Egypt. J. Chem. **Vol. 64,** No. 11 pp. 6323 - 6332 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Efficient Method for Synthesis of New Tetra Substituted Pyrroles Under Catalytic Phosphine

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Abstract

The main precursor to the synthesis of new tri substituted Pyrroles (1&2**)** 4-((z)-(E)-2,3,5-tri aryl allylidene amino)-N-(thiazole-2-yl) benzene sulfonamide (3&4). The last one was under went multicomponent witting reaction in presence of acid chloride and tri phenyl phosphine in basic media from tri ethyl amine to afford the substituted pyrrole named 4-(2,3,5-tri aryl-1H-pyrrole-1-yl)-N-(thiazole-2-yl) benzene sulfonamide (5a-g). The structure of prepared compounds were determined by the available physical and spectral methods M.P. ,T.L.C , U.V , FT-IR & ^{1}H-NMR.

Keywords: - Wittig reaction, sulfathiazole, pyrrole, chalcone, multicomponent reaction.

1. Introduction

Heterocyclic small molecules play an important role in the search for new physiological and pharmacological activities [1] . Pyrroles are an important class of heterocyclic compounds and are structural units found in vast away of natural products[2] , synthetic materials[3], and bioactive molecules such as hem [4], vitamin B_{12}[5], and cytochrome[6, 7].Actually, pyrroles show broad spectrum of activity in pharmaceutical and medical field , such as non-steroidal anti-inflammatory drugs (NSAIDs)[8], antitumor[9], antimicrobial[10], antibacterial, antifungal[11], analgesic[12], anticonvulsant[13], anticancer[14] and anti HIV [15]. and can also be used as an enzyme inhibitors in the organism such as COX-1/COX-2 inhibitors[16]. Pyrroles in general were prepared by the classical methods represented by Knorr[17], Hantzsch [18], and Pall Knorr condensation reaction[19] , some of the other methods for synthesis of pyrroles include conjugated addition reaction[20], multicomponent reaction[21] and finally must active procedure , which used nowadays is aza-Wittig reaction[22].In this presentation and because of the above supreme introduction, pyrroles were prepared through multicomponent reaction represented by catalytic phosphine mediated aza-wittig reaction in basic media and in presence of acid chloride derivatives . Herein, sulfathiazole was used as a source for primary aromatic amine which reacted firstly with heterochalcone (1&2) to give the α-β-unsaturated imine represented by compounds (3&4) followed by intracyclization reaction with acid chlorides through wittig reaction in basic condition to afford the pyrroles compounds (5a-g). 1. Experimental

Starting material and solvents were procured from Fluka,BDH and Aldrich companies and used without futther purification . Melting points (M.P.) were measured on Electrothermal SMP30- Stuart melting point apparatus and were uncorrected. 1H-NMR spectra were recorded using Bruker Bio Spin GmbH Spectrophotometer (400 MHz by using TMS as internal standard and using DMSO-d6 as a solvent) in University of Gazi Othman Basha, Turkey, [(s) singlet, (d) doublet, (m) multiplet]. Infrared (FT-IR) spectra were recorded using FT-IR Spectrophotometer, Shimadzu 8400s (Japan). Ultraviolet (U.V) spectra were performed on (Jasco V-630 UV–Vis) Spectrophotometer using methanol as a solvent. The Thin-layer chromatography (TLC) was carried out on an eastman chromatogram sheet (20x20) cm, 13181 silica gel with the fluorescent indicator (No. 6060) using solvent system benzene: methanol in the ratio (80:20).

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Receive Date: 18 May 2021, Revise Date: 04 June 2021, Accept Date: 06 June 2021
DOI: 10.21608/ejchem.2021.76540.3754

Synthesis of *Chalcones* (1&2)[23, 24]:

A mixture of (0.023 mol) of ketone (2-acetyl furan or 2-acetyl pyridine) and (0.023 mol) of piperonal was dissolved in (40 ml) ethanol in presence (1 gm) NaOH , the reaction mixture was stirred at room temperature for (20 hrs). this mixture was filterated and washed with the water several times, dried to afford the chalcone (1&2) which show the following data :-

Chalcone (1) **(E)-3(benzo [1,3-d] dioxol-5-yl)-1-(furan-2-yl)prop-2-en-1-one:-**

yellow powder , m.p (°C): (176-178), yield (%): 87% ; T.L.C (R_f): 0.761, λ_{max}(nm)(349-260); FT-IR (ν cm^{-1}): NH(3406), CH_3(asym 2899 & sym 2800), C=O(1663), C=C(acycl. 1593 & cycl. 1584), C-O-C(asym 1447 & sym 1261).

Chalcone (2) **(E)-3(benzo [1,3-c] dioxol-5-yl)-1-(pyridin-2-yl)prop-2-en-1-one:-**

yellow powder, m.p (°C): (196-198), yield (%): 77%, T.L.C (R_f) : 0.706, λ_{max}(nm)(364-252), FT-IR (ν cm-1): NH(3435), CH_3(asym 2915 & sym 2855), C=O(1663), C=C(acycl. 1564 & cycl. 1503), C-O-C(asym 1445 & sym 1254).

