SYNTHESIS OF SOME NEW 6-ARYL-2-(3-OXO-1, 4-BENZOXAZIN-6-YL)PYRIDINES

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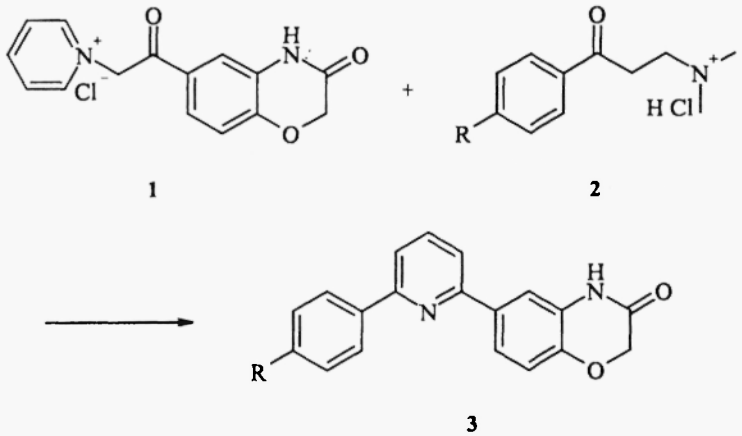
Abstract

A series of some new 6-aryl-2-(3-oxo-1,4-benzoxazin-6-yl)pyridines (3a-g) have been prepared.

Introduction

A large number of pyridines are known as pharmaceutical agents, herbicides and insecticides. Also, pyridine ring forms a part of many biologically important natural products[1]. Certain functionalized pyridines have been reported as HIV reverse transcriptase inhibitors[2]. Diaryl pyridines like Etoricoxib is a selective COX-2 inhibitor[3]. These findings give an impetus for the synthesis of diverse types of substituted pyridines. Furthermore, 1,4-benzoxazine is an active pharmacophore in a number of compounds with anticancer[4], antibacterial[5], antihypertensive[6], anticoagulant[7], antiparasitic[8], blood platelet aggregation inhibitors[9] and herbicidal activities[10]. Earlier communication from this laboratory described the synthesis of benzopyranopyridinyl benzoxazines[11]. In continuation of our work on benzoxazines we now report the synthesis of some new 2,6-disubstituted pyridines with 1,4-benzoxazinone pharmacophore as one of the substituent.



1 2 3

SCHEME-1

Results and Discussion

6-Benzoxazinoylmethylpyridinium salt (**1**) was prepared by reaction of 6-chloroacetylbenzoxazinone with pyridine. **1** reacted with various β-dimethyl aminopropiophenone hydrochlorides (**2**) in the presence of ammonium acetate in refluxing acetic acid under Kröhnke's conditions to give the desired 6-aryl-2-(benzoxazinoyl)pyridines **3** in good to moderate yields. The structures of the products were established based on their ^{1}H NMR, IR and mass spectra. In the ^{1}H NMR spectra compounds **3** exhibited two singlets around δ 4.34-4.56 and 10.57-10.62 for benzoxazine ring $-OCH_2$ and lactam carbonyl NH protons apart from other aromatic and pyridine protons.

The formation of **3** involves the Kröhnke's mechanism[12] in which the Mannich base **2** forms the source of α, β-unsaturated ketone under the reaction conditions, which undergoes Michael addition by pyridinium salt followed by cyclization of the resulting 1,5-dicarbonyl derivative in the presence of ammonium acetate and acetic acid to give the pyridine ring.

Experimental

Melting points were determined in open capillaries and are uncorrected. IR spectra was recorded in KBr pellets. ^{1}H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard and chemical shifts are expressed in δ ppm and Mass spectrum on a Hewelett Packard mass spectrometer operating at 70eV. All the compounds were purified by column chromatography using silica gel.

