A Facile Solvent Free Microwave Induced Synthesis and Antibacterial Activity of Some 3-(2'-Hydroxyphenyl)-5-(Substituted Aryl)-2- Pyrizoline-N¹-Caboxaldehydes

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Abstract: A novel one pot formylation of 3-(2'-hydroxyphenyl)-5-(substituted 2-pyrazolines has been carried out using microwave irradiation with formic acid solvent free reaction afforded title compounds in 80-90% yield with high purity synthesized compounds were tested for their antibacterial activity using standard drug.

Keywords: N-formylation, Pyrazoline, microwave irradiation, antibacterial activity

Introduction

Pyrazolines and their derivatives are known to possess impressive biological activities. They have been reported to have bactericidal^{1,2}, acaricidal^{3,4}, anti-inflammatory⁵, antidepressant⁶, anipyretic⁷, antibacterial⁸ and antifungal⁹ properties. Certain pyrazolines due to their non toxic properties have been used as local anesthetics also¹⁰. Recently reported studies on the microwave irradiation for the synthesis of heterocyclic compounds revealed that it is safe, rapid, economic and convenient, eco friendly method for chemical synthesis. Pollution free synthesis, lesser reaction time, easy workup, and minimum use of solvent are the major advantages of this technique¹¹⁻¹³. A serious constrain of this method is selection of appropriate solvent, which can be avoided by synthesis under solid phase solvent free condition¹⁴.

These facts have prompted us to synthesis some new pyrazoline carboxaldehydes using microwave irradiation under solvent free condition .3-(2'-hydroxyphenyl)-5-(substituted aryl)-2-pyrazolines were treated with formic acid under microwave irradiation to afford the title compounds. Alternatively 2'-hydroxy Chalcones were heated with hydrazine hydrate in presence of formic acid under MWI to get the compound (3a-e).The identity of the synthesized compounds was established on the basis of co-TLC, m.m.ps, elemental analysis and spectral data.

Experimental

Melting points were measured on a Buchi 530 melting point apparatus in open capillaries and are uncorrected (Table 1). The purity of the compounds was checked by TLC using silica gel-G. adsorbent and benzene-ethyl acetate (9:1v/v) as the eluent. IR spectra were recorded on Pekin-Elmer1600 spectrometer using KBr (cm^{-1}). $^1\text{H-NMR}$ spectra were taken on Bruker-DRx-600 Spectrometer using TMS as internal standard and CDCl_3 or DMSO-d_6 as solvent. Mass spectra were obtained on JEOL-SX-DA-600 mass spectrometer (FAB) using m-nitro benzyl alcohol as Matrix. Matrix peaks appeared at m/z 136,137,154,289 and 307.

Table 1. Physical data of some 3-(2'-hydroxyphenyl)-5-(substituted aryl)-2-pyrazoline- N^1 -caboxaldehydes

Compd.	Ar	Molecular formula (M. Wt.)	M P. ($^{\circ}\text{C}$)	Reaction Time (min)	Yield (%)
3a	phenyl	$\text{C}_{16}\text{H}_{14}\text{O}_2\text{N}_2$ (266)	152	6	80
3b	4-methoxy Phenyl	$\text{C}_{17}\text{H}_{16}\text{O}_3\text{N}_2$ (296)	186	6	84
3c	3,4-dimethoxy Phenyl	$\text{C}_{18}\text{H}_{18}\text{O}_4\text{N}_2$ (326)	180	7	85
3d	4-chloro Phenyl	$\text{C}_{13}\text{H}_{13}\text{O}_2\text{N}_2\text{Cl}$ (300)	198	8	87
3e	N,N di-methyl amino Phenyl	$\text{C}_{18}\text{H}_{19}\text{O}_2\text{N}_3$ (309)	176	7.5	85

Synthesis of 3-(2'-hydroxyphenyl)-5-(substituted-aryl)-2-pyrazoline- N^1 -caboxaldehydes (3:)

Method- A

3-(2'-hydroxyphenyl)-5-(substituted aryl)-2-pyrazoline (0.05 mole) and formic acid (0.1mole) were taken in a borosil conical flask, covered loosely with a funnel. The reaction mixture was thoroughly mixed and irradiated under microwave at 600 watt. power for 6-8 minutes. After completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature and extracted with ethyl acetate. After concentration under reduced pressure it was left at room temperature .The solid separated was filtered, dried, and recrystallized to afford analytical sample of 3(a-e).

Method –B

A slurry of 2'-hydroxy chalcone (0.05 mole), hydrazine. hydrate (0.05 moles) and formic acid (0.10 mole) was irradiated under microwave at 450 watt. for 5-6 minis. After completion of reaction as indicated by TLC, the reaction mixture was cooled to room temperature and extracted with ethanol. The separated solid on crystallization was identified as 3(a-e).

Scheme 1.

Reagents and conditions

(a) Hydrazine Hydrate, MWI, 180 watt, -5 min. (b) Formic acid, MWI, 600 watt, 6-7 min

Antibacterial Activity

All the synthesized compounds were screened for their antibacterial activity against gram positive *S.aureus* and *S.albus* and gram negative *E.coli*, *K. pneumonia* and *P.vulgaris* organism. In the determination of antibacterial activity peptone nutrient broth was used, the media was used for gram negative organism by adding 2% meconkey agar to the nutrient broth and for gram positive organism it was prepared by adding 10% sheep blood to 2% nutrient agar. Paper disc diffusion plate method was followed by using special microbial filter paper disc. The compound were screened at maximum concentration of 250 µg/mL in DMF. Results were compared with standard drug Amicacin and coffrioxane at concentration 30 µg/disc. The results of antibacterial activity were tabulated in the form of activity index (Table 2.)