Synthesis of 4-((Z)-(E)-2,3,5-tri aryl allylidene) amino)-N-(thiazole-2-yl) benzene sulfonamide (3&4)[25]:

A mixture of (0.013 mol) of sulfathiazole and (0.013 mol) of chalcones (1&2) was dissolved in (30 ml) DMSO , the reaction mixture was refluxed for (6 hrs) in presence of catalytic amounts of glacial acetic acid (3drops). This mixture was cooled and poured in crushed-ice followed by filtration and washed with the water several times , dried to afford the Schiff bases (2&4) which show the following data :-

Schiff base (3) (furyl ring) :-

green powder, m.p (°C):(137-140) , yield (%):60% , T.L.C(R_f):0.647, λ_{max}(nm)(257-230), FT-IR (ν cm^{-1}): NH(3370), C=C(acycl. 1630), C=C(cycl. 1593), C=N (acycl.1537) , C=N (cycl.1497) ,C-O-C (asym 1242 & sym 1086) ,SO_2 (asym 1327 & sym 1138) , C-S=(810).

Schiff base (4) (pyridyl ring):-

yellow powder, m.p(°C):(146-148), yield (%):59%, T.L.C(R_f):0.741, λ_{max}(nm)(247-225), FT-IR (ν cm^{-1}): NH(3368) , C=C(acycl. 1657), C=C (acycl. 1597), C=N (acycl. 1536), C=N (cycl.1501), C-O-C (asym 1251 & sym 1086), SO_2 (asym 1321 &sym 1138), C-S=(824).

Synthesis of 4-(2,3,5-tri aryl-1H-pyrrole-1-yl)-N-(thiazole-2-yl) benzene sulfonamide (5a-g)[26]:-

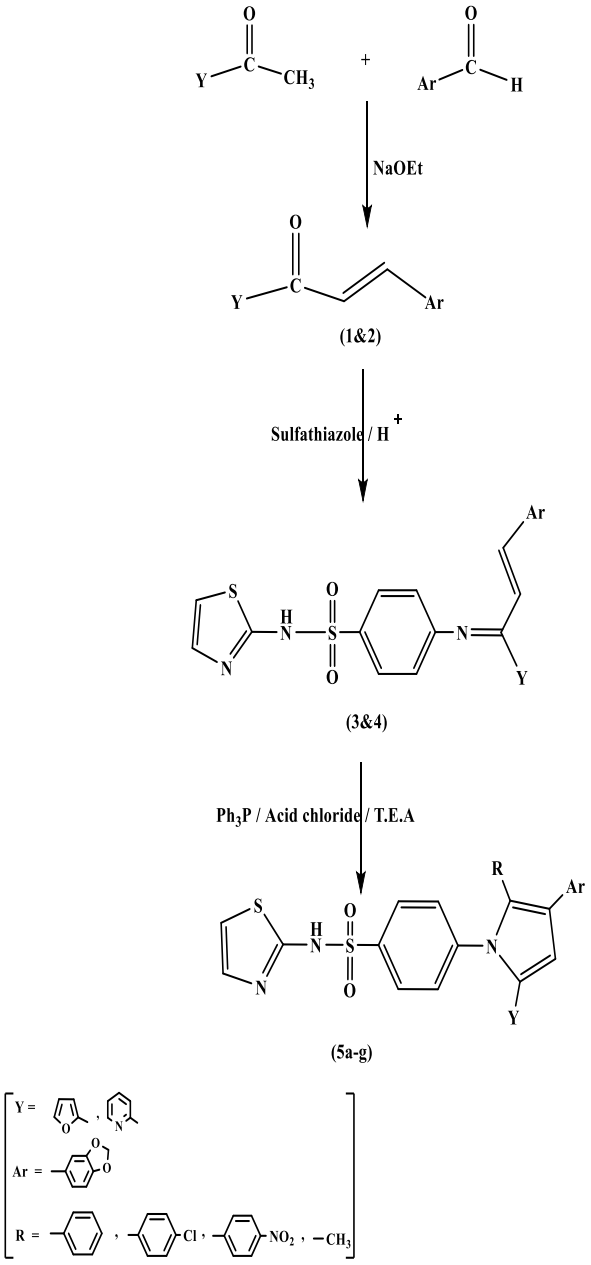
Equimolar of Schiff bases (3&4), tri phenyl phosphine and acid chlorides (0.001 mole) were dissolved in (20ml) DMSO in presence of catalytic amounts of tri ethyl amine (3 drops), followed by refluxed (6 hrs.) . The reaction was then cooled and poured in crushed-ice and the gummy product was treated several times with pet-ether (60-80) followed by washing with benzene to afford the compounds (5a-g). The physical and spectral data were listed in the table (1&2).

