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Synthesis and Identification of some Benzoxazole Derivatives via Mannich Reaction

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ABSTRACT

The p-Hydroxybenzyldehyde is one of the aromatic compounds which contains two important functional groups (OH, CHO). In this work, the p-hydroxybenzyldehyde has been introduced into different reactions. The first one involves the synthesis of ether via Williamson reaction, in which p-hydroxybenzyldehyd reacts with chloroacetic acid to afford compound (1), then compound (1) in presence of sodium bicarbonate gives the anion (2). Which reacts with propargyl bromide to give the acetylenic compound (3). The compound (3) in turn reacts with secondary amine via Mannich reaction to give the acetylenic amines(4a-f). Finally, the compounds (4a-f) undergo reaction with o-amino phenol to give benzoxazole derivatives (5a-f). The structure of synthesized compounds had been elucidated by the available physical and spectral data.

Keywords: Mannich reaction, benzoxazole, p-hydroxybenzyldehyde, acetylenic amines.

تحضير وتشخيص بعض مشتقات البنزوكسازول باستخدام تفاعل مانخ

الملخص

يعد البارا هيدروكسي بنزالديهايد من المركبات الاروماتية المهمة في الكيمياء العضوية لاحتوائه على مجموعتين فعالتين هما (الهيدروكسيل والالديهايد) في هذا البحث ادخل هذا المركب تفاعلين مختلفين. تضمن التفاعل الأول تحضير الايثر باستخدام تفاعل وليامسون، حيث تم مفاعلة البارا-هيدروكسي بنزالديهايد مع كلورو حامض الخليك ليعطي المركب (1)، ومن ثم حول المركب (1) الى الآنيون (2) بمفاعلته مع بيكاربونات الصوديوم، الذي أدخل تفاعلا مع بروميد البروبارجيل ليعطي المركب الاستيليني(3)، تمت مفاعلة المركب (3) مع الأمينات الثانوية عبر تفاعل مانخ ليعطي الأمينات الاستلينية (4a-f). أخيرا أجري تفاعل المركبات (4a -f) مع الأورثو- أمينو فينول للحصول على مشتقات البنزوكسازول (5a-f) .شخصت المركبات المحضرة باستخدام الطرائق الطيفية والفيزيائية المتوفرة.

الكلمات الدالة: تفاعل مانخ، بنزوكسازول، بارا-هيدروكسي بنزالديهايد، الامينات الاستيلينية.

INTRODUCTION

The five membered hetero cyclic compounds attracted a significant interest in medical, pesticide chemistry, polymer and material science (Annji *et al*., 2008), benzoxazole is known to possess an antibiotic effect (Evens *et al*., 1979) antiviral activity (Amidon *et al*., 2005), anticancer effect (Carturk *et al*., 2004), and antimicrobial activity (Agarwal, 2005).

Mannich reaction involves reaction of compounds containing active hydrogen with formaldehyde and amminonia, primary or secondary amine. Mannich reaction has been employed in the organic synthesis of neutral compounds such as peptides, nucleotides, antibiotics, and alkaloids (Hussin, 2009). Other applications were in agrochemicals such as plant growth,

regulators (DaRosa, 2003). The Mannich products (acetylenic amine derivatives) were considered pharmaceutically active compounds for possessing several biological activities such as antispasmodic (Sheat and Ali, 2005), hypertensive (Sheat and Dawood, 2005) anticancer (Al-Iraqi and Yahya, 2009), and antibacterial activities (Sheat and Saeed, 2006).

EXPERIMENTAL

Melting points were determined using electrothermal 9300 melting point apparatus and are uncorrected. The IR spectra were recorded on pye-Unicam SP1100 spectraphotometer as (KBr) disc. UV spectra were recorded on Shimadzu (UV-160) UV-visible spectrophotometer using CHCl3 as a solvent.

Preparation of 2-(4-formyl phenoxy) acetic acid (1) (Vishnoi, 1982):

A solution of sodium (0.3 g) in absolute ethanol (25 ml) was cooled then para-hydroxybenzaldehyde (0.033 mole, 5 gm) and (0.048 mole, 8 gm) chloroacetic acid were added slowly. The reaction mixture was refluxed with stirring for 3 hr, then cooled in an ice-bath. The formed precipitate was filtered off, washed with ethanol and recrystallized from ethanol to give white crystals of 70% yield and mp (180 -182) °C. The IR spectrum of compound (1) showed the following characteristic absorption band cm^{-1}: 1238(C-O-C), and 1723(C=O) acid, 1675 (C=O) aldehyde.

