SYNTHESIS OF SOME NEW 1,5-BENZOTHIAZEPINES CONTAINING 2H-1-BENZOPYRAN-2-ONE HETEROCYCLE

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Abstract : A facile procedure has been developed for the synthesis of 2-aryl/heteryl-4-(2H-1-benzopyran-2-one-8-yl)-2,3-dihydro-1,5-benzothiazepines (**5a-o**) by the reaction of 1-(2H-1-benzopyran-2-one-8-yl)-3-aryl/heteryl-2-propenones (**3a-k**) with 2-aminothiophenols (**4a,b**) in toluene in the presence of triflouroacetic acid.

Introduction

Synthesis of 1,5-benzothiazepine derivatives has gained much significance owing to their wide range of biological activities like coronary vasodilatory [1], tranquilizer [2,3], antidepressant [4], antispasmodic [5], neuroleptic [6], anticonvulsive [3], and CNS activity [7]. 2H-1-Benzopyran-2-one(coumarin) derivatives find wide pharmacological applications. Literature survey reveals that 1,5-benzothiazepine derivatives synthesized so far have an alkyl or aryl groups but not a heterocyclic moiety on the benzothiazepine nucleus at 4-position . It was therefore thought of to incorporate heterocyclic moieties into 1,5-benzothiazepines. Earlier, we reported[8] , synthesis of some new 1,5-benzothiazepines havinga α-pyrone moiety at 4- position. In continuation of our work on the synthesis of new 1,5-benzothiazepines, we report here synthesis of some new 1,5-benzothiazepines containing 2H-1-benzopyran-2-one heterocycle from 1-(2H-1-benzopyran-2-one-8-yl)-3-aryl/heteryl-2-propenones (**3a-k**) and 2-aminothiophenols (**4a,b**).

Results and Discussion

The required starting materials, 8-acetyl-7-hydroxycomourin (**1a**) and its 4-methyl derivative (**1b**) have

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been prepared[9] by the Fries migration of 7-acetyloxycoumarin and 7-acetyloxy-4-methylcomourin respectively. On condensation of 8-acetyl-7-hydroxy 2H-1-benzopyran-2-ones(coumarines) **(1a,b)** with aromatic aldehydes **(2a-i)** in ethanol in the presence of piperidine afforded 1-(2H-1-benzopyran-2-one-8-yl)-3-aryl/heteryl-2-propenones **(3a-k)** whose physical and spectroscopic data is comparable with literature data[10]. 2-Propenone derivatives **(3a-k)** on stirring and refluxing with 2-aminothiophenols **(4a,b)** in toluene in the presence of few drops of triflouroacetic acid afforded the corresponding 2-substituted-4-(7-hydroxy-2H-1-benzopyran-2-one-8-yl)-2,3-dihydro-1,5-benzothiazepines **(5a-o)** in

