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A Short Synthesis and Antimicrobial Activity of 9-Substituted 2-Aroyl-Benzopyranopyridazin-3-ones

S. D. Shirke[a]* and M. B. Deshmukh[b]
[a]Department of Chemistry, Vivekanand College, Kolhapur ,416 001, M.S., India
[b]Department of Chemistry, Shivaji University, Kolhapur, 416004, M.S., India
Corresponding author : sds.orgchem@gmail.com

Abstract

The various derivatives of benzopyranopyridazin -3-one of substituted aryl, aryloxy and alkoxymethyl hydrazides were synthesized for their study of biological activities. The structures of the synthesized compounds were assigned on the basis of IR, NMR and elemental analysis. The biological screenings of these synthesized compounds were done against gram positive and gram negative bacteria with a view to explore their antimicrobial action.

Keywords: *Benzopyranopyridazin-3-one, Dimethylacrylic acid, Benzopyran-4(1H)-one, Methyl chloroacetate, Carbonyl hydrazides, Benzopyranopyridazins, Antimicrobial activity.*

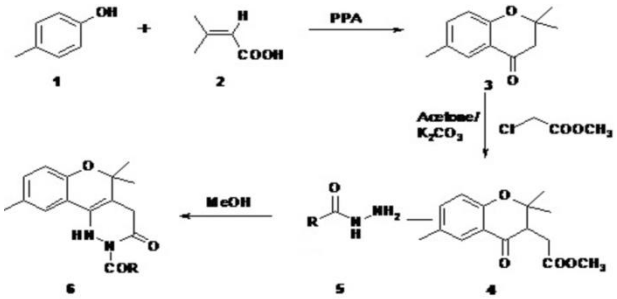
1.0 INTRODUCTION

Benzopyranopyridazine derivatives are extensively studied because of their broad spectrum biological[1] activities like anticoagulant[2-5], spasmolytic[6-8], rodenticidal[10] and estrogenic etc. Some coumarin derivatives possess antifungal, anti-inflammatory and anti-HIV activities[11-13]. Many of the benzopyrans are physiologically active compounds and widely distributed in various plants[14-16]. A novel chroman derivatives act as anti-inflammatory, antipyretic and analgesic agents showing low toxicity and reduced side effects such as gastrointestinal disorders and formation of ulcers in digestive tracts, compared to conventional non-steriodal anti-inflammatory agents[17-18]. It is also used for the preparation of variety of heterocyclic compounds[19-20]. Benzopyran derivatives have excellent herbicidal activity, selective in action for the control of the pests in paddy rice, soyabeans and cotton[21-22] 2-Aryl-4H-1-benzopyran-4-one showed moderate activity against S.aureus whereas high activity against Aspergillus niger.

2.0 RESULTS AND DISCUSSIONS

The various aroyl-benzopyranopyridazin-3-one derivatives were synthesized as described in the Scheme 1 shown below. The compound (3) was obtained in high yields by refluxing substituted phenol (1) with 3-3 dimethyl acrylic acid (2) in polyphosphoric acid (PPA). The reaction of (3) with methyl chloroacetate in presence of K_2CO_3 as a base in acetone yielded compound (4) which on treatment with the various carbonyl hydrazides (5) afford the desired derivatives 6a-6f (Table 1) in high to excellent yields. The structures of all the compounds have been confirmed on the basis of IR, and 1H NMR data. The formation of compound (3) was evidenced by C=0 band at 1620 cm-1, disappearance of –OH band in IR spectrum

Antimicrobial Activity: The disc diffusion method was used for assessing antimicrobial activity against gram positive bacteria (S. aureus and S. citrus) and gram negative bacteria (E. coli and P. aerugenosa) at the concentration 50 μg/mL and 100 μg/mL using aploxacin as standard. DMF waused as a control of the solvent and nutrient agar was used as culture medium. The zones of inhibition formed were measured in mm and are shown in Table 2.



