

Preparation, Characterization and Antibacterial Study of Novel 2-[5-(4-Chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl] Compounds

Kiran V. Mehta

Department of Chemistry, R. R. Mehta College of Science and C. L. Parikh College of Commerce,
PALANPUR-385001, Dist. – Banaskantha, State – Gujarat (India)
Corresponding author. Email address: kiranvmehta@ymail.com

Received December 10, 2014; Accepted April 17, 2015

Abstract

This research paper describes a study about synthesis, structure determination and antibacterial activity evaluation of some novel heterocyclic compounds having 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl] fragment. To prepare this kind of compounds, 3-(4-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one was prepared. Its coupling reaction was carried out with diazonium salt of 1° aromatic amine. The coupled product was separated and reacted with hydroxylamine hydrochloride. The final product containing 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl] fragment was characterized with the help of melting point determination and elemental analysis of carbon, hydrogen, nitrogen and chlorine elements. Further characterization was performed with the help of IR, ¹H NMR and Mass spectroscopic methods. The characterization study supports the projected structures of heterocyclic derivatives. Antibacterial assay in vitro for these compounds was carried out for *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Erwinia carotovora* and *Escherichia coli*. It showed good antibacterial activity.

Key Words: 1,2-oxazol-3-yl; Synthesis; Structure; Antibacterial.

Introduction

Besides carbon and hydrogen atoms, oxazole and oxazoline derivatives contain nitrogen and oxygen as hetero atoms. The research work done in this area throws light on structures and mysterious pharmacological perspectives of such molecules (Al-Majidi, et al., 2013; Dabholkar and Syed, 2010; Narwade et al., 2008; Zwawiak et al., 2008; Reddy et al., 2013; Sadek and Fafelelbom, 2011; Silva et al., 2014; Uno et al., 1979; Youn et al., 2009). In this way, these kinds of compounds have been screened for various pharmacological actions. Hence, it was thought to prepare some novel heterocyclic compounds containing 1,2-oxazol-3-yl moiety for studying their activity against selected bacterial species.

Experimental

The general synthetic pathway employed is depicted in Figure 1.

Procedure for preparation of compounds (1)

A solution of absolute ethanol (50 ml) and o-hydroxy acetophenone (0.1 mol, 12.041 ml) was warmed and crystals of p-chloro benzaldehyde (0.1 mol, 14.056 g) were added to get clear solution into which aqueous

solution of sodium hydroxide (10 N, 15 ml) was poured gradually. The solution was stirred at ambient temperature by a mechanical stirrer for 6 h to get the orange mass which was decomposed with chilled HCl (10-15°C, 50%, 40 ml). Thus, yellow granules were obtained which were filtered and washed with aqueous solution of sodium bicarbonate (10%, 20 ml). The granules were dried and crystallized with absolute ethanol. Thus, yellow crystals of compound (1, C₁₅H₁₁O₂Cl, (3-(4-chlorophenyl)-1-(2-hydroxyphenyl)prop-2-en-1-one) were synthesized. The yield of the product was 86% and the melting point was 150°C.

General procedure for preparation of compounds (2-a to 2-f)

These compounds were prepared according to the way depicted in the literature (Chopde et al., 2010; Shah, 1998). The general process which was espoused was as follows: Primary (1°) aromatic amine (0.01 mol) was added into the mixture of concentrated hydrochloric acid (2.8 - 3.6 ml) and water (2.8 ml - 3.6 ml) in a conical flask kept in an ice bath. The solution was gently stirred till its temperature decreased to 0°C (solution 1). Sodium nitrite (NaNO₂, 0.689 g) was dissolved in distilled water (6.9

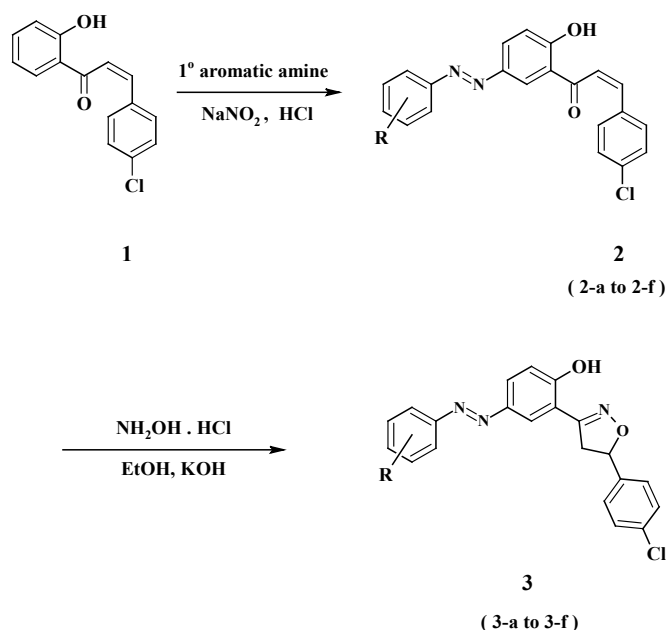


Figure 1 General outline of preparation of compounds

ml) and the solution was cooled to 0°C in the ice bath (solution 2). Small portions of solution 2 were poured into solution 1 and the consequent solution was vigorously stirred and maintained at the temperature between 0-5°C. Presence of a slight excess of nitrous acid was checked with a potassium iodide-starch paper.

