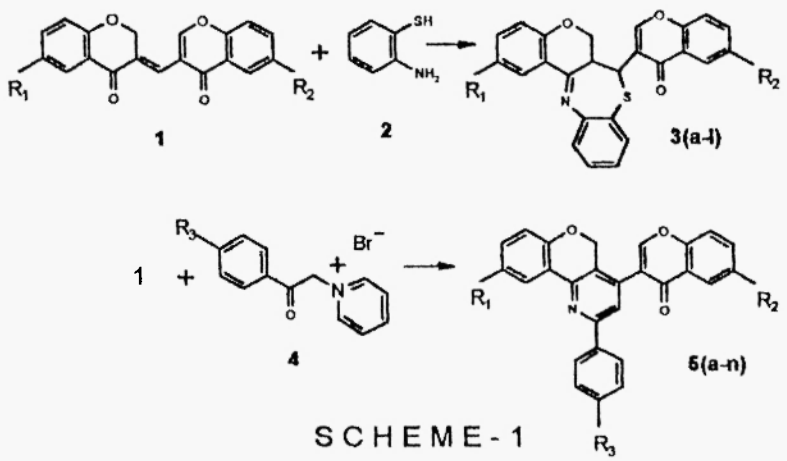
Abstract

A series of 7-(chromon-3-yl)-6*a*,7-dihydro-6*H*-[1]benzopyrano[3,4-*c*][1,5] benzothiazepines (**3a-l**) and 2-Aryl-4-(chromon-3-yl)benzopyrano[4,3-*b*]pyridines (**5a-n**) have been synthesized from benzopyranomethynylbenzopyranones (**1**).

Introduction

1,5-Benzothiazepine compounds are of considerable interest because of their diverse types of pharmacological activities[1-4]. Several fused 1,5-benzothiazepine derivatives have been synthesized with a view to enhance the biological profile of the parent ring system[5]. In addition, a number of benzopyranopyridines[6] have been reported as antiallergic agents and the biological activities exhibited by chromones are well documented[7]. In view of this and in continuation of our work on 3-formylchromone based heterocycles[8], we report herein the synthesis of hitherto unreported chromonyl substituted benzopyrano[3,4-*c*][1,5]-benzothiazepines (**3a-l**) and benzopyrano[4,3-*b*] pyridines (**5a-n**).



SCHEME-1

Results and Discussion

In general, the synthesis of 1,5-benzothiazepines involves the reaction of α,β-unsaturated ketones with 2-aminobenzenethiol. Similarly, they react with phenacylpyridinium salts under Krohnke's conditions to give 2,4,5-trisubstituted pyridines. In the present work, we have utlilized 3-(4-oxo-4*H*-1-benzopyrano-3-methynyl)-2,3-dihydro-4*H*-benzopyran-4-ones (**1**) as a source of α,β-unsaturated ketone which undergoes cyclocondensation under the above conditions leading to the formation of chromone substituted benzopyranobenzothiazepines and benzopyranopyridines.

Compounds **1** were prepared by reaction of chromonones with 3-formylchromones according to the method described earlier[9]. Reaction of various substituted benzopyranomethynylbenzopyranones (**1**) with 2-aminobenzenethiol (**2**) in refluxing ethanol in presence of catalytic amount of acetic acid gave the corresponding benzopyranobenzothiazepines (**3**) in moderate yields. Similarly **1** underwent smooth cyclocondensation when reacted with different phenacylpyridinium salts (**4**) in presence of ammonium acetate in refluxing acetic acid to give benzopyranopyridines (**5**) in good yields (**Scheme-1**). Compounds **3** & **5** were characterized based on their IR and NMR spectral data.