Preparation of β-dimethylaminopropiophenone Hydrochlorides 2. General procedure 2

A mixture of acetophenone (0.01 mole), dimethylamine hydrochloride (0.01 mole), paraformaldehdye (0.01 mole) and concentrated HCl (0.5 ml) in ethanol (100 ml) was heated at 60° for 4-6 hrs. Progress of the reaction was checked by TLC, at the end of reaction acetone was added and the solution was cooled overnight, the resulting white solid was filtered and washed with cold ethanol. The salt was used as such in the next step without further purification.

Preparation of 6-aryl-2-(3-oxo-1,4-benzoxazin-6-yl)pyridine. General procedure 3

A mixture of benzoxazinoylmethylpyridinium chloride (1, 0.001 mole), ammonium acetate (0.01 mole), Mannich base (2, 0.001 mole) and glacial acetic acid (10 ml) was refluxed for 4-5 hrs. The reaction mixture was poured onto crushed ice, the solid obtained was filtered washed with water and extracted with dichloromethane. The organic extract was washed with water, 5% $NaHCO_3$ water, dried and purified by column chromatography (Hexane : ethylacetate, 90:10) to give pure **3** as crystalline solid.

Table –1: Physical data of 6-Aryl-2-benzoxazin-6-yl pyridines[3]

Compd*	R	m.p °C	Yield %	Mol. Formula	^{1}H NMR (δ ppm) 200 MHz ($CDCl_3$ + DMSO-d_6)
3a	H	189	67	$C_{19}H_{14}N_2O_2$	4.56(s, 2H), 6.94(d, 1H), 7.42-7.78(m, 8H), 8.12(d, 2H), 10.57(s, 1H)
3b	F	227	68	$C_{19}H_{13}FN_2O_2$	4.56(s, 2H), 6.93(d, 1H), 7.19(m, 2H), 7.76(m, 5H), 8.13(m, 2H), 10.67(s, 1H)
3c	Cl	215	69	$C_{19}H_{13}ClN_2O_2$	4.58(s, 2H), 6.96(d, 1H), 7.85(m, 8H), 8.47(d, 1H), 10.61(bs, 1H)
3d	Br	218	72	$C_{19}H_{13}BrN_2O_2$	4.34(s, 2H), 6.92(d, 1H), 7.58(m, 7H), 7.94(d, 2H), 10.61(bs, 1H)
3e	CH_3	225	65	$C_{20}H_{16}N_2O_2$	2.41(s, 3H), 4.51(s, 2H), 6.93(d, 1H), 7.21(d, 2H), 7.81(m, 5H), 7.98(d, 2H), 10.62(s, 1H)
3f	OCH_3	207	64	$C_{20}H_{16}N_2O_3$	3.84(s, 3H), 4.53(s, 2H), 6.95-7.31(m, 3H), 7.83(m, 5H), 8.12(d, 2H), 10.58(s, 1H)
3g	SCH_3	245	63	$C_{20}H_{16}N_2O_2S$	3.78(s, 3H), 4.57(s, 2H), 6.94(d, 1H), 7.23(d, 2H), 7.83(m, 5H), 7.98(d, 2H), 10.62(s, 1H)

*a) All the compounds gave satisfactory C, H and N analyses
b) All the compounds exhibited lactam carbonyl absorption around 1680-90 cm^{-1} in IR spectra

6-Phenyl-2-(3-oxo-1,4-benzoxazin-6-yl)pyridine 3a

A mixture of **1** (1.35 g, 0.005 mole), **2** (R = H, 1.0 gm, 0.005 mole) ammonium acetate (0.05 mole) acetic acid (5 ml) was refluxed for 4-5 hrs and worked up as above to give pure **3a**. Yield: 1.00 gm (67%), m.p: 189°C, ms (70eV): m/z (%): 302 (100%, M^+), 273 (20%), 231 (20%). ^{1}H NMR ($CDCl_3$ + DMSO-d_6): δ 4.56 (s, 2H), 6.94(d, 1H), 7.42-7.78(m, 8H), 8.12(d, 2H), 10.57(bs, 1H) (found: C, 7.52; H, 4.87; N, 9.43 $C_{19}H_{14}N_2O_2$ requires C, 75.43; H, 4.63; N, 9.27%).

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