Scheme 1. Synthesis of benzopyranopyridazin-3-one derivatives

3.0 EXPERIMENTAL

3.1 General Remarks:

^{1}H NMR spectra were recorded on a Brucker AC (300 MHz for ^{1}H NMR) spectrometer using D_2O and DMSO-d_6 as solvent and tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer FTIR spectrometer. The samples were examined on KBr discs 5% w/w. Melting points were determined with a DBK melting point apparatus and are uncorrected. All the chemicals were obtained from local suppliers and were used without further purification. The compounds 3a-3c[23] and 4a-4c[24] were prepared by the literature procedure[25-28].

3.2. Synthesis of 3-methoxy-carbonyl-methyl –2,2,6–trimethyl–benzopyran–4-(1H)–one (4)

To the stirred mixture of compound (3) (3.8 g, 0.02 mol) and methyl chloroactetate (4.0 gm, 0.02 ml) acetone (25 ml.), K_2CO_3 (2.5 g) was added and the reaction mixture refluxed for 20 hrs. It was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting solid was poured in ice-water mixture and extracted in chloroform, the organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent and purification by column chromatography gave the desired compound(4) in Yield 78 %; IR (KBr): υ= 1780 (ester C=0), 1710 (C=O), 1600 (C = C) and 1060 cm-1; 1H NMR (300MHz, DMS0-d_6):δ 2.3 (s, 3H, Ar-CH_3), 2.6 (d, 2H, J = 8Hz, $COCH_2$), 3.2 (t, 1H, J = 8Hz, -CH), 3.8 (s, 3H, OCH_3), 6.8 – 7.1 (m, 3H, Ar-H) ppm. Elemental analysis, calcd for $C_{15}H_{17}O_4$: C, 68.98; H, 6.52. Found : C, 68.96; H, 6.51.

3.3 Synthesis of 2-aroyl–5,5,9–trimethylbenzopyrano–[3, 4 -c] pyridazin–3-one (6)

A mixture of compound (4) (0.25 g, 0.001 mol.) and 4-dinitrophenoxyacetic acid hydrazide (0.001 mol.) (5) in methanol (25 ml) was refluxed on a hot water bath . After completion of the reaction which was monitored by TLC, the solvent was removed under reduced pressure. The residual solution was poured in ice water (150 ml) to get a crude product which was recrystallized from methanol to yield 6a in excellent yield (88 %).

Table 1: Synthesized Benzopyranopyridazine-3-one derivatives.

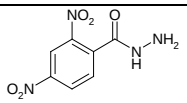
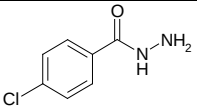
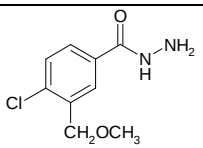
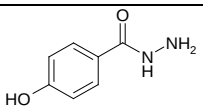
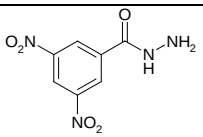
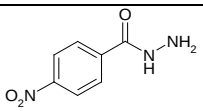
Entry	Phenyl hydrazones (5)	Products (6)	Yield (%)	M.P.(°C)
a		6a	88	180
b		6b	82	195
c		6c	88	177
d		6d	88	220
e		6e	79	251
f		6f	76	182

Table 2: Antimicrobial screening data of benzopyranopyridazin-3-one derivatives.

Entry	Compound	Antibacterial Activity (zone of inhibition in mm)			
		Gram +ve		Gram -ve	
		S. aureus	S. citrus	E.coli	P.aerugenosa
1	6a	8	10	14	15
2	6b	12	11	8	10
3	6c	12	13	14	15
4	6d	14	12	15	12
5	6e	09	9	13	15
6	6f	10	12	13	14
Standard compounds	Tetracycline	20	22	-	-
	Streptomycin	-	-	18	20

4.0 CONCLUSION

The titled compounds 9-substituted benzopyranopyridazines were synthesized using a short method from acetate of benzopyrone when treated with various carbonyl hydrazides. The antimicrobial activity of these compounds was studied by disc diffusion method and it was found to show moderate to good antimicrobial activity particularly for compounds 6a, 6c, 6d and 6e (Table 2) against gram negative bacteria. However they showed moderate activity against gram positive bacteria. The compounds having nitro and chloro substituents were found to be more active than otherwise substituted compounds.

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