Preparation of sodium 2-(4-formyl phenoxy) acetate (2) (Saeed, 2010):

The compound (1) (0.03 mole) was dissolved in an aquous solution of sodium bicarbonate (0.03 mole, 5gm) in (20 ml) of water. The solution was evaporated to dryness to obtain a white powder of compound (2).

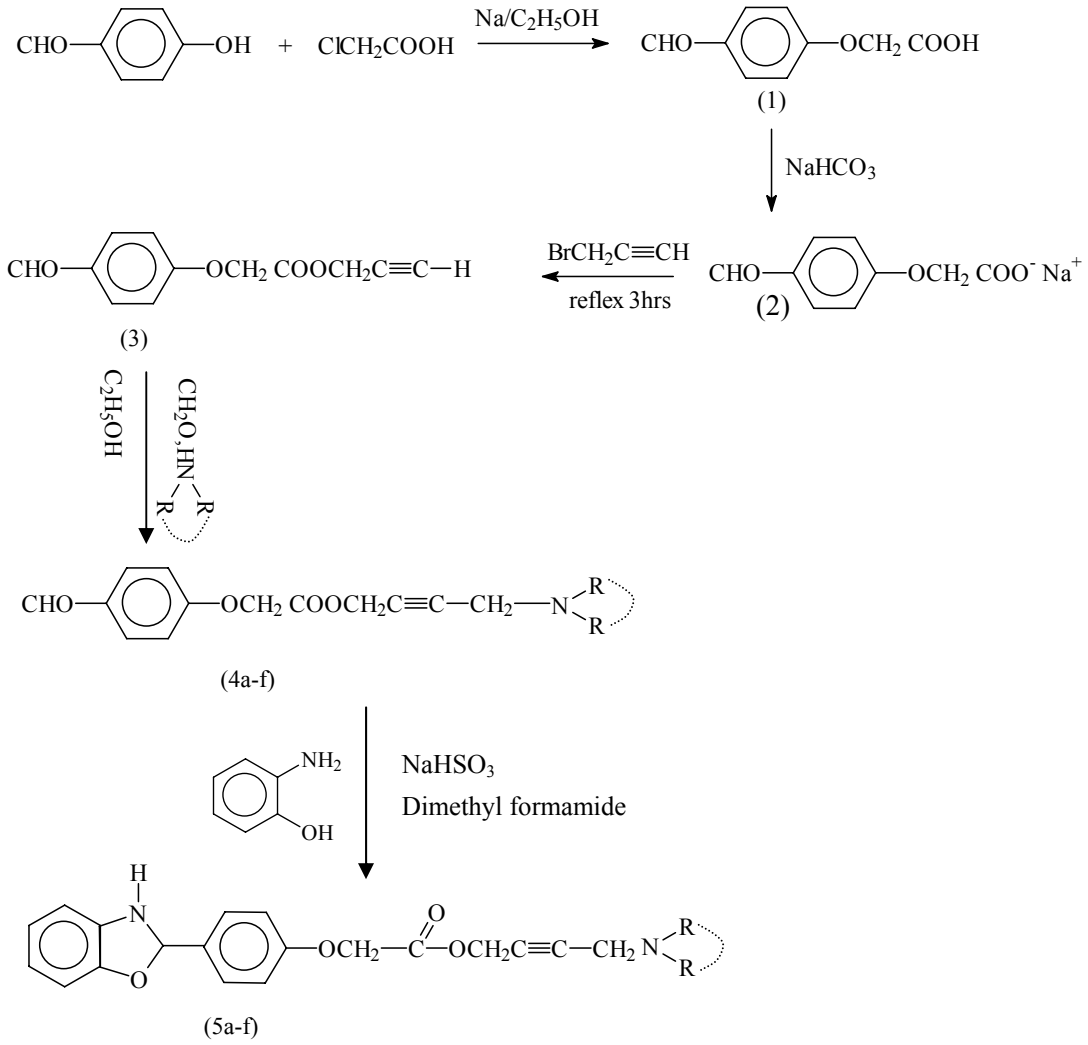
Preparation of propargyl 2-(4-formyl phenoxy) acetate (3) (Saeed, 2010):

