Synthesis and cytotoxic activity study of 3-(2,4-dichlorophenyl)-1-(4'-methoxyphenyl)-3-hydroxypropan-1-one

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Abstract:-

A new methodology was used to synthesis β-hydroxyketone compound namly 3-(2,4-dichlorophenyl)-1-(4'-methoxyphenyl)-3-hydroxypropan-1-one
directly from α,β-unsaturated compound (p-methoxychalcone) in basic medium. Elemental analysis show good agreement between measured and calculated percentage. FT-IR and NMR Spectra techniques were used to identify structure of prepared compound. Minimum inhibitory concentration(MIC) and cytotoxic activity were investigated. The new compound have a limited ability to inhibit microorganisms but have significant cytotoxicity,

Key word:- β-hydroxyketone, chalcone, aldol reaction, MIC Activity, Cytotoxic activity

1-Introduction

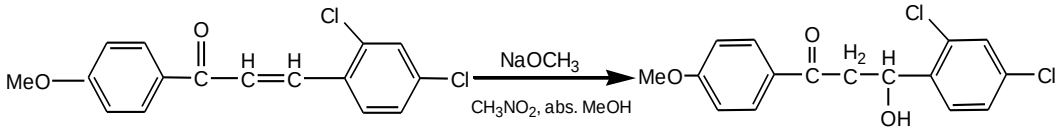
such as self-condensation and polycondensation. The synthetic limitation arises because the reaction is reversible and cannot be driven to completion if the aldol is less stable than the parent carbonyl compounds. In addition, the reverse reaction, in the presence of acid or base, generates regioisomeric enols or enolates, which in turn attack the carbonyl compounds to yield a mixture of aldols. Furthermore, the aldols are often dehydrated and the resulting unsaturated carbonyl compounds may undergo a Michael addition between enolate anions to give a complex reaction mixture.

During the last decade new methods have been developed for the directed coupling of two different carbonyl compounds (or carbonyl equivalents) to give specific β-hydroxyketones. (Yusada, et al.,2005, Jung, *et al*.,2006, Chintareddy, 2009 and Inamoto *et al*., 2012). These methods provide regiospecific reactions for forming β-hydroxyketone and allow the synthesis of a wide variety of aldols by directed self- or cross-coupling.

The aim of this research involves the development of new and practical method for the construction of these important target structure(β-hydroxykrtone) directly from α,β-unsaturated ketone (chalcone). Scheme 1

The aldol reaction is a powerful means of forming carbon–carbon bonds in organic chemistry (Smith and March, 2001, Mahrwald, 2004 and Wade,2005). The reaction combines two carbonyl compounds (the original experiments used aldehydes) to form a new β-hydroxy carbonyl compound. These products are known as aldols, from the aldehyde and alcohol, a structural subunit seen in many of the products. Aldol structural units are found in many important molecules, whether naturally occurring or synthetic(Heathcock, 1991, Mukaiyama, 1982 and Paterson, 1988). The aldol subunit have potent biological properties: the powerful immunosuppressant FK506 (Kino *et al*.,1987), the anti-tumour agent discodermolide (Longley *et al*., 1991) or the antifungal agent amphotericin B (Moen *et al*., 2009).

The aldol reaction, usually carried out in portic solvents with base or acid as the catalyst, is one of the most versatile methods in organic synthesis. By application of this reaction a great number of aldols and related compounds have been prepared from various carbonyl compounds. However, because of difficulty in directing the coupling, the conventional method has serious synthetic limitations. This is particularly notable when two different carbonyl compounds are used in a cross-coupling; the reaction is often accompanied by undesirable side reactions



Scheme 1

2-Experimental

2.1-Preparation of 3-(2,4-dichlorophenyl)-1-(4'-methoxyphenyl)-3-hydroxypropan-1-one:-