Powder of compound (1,0.01 mol) was added little by little in the solution of sodium hydroxide (0.564 g) in water (15.8 ml) and absolute ethanol (15.8 ml). The mixture was stirred for 50 min. It was heated gently up to 50-55°C with vigorous stirring to obtain clear solution and then cooled with continuous stirring. The diazonium salt solution was added slowly maintaining the temperature between 0-5°C for a coupling reaction. The mixture was stirred for 3 h at 0-5°C to yield the compound (2). It was then filtered, washed with water and dried. Its crystallization was carried out using absolute ethanol as a solvent.

General procedure for preparation of compounds (3-a to 3-f)

For cyclisation in compounds, the reaction with hydroxylamine hydrochloride is useful (Ingle et al., 2011; Gantla, 2009). The general method used for the preparation of compounds (3-a to 3-f) is as follows: Compound (2, 0.01 mol), hydroxylamine hydrochloride (0.02 mol) and potassium hydroxide (1.122 g) in ethanol (35 ml) were refluxed for 11-12 h. The reaction mixture was cooled, slightly acidified with glacial acetic acid and poured into cold water (5-10°C). The product was filtered, washed with water, dried and crystallized with absolute ethanol.

The progress of the reaction was monitored by TLC which was performed on silica gel (Merck) plates using a mixture of methylene chloride and methanol (9:1, v/v) as eluent. The spots were observed in the ultraviolet light ($\lambda = 254 \text{ nm}$).

Antibacterial activity

Compounds (3-a to 3-f) were evaluated for activity against *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Ervinia Carotovora* and *Escherichia coli*. Ampicillin 100 $\mu\text{g/ml}$ was taken as a standard antibiotic. DMSO (1%) was used as a solvent control. The strains of bacteria were maintained on nutrient agar slant for 2 h at 37°C. The antibacterial activity was assessed using nutrient agar plate seeded with 0.1 ml of bacterial culture prepared in sterile saline (0.85%) of 10^5 CFU (Colony Forming Unit)/ml. The wells of 6 mm diameter were dug with a sterile metallic borer. The wells were filled with 0.1ml solution of concentration 100 $\mu\text{g/ml}$. All plates were incubated for 24 h at 37°C. The zone of inhibition was measured in mm units, with a Vernier Calliper having precision 0.1 mm. The growth inhibition was calculated with reference to ampicillin as a positive control.

Results and discussion

The melting points of all these compounds (3-a to 3-f) were taken in open capillary glass tubes using paraffin bath and are uncorrected. They are shown in Table 1. The elemental analyses of carbon, hydrogen, nitrogen and chlorine were performed using Carlo-Erba 1108 analyser, Thermo Finnigan FLASH EA 1112 analyser and

Table 1 Basic information about compounds prepared

Comp.	R	M.F. and Name of compound	Molar mass (g/mol)	Yield (%)	M.P.
3-a	H	C ₂₁ H ₁₆ N ₃ O ₂ Cl 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-[phenyldiazenyl]phenol	377.83	65	139
3-b	2 - CH ₃	C ₂₂ H ₁₈ N ₃ O ₂ Cl 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-[(2-methylphenyl)diazenyl]phenol	391.85	60	132
3-c	3-Cl	C ₂₁ H ₁₅ N ₃ O ₂ Cl ₂ 4-[(3-chlorophenyl)diazenyl]-2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	412.27	75	164
3-d	4 - NO ₂	C ₂₁ H ₁₅ N ₃ O ₄ Cl 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-[(4-nitrophenyl)diazenyl]phenol	422.82	62	170
3-e	2-Br	C ₂₁ H ₁₅ N ₃ O ₂ ClBr 4-[(2-bromophenyl)diazenyl]-2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]phenol	456.72	58	123
3-f	3 - OCH ₃	C ₂₂ H ₁₈ N ₃ O ₃ Cl 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl]-4-[(3-methoxyphenyl)diazenyl]phenol	407.85	64	141

Mitsubishi NSX-2100H elemental analyser. The elemental analysis is shown in Table 2. The analyses go well with the predicted structures of compounds (3-a to 3-f). IR spectra were run on Shimadzu FTIR-8300 spectrometer and Perkin Elmer spectrometer using KBr pellets technique. ¹H-NMR Spectra were recorded on a Bruker-Ultrashield (300 MHz) spectrometer using DMSO-d₆ as a solvent and TMS as an internal standard. Mass spectra were recorded on a Joel D-300 spectrometer. The significant spectral characteristics of compounds are given in Table 3.