Table 1 Physical properties of compounds5a-g)

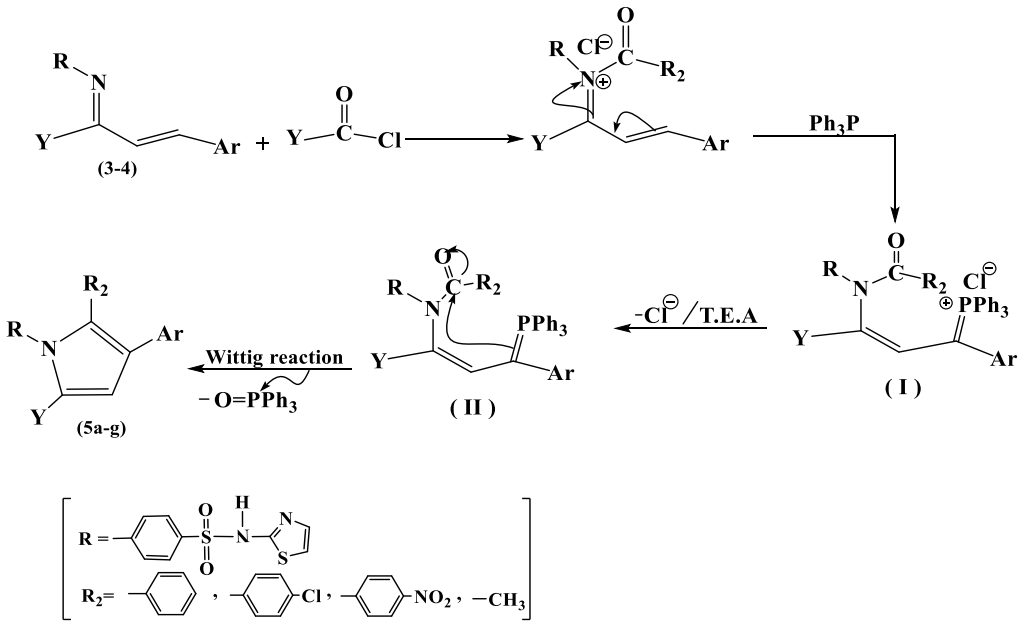
Comp. No.	Y	X	M.P (˚C)	Yield (%)	Colour	T.L.C Benzene Methanol (8:2)
5a		$-CH_3$	213-215*	63	Black	0.831
5b			282-285*	53	Black	0.725
5c			162-165	55	dark brown	0.518
5d		$-CH_3$	328-330	52	Brown	0.736
5e			158-160	92	Brown	0.860
5f			153-155	56	Brown	0.7674
5g			107-108	52	Brown	0.6451

3- Results and Discussion

A series of new tri substituted pyrroles were designed and synthesized by catalytic phosphine mediated multicomponent reaction route according to general synthetic pathway Scheme(1) First of all, the hetero chalcone (1&2) were prepared according to the literature procedure using 2-acetyl furan and 2-acetyl pyridine which used as active ketone to prepared the hetero chalcones (1&2).These compounds used as conjugated carbonyl source to afford the conjugated imines represented by compounds (3&4),through it's reaction with sulfathiazole and according to the following mechanism reaction[27], (Scheme 2) It has been found that these imines were shown in FT-IR spectroscopy stretching absorption bands at ν(cm^{-1}) (1537 & 1536), due to the (C=N) functional group in Schiff base structure . In addition to the other absorption bands has been mentioned experimental section. In U.V. spectroscopy they show an oxochromic shift at λ_{max} (nm), (257) & (225) due to the n→π* and π→π* respectively[28].Wherease in ^{1}H-NMR spectroscopy compound (3) gave clear signals at (δppm) :- (d,1H,5.82)&(d,1H, 6.1) refer to the CH=CH functional group additionally to the other functional groups signals were listed in Table(3) which came in agreement with the expected structure. These conjugated imines were undergone intracyclization wittig reaction in presence of different acid chlorides and catalytic amounts of tri phenyl phosphine and tri ethyl amine to afford the substituted pyrroles represented by compounds (5a-g) , as shown in the following scheme[29] According to Scheme (3) , the ammonium salt was formed via direct attaching of nitrogen atom of imine on the carbonyl group which reacted rapidly with tri phenyl phosphine to give the intermediate (I) which losing the chloride ion by the action of the base to give the compounds (II) ; and the later was underwent Wittig reaction through losing of $O=PPh_3$ molecule to give tri substituted pyrroles (5a-g). Tables (1&2) shown the physical properties and spectral data respectively. The absence of (C=N acycl.) stretching vibration in FT-IR spectra gave evidence of the output structure in addition to the other absorption vibrations (Table 1). On the other hand , these compounds showed two electronic transition in UV spectra due to n→π* & π→π* at λ_{max}(nm) , (341)& (246) Respectively and due to the ring system[28], Whereas in ^{1}H-NMR spectroscopy compounds (5c&5g) as example gave complex absorption peaks as shown in (Table 3), the appearance of the pyrrole proton peak at (δ ppm): (s,1H, 7.09) and (s,1H, 6.88) respectively give a good indication that Wittig reaction was take place and supporting the pyrrole ring formation.



