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Green chemistry as efficient approache to achieve a new series of heterocyclic compounds

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***Abstract*---**Solid phase one-pot Multicomponent reaction was used widely to achieved a board spectrum of heterocyclic compounds due to it's supreme properties starting from four component mixture of piperonal binzil, p-phenylene diamine and ammonium acetate which was reacted directly through grinding then microwave irradiation at (270 watt) for (8 min) in a cidic media to afford 1-N(p-aminophenyl)-2-(piperonyl-5-yl)-5-hydroxy-4, 5-diphenyl-2H-imidazole (1) which then converted to its N'-aroyl derivatives (2-4) through it's reaction with substituted benzoyl chloride in basic media terminated by direct reaction with acetic anhydride to obtained N'-acetyl-N'-aroyl derivative (5-7) followed by inter cyclization reaction with hydrazine hydrate (99%) to achieve 1,2,4-trizole derivatives (8-10) in basic media. The assigned structure of the prepared compounds were corroborated by the available physical and spectral methods.

***Keywords*---**green chemistry, one-pot multicomponent reaction, grinding technique, microwave irradiation, imidazole, 1,2,4 triazole.

Introduction

Recently, solid phase on-pot multicomponent reaction as a green chemistry approach it was used to achieve wide rang of heterocyclic compounds [1-3], due to it's supreme properties such as safety, rapid, environmentally friendly, in expensive and yield enhancement [4-5]. On the other hand, heterocyclic compounds received a great deals of attention due to their structure which can be suitably manipulated to achieve a required modification in function[6]. Imidazole in one of the must important type of heterocyclic compounds which exhibit extensively potential application in medical field as anti cancer [7], antitubercular

[8], anti HIV-1[9], anti obesity[10], antihypertensive[11], antidiabetic[12], and inflammation of the nerves[13], antifungal[14], antiparasitic[15], antibacterial[16]. further more imidazole have emerged as herbicides[17] and also in industrial field as anti corrosion[18] and to improve the mechanical properties of polymers[19]. According to the above mentioned, herein in this presentation the imidazole (1) represented by compound 1-N-(p-aminophenyl)-2-(piperonal-5-yl)-5-hydroxy-4,5-diphenyl-2H-imidazole have been prepared through green chemistry approach represented by solid phase one-pot multicomponent reaction using grinding and microwave irradiation techniques. In fact the imidazole (1) was used in this work as active precursor to prepare a new series of heterocyclic compound starting by conversion to it's N-aroyl derivatives (2-4) then to N- acety-N-aroyl derivatives (5-7) finally to the 1,2,4-triazole derivatives (8-10). Basically, the final products pyrazoles are very attractive type of heterocyclic compounds due to exhibit various pharmaceutical properties [20-23] and wide application in a agricultural and industrial fields [24-27].

Experimental

Melting points (M.P.) were measured on Electrothermal SMP30-Stuart melting point apparatus. Infrared (FT-IR) spectra were recorded FT-IR-spectrophotometer, Shimadzu. 8400S (Japan). The nuclear magnetic response ^{1}H-NMR were recorded using Bruker Biospin Gmb H spectrophotometer (400 Hz). Turkey and also using [DMSO-d_6 as solvent, TMS as internal standard, (s). singlet, (d) doublet, (t) triplet, (m) multiplet ,b,broad]. Ultra violate (U.V) spectra were performed on Ta2+U.V spectrophotometer using methanol as absolute ethanol as solvent. Thin layer chromatography (T.L.C.) was carried out on glass plate coated by silica gel (60˚A) with gypsum (13%) using solvent system Benzon: Methanol in ratio (8:2).

Synthesis of 1-N-(p-amino phenyl)-2-(piperonal-5-yl)-5-hydroxy-4,5-diphenyl-2H-imidazole. (1): [28]

In a small mortar equimolar (0.01 mole) of piperonal, binzil, p-phenylen diamine and ammonium acetate was well grinded for (5 min) in presence of glacial acetate acid followed by irradiation using microwave irradiation in domestic microwave oven at power (270 watt) for (8 min), Cooling., followed by adding ice-water with stirring until a solid mass separates which is then filtered off and washed thoroughly with ice-water (5×5 ml) to remove the formed acid during the reaction. Drying and recrystallized from ethanol to afford compound (1): M.P: 232-234°C, Yield: 97%, T.L.C (R_f) 0.320.