Table 2. Antibacterial activity of synthesized compounds

S.No.	Compound	<i>S.aureus</i>	<i>S.albus</i>	<i>E.coli</i>	<i>K. pneumonia</i>	<i>P. vulgaris</i>
1	3a	-	-	1.4	0.72	-
2	3b	-	-	-	0.66	1.0
3	3c	-	-	-	0.66	-
4	3d	-	-	-	-	-
5	3e	-	-	-	0.66	-
6	Amicacin	1.0	1.0	1.0	1.0	1.0

$$\text{Activity Index} = \frac{\text{Zone of inhibition of compound in mm}}{\text{Zone of inhibition of std. drug in mm}}$$

The observation show that Activiy index of compound 3a., 3b., 3c., 3e., is maximum against Klebsiella pneumonia, compound 3a., 3e., show good index against *E.coli*. All the compounds are inactive against gram positive *S.aureus* and *S.albus*

Synthesis of some 3-(2'-hydroxyphenyl)-5-(substituted aryl)-2-Pyrazoline-N¹-Caboxaldehydes:

3-(2'-hydroxyphenyl)-5-phenyl-2-pyrazoline-N¹-caboxaldahyde (3a)

IR(KBr,Cm⁻¹)- 3400 (OH), 2885 (C-H Stret.), 1664,1660 (CHO), 1430, 2350 (C=C and C=N). ¹H -NMR(CDCl₃) δ-3.29-3.37(DD, 1H,C-Ha),3.83-3.93 (dd, 1H,C-Hb), 5.46-5.52 (dd,1H,C-Hx),6.90-7.39(m,9H,Ar-H),8.90(s,1H,OH),10.12(s,1H,CHO).
MASS FAB(*m/z*) 295 [M⁻¹], 296 [M⁺], 265, 264, 161, 100 ,89

3-(2'-hydroxyphenyl)-5-(4-methoxy phenyl)-2 -pyrazoline-N¹-caboxaldahyde (3b).

IR(KBr,Cm⁻¹)- 3380 (OH), 2935 (C-H Stret.), 1676 (CHO), 1495-1365 (C=C and C=N). ¹H - NMR(CDCl₃) δ-3.30-3.38(dd, 1H,C-Ha),3.83-3.93 (dd, 1H,C-Hb), 5.44-5.50(dd,1H,C-Hx), 6.96-6.86 (m,8H,Ar-H), 8.90 (S,1H,OH), 10.12 (s,1H,CHO), 1.01 (s,3H,OCH₃).
MASS FAB(*m/z*) 266[M⁻¹],267 [M⁺], 251, 237, 154, 134, 121 ,96.

3-(2'-hydroxyphenyl)-5-(3,4-dimethoxy phenyl)-2-pyrazoline-N¹-caboxaldahyde (3c)

IR(KBr,Cm⁻¹)-3400(OH), 2840 (C-H Stret.), 1676 (CHO), 1490-1320 (C=C and C=N). ¹H-NMR(CDCl₃) δ-3.32-3.39(dd, 1H,C-Ha),3.80-3.95 (dd, 1H,C-Hb), 5.44-5.49 (dd,1H,C-Hx), 6.77-6.41 (m,7H,Ar-H), 8.93 (s,1H,OH), 10.13 (s,1H,CHO), 1.08 (s,6H,OCH₃).MASSFAB(*m/z*)327 [M⁻¹],326[M⁺],297, 282, 281 ,266, 263, 230, 207, 189, 161, 154.

3-(2'-hydroxyphenyl)-5-(4-chloro phenyl)-2-pyrazoline-N¹-caboxaldahyde (3d)

IR(KBr,Cm⁻¹)-3387(OH), 2932 (C-H Stret.), 1670 (CHO), 1496-1440 (C=C and C=N). ¹H - NMR(CDCl₃) δ-3.24-3.30(dd, 1H,C-Ha),3.85-3.95 (dd, 1H,C-Hb), 5.44-5.49(dd, H,C-Hx),6.40-6.91(m,8H,Ar-H),8.89(s,1H,OH),10.05(s,1H,CHO).MASSFAB(*m/z*)300 [M⁺], 271, 256, 255, 243, 189, 178, 120, 107 ,89.

3-(2'-hydroxyphenyl)-5-(4-N,Ndimethylaminophenyl)-2-pyrazoline-N¹-caboxaldahyde (3e)

IR(KBr,Cm⁻¹)-3403(OH), 2938 (C-H Stret.), 1665 (CHO), 1524-1440 (C=C and C=N). ¹H- NMR(CDCl₃) δ-3.31-3.38(dd, 1H,C-Ha),3.78-3.86 (dd, 1H,C-Hb), 5.41-5.45(dd, 1H,C-Hx), 6.65-6.39 (m,8H,Ar-H), 8.88 (s,1H,OH), 10.19 (s,1H,CHO),1.01(s,6H,CH₃)
MASS FAB(*m/z*) 309[M⁺], 308[M⁻¹],280, 265, 259, 237, 189, 154, 136, 122.

Conclusions

In above synthetic scheme we use microwave irradiation technique, this is a solvent free reaction condition that leads to considerable saving in the reaction time and energetically profitable. The solvent free condition contributes to saving in cost and diminishes the waste disposal problem. Some compounds show potential antibacterial activity

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