Scheme (1)
Steps for synthesis tri substituted pyrrole

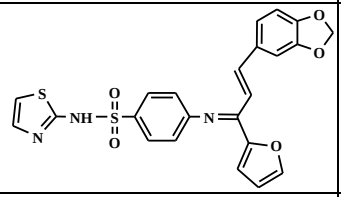
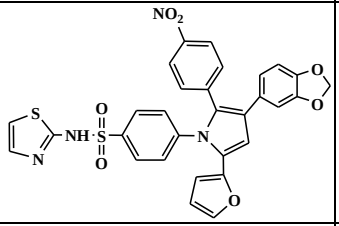
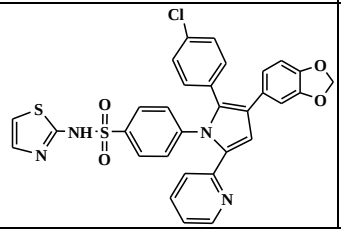


Scheme (3)
Synthesis of tri substituted pyrroles (5a-g)

Table (2): Specrtral data for compounds (5a-g)

Comp. No.	Y	X	FT-IR , ν (cm^{-1})							UV(MeOH) λ_{max}(nm)
			N-H	C=C arom.	C=N	C-O-C	SO_2	C-S	Other	
5a		-CH_3	3333	1595	1505	asym.1290 sym.1088	asym 1368 sym 1142	816	CH_3 asym. 2920 sym. 2827	341-304
5b			3371	1595	1503	asym.1285 sym.1086	asym 1362 sym 1140	814	-----	341-302
5c			3297	1599	1505	asym.1283 sym.1088	asym 1350 sym 1140	818	NO_2 asym. 1435 sym. 1238	341-316
5d		-CH_3	3376	1595	1505	asym.1291 sym.1088	asym 1362 sym 1142	814	CH_3 asym 2915 sym 2800	341-304
5e			3340	1595	1505	asym.1244 sym.1036	asym 1358 sym 1142	813	-----	289-285
5f			3345	1579	1505	asym.1289 sym.1088	asym 1364 sym 1140	814	NO_2 asym 1480 sym 1238	262-246
5g			3273	1593	1507	asym.1290 sym.1088	asym 1364 sym 1140	813	C-Cl 764	341-311

Table (3): The ^{1}H-NMR spectroscopy for compounds (3,5c&5g)

Comp. No.	Structure	^{1}H-NMR , DMSO-d6, δ (ppm)
3		NH-SO$_2$ (s,1H,5.0), O-CH$_2$-O (s,2H,6.03), =CH-C=N(d,1H,5.82), CH=CH-C=N(d,1H, 6.1), piperonal protons (m,3H,6.52-6.57), thiazole protons (d,1H,6.72) &(d,1H, 7.17), furan protons (d,1H,6.79), (s,1H, 6.74)& (d,1H,7.07), sulfathiazole aryl protons AB system (d-d,4H,8.58-8.69)
5c		NH-SO$_2$ (s,1H,4.35), O-CH$_2$-O (s,2H,4.37), piperonal protons (m,3H,6.59-6.60), furan protons (m,3H,6.62-6.63), thiazole protons (d,1H,7.07) &(d,1H, 7.08), pyrrole proton (s,1H, 7.09), ,2-aryl pyrrole protons AB system (d-d,4H,7.16-7.72), sulfathiazole aryl protons AB system (d-d,4H,7.76-7.99)
5g		NH-SO$_2$ (s,1H,5.06), O-CH$_2$-O (s,2H,5.0), piperonal protons (m,3H,5.01-5.06), thiazole protons (d,1H,6.72) &(d,1H, 6.74), pyrrole proton (s,1H, 6.88), pyridine protons (m,3H,7.37-7.40),2-aryl pyrrole protons (m,4H,7.54-7.65), sulfathiazole aryl protons AB system (d-d,4H,8.18-8.36)

