



A Novel Synthetic Approaches of Tetra Substituted Pyridine via an Efficient One-Pot Multicomponent Reaction

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Abstract

Recently, one-pot multicomponent reaction as a green, simple friendly environmental and cheap procedure has been developed to achieve wide range of heterocyclic compounds especially when it possess an application in many applied fields. The imidazole is one of the most important five membered heterocyclic compounds, which prepared in this presentation through solid phase one-pot multicomponent reaction among piperonal, p-phenylenediamine, benzil and ammonium acetate enhancement by grinding and microwave irradiation at (270 watt) for (8 min). The prepared imidazole (1) used later as active units building to obtain the N-acetyl derivative (2) via its reaction with acetic anhydride and the later underwent Claisen-Schmidt reaction to afford the chalcones (3-8) in basic media followed by three component reaction with malononitrile and ammonium acetate to achieve the tetra substituted pyridine (9-14).

All prepared compound, were illustrated by the available physical and spectral methods.

Keyword:- Multicomponent reaction, Imidazole, chalcones, pyridine, microwave irradiation.

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and microwave irradiation for (8 min) at (270 watt), then it converted to its N-acetyl derivative (2) via its reaction with acetic anhydride which then in turn underwent Claisen-Schmidt reaction in basic media to afford the chalcones (3-8). Finally, tetra substituted pyridines (9-14) were achieved through one-pot three component reaction among the chalcones (3-8), malononitrile and ammonium acetate.

Basically, substituted pyridines are one of the most important heterocyclic compounds that possess medicinal⁽⁶⁾ and functional properties with attractive application as pharmaceutical⁽⁷⁾ as well as general synthetic building blocks⁽⁸⁾, moreover, it is an integral part of anti-inflammatory⁽⁹⁾ and anti-cancer agent⁽¹⁰⁾.

Introduction

One-pot multicomponent reaction received considerable attention in recent years in organic synthesis, due to its supreme properties as economic, reducing the reaction time, simple, efficient, friendly environment and yield enhancement. It used to prepare wide range of heterocyclic compounds which have an application in medicinal and pharmaceutical field as well as in industrial and agricultural field between these heterocyclic compounds, the imidazole has a long history of application in various medical⁽¹⁾, pharmaceutical⁽²⁾, biological⁽³⁾, agrochemicals⁽⁴⁾ and industrial field⁽⁵⁾. In this presentation, imidazole used as active precursor to prepare tetra substituted pyridine through many sequence steps. First of all, the imidazole (1) was prepared through solid phase one-pot four component reaction among benzil, piperonal, p-phenylenediamine and ammonium acetate accelerated by grinding



Synthesis of the imidazole. (1): ⁽¹¹⁾

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 acetic 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 filtered off and then 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.

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 resonance ¹H-NMR were recorded using Bruker Biospin Gmb H spectrophotometer (400 Hz). Turkey and also using [DMSO-d₆ as solvent, TMS as internal standard, (s) Singlet, (d) doublet, (t) triplet, (m) multiplet]. Ultra violet (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 silicagel (60°A) with gypsum (13%) using solvent system Benzene: Methanol in ratio (8:2).

Table (1): Spectral data 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).

abs. ethanol to afford the compound with M.P= 216-218 °C, yield=95,T.L.C (R_f) =0.200.

Synthesis of chalcones (3-8) ^(13,14):

Equimolar (0.001 mole) of compound (2) and substituted benzaldehyde was dissolved in (20 ml) ethanol in presence of (2 ml/10%) NaOH with stirring for (20 min), followed by reflux for (4 hrs.), cooling and filtered off then recrystallized from ethanol. Table (2).

