Synthesis of 6-(1,5-Benzothiazepinyl/pyridyl)-2H-[1,4]-benzoxazin-3[4H]-ones from 6-Acetyl-2H-[1,4]-benzoxazin-3(4H)-ones

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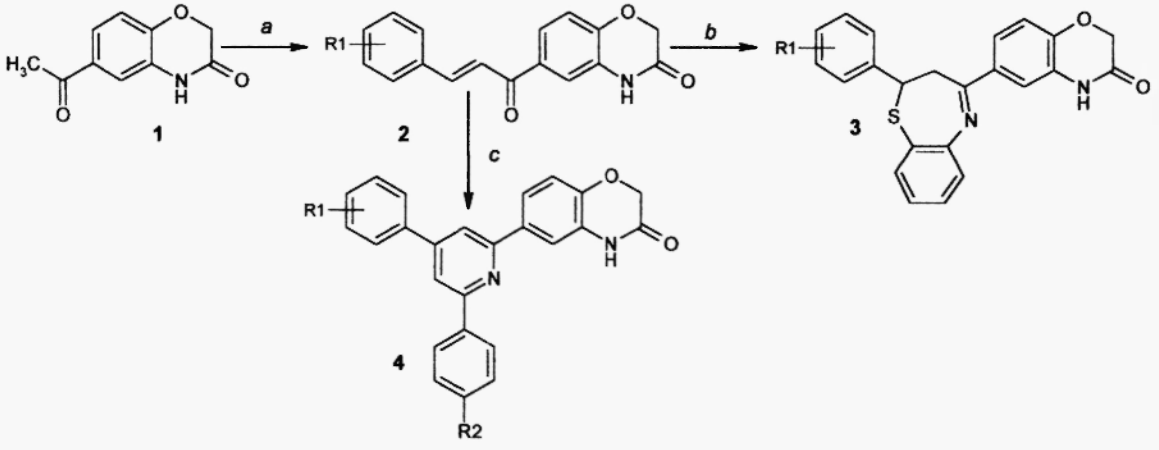
Abstract

A series of 6-(2,3-dihydro-1,5-benzothiazepinyl/pyridyl)-2H-[1,4]-benzoxazin-3[4H]-ones (**3a-d** & **4a-h**) have been synthesized from 1-(3-oxo-[1,4]-benzoxazin-6-yl) 3- arylpropen-1-ones (**2a-d**).

Introduction

Benzoxazinones substituted with a variety of heterocycles in the aromatic ring such as pyridazinyl, thiazolyl and imidazolyl systems have been synthesized and reported to exhibit interesting cardiotonic, antiinflammatory, α-adrenoceptor and antimicrobial activities[1-4]. Furthermore several 1,5-benzothiazepines, di and tri substituted pyridines have been found extensive utility as pharmaceutical agents[5,6]. In continuation of our work on biologically active benzoxazinones[7,8], we now report, the synthesis of some new 1,5-benzothiazepinyl and pyridylbenzoxazines from benzoxazinonepropen-1-ones (Scheme 1).



a) Aromatic aldehydes, Na, MeOH b) 2-aminothiophenol, alcohol, AcOH
c) Phenacylpyridinium bromides, NH_4OAc, AcOH.

SCHEME-1

Results and Discussion

The required starting materials 1-(3-oxo-1,4-benzoxazin-6-yl)-3-aryl-propen-1-ones (**2**) were prepared by condensation of various substituted aromatic aldehydes with 6-acetyl-2H-[1,4]-benzoxazin-3(4H)-ones (**1**) in methanol in presence of sodium. The propen-1-ones **2** were reacted with 2-aminothiophenol in ethanol in presence of acetic acid to give 6-(2,3-dihydro-1,5-benzothiazepinyl)benzoxazinones (**3**) in moderate yields. **2** were also reacted with various phenacylpyridinium bromides in presence of ammonium acetate in acetic acid under Kröhnke's conditions[9] to give 6-(4,6-diaryl-pyridin-2yl)-2H-[1,4]-benzoxazin-3(4H)-ones (**4**) in good yields. The structures of **3** were established, based on analytical and spectral data. IR spectra of **3** exhibited absorption band at 1700 cm^{-1} for benzoxazine carbonyl group. The ^{1}H-NMR spectra of **3** are very much characteristic of the structures of the products. Thus $-OCH_2$ and NH proton of benzoxazine ring appeared as singlets at δ 4.6 and 10.6 respectively. The –SCH and CH_2 proton of benzothiazepine ring appeared as one proton multiplet and two proton multiplet at δ 5.1 and 2.8 - 3.3 respectively. 6-(2-Pyridyl)-benzoxazinones (**4**) were also characterized by IR and ^{1}H-NMR spectra. For example ^{1}H-NMR spectra of **4b** exhibited the following signals at δ 3.8(s, 3H, OCH_3) 4.6(s, 2H, $-OCH_2$); 6.9-8.2(m, 13H, aromatic & pyridine protons); 10.6(br, 1H, NH).