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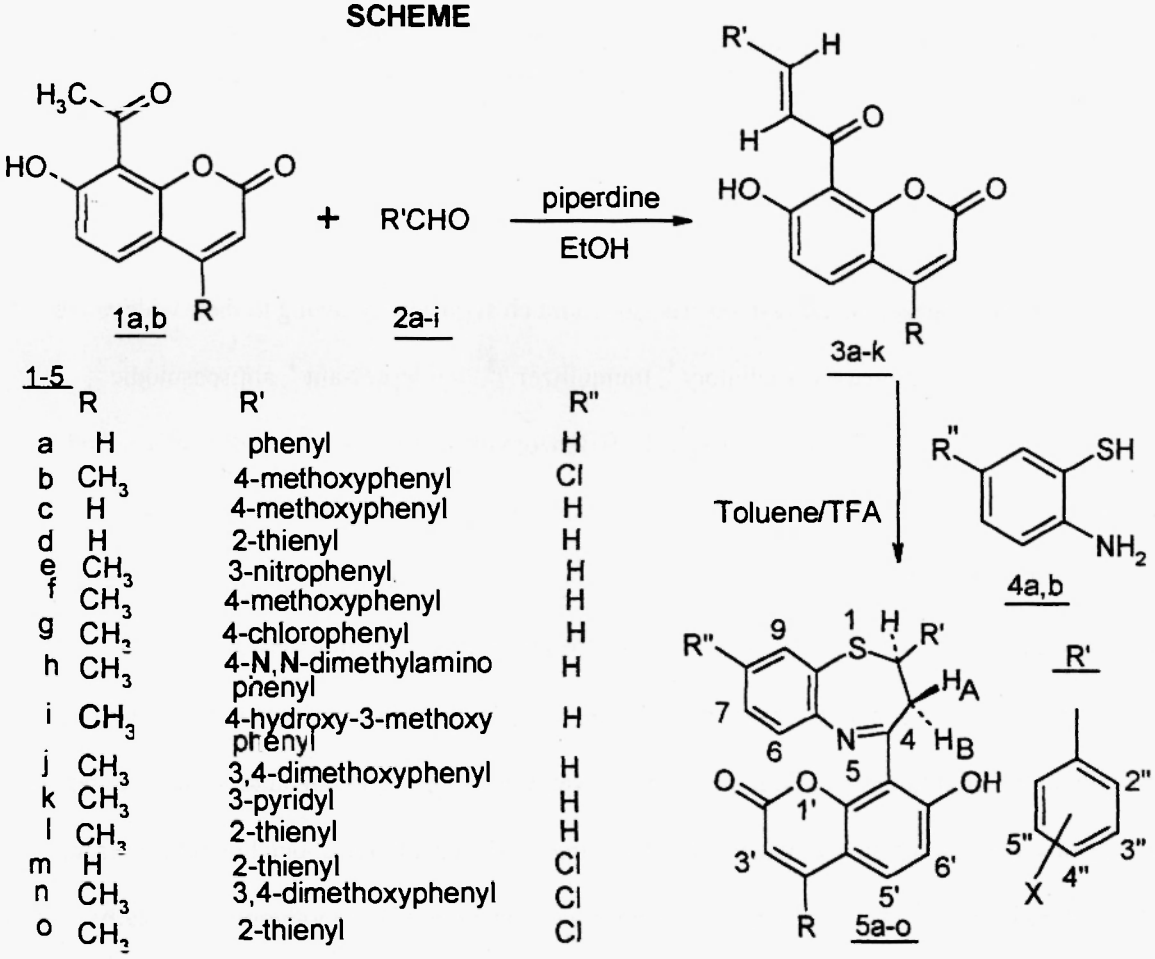

1-5	R	R'	R"
a	H	phenyl	H
b	CH_3	4-methoxyphenyl	Cl
c	H	4-methoxyphenyl	H
d	H	2-thienyl	H
e	CH_3	3-nitrophenyl	H
f	CH_3	4-methoxyphenyl	H
g	CH_3	4-chlorophenyl	H
h	CH_3	4-N,N-dimethylamino phenyl	H
i	CH_3	4-hydroxy-3-methoxy phenyl	H
j	CH_3	3,4-dimethoxyphenyl	H
k	CH_3	3-pyridyl	H
l	CH_3	2-thienyl	H
m	H	2-thienyl	Cl
n	CH_3	3,4-dimethoxyphenyl	Cl
o	CH_3	2-thienyl	Cl

moderate to good yields. Structures of these compounds have been elucidated from elemental analysis, IR and proton NMR spectral data. A C=N band characteristic for such 2,3-dihydro-1,5-benzothiazepines has been observed between 1600-1616 cm^{-1} . In the proton NMR spectra, chemical shift values, coupling constants and multiplicity of protons attached to carbon atoms C-2 and C-3 unequivocally prove the structure of new 1,5-benzothiazepines. In the proton NMR spectra of all the compounds synthesized a triplet signal was found at 2.98-3.00 ppm with coupling constant 12.4 Hz and a double doublet signal at 3.8 ppm with coupling constants 12.4 and 4.4 Hz. These signals can be assigned to the H_A and H_B protons of C-3 atom of 1,5-benzothiazepines. While a double doublet signal was found at 5.8-6.1 ppm with coupling constants 15.3and 4.4 Hz belong to the proton of C-2 atom. All the 1,5-benzothiazepines synthesized were characterized by mp's ,^{1}H NMR and IR data (Table).The biological activity testing of these new 1,5-benzothiazepines is under process and the results will be published elsewhere.

In conclusion, few new1,5-benzothiazepines containing an important heterocycle (2H-1-benzopyran-2-one) have been synthesised in a facile manner in a one step process.