Synthesis of N'-4-(2-piperonal-5-yl)-5-hydroxy-4,5-diphenyl-2H-imidazole-1-yl) aryl benzamide (2-4) [29]:

In round bottomed flask (100 ml) equipped with magnetic stirrer bar, dissolve (0.002 mole/0.864 gm) of compound (1) in abs. ethanol (20 ml) with (3 drops) of triethyl amine followed by adding dropwise of alcoholic solution of (0.005 mol) of substituted benzoyl chloride for (30 min.) then the reaction mixture was refluxed for (3 hrs.), Cooling and poured in beaker with ice-water with stirring to afford the solid mass which filtered off and washed several time with ice-water, drying

followed by recrystallization from abs. ethanol to afford compounds (2-4). Table (1).

Table (1): Physical properties for compounds (2-4)

Comp No.	X	M.P. (°C)	Yield %	T.L.C Benzene: MeOH (8: 2)
2	H	235-236	95	0.882
3	m-NO_2	227-229	94	0.838
4	p-Cl	168-170	96	0.750

Synthesis of N'-acetyl-N'-4-(2-piperonal-5-yl)-5-hydroxy-4,5-diphenyl -2H-imidazole-1-yl) aryl benzamide (5-7) [30]

(0.001 mole) of compounds (2-4) was dissolved in abs. ethanol (20 ml) then acetic anhydride (0.003 mole/0.28 ml) was added drop wise with stirring in presence of conc. sulfuric acid, the stirring was continued for (4 hrs). followed by pouring in beaker equipped with ice-water with stirring until the solid mass is separates, filtered off ,drying followed by recrystallized from abs. ethanol to afford the compounds (5-7). Table (2).

Table (2): Physical properties for compounds (5-7)

Comp No.	X	M.P (°C)	Yield %	T.L.C Benzene: MeOH (8: 2)
5	H	239-240	88	0.769
6	m-NO_2	235-236	76	0.750
7	p-Cl	228-230	86	0.833

Synthesis of 4-N-(4-(2-piperonal-5-yl)-5-hydroxy-4,5-diphenyl-2H-imidazole-1-yl) phenyl)-3-methyl-5-aryl-1,2,4-triazole (8-10) [30]

In round bothomed flask (100 ml) dissolve equimolar (0.001 mole) of compounds (5-7) and hydrazine hydrate (99%) in abs. ethanol (20 ml) in basic media from pyridine (1 ml). The reaction mixture was refluxed for (3 hrs), cooling then poured in beaker equipped with ice-water with stirring. The formed solid mass was filtered off and washed thoroughly with ice-water to remove the excess of pyridine followed by drying and recrystallization from abs. ethanol to achieved compounds (8-10). Table (3).

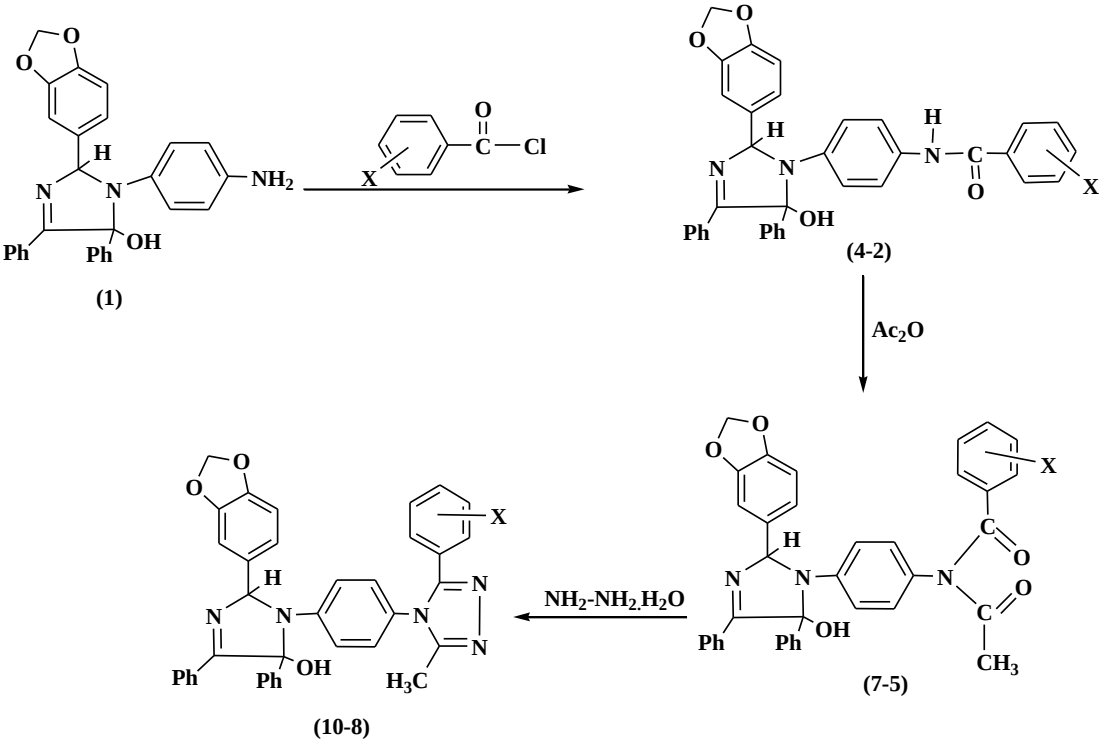
Table (3): Physical properties for compounds (8-10)