To a solution of the compound (2) (0.02 mole) in water (20 ml), propargyl bromide (0.02 mole, 20 ml) was added. The mixture was heated on water bath at (70 -80 °C) for 2 hours with stirring. After cooling, cold water (40 ml) was added with stirring and the oily product was changed to a precipitate. The precipitate was filtered off, washed with cold water and dried, then recrystallized from benzene to afford brown crystals of 66% yield and mp (58 - 60°C). The spectral data of compound (3) showed the following characteristic absorption bands cm^{-1}: 1677 (C=O aldehyde), 2123 (C≡C) 3150 (≡C-H) 1761 (C=O ester). The UV spectrum showed λ_{max} at 256 nm .

Preparation of 2-(4-formylphenoxy)-4-amino-2-butynyl acetate derivatives (4a-f) (Sheat and Saeed, 2006):

General method (Mannich reaction) (Hussin,2009)

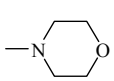
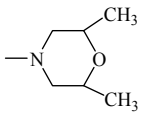
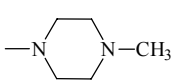
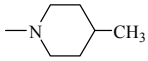
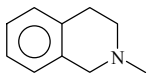
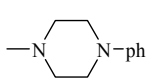
A mixture of paraformaldehyde (0.001 mole, 0.9 g) and appropriate secondary amine (0.015 mole) in absolute ethanol (10 ml) was refluxed till clear solution was obtained. The acetylenic compound (3) (0.04 mole, 0.59 g) in absolute ethanol (10 ml) was added to the first reaction mixture and the resulted mixture was refluxed for 2 hr. The mixture was concentrated by evaporation of the solvent and the residue was filtered off and recrystallized from petroleum ether (80-100 °C) to give the desired compounds (4a-f) (Table 1).



Scheme 1

Table 1: Physical and spectral data of the synthesized compounds (4a-f)

Compd. No.	Yield %	m.p.°C	IR (KBr) υ cm^{-1}					UV ($CHCl_3$) λ_{max}, nm
			C-O-C	C≡C	C=O ester	N-H	C=O aldehyde	
4a	63	110-112	1239	2150	1727	3370	1695	250
4b	55	188-190	1262	2128	1740	3352	1696	255
4c	40	145-147	1236	2132	1750	3340	1699	267
4d	38	280-282	1228	2154	1755	3332	1705	251
4e	45	95-97	1230	2125	1740	3350	1710	253
4f	48	132-134	1232	2140	1735	3360	1715	282

4a:  4b:  4c:  4d:  4e:  4f: 

Preparation of benzoxazoline derivatives (5a-f) (Gupta, 2011):

To a stirred solution of the compounds (4a-f) (0.011 mole) in ethanol, sodium bisulfite (0.0023 mole, 5 g) was added at room temperature. Then a solution of o-aminophenol (0.0023 mole, 5 g) in dimethylformamide (20 ml) was added and boiled under reflux for 3 hr. The reaction mixture was poured on an ice cold water (20 ml) and the precipite formed was filtered off and recrystallized from ethanol. The physical and spectroscopic data of synthesized compounds (5a-f) were listed in (Table 2).

Table 2: Physical and spectral data of compounds (5a-f)

Compd. No.	Yield %	m.p.°C	IR (KBr)υcm^{-1}			UV ($CHCl_3$) λ_{max}, nm
			C=N	C -O-C Asy , sy	C≡C	
5a	55	dec. 200	1559	1246 1166	2141	329
5b	42	215-217	1563	1276 1182	2125	320
5c	30	dec. 180	1558	1247 1167	2123	325
5d	60	dec. 132	1565	1270 1173	2132	315
5e	32	200-203	1568	1243 1165	2150	310
5f	32	140-143	1572	1250 1169	2152	326

RESULTS AND DISCUSSION

The synthetic route in this research was illustrated in scheme 1.The IR spectrum of compound (1) showed characteristic absorption bands at the region: 3060 cm^{-1} for the O-H bond stretching, (2852,2918) cm^{-1} for the aliphatic C-H stretching vibration, 1677and 1724 cm^{-1} for the c=o bond stretching of the formyl and carboxyl moieties, in addation to absorption bond at 1238 and 1053 cm^{-1}for the asy. and sy. c-o-c bond. The UVspectrum showed λ_{max} at (254) nm. The other supporting evidence for this compound is the negative ferric chloride test.