Synthesis of N-acetyl derivative (2) ⁽¹²⁾:

A mixture of (0.00432 mole/4.32 gm) of compound (1) and (0.0015 mole) acetic anhydride in presence of acetic acid (1 ml) as catalyst, were irradiated under microwave oven using energy (450 watt) for (6 min),cooling , followed by adding ice-water (15 ml) with stirring until the chemical precipitate separates , filtered off followed by recrystallization from

Table (2): Physical properties and Spectral properties of compounds (3-8)

Comp. No.	X	M.P (°C)	Yield (%)	T.L.C Benzene : Ethylacetate (8: 2)	FT-IR (v cm ⁻¹)									U.V (ETO H) λ _{max} (nm)
					OH	NH	=C-H	CH ₂	C=O	C=C	C=N	O-C-O	Other	
3	H	287-290	74	0.770	3300	3188	3052	2917 , 2771	1661	1599	15 16	1236, 1038	---	294,234
4	o-C1	297-299	70	0.400	3430	3300	3050	2917 , 2770	1663	1601	15 16	1236, 1038	---	292,243
5	m - NO ₂	299-300	69	0.390	3300	3189	3050	2917 , 2789	1661	1599	15 18	1236, 1038	NO ₂ asym:1406 sym:1302	236,212
6	4 - N , N - di methyl amino	223 - 225	65	0.570	3300	3190	3052	2917 , 2789	1661	1597	15 18	1236, 1036	---	280,210
7	p - OH	307-309	73	0.730	3300	3190	3052	2920 , 2789	1661	1601	15 16	1236, 1038	---	256,212
8	m - OCH ₃	225-227	64	0.790	3300	3187	3052	2918 , 2790	1661	1599	15 16	1236, 1036	---	254,216

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Synthesis of tetra substituted pyridines (9-14) ⁽¹⁵⁾:

Equimolar (0.001 mole) of chalcones (3-8), malononitrile and ammonium acetate were dissolved in (20 ml) abs. ethanol with stirring followed by refluxed for (3 hrs.), cooled and leave to subside at room temperature for (24 hours). The formed product then filtered off and washed thoroughly with water (10 ml × 4), followed by drying and recrystallized from ethanol. Table (3).

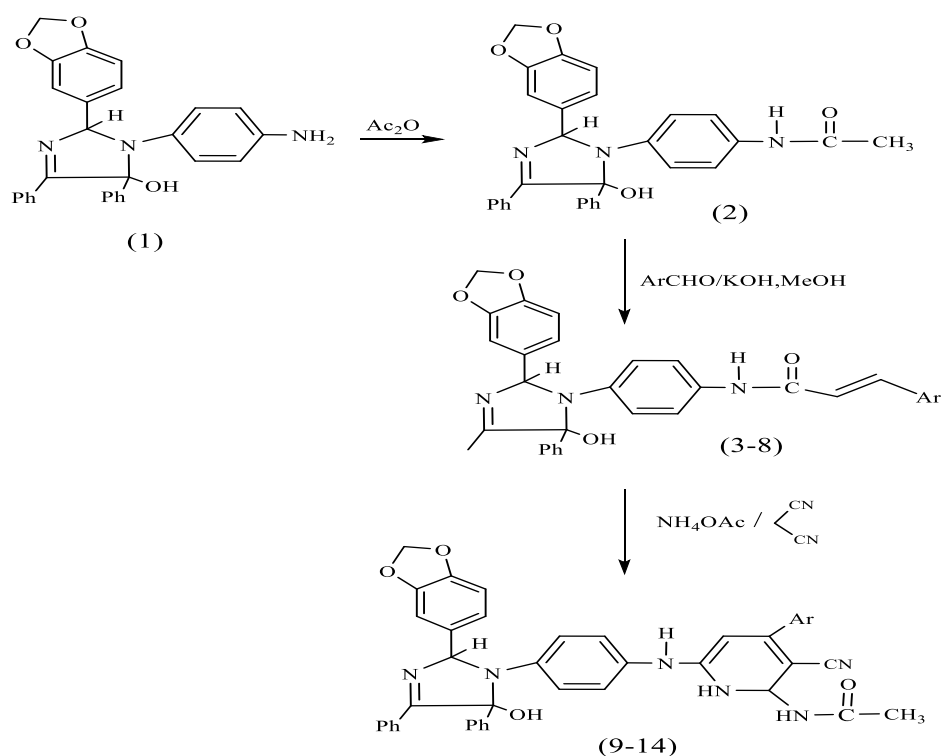


Table (3): Physical properties and spectral properties U.V.,I.R for compounds (9-14)