Comp No.	X	M.P (°C)	Yield (%)	T.L.C Benzene: MeOH (8: 2)
8	H	280-281	80	0.694
9	m-NO_2	290-291	83	0.628

10	p-Cl	243-244	85	0.683

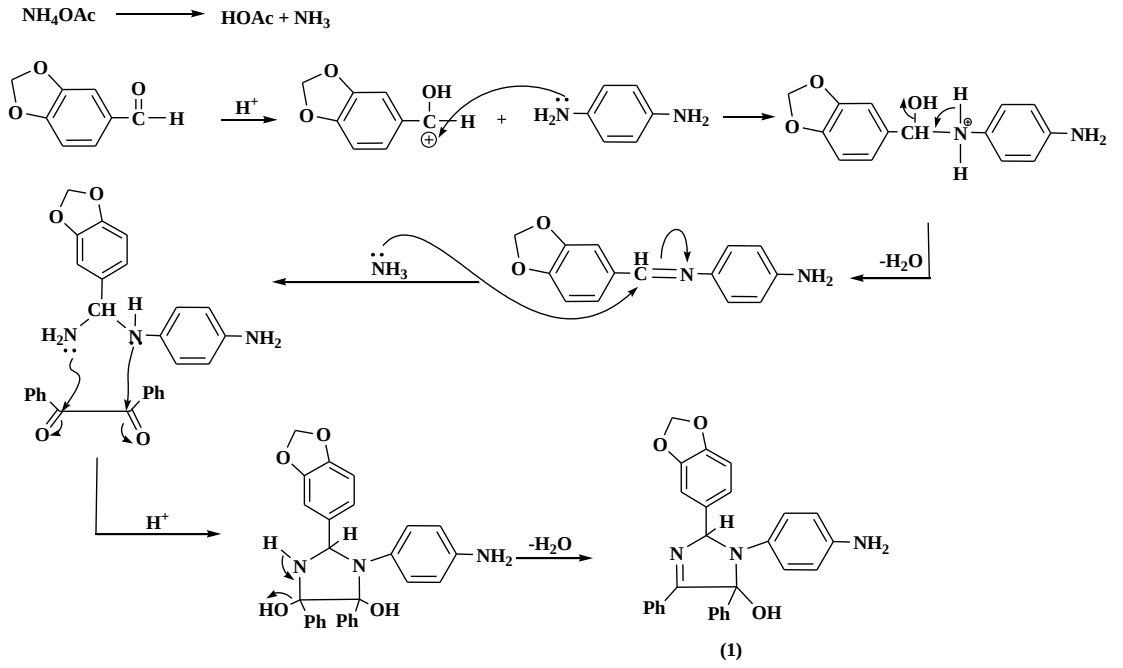
Result & Discussion

Actually, all compounds were prepared according to the following pathway, Scheme (1).



Scheme (1): Synthesis compound (8-10)

First of all, the imidazole (1) was prepared through solid phase one-pot multicomponent reaction as shown in the following mechanism, Scheme(2)[31].