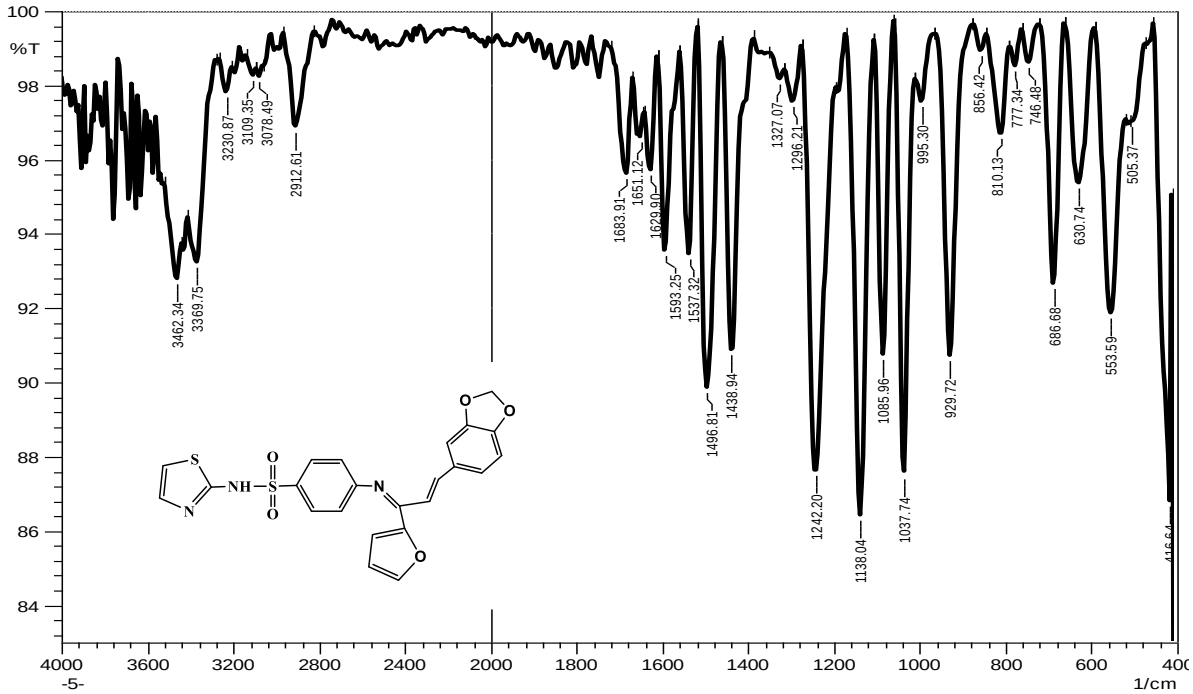


Figure (1): FT-IR Spectrum of compound (3)

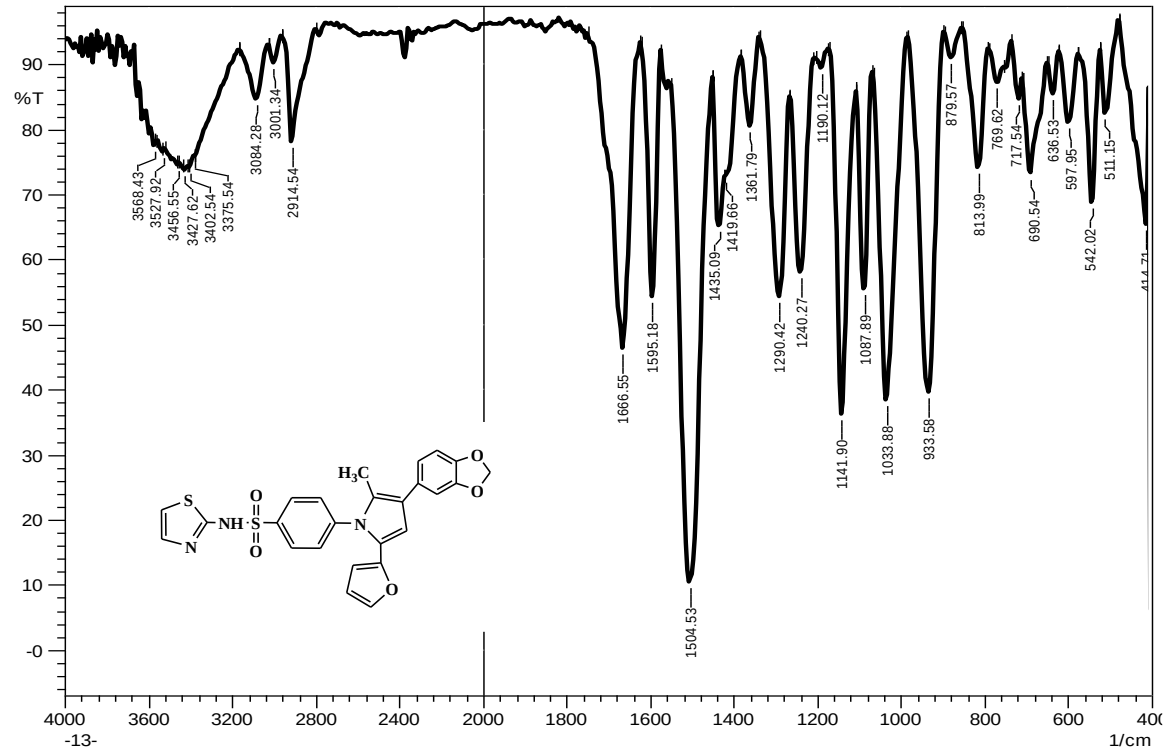


Figure (2): FT-IR Spectrum of compound (5a)