Comp. No.	X	M.P (°C)	Yield (%)	T.L.C Benzene: Ethylacetate (8: 2)	FT-IR (ν cm ⁻¹)										U.V (ETO H) λ_{max} (nm)
					OH	NH	=C-H	CH ₂	C \equiv N	C=O	C=C	C=N	O-C-O	Other	
9	H	248-250	75	0.810	3430	3304	3059	2903, 2779	2200	1678	1605	1514	1238, 1036	---	285,259
10	o-Cl	244-245	69	0.630	3254	3192	3063	2907, 2778	2400	1662	1603	1547	1236, 1040	C-Cl 777	305,255
11	m-NO ₂	188-189	81	0.220	3433	3250	3057	2907, 2779	2342	1678	1605	1514	1238, 1036	NO ₂ asym:1550 sym:1321	297,265
12	4-N,N-dimethylamino	143-145	94	0.700	3298	3262	3059	2906, 2779	2209	1678	1611	1516	1238, 1036	---	368,265
13	p-OH	149-150	90	0.260	3430	3302	3057	2902, 2776	2105	1678	1605	1516	1238, 1036	---	322,202
14	m-OCH ₃	144-145	78	0.370	3430	3298	3059	2902, 2775	2368	1678	1605	1514	1238, 1036	---	304,204

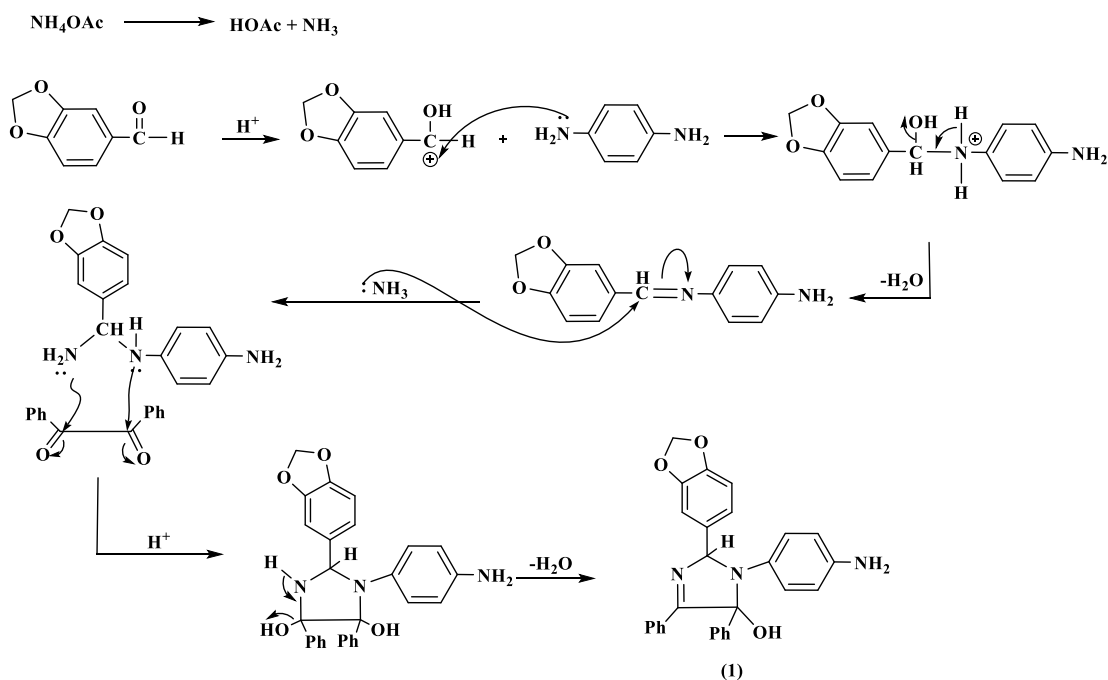
Result & Discuss:

All compounds prepared according to the following synthetic pathway .



Scheme (1): Synthetic pathway of compound (9-14)

First of all, the unit building imidazole (1) was prepared according the following mechanism, Scheme(2)^(16,17).