A new methodology for the synthesis of β-hydroxyketone was developed. 0.5 gm (0.0016 mole) of 3-(2,4-dichlorophenyl)-1-(4'-methoxyphenyl)propan-1-one(chalcone) (Perjessy, *et al*., 2011) dissolved in (10 ml) nitromethane and (50 ml) abs. methanol . Sodiummethoxid salt 0.086 gm (0.0016 mole) dissolved in (70 ml) abs. methanol and left in cool water bath for 10 minutes. The chalcone solution was gradually added to cold sodiummethoxid salt solution with stirring. The reaction mixture was left with stirring overnight. Later, the stirring turned off and left the mixture to stable for 15 minute. Distilled water (200 ml) was added to the reaction mixture (white loblolly suspension was formed). A white-green solid product was obtained by left the mixture to stable for 2hr. at room temperature. The product was filtered and purified by recrystallization from n-hexane given white powder product. Mp. 120-121° C, R_f = 0.38 (from 1:3 ethylacetate : n-hexane).

3-Identification:

3.1-Elemental analysis

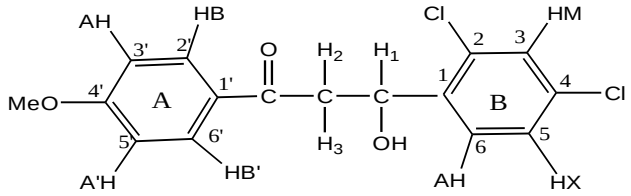
The measured percentage of C, H and N atoms of prepared compound show good agreement with the calculated results: measured (cal.) %C: 60.31(59.50), %H: 4.22(4.24), %N: 0.00(0.00).

3.2-Infrared Spectra:

IR spectra of prepared compound was measured as KBr disk using FT IR-8400S SHIMADZU

3.3-NMR Spectra:

Proton NMR spectrum measurement was recorded on a Varian VXR 300 NMR spectrometer (299.943 MHz) in $CDCl_3$ solvent at 25 °C . ^{13}C NMR spectra was recorded on the same spectrometer at (75.429 MHz) in $CDCl_3$ solvent at 25 °C and reference with respect to TMS in ppm. Scheme 2 shows proton designation and carbon atom numbering.



Scheme 2

4-Results and dissection

4.1-Infrared Spectra:

The spectrum of this compound (Figure 1) show v. strong sharp band at 3498 cm^{-1} of -OH alcohol stretching. Strong peaks at 1259 cm^{-1} of secondary C-O stretching (Cross and Alan) . Also the aliphatic –CH_2- and -CH- stretching at 2933 cm^{-1} and 2900 cm^{-1} respectively and –CH_2- and -CH- deformation at 1482 cm^{-1} and 1355 cm^{-1} respectively. The strong band at 1660 cm^{-1} is attributed to C=O stretching

(Silverstein *et al.*, 1997). Two strong bands at 1027 cm^{-1} and 1259 cm^{-1} are attributed respectively to symmetry and asymmetry C-O-C stretching band of methoxy group (Hanoy 1999).