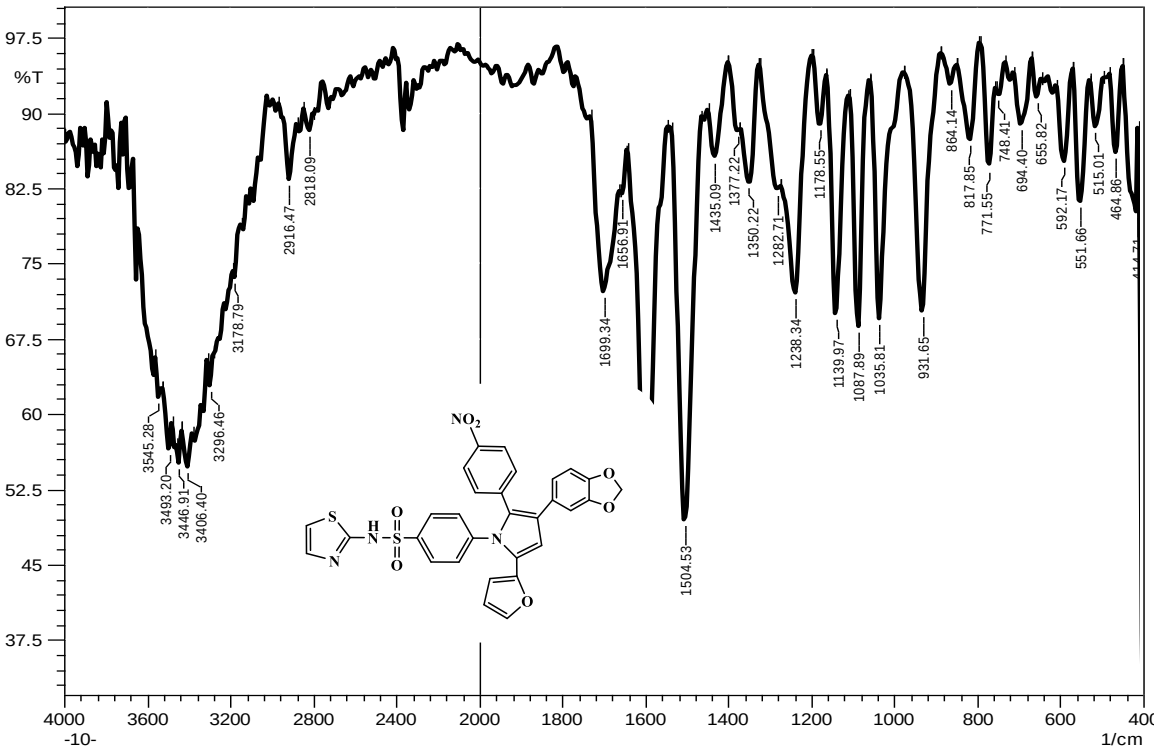


Figure (3): FT-IR Spectrum of compound (5c)

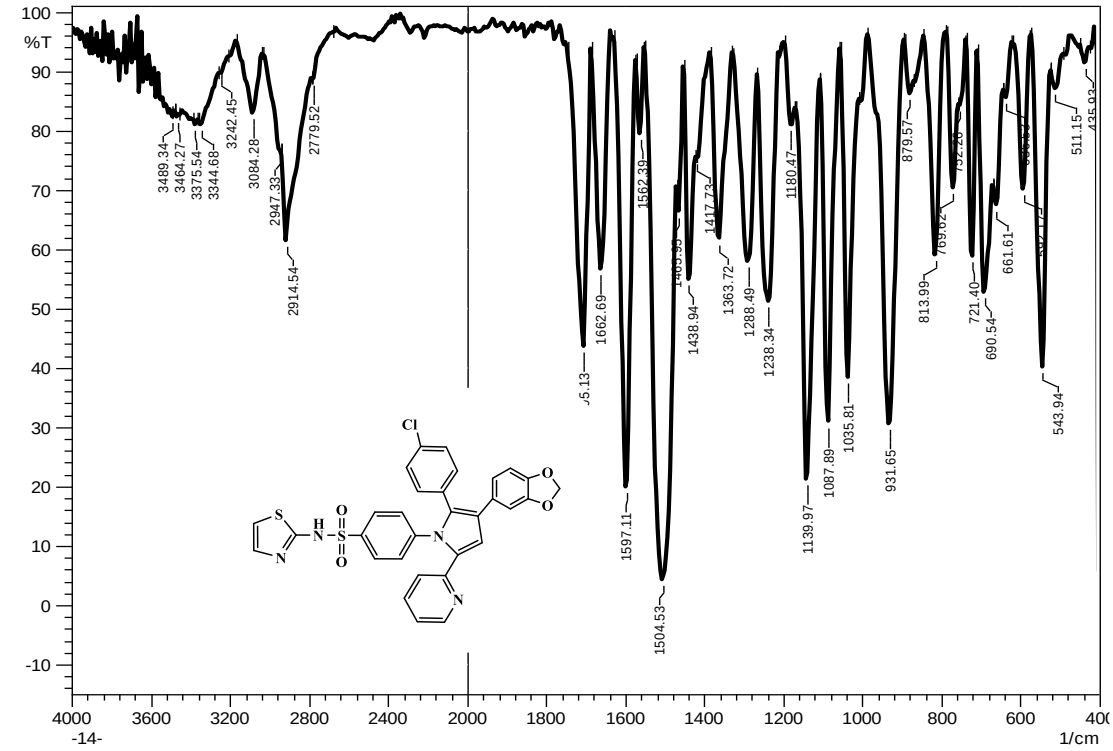


Figure (4) FT-IR Spectrum of compound (5g)