Experimental

Melting points were taken in capillary tube and are uncorrected. Proton NMR spectra were recorded on a Varian Gemini 200MHz Spectrometer in $CDCl_3$. Proton chemical shift values are reported in δ (ppm) , down field from TMS which is an internal standard and J values are in Hertz. IR spectra were obtained as KBr pellets. Purity of the compounds was checked by TLC on silica gel G plates. Spots are located under UV light.

8-Acetyl-7-hydroxy-2H-1-benzopyran-2-one (1a) : This was prepared by Fries migration of acetyl group of 7-acetyloxycoumarin which was prepared by acetylation of 7-hydroxycoumarin which in turn was prepared from resorcinol and malic acid by following the literature method[11].

Fries migration of 7-acetyloxycoumarin : 7-Acetyloxycoumarin (10.2g ,0.05M) and aluminium chloride (20g, 0.15M) were taken in a RB flask and shaken well to mix the contents. Initially the temp. was maintained at 125°C and slowly it was raised to 175°C over a period of 2 hrs. It was cooled and decomposed with 1:7 HCl (160ml) and the solid seperated was filtered , washed with cold water . It was crystallized from 95% ethanol to get pure 8-acetyl-7-hydroxy-2H-1-benzopyran-2-one **1a**,5g, mp162°C.

8-Acetyl-7-hydroxy-4-methyl-2H-1-benzopyran-2-one[9] (1b) and 5-chloro-2-aminothiophenol [12](4b) These two compounds were made by following the reported literature methods.

1-(2H-1-Benzopyran-2-one-8-yl)-3-aryl/heteryl-2-propenones (3a-k) : *General Procedure.* A mixture of 8-acetyl-7-hydroxy-2H-1-benzopyran-2-one (**1a,b,**0.01M) and aromatic aldehyde(**4a-i,** 0.012M) in 30ml ethanol in the presence of 0.3ml piperidine was refluxed for 3-4 hrs. While refluxing yellow to red solids precipitated out. After the reaction is complete (tlc monitoring) , half of the ethanol was removed under reduced pressure and cooled to RT. The solid seperated was filtered, washed with cold ethanol and crystallized from alcohol to obtain compounds **3a-k.** Physical and spectroscopic characteristics of these compounds were respondent to known data[10].

2-Aryl/heteryl-4-(7-hydroxy-2H-1-benzopran-2-one-8-yl)-2,3-dihydro-1,5-benzothiazepines (5a-o) *General Procedure.* 1-(2H-1-benzopyran-2-one-8-yl)-3-aryl/heteryl-2-propenones (**3a-k,** 0.01M) was disolved in hot toluene(50 ml) and to this solution was added 2-aminothiophenol (**4a,b,** 0.012M) and few drops of trifluroacetic acid . The mixture was refluxed on a steam bath for 4-6 hrs. After completion of the reaction (tlc monitoring), toluene was completely removed under reduced pressure and 30 ml of ethanol was added and cooled to 10° C . The solid seperated was filtered and washed with cold ethanol and dried . They were crystallized from ethanol or column chromatographed to get pure 1,5-benzothiazepine derivatives **(5a-o).** Physical and spectral data were recorded in table.