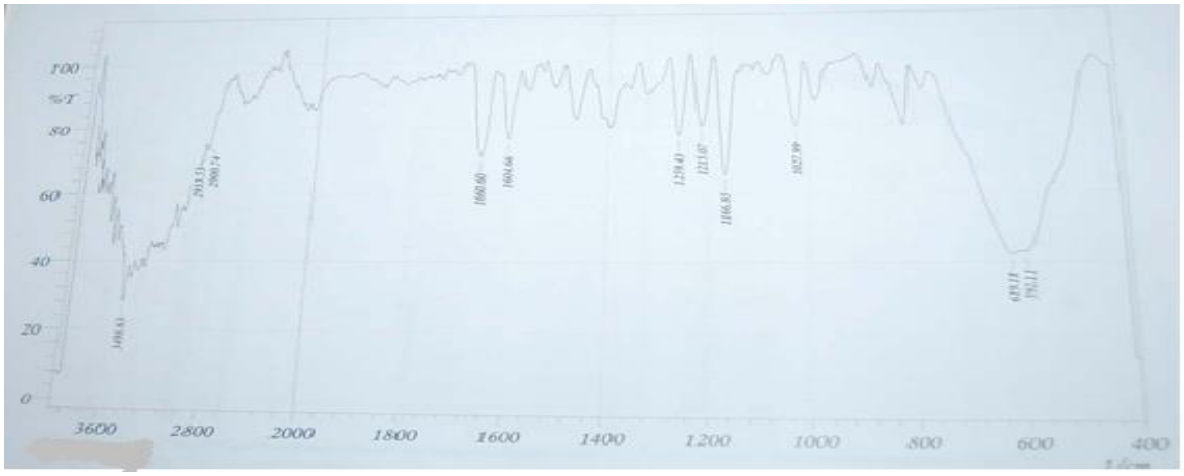


Figure (1) IR spectrum of new compound

4.2-Proton NMR spectra:

Table 1and Figure 2 shows proton NMR spectrum. Protons on ring B showed an AMX pattern of splitting, while protons on ring A showed an AA'BB' pattern of splitting (Crews *et al.*,1998 and Hanoy 1999). The alphatic protons gave different pattern of splitting. Scheme 2

Table 1. Bands of ^{1}H- NMR spectra of new compound

Comp.	H-AA'	H-BB'	H-A	H-X	H-M	J_A x	J_M x	CH(OH)(1) doublet	CH_2 (2) quartet	CH_2(3) quartet	others
p-OCH3	6.954-6.926	7.950-7.920	7.663	7.317	7.373	8.7	1.8	5.597	3.499	3.032	3.87(OCH$_3$) 4.073(OH)

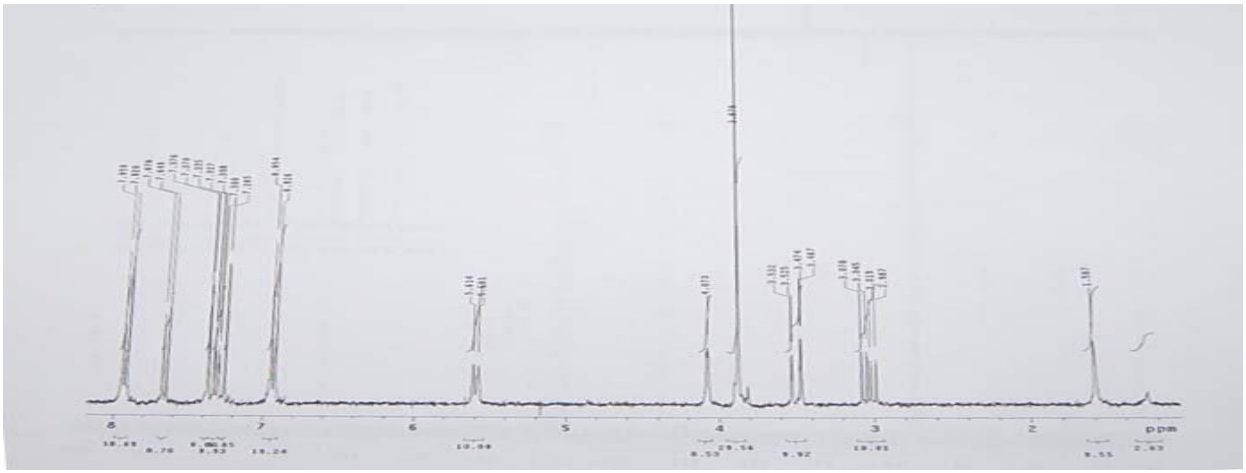


Figure (2) ^{1}H-NMR spectrum of new compound

4.3- ^{13}C NMR spectra assignment

Table 2 and Figure 3 presents the measured ^{13}C-NMR CS. The spectra of ^{13}C-NMR of this compound assign depending on additivity method using CS-ChemDraw program (Chemical Structure Drawing Standard, copyright by Cambridge soft Corporation, publication 1997).