Infrared spectra of **3** showed strong absorption bands at 1650 cm^{-1} for pyrone carbonyl and at 1580 cm^{-1} for C=N bond characteristic of benzothiazepines. This observation coupled with the absence of absorption bands at 1670 cm^{-1} (CO) and at 3450-3350 cm^{-1} (NH_2), confirmed the condensation of amino group of 2-aminobenzenethiol with benzopyranone carbonyl resulting in the formation of benzopyranobenzothiazepines. ^1H NMR spectra of compound **3b** exhibited signals at δ 3.6, 4.1 and 5.0 for C-7, C-6, C-6a bridgehead protons respectively and a singlet at δ 2.4 for CH_3 apart from other aromatic protons and chromone proton in the region of δ 6.9-8.3, thus confirming the Michael addition of mercapto group to the β-carbon of the α,β unsaturated ketone system present in **1**, followed by ring closure by addition of amino group to carbonyl system leading to the formation of benzopyrano fused benzothiazepine **3** with chromone substituted in the position 7.

Similarly IR spectra of **5** exhibited strong absorption bands around 1649 cm^{-1} and 1579 cm^{-1} indicating the presence of benzopyranone carbonyl and a C=N bond. ^1H NMR spectrum of **5a** showed a two proton singlet at δ 5.1 for $-OCH_2$ protons, another singlet at δ 8.7 for C-2 of chromone proton apart from other aromatic and pyridine protons.

All the compounds reported in **Table-1** were further confirmed by mass spectra and correct elemental analyses.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra was recorded in KBr. ^1H NMR spectra on a varian 200 MHz instrument with

TMS as internal standard and chemical shifts were expressed in δ ppm and mass spectra on a Hewelett packard Mass spectrometer operating at **70** ev.

7-(6-Methylchromon-3-yl)-6a,7-dihydro-6H[1]-benzopyrano[3,4-c[[1,5]-benzothiazepine (3b).

A mixture of benzopyranomethynylbenzopyranone (**1b**, R_1=H, R_2=CH_3, 3.18 g, 0.01 mole), 2-aminobenzenethiol (**2**, 1.25 g, 0.01 mole) ethanol (20 ml) and acetic acid (4-5 drops) was refluxed for 4-6 hrs and the progress of the reaction was monitored by T.L.C. At the end of the reaction, solvent was removed and the solid was filtered, washed with water, ethanol and recrystallized from DMF. Yield 2.2g (52%), m.p 176°C IR(KBr): 1650 (C=O) 1580 cm^{-1} (C=N) PMR (DMSO-d_6): δ 2.40 (s, 3H, -CH_3), 3.58 (d, 1H, *J*=12.5 Hz), 3.99 (d, 1H, *J*=8.3 Hz), 4.13 (dd, 1H, *J*=8.3 Hz, 3.2 Hz), 5.05 (d, 1H, *J*=12.5 Hz), 7.00 (d, 1H, *J*=8.3 Hz, ArH), 7.02-7.60 (m, 8H, ArH), 7.85 (s, 1H, Hchrom), 8.25 (d, 2H, *J*=8.3 Hz, ArH). Mass: (m/z) 425(100%), 392(100%), 290(30%), 251(50%), 199(100%). Found: C, 73.16; H, 4.51; N, 3.25 $C_{26}H_{19}NO_3S$ requires C, 73.14; H, 4.47; N, 3.29%.

Compounds 3a and 3c-l were similarly prepared.

2-(4-Chlorophenyl)-4-(chromon-3-yl)benzopyrano[4,3-b]pyridine 5a.

A mixture of **1a** (3.04 g, 0.01 mole), phenacyl pyridiniumbromide (2.33 g, 0.01 mole) ammonium acetate and acetic acid (50 ml) was refluxed for 4-6 hrs (4.62 g, 0.06 mole). The reaction was followed by TLC. At the end of the reaction, it was cooled, filtered and the solid was washed with acetic acid. Recrystallization from DMF –H_2O gave pure **5a** as white crystalline solid. Yield 1.69 g(75%), m.p 220°C IR(KBr): 1649 (C=O), 1579 cm^{-1} (C=N). ^{1}H-NMR (DMSO-d_6): δ 5.1 (s, 2H, OCH_2) 7.0-8.3(m, 13H, HAr & Hpyr) 8.7(s, 1H, Hchromone); Mass: m/z(M^+) 437(found: C, 74.17; H, 3.68; N 3.19; $C_{27}H_{16}ClNO_3$ required C, 74.05; H, 3.65; N, 3.20 %).