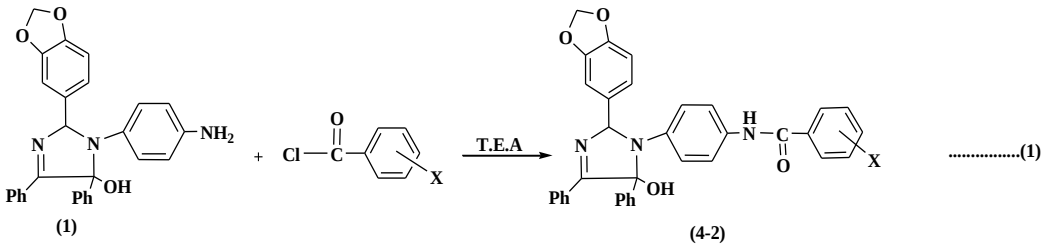
Scheme (2): Synthestic mechanisum compound(1)

As shown in the in the above scheme (2) the ammonium acetate act as a source for the acetic acid and ammonia respectively. The formed acid was used to achieve a poor electronic center in piperonal followed by nucleophilic attack from p-phenylene diamine to afford the Schiff base as active intermediate which react directly with the firshly formed ammonia followed by intercyclization reaction with binzil accompanied by losing of one molecule of water to obtained the imidazole(1). Which shown a significant absorption bands in FT-IR spectroscopy that came in agreement with the suggested structure especially when it shown a stretching vibration of hydroxyl and amino group at (3475 cm^{-1}) and (3360 & 3540 cm^{-1}) respectively , whereas in ^{1}H-NMR it gave a clear peak at δ(8.62 ppm) refer to the hydroxyl group in addition to the (AB system) for p-substituted phenyl ring at (6.42-6.46 ppm) and the amino group at δ(5.33 ppm) that gave clear evidence for the suggested structure compound one.

Table (4): Spectral properties of compound (1)

UV / λ_{max} (nm)	306 & 326
FT-IR (ν cm^{-1})	OH (3475);NH_2 (3360 & 3340) ; CH_2 (2853 & 2922); C=C (1622); C=N (1514); C-O-C (1232 & 1458)
^{1}H-NMR (δppm)	NH_2(s,5.33,1H); CH_2-piperonal(s,6.02,2H); CH-imidazole (s,6.03,1H); p-amino(AB system) (d-d, 6.42-6.46,4H); ph-piperonal (m,6.86-6.91,3H); 2phenyl ring (m, 7.15-7.50,10H) ; OH(s,8.62,1H).

Then converted to N'-aryl dervatives (2-4) via it's reaction with the substituted benzoyl chloride in basic media as shown in the following equation[29,32].



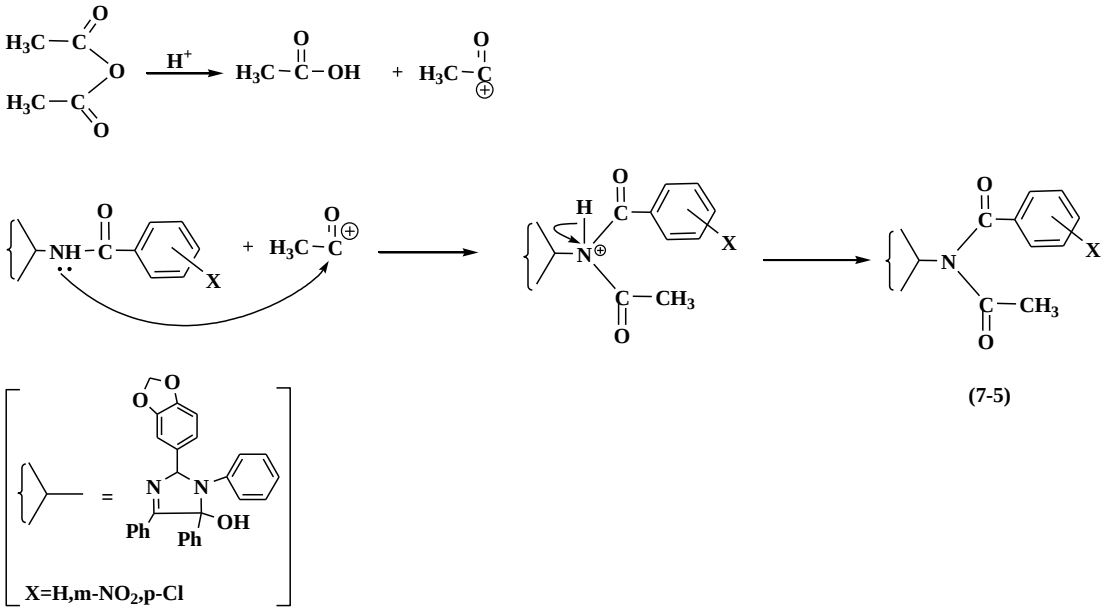
As shown from the above Table the N'-aroyl derivatives shown in FT-IR spectroscopy a stretching vibration band at (1710-1720 cm^{-1}) offer to the amide carbonyl group in addition to the other vibration bands which came in agreement with suggested structure, while in ^{1}H-NMR spectroscopy, these compounds shown the absence of NH_2 peak and the appearance addition aromatic protons in aromatic area and also this is a clear evidence that the reaction was occurred and the compound (2-4) were formed , especially when compound (2&4) the shown NH group appeared at (5.45-3.86 ppm) rather than the amino group (NH_2) in compound (1).