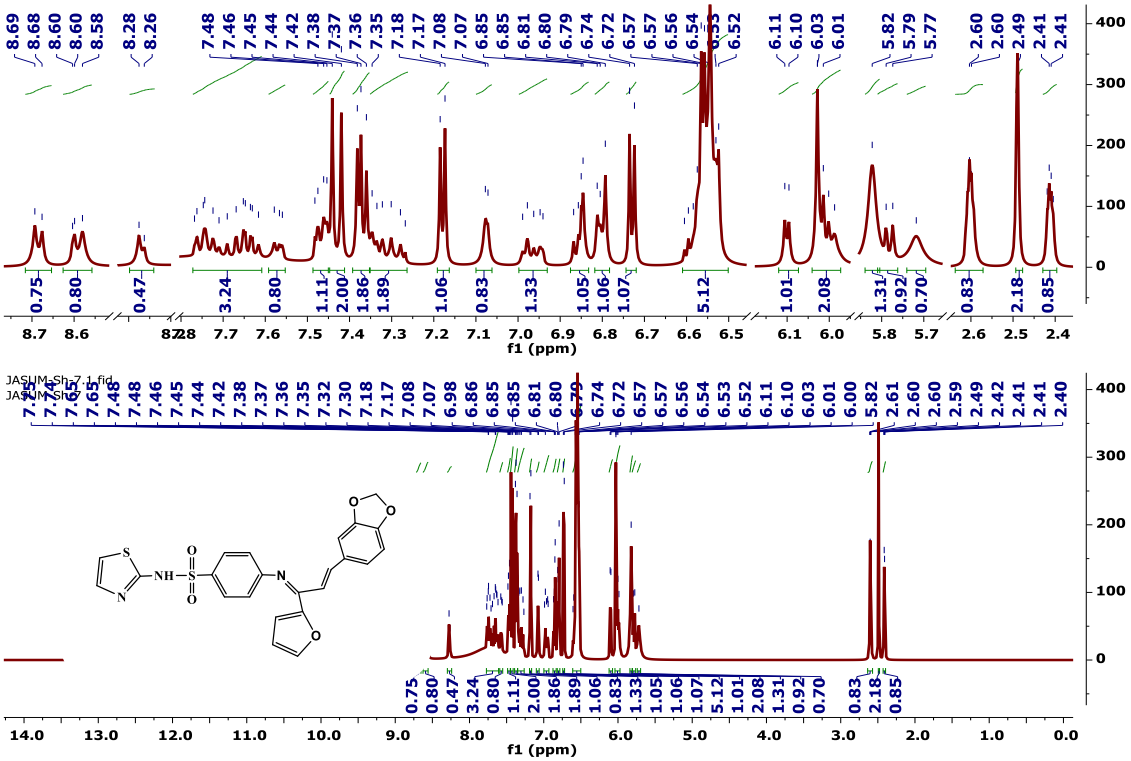


Figure (5): ^{1}H-NMR Spectrum of compound (3)