Compounds 5**b-n** reported in Table -1 were similarly prepared.

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10. Representative ^{1}H-NMR spectra: **3a** (DMSO-d_6): δ 3.5 (d, 1H, *J*=12.5 Hz), 3.9(d, 1H, *J*=8.3 Hz), 4.05(dd, 1H, *J*=8.3, 3.2 Hz), 4.9 (d, 1H, *J*=12.5 Hz), 6.9 (d, 1H, *J*=8.3 Hz, ArH), 7.05-6.65 (m, 9H, ArH), 7.95 (s, 1H, Hchrom), 8.1 (d, 1H, ArH), 8.25 (d, 1H, ArH) **3d** (DMSO-d_6): δ 2.3 (s, 3H, $ArCH_3$), 3.45 (d, 1H, *J*=12.5 Hz), 3.95 (d, 1H, *J*=8.3 Hz), 4.15 (dd, 1H, *J*=8.3 Hz, 3.2 Hz), 5.05 (d, 1H, *J*=12.5 Hz), 6.9 (d, 1H, *J*=8.3 Hz, ArH), 7.1-7.7 (m, 8H, ArH), 8.0 (s, 1H, Hchrom), 8.1 (m, 2H, ArH) **3e** (DMSO-d_6): δ 2.3 (s, 3H, $ArCH_3$), 2.45 (s, 3H, $ArCH_3$), 3.4 (d, 1H, *J*=12.5 Hz), 3.9 (d, 1H, *J*=8.3 Hz), 4.1 (dd, 1H, *J*=8.3 Hz, 3.2 Hz), 5.05 (d, 1H, *J*=12.5 Hz), 6.85 (d, 1H, *J*=8.3 Hz, ArH), 7.1-7.6 (m, 7H, ArH), 7.95 (m, 2H, ArH), 8.1 (s, 1H, Hchrom) **3f** (DMSO-d_6): δ 2.35 (s, 3H, $ArCH_3$), 3.45 (d, 1H, *J*=12.5 Hz), 3.9 (d, 1H, *J*=8.3 Hz), 4.1 (dd, 1H, *J*=8.3 Hz, 3.2 Hz), 5.0 (d, 1H, *J*=12.5 Hz), 6.85 (d, 1H, *J*=8.3 Hz, ArH), 7.1-7.5 (m, 7H, ArH), 7.8 (dd, 1H, *J*=3.2 Hz, ArH), 7.95 (s, 1H, Hchrom), 8.1 (m, 1H, ArH) **5b** (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 5.1 (s, 2H, OCH_2), 6.8-8.35 (m, 12H, ArH), 8.4 (s, 1H, Hchrom) **5d** (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 5.0 (s, 2H, OCH_2), 6.8-8.3 (m, 12H, ArH), 8.4 (s, 1H, Hchrom) **5e** (DMSO-d_6): δ 2.4 (s, 3H, CH_3), 2.5 (s, 3H, CH_3), 5.0 (s, 2H, OCH_2), 6.8-8.2 (m, 11H, ArH), 8.3 (s, 1H, Hchrom) **5k** (DMSO-d_6): δ 5.05 (s, 2H, OCH_2), 6.9-8.2 (m, 11H, ArH), 8.6 (s, 1H, Hchrom) **5m** (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 5.05 (s, 2H, OCH_2), 6.8-8.1 (m, 12H, ArH), 8.4 (s, 1H, Hchrom) **5n** (DMSO-d_6): δ 5.0 (s, 2H, OCH_2), 6.8-8.2 (m, 12H, ArH), 8.5 (s, 1H, Hchrom).

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