Table (5): Spectral properties of compound (2-4)

Comp No.	FT-IR (υcm^{-1})										U.V (EtOH) λ_{max} (nm)	^{1}H-NMR (δ ppm)
	OH	NH	C –H	CH_2	C=O amide	C-C	C=N	C-O-C asym.	C-O-C sym.	Other		
2	3395	3198	3055	2890, 2782	1715	1659	1599	1234	1036	----	224, 218	NH (s,5.45,1H);CH_2-piperonal(d,6.02&6.09, 2H); CH-imidazole(s,6.09,1H); piperonal ring(m,6.87-6,95,3H);2ph (m,7.17-7.34,10H);Ph-C=O (m,7.45- 7.61,5H); ph (AB system) (d-d,7.73-7.93,4H);OH(s,10.37,1H).
3	3302	3194	3065	2895, 2772	1710	1649	1527	1236	1038	NO_2 asym 1349, sym1316	282, 212	–
4	3376	3198	3069	2982, 2886	1720	1659	1597	1279	1098	C-Cl	272, 234	NH(s,3.86,1H);CH_2-piperonal(d,6.02&6.09, 2H); CH-imidazole(s,6.09,1H); piperonal ring(m,6.85,6,94,3H);P

											h-C=O (AB system) (d-d,6.09 6.46,4H); 2ph (m,7.17–7.63,10H); ph (AB system) (d-d,7.73 7.97,4H); OH(s,10.45, 1H).

Compound (2-4) then converted to N'-acetyl-N'-aroyl derivatives by it's reaction with acetic anhydride to obtained the compounds (5-7) as shown in the following Scheme[32,33]:



Scheme (3): Synthesis compound (5-7)

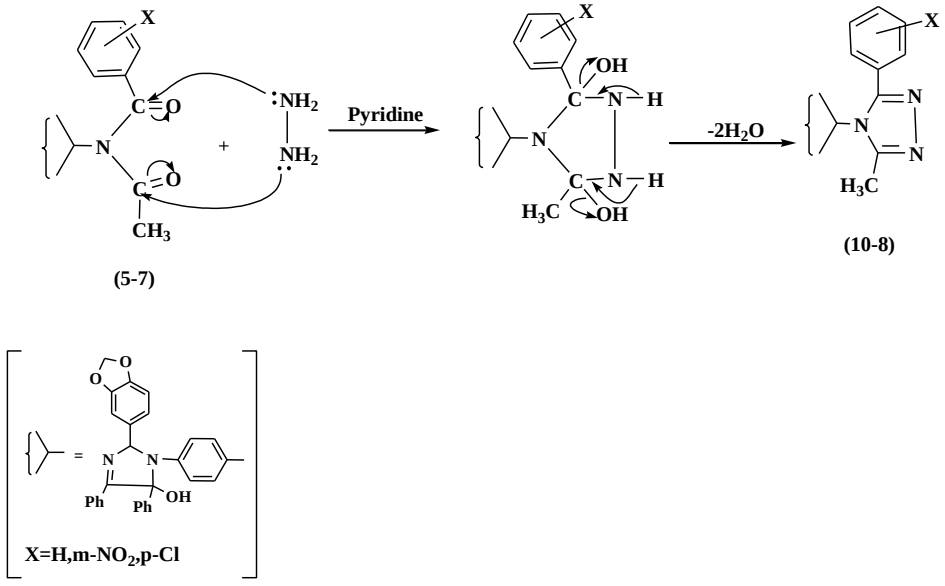
These compounds shown in FT-IR spectroscopy two carbonyl absorption bands the first one refer to the carbonyl of aroyl group at (1678-1721 cm^{-1}) and to the carbonyl of acetyl group at (1667-1680 cm^{-1})respectively, as well as in ^{1}H-NMR they shown the absence of the NH peak and the appearance of CH_3 peak at (1.34 & 2.02 ppm) for compound (5&7) respectively, Table (2).