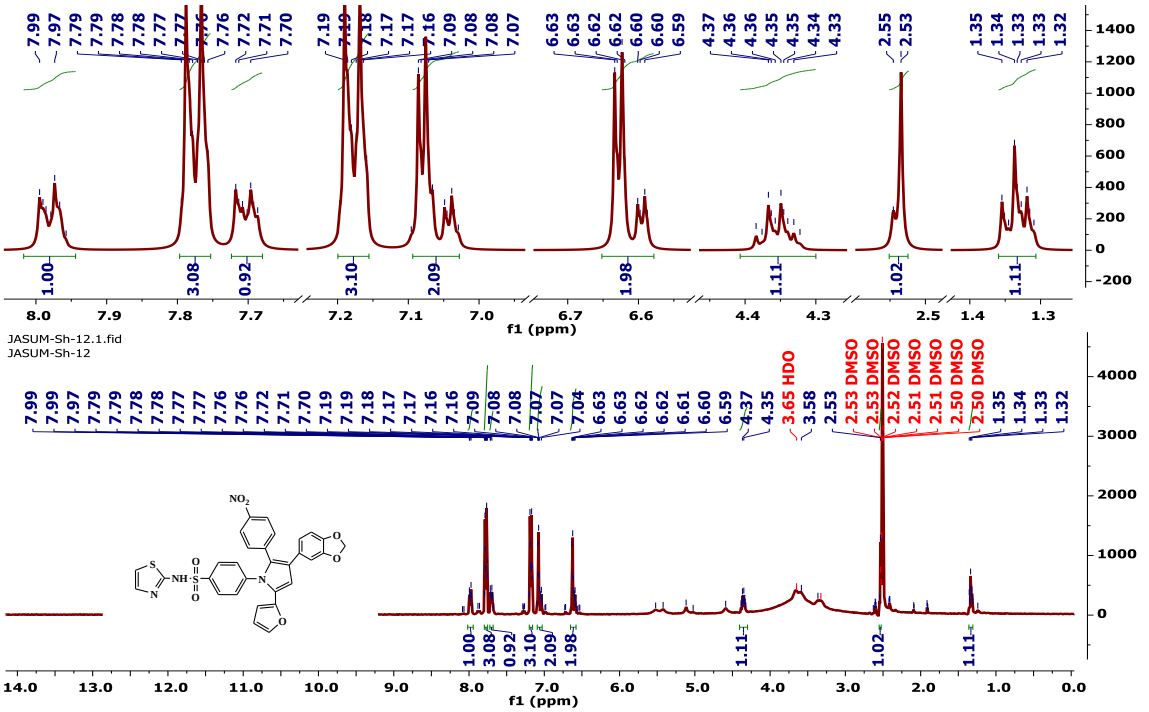


Figure (6): ^{1}H-NMR Spectrum of compound (5c)

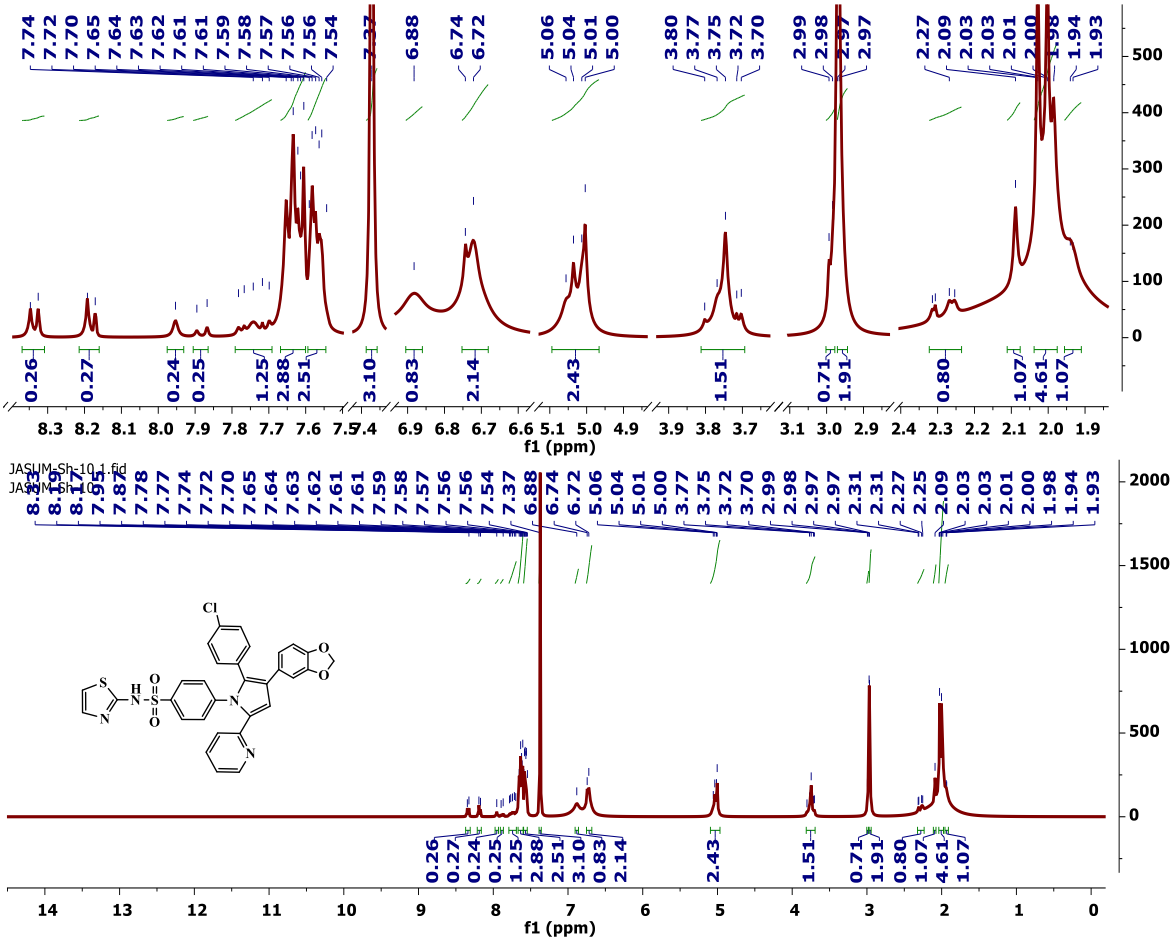


Figure (7): ^{1}H-NMR Spectrum of compound (5g)

4-Conclusion

Efficient protocol for synthesis tri substitutes pyrrole was used through catalytic phosphine mediated multicomponent reaction, and also it was found that using of catalytic amount of tri ethyl amine was very important to complete the wittig reaction. The workup of the reaction was very simple which made it easier to isolate the products.

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