Physical & spectral data of 1,5-benzothiazepines, **5a-o**

Compd.,	mp	yield (%)	^{1}H-NMR (200 MHz, $CDCl_3$), ppm.
5a	214	52	3.00 (1H,t,J=12.4,H_A -3), 3.8 (1H,dd,J=12.4,4.4,H_B-3), 5.8 (1H,dd,J=15.2,4.4,H-2), 6.3 (1H,d,J=10,H-3'), 7.00 (1H,d, J=8.5,H-6'), 7.5 (1H,d,J=8.5,H-5'), 7.7 (1H,d,J=10,H-4'), 7.4-7.6 (3H,m,H-6,7,8) & 7.8 (1H,d,J=8.5,H-9).
5b	186	58	2.45 (3H,s,CH_3 -4'), 3.8 (3H,s,OCH_3-4''), 2.95 (1H,t,J=12.4, H_A -3), 3.72 (1H,dd,12.4,4.4,H_B -3), 5.8 (1H,dd,J=15.3,4.4, H-2), 6.2 (1H,s,H-3'), 6.85 (2H,d,J=8.5,H-3'&5'), 7.00 (1H, d,J=8.5,H-6'), 7.1 (1H,d,J=8.5,H-5'), 7.5 (2H,m,H-6,7), 7.6 (2H,d,J=8.5,H-2''&6''), 7.8 (1H,d,J=2.4,H-9).
5c	180	60	3.00 (1H,t,J=12.4,H_A-3), 3.75 (1H,dd,J=12.4,4.4,H_B -3) 3.8 (3H,s,OCH_3 -4''), 5.8 (1H,dd,J=15.3,4.4, H-2) 6.3 (1H,d,J=10.00,H-3'), 6.85 (2H,d,J=8.5,H-3''&H-5'') 7.00 (1H,d,J=8.5,H-6'), 7.4-7.45 (3H,m,H-6,7,8), 7.5 (1H, d,J=8.5,H-5'), 7.6 (2H,d,J=8.5,H-2''&6''), 7.8 (1H,d,J=10, H-4') & 7.85 (1H,d,J=8.5,H-9).
5d	226	65	3.00 (1H,t,J=12.4,H_A -3), 3.9 (1H,dd,J=12.4,4.4,H_B-3) 6.1 (1H,dd,J=15.3,4.4,H-2), 6.35 (1H,d,J=10,H-3') 6.98 (2H,m,H-6',H-4''), 7.4 (3H,m,H-7,8,3''), 7.5 (1H,d, J=8.5,H-5'), 7.6 (1H,d,J=8.5,H-5''), 7.7 (1H,d,J=10,H-4'), 7.85 (1H,d,J=8.5,H-9).

5e	236	70	2.4 (3H,s,CH_3 –4'), 2.9 (1H,t,12.4,H_A –3), 3.8 (1H,dd,J=12.4, J=12.4,4.4,H_B-3), 5.8 (1H,dd,J=15.3,4.4,H-2), 6.1 (1H,5, H-3'), 7.00 (1H,d,J=8.5,H-6'), 7.6 (1H,d,J=8.5,H-5'), 7.7 (2H, m,H-2''& 4''), 7.2 (2H,m,H-5''& 6''), 7.5 (1H,d,J=8.5,H-6), 7.6 (2H,m,H-7,8) & 7.81 (1H,d,J=8.5,H-9).
5f	170	55	2.4 (3H,s,CH_3 –4'), 2.9 (1H,t,J=12.4,H_A –3), 3.7 (1H,dd, J=12.4,4.4,H_B –3), 3.78 (3H,s,OCH_3 –4''), 5.8 (1H,dd,J=15.3, 4.4,H-2), 6.1 (1H,s,H-3'), 6.9 (2H,d,J=8.5,H-3''& 5'') 7.6 (2H,d,J=8.5,H-2''& 6''), 7.4-7.5 (3H,m,H-6,7,8) & 7.85 (1H,d,J=8.5,H-9).
5g	172	50	2.35 (3H,s,CH_3 –4'), 2.9 (1H,t,J=12.4,H_A –3), 3.7 (1H, dd,J=12.4,4.4,H_B –3), 5.8 (1H,dd,J=15.3,4.4,H-2), 6.1 (1H,s,H-3'), 7.4-7.5 (7H,m,H-2'',3'',5'',6'',6,7,8) & 7.8 (1H,d,J=8.5,H-9).
5h	188	58	2.4 (3H,s,CH_3 –4'), 3.5 (6H,s,$N(CH_3)_2$, 2.9 (1H,t,J=12.4, H_A-3), 3.7 (1H,dd,J=12.4,4.4,H_B-3), 5.8 (1H,dd,J=15.3, 4.4,H-2), 6.1 (1H,s,H-3'), 7.00 (2H,d,J=8.5,H-3''& 5''), 7.6 (2H,d,J=8.5,H-2''& 6''), 7.4-7.6 (3H,m,H-6,7,8) & 7.89 (1-H,d,J=8.5,H-9).
5i	230	70	2.4 (3H,s,CH_3 –4'), 2.9 (1H,t,12.4,H_A –3), 3.8 (1H,dd, J=12.4,4.4,H_B –3), 3.9 (3H,s,OCH_3 –3''), 5.8 (1H,dd, J=15.3,4.4,H-2), 6.2 (1H,s,H-3'), 7.00 (1H,d,J=8.5,H-6'), 7.6 (1H,d,J=8.5,H-5'), 6.8 (1H,d,J=8.5,H-5''), 7.2 (1H,d, J=8.5,H-2''),7 .45 (3H,m,H-7,8,6''), 7.5 (1H,d,J=8.5,H-6), 7.82 (1H,d,J=8.5,H-9).
5j	218	70	2.4 (3H,s,CH_3 –4), 2.8 (1H,t,J=12.4,H_A –3), 3.7 (1H,dd, J=12.4,4.4,H_B –3), 3.8-85 (6H,2 X OCH_3), 5.8 (1H,dd, J=15.3,4.4,H-2), 6.15 (1H,s,H-3'), 6.8 (1H,d,J=8.5,H-5''), 7.0 (1H,d,J=8.5,H-6'), 7.2 (1H,d,J-8.5,H-2''), 7.6 (1H,d, J=8.5,H-5'), 7.3 (3H,m,H-7,8,6''), 7.8 (1H,d,J=8.5,H-9).
5k	235	66	2.45 (3H,s,CH_3 –4'), 2.9 (1H,d,J=12.4,H_A –3), 3.7 (1H,dd, J=12.4,4.4,H_B –3), 5.8 (1H,dd,J=15.3,4.4,H-2), 6.15 (1H,s, H-3'), 6.95 (1H,d,J=8.5,H-6'), 7.3 (3H,m,H-7,8&5''), 7.5 (1H,d,J=8.5,H-6''), 7.6 (1H,d,J=8.5,H-5'), 7.8 (1H,d,J=8.5, H-6), 8.00 (1H,d,J=8.5,J=8.5,H-9), 8.5 (1H,d,J=8.5,H-4'') & 8.9 (1H,s,H-2'').
5l	210	68	2.45 (3H,s,CH_3 -4'), 2.95 (1H,t,J=12.4,H_A –3), 3.85 (1H,dd, J=12.4,4.4,H_B –3), 6.1 (1H,dd,J=15.3,4.4,H-2), 6.15 (1H,s,