Table (6): Spectral properties of compounds (5-7)

Comp. No.	FT- IR (υcm^{-1})									U.V (EtOH) λ_{max} (nm)	^{1}H-NMR (δ ppm)
	OH	NH	C-H	Ar-C=O	CH_3-C=O	C=C	C=N	C-O-C	Other		
5	3396	3279	3067	1678	1667	1602	1516	1238, 1038	---	368,236	CH_3(s,1.34,3H); CH_2 piperonal (s,6.01,2H) ; CH-imidazole (s,6.08,1H) ph-piperonal (m,6.85-

										6.96,3H); 3phenyl ring (m,7.15-7.76,15H); phenyl ring (AB system) (d-d,7.91-7.93,4H); OH(s,10.38,1H)
6	3300	3177	3061	1721	1680	1603	1527	1240, 1037	NO_2 asym1550 sym1319	230,212	–
7	3374	3200	3059	1717	1667	1599	1513	1236, 1038	Cl 843	294,234	CH_3(s,2.02,3H); CH_2-piperonal (s,6.02,2H) ; CH-imidazole (s,6.03,1H) ph-piperonal (m,6.85-6.95,3H); 2phenyl ring (m,7.15-7.37,10H); phenyl ring (AB system) (d-d,7.59-7.67,4H); p-ch phenyl (AB system)(d-d,7.72-7.97,4H) ;OH(s,10.44,1H)

Finally , the compounds (5-7) were underwent inter cyclization reaction with hydrazine hydride (99%) to afford compounds (8-10) and according to the following mechanism scheme (5)[34].



Scheme (5): Synthesis compound (8-10)

The 1,2,4-triazole derivatives (8-10) gave significant absorption band in FT-IR spectroscopy as listed in the Table (7) and they show the absence of the two carbonyl groups and this is a clear improvement that the 1,2,4-triazole ring was formed and also the appearance of the methyl group in ^{1}H-NMR at (3.44 & 3.79

ppm) for compound (8 & 10) higher than that in compound (2,4) indicate clearly the formation of the 1,2,4-triazole ring. Table (7).

Table (7): Spectral properties of compounds (8-10)

Comp No.	FT- IR (υcm^{-1})							U.V (ETOH) λ_{max}(nm)	^{1}H-NMR (δ ppm)
	OH	C-H	CH_2	C=C	C=N	C-O-C	Other		
8	3397	3053	2924, 2855	1657	1518	1236, 1038	---	278, 214	CH_3(s,3.44,3H); CH_2- piperonal (d,6.02& 6.03,2H) ; CH-imidazole (s6.09,1H); ph−C=O (m,6.09 – 6.94,4H); piperonal ring (7.17-7.34,3H); 2ph (m,7.46-7.60,10H); phenyl (AB system) (d-d,7.7-7.93,4H); OH(s,10.45,1H)
9	3302	3063	2924, 2855	1676	1525	1240, 1036	NO_2 asym1349 sym1316	234, 218	
10	3378	3057	2891, 2776	1667	1599	1236, 1038	C-Cl 842	224, 216	CH_3(s,3.79,3H); CH_2 -piperonal (d,6.08,2H) ;CH-imidazole (s,6.09,1H); ph-piperonal (m,6.96 – 6.98,3H); p-chlorophenyl (AB system) (d-d,7.26-7.35); 2ph ring (m,7.11-7.19,10H); phenyl ring (AB system) (d-d,7.26-7.35,4H); OH(s,11.70,1H)

Conclusion

An efficient protocol for synthesis the unite building imidazole (1) through green chemistry approach which reducing the reaction time and yield enhancement as well as it supporting with thin layer chromatography (T.L.C) which used for determine the purity and the reaction time for all prepared compounds. The workup for all prepared compound very simple and so easy.

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