All the compounds reported in Table -1 were established, based on their IR, ^{1}H-NMR, Mass spectra and correct elemental analyses.

Experimental

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 pellet. ^{1}H-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 Hewelett Packard Mass spectrometer operating at 70ev.

Preparation of 1-(3-oxo-1,4-benzoxazin-6-yl)-3-arylpropen-1-ones (2): General Procedure

To a mixture of 6-acetylbenzoxazinone (**1**, 0.01 mole) and aromatic aldehyde (0.015 mole) in methanol (50 ml) was added sodium (0.02 mole) and stirred at room temperature until the disappearance of the starting materials as monitored by TLC (3:1, Hexane:Ethylacetate). The separated solid was filtered to give **2** in pure form.

6-[2-(4'-Methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4-yl]-2H-[1,4]-benzoxazin-3(4H)-one (3b)

To a mixture of 1-(3-oxo-1,4-benzoxazin-6-yl) 3-(4'-methoxylphenyl)-propen-1-one (**2b**, R_1=4-OCH_3, 3.09 gm, 0.01 mole) and 2-aminothiophenol (1.25 gm) in ethanol (50 ml) was added few drops of acetic acid and the mixture was refluxed for 4 to 5 hrs, until the disappearance of starting materials as monitored by TLC. It was cooled, the

Table –1. Characterization data of compounds 3 & 4

Compound	R_1	R_2	m.p	Yield %	Mol. Formula	found %N	Calc
3a	H	-	201	52	$C_{23}H_{18}N_2O_2S$	7.24	7.25
3b	4-OCH_3	-	200	57	$C_{24}H_{20}N_2O_3S$	6.76	6.73
3c	2-Cl	-	242	58	$C_{23}H_{17}ClN_2O_2S$	6.61	6.65
3d	4-Cl	-	280	51	$C_{23}H_{17}ClN_2O_2S$	6.62	6.65
4a	H	F	>300	61	$C_{25}H_{17}FN_2O_2$	6.98	7.00
4b	4-OCH_3	F	242	65	$C_{26}H_{19}FN_2O_3$	6.54	6.57
4c	2-Cl	F	>300	68	$C_{25}H_{16}ClFN_2O_3$	6.47	6.50
4d	4-Cl	F	292	67	$C_{25}H_{16}ClN_2O_3$	6.51	6.50
4e	H	Cl	>300	63	$C_{25}H_{17}ClN_2O_2$	6.73	6.75
4f	4-OCH_3	Cl	250	67	$C_{26}H_{19}ClN_2O_3$	6.35	6.32
4g	2-Cl	Cl	>300	71	$C_{25}H_{16}Cl_2N_2O_2$	6.29	6.26
4h	4-Cl	Cl	>300	68	$C_{25}H_{16}Cl_2N_2O_2$	6.28	6.26

separated solid was filtered, washed with ethanol, dried and recrystallized from dimethylformamide to give pure **3b** as light yellow crystalline solid. Yield: 2.37 gm (57%); m.p: 200°C; MS: 416(M^+); IR: 1700 cm^{-1} (C=O of benzoxazine); ^{1}H-NMR(DMSO-d_6); δ 3.2(m, 2H, CH_2 of benzothiazepine); 3.8(s, 3H, OCH_3); 4.6(s, 2H, OCH_2); 4.9(m, 1H, -SCH of benzothiazepine); 6.8-7.8(m, 11H, ArH); 10.6(s, 1H, NH) found: C, 69.25; H, 4.81; N, 6.76 $C_{24}H_{20}N_2O_3$ requires C, 69.23; H, 4.80; N, 6.73%).

Compounds **3a** & **3c-d** reported in Table -1 were similarly prepared.

6-[4-(4'-Methoxyphenyl)-6-(4-chlorophenyl)-pyrid-2-yl]-2H-[1,4]-benzoxazin-3[4H]-one (4f)

A mixture of **2**b (0.01 mole), 4-chlorophenacylbromide (0.01 mol) ammonium acetate (10gm) in glacial acetic acid (50ml) was refluxed for 4-6 hrs. The reaction mixture was allowed to cool to room temperature. It was poured onto ice cold water and the solid obtained was filtered, washed with water, dried and recrystallized from dimethylformamide to give **4f** as colourless crystalline solid. Yield: 2.64 g (62%); m.p: 250°; MS; 426(M^+); IR: 1690 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 3.8(s, 3H, OCH_3); 4.6(s, 2H, OCH_2); 7.0(m, 3H, ArH & pyridine protons); 7.45(d, 2H, ArH); 7.8(m, 6H, ArH); 8.2(d, 2H, ArH); 10.7(bs, 1H, NH). (Found: C, 70.49; H, 4.27; N, 6.35 $C_{26}H_{19}ClN_2O_3$ requires C, 70.50; H, 4.29; N, 6.32%).

Compounds **4**a-e & **4**g-h reported in Table –1 were similarly prepared.

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