			H-3'), 7.65 (1H,d,J=8.5,H-5'), 6.95 (1H,m,H-4''), 7.15 (1H, d,J=8.5,H-5''), 7.35 (3H,m,H-7,8,3''), 7.5 (1H,bd,J=8.5,H-6), 7.7 (1H,d,J=8.5,H-9).
5m	230	55	3.00 (1H,t,J=12.4,H_A -3), 3.9 (1H,dd,J=12.4,4.4,H_B -3), 6.1 (1H,dd,J=15.3,4.4,H-2), 6.34 (1H,d,J=10,H-3), 7.6 (1H, d,J=10,H-4'), 6.9 (2H,m,H-6'&H-4''), 7.5 (1H,d,J=10,H-5'), 7.3 (1H,d,J=8.5,H-6), 7.5 (1H,dd,J=8.5,2.5,H-7) & 7.8 (1H, d,J=2.5,H-9).
5n	226	61	2.45 (3H,s,CH_3 -4'), 2.90 (1H,t,J=12.4,H_A -3), 3.75 (1H, dd,J=12.2,4.4,H_B -3), 3.85-3.9 (6H,s,OCH_3 X 2), 5.8 (1H, dd,J=15.3,4.4,H-2), 6.15 (1H,s,H-3'), 6.82 (1H,d,J=8.5, H-5''), 7.00 (1H,d,J=8.5,H-6'), 7.15 (1H,dd,J=8.5,2.3,H-6''), 7.3 (2H,m,H-6,2''), 7.5 (1H,dd,J=8.5,2.5,H-7), 7.89 (1H,d, J=2.5,H-9).
5o	218	63	2.4 (3H,s,CH_3 -4'), 2.94 (1H,t,J=12.4,H_A -3), 3.72 (1H,dd, 12.4,4.4,H_B -3), 5.8 (1H,dd,J=15.3,4.4,H-2), 6.2 (1H,s,H-3'), 6.95 (1H,m,H-4''), 7.00 (1H,d,J=8.5,H-6'), 7.15 (1H,d, J=8.5,H-5''), 7.36 (2H,m,H-7,3''), 7.5 (1H,d,J=8.5,H-6), 7.6 (1H,d,J=8.5,H-5'), & 7.8 (1H,d,J=2.5,H-9).

All the compounds gave satisfactory elemental analysis

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Received on October 25, 2000