Table 1. Bands of ^{13}C-NMR spectra of new compound

Comp.	CO	-CH_2-CO-	CH(OH)	C-1' C-1	C-2' C-2	C-3' C-3	C-4' C-4	C-5' C-5	C-6' C-6	Others (OCH_3)
p-OCH3	198.7	44.5	66.7	129.6 139.1	130.5 131.7	113.9 129.1	164.1 133.6	113.9 127.5	130.5 128.4	55.6

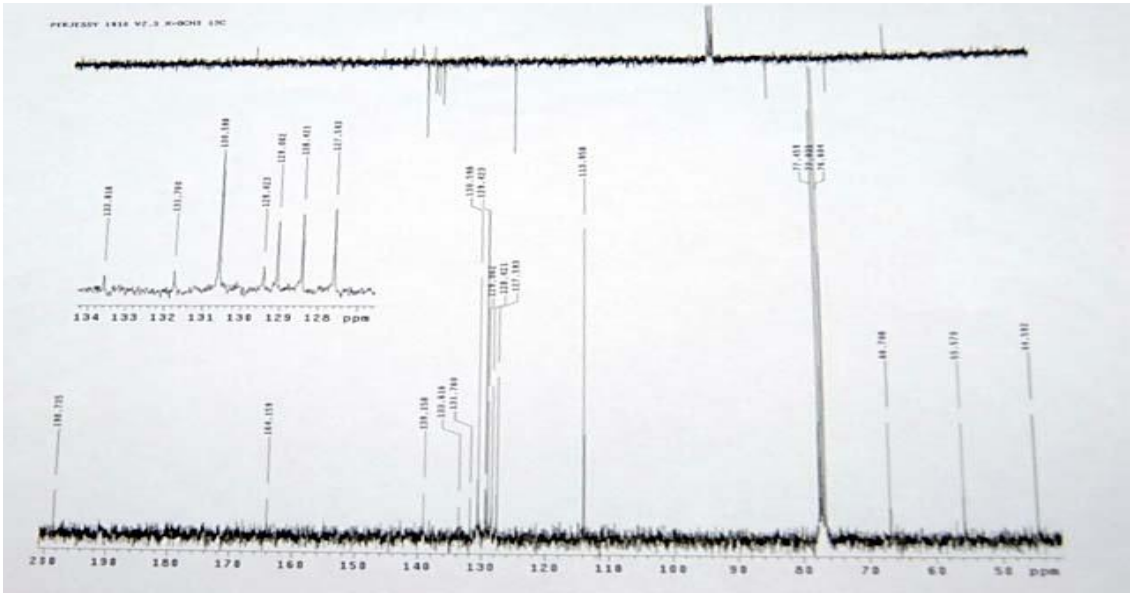


Figure (3) ^{13}C-NMR spectrum of new compound

5-Bioactivity study

5.1-Minimum inhibitory concentration (MIC) assay.

The Minimum inhibitory concentration (MIC) of new compound was determine against to two standard bacterial species: *Escherichia coli* (Gram negative bacteria ATCC25922) and *Staphylococcus aureus* (Gram positive bacteria ATCC25923) according to Hanoy *et al.*, 2013, in different concentrations ranging (75,50,25,15,10,5 and 2.5) µg/ml.

5.2-Cytotoxicity assay

Any drug that has a toxic effect on cells; commonly used in chemotherapy to inhibit the proliferation of cancerous cells.

Cytotoxicity of new compound against human red blood corpuscles RBCs was tested according to Nair *et al.*, 1989, in different concentrations ranging from (0.5 - 250) µg/ml. dissolved in DMSO. DMSO was used as a control sample.