To synthesize the ester (3), the carboxylic acid was treated with sodium bicarbonate to produce the enolate anion (2) which upon treatment with propargyl bromide afforded the propargyl ester (3). The IR spectrum of compound (2) showed a strong band at 1240 and 1163 cm^{-1} for the asy. And sy. c-o-c bond stretching respectively. The UV spectrum of compound (2) showed λ_{max} at (256) nm.

The spectrum of compound (3) showed characteristic absorption bands: 1761 **and** 1677 cm^{-1} for the ester and aldehydic c=o bond stretching, at 2123 cm^{-1}for the c≡c bond stretching and at 3250 cm^{-1}for the ≡C-H bond stretching. The UV spectrum of compound (3) showed λ_{max} at (256) nm due to the (n $\longrightarrow \pi^*$) electronic transition.

The other supporting evidence for the formation of this compound is the positive tollens test for the terminal acetylenic compounds. The acetylenic compound (3) was converted to the Mannich base by its reaction with secondary amines in presence of paraformaldehyde. The structure investigation of the synthesized acetylenic amines derivatives (4a-f) was achieved according to their physical and spectroscopic data (IR, UV) (Table 1).

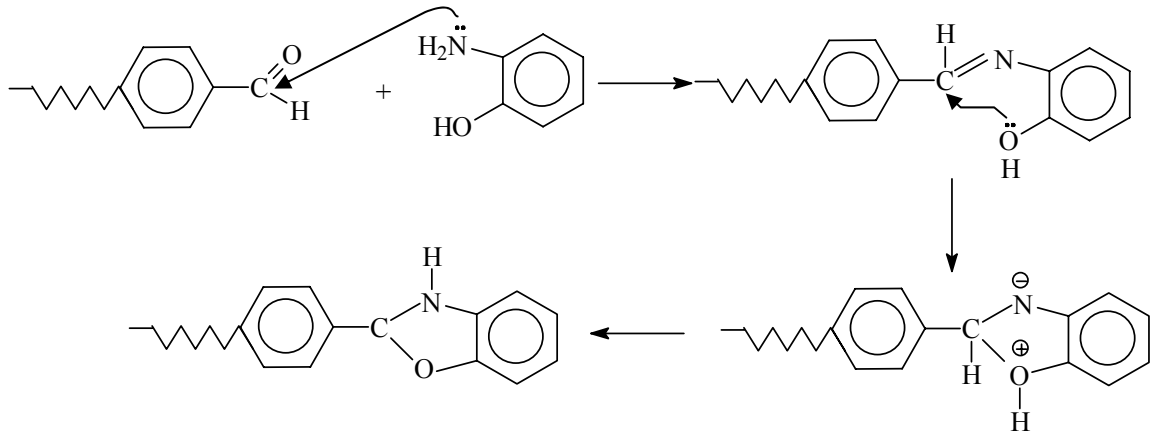
The IR spectra of compounds (4a-f) showed a strong absorption band for esteric as indicated in (Table 1) showed a strong absorption band for esteric c=o at (1755-1727) cm^{-1}, weak band for

C≡C at (2154 -2125) cm^{-1}, the IR spectra indicated the disappearance of ≡C-H bond stretching at 3150 cm^{-1} (Parikh,1974).

The UV spectra of compounds (4a-f) showed a bathochromic shift in λmax (250-282) nm as compared with compound (3) (λmax 256 nm).

Other supporting evidences are that the acetylenic hydrogen in compound (3) showed positive Tollens test which become test negative in Mannich products (4a-f)

The aldehydic group can be used to synthesize the benzoxazoline derivatives (5a-f) by its reaction with o-amino phenol. The formation of these compounds was proceeded according to the following suggested mechanism.



IR spectra of compounds (5a-f) as indicated in Table (2) show strong absorption band for benzoxazole C=N at (1558-1572)cm^{-1}. The disapperance of the absorption bands for the aldehydic C=O band stretching in the range of (1715-1695) cm^{-1} give a good indication for the formation of the oxozoline ring in compounds (5a-f).

The UV spectra of compounds (5a-f) showed bathochromic shift λmax at(310-329) nm due to the conjugation effect on electronic transition (n ⟶ π*) in the synthesized compounds (5a-f) as shown in Table (2) (Parikh,1974).

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