In this way, the compounds synthesized (3-a to 3-f) were subjected to elemental analysis and ¹H NMR, IR and Mass spectral analysis. These analyses support the predicted structures of the compounds (3).

The antibacterial activity data is given in Table 4. The antibacterial assessment indicates that the compound 3-c showed higher activity against *Pseudomonas aeruginosa* in comparison to the standard antibiotic.

Good antibacterial activity of compounds 3-f and 3-d was noticed against *Bacillus subtilis*, while 3-a and 3-e

showed good results against *Erwinia carotovora*. Compounds 3-c and 3-e showed remarkable anti-*Escherichia coli* activity which is just slightly lower than that of standard antibiotic.

Conclusion

Thus, some novel compounds containing 2-[5-(4-chlorophenyl)-4,5-dihydro-1,2-oxazol-3-yl] fragment can be prepared satisfactorily (58% to 75% yield) by the chemical steps described in this research paper.

These compounds possess notable antibacterial property against the bacterial species: *Pseudomonas aeruginosa*, *Bacillus subtilis*, *Erwinia carotovora* and *Escherichia coli*. It is an important feature of these compounds which make them valuable organic molecules. The insights achieved in this study would be helpful for the development of novel antimicrobial agents.

Table 2 Elemental analysis of compounds

Compound	Elemental analysis (Found Calcd.)							
	% C		% H		% N		% Cl	
3-a	66.76	66.75	4.28	4.26	11.11	11.12	9.47	9.40
3-b	67.39	67.43	4.62	4.63	10.74	10.72	9.00	9.06
3-c	61.14	61.18	3.69	3.66	10.18	10.19	17.19	17.22
3-d	59.67	59.65	3.55	3.57	13.24	13.25	8.32	8.40
3-e	55.19	55.22	3.27	3.31	9.21	9.20	7.79	7.77
3-f	64.74	64.78	4.46	4.44	10.27	10.30	8.68	8.70

Table 3 Spectral characteristics of compounds

Compound	IR	¹ H NMR	Mass(m/z)
3-a	3200, 3054.99, 1601.57, 1564.92, 1246.69 cm ⁻¹	δ = 8.41 (s, 1H, -OH), 6.8-7.98 (m, 12H, Ar-H), 5.69-5.75, 5.19-5.22, 3.91-4.01 (three dd, -CH ₂ -CH)	Calcd. 377.09, Found 377.18 (M ⁺)
3-b	3206, 3010, 1602.89, 1580.2, 1233 cm ⁻¹	δ = 2.49 (s, 3H, -CH ₃), 8.18 (s, 1H, -OH), 6.8-8.1 (m, 11H, Ar-H), 5.63-5.72, 5.21-5.15, 3.70-3.79 (three dd, -CH ₂ -CH)	Calcd. 391.10, Found 391.12 (M ⁺)
3-c	3270, 3017, 1609.21, 1586, 1230.85 cm ⁻¹	δ = 8.35 (s, 1H, -OH), 6.7-8.1 (m, 11H, Ar-H), 5.67-5.71, 5.12-5.19, 3.79-3.84 (three dd, -CH ₂ -CH)	Calcd. 411.05, Found 411.01 (M ⁺)
3-d	3245.93, 3060.78, 1599.64, 1580.35, 1246.69 cm ⁻¹	δ = 8.39 (s, 1H, -OH), 6.75- 8.20 (m, 11H, Ar-H), 5.70- 5.74, 5.20-5.24, 3.85-3.90 (three dd, -CH ₂ -CH)	Calcd. 422.07, Found 422.08 (M ⁺)
3-e	3359.16, 3070, 1618, 1576.1, 1246.2 cm ⁻¹	δ = 8.38 (s, 1H, -OH), 6.63-7.9 (m, 11H, Ar-H), 5.20-5.28, 5.62-5.69, 3.78-3.88 (three dd, -CH ₂ -CH)	Calcd. 455.00, Found 455.09 (M ⁺)
3-f	3257.5, 3008.1, 1613.7, 1561.6, 1246.8 cm ⁻¹	δ = 3.25 (s, 3H, -OCH ₃), 8.32 (s, 1H, -OH), 6.75-7.89 (m, 11H, Ar-H), 4.89-5.0, 5.67- 5.75, 3.77-3.85 (three dd, -CH ₂ -CH)	Calcd. 407.10, Found 407.05 (M ⁺)

Table 4 Antibacterial activity of compounds

Compound	Inhibition zone (mm)			
	<i>Pseudomonas aeruginosa</i>	<i>Bacillus subtilis</i>	<i>Erwinia carotovora</i>	<i>Escherichia coli</i>
3-a	08	14	17	09
3-b	11	10	13	15
3-c	22	15	10	18
3-d	09	19	11	12
3-e	14	08	15	20
3-f	10	23	12	10
Ampicillin (100 µg/ml)	20	27	26	23

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