Results and dissection of biological 6 -activity:

6.1-Minimum inhibitory concentration (MIC)

Table 3 show the result of the MIC of new compound. When comparing this result with the MIC of starting material (p-methoxychalcone) (Table 3) we found that the p-methoxychalcone is more reactive against bacterial microorganism than new compound. The activity of chalcones was attributed to α , β-unsaturated ketone system (Hanoy *et al.,* 2013).

Table 3. MIC of new compound

microorganism	*Escherichia coli*	*Staphylococcus aureus*
MIC of new compound (µg/ml)	>75	50
(MIC of p-MeO chalcone) (µg/ml) (Hanoy *et al.,* 2013).	10	2.5

6.2-The cytotoxicity of the compounds:

The result in Table 4 and Figures 4 and 5 , show the cytotoxicity for both p-methoxychalcone and the new compound, against the human red blood cells within a concentration ranging from 0.5 - 250 µg/ml for each compound, by using DMSO solvent as a control. From Table 4 and Figure 5 seen that the new compound is more cytotoxic than p-methoxychalcone at 100, 200 and 250 µg/ml. This cytotoxicity can be attributed to stereogenic aldol units which are especially common in polyketides(Polyketides are structurally a very diverse family of natural products with diverse biological activities and pharmacological properties) (Leonard 1997) .

Table 4: The cytotoxicity of the compounds

Compound	**(No.) Concentration** µg/ml	**Toxicity against RBC**
DMSO	-	NT
p-methoxychalcone	(1) 0.5 (2) 10 (3) 50 (4) 100 (5) 200 (6) 250	NT NT NT NT NT NT

New compound	(1) 0.5	NT
	(2) 10	NT
	(3) 50	NT
	(4) 100	T
	(5) 200	T
	(6) 250	T

T: Toxic NT: Not Toxic DMSO: Dimethylsulfaoxide

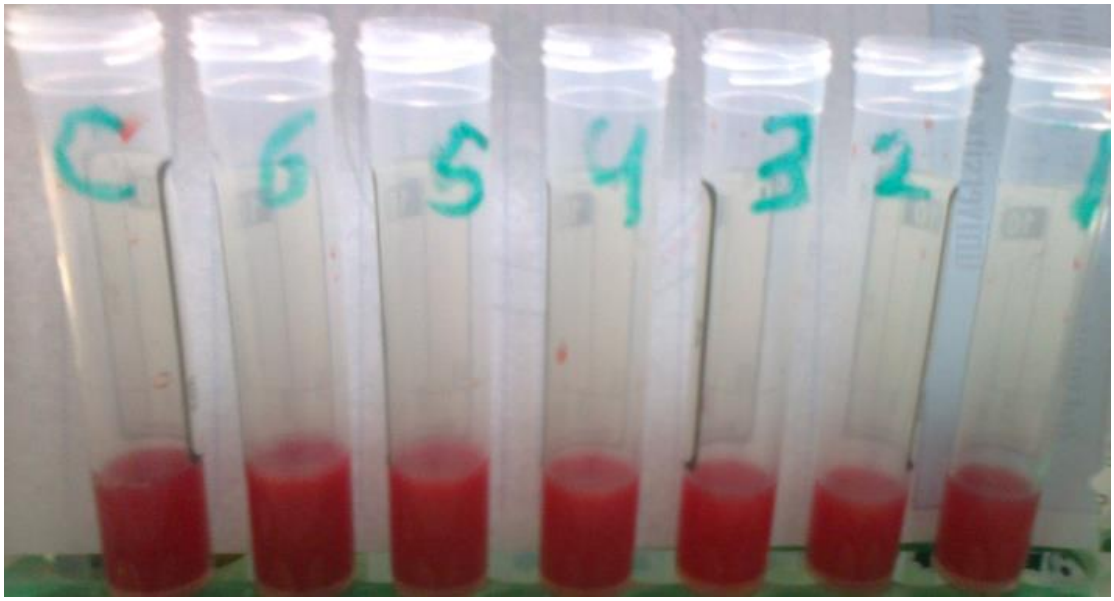


Figure 4 : The cytotoxicity of the p-methoxychalcone

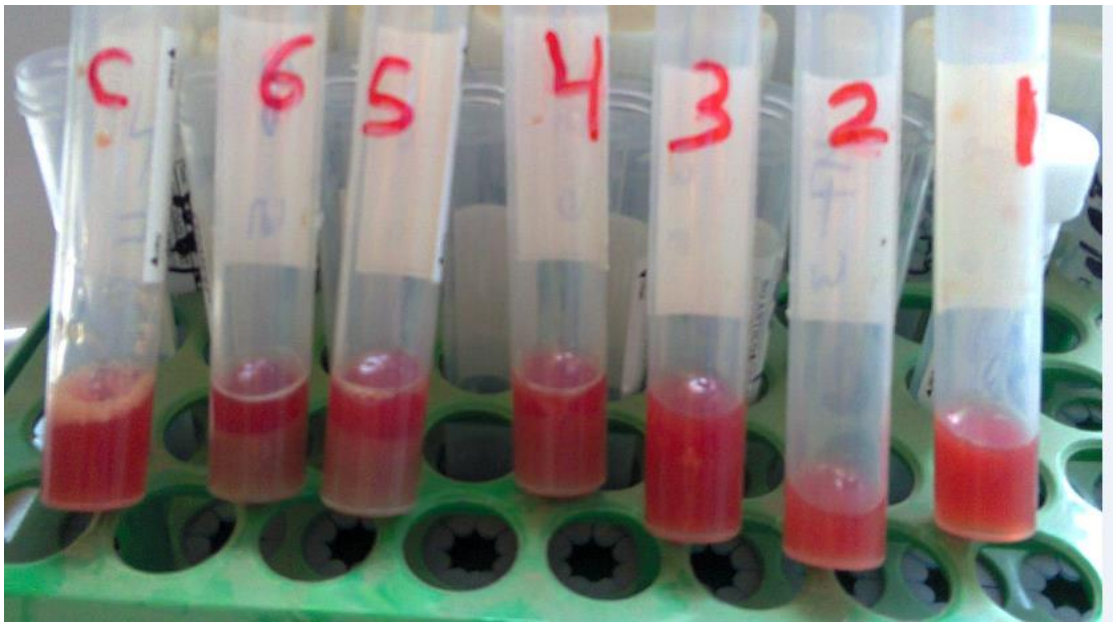


Figure 5 : The cytotoxicity of the new compound

7-Conclusions

This directed hydroxylation of chalcone is an efficient method for the regiospecific formation of new compounds and can be used for the preparation of key intermediates in the synthesis of important natural products.

New compound have a limited ability to inhibit microorganisms but have significant cytotoxicity,

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تحضير ودراسة الفعالية السمية الى 3-(4,2-ثنائي كلوروفنيل)-1-(4'-ميثوكسي فنيل)-3-هيدروكسي-1-اون

هانوي كمال العامود
جامعة البصرة-كلية العلوم-قسم الكيمياء

الخلاصة:-

استخدمت طريقة جديدة لتحضير احد مركبات البيتا-هيدروكسي كيتون والمسمى3-(2,4-ثنائي كلوروفنيل)-1-(4"-ميثوكسي فنيل)-3-هيدروكسي بروبان-1-اون من الجالكون المقابل (بارا-ميثوكسي جالكون) في وسط قاعدي. التحليل العنصري الدقيق اظهر توافق جيد بين القيم المحسوبة نظريا والقيم المقاسة عمليا. استخدمت تقنية مطيافية تحت الحمراء ومطيافية الرنين النووي المغناطيسي لغرض تشخيص المركب. تم فحص التركيز المثبط الادنى والسمية للمركب الجديد حيث اظهر قدرة أقل من الجالكون على التثبيط ولكنه في الوقت نفسه اظهر فعالية نسبية من السمية.