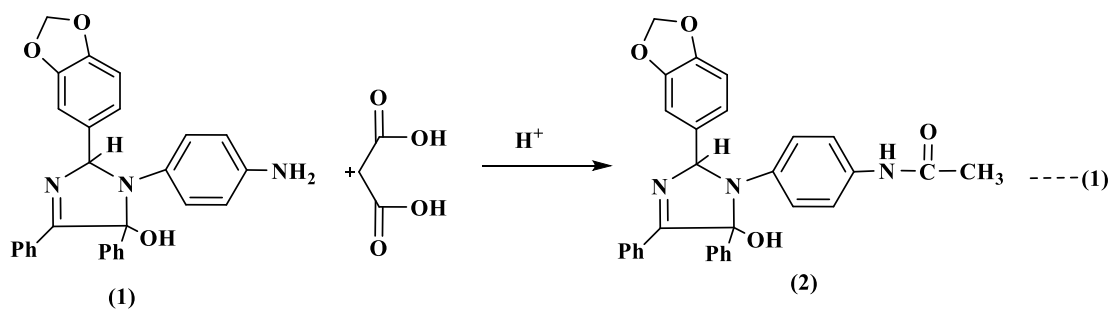


Scheme (2):

Synthetic mechanism of compound (1)

Also, it shown a significant absorption bands in FT-IR (ν) at ($3475, 3340-3360\text{cm}^{-1}$) refer to the hydroxyl, amino functional groups respectively in addition to the other absorption bands which listed in the, whereas, in $^1\text{H-NMR}$ spectroscopy it gave a singlet peak at (8.62 ppm) refer to the hydroxyl group and at (5.33 ppm) refer to the amino group as well as at (6.03 ppm) refer to the H-imidazole ring which came in agreement with the suggested structure.

Fortently, the presence of primary aromatic amino group in the imidazole structure lead to used it as active precursor to prepare the N-acetyl derivative (2) via it's reaction with the acetic anhydride through direct nucleophilic substitution reaction as shown in equation(1)



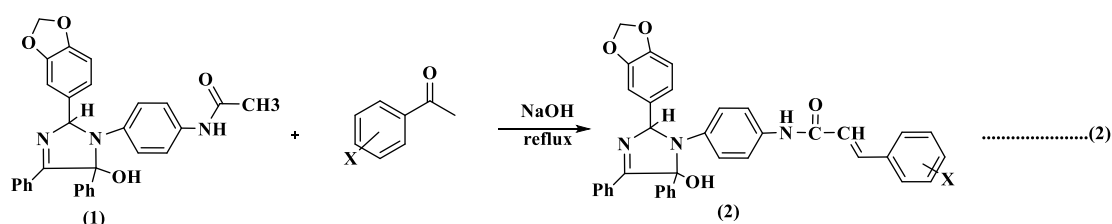
Which isolated and identity by physical and spectral methods. Actually, it shown a significant bond at (1661 cm^{-1}) refer to the carbonyl group in addition to the significant band at (3300 cm^{-1}) refer to the secondary amino group and also these two absorption bands gave initial proofment for the suggested structure, while in $^1\text{H-NMR}$, the absence of NH_2 peak and the appearance NH group at (2.20 ppm) indicat clearly the formation of the N-acetyl derivative (2). Table (4).

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

UV / λ_{max} (nm)	322 & 350
FT-IR (ν cm^{-1})	OH (3300);NH (3188) ;=C-H(3052); CH ₃ (2918 & 2787); C=O (1661); C=C (1599); C=N (1516); C-O-C (1236 & 1036)
¹ H-NMR (δ ppm)	CH ₃ (s,2.10,3H); NH(s,2.20,1H); CH ₂ -piperonal(s,6.02,2H); CH-imidazole (s,6.03,1H); ph-piperonal (m,6.85-6.93,3H); 2phenyl ring (m, 7.17-7.32,10H) ; phenyl(AB system) (d-d, 7.47-7.54,4H); OH(s,10.06,1H).

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On the other hand, compound (2) underwent Claisen-Schmidt reaction in basic media to afford the α - β -unsaturated carbonyl compounds (chalcones) (3-8) as shown in the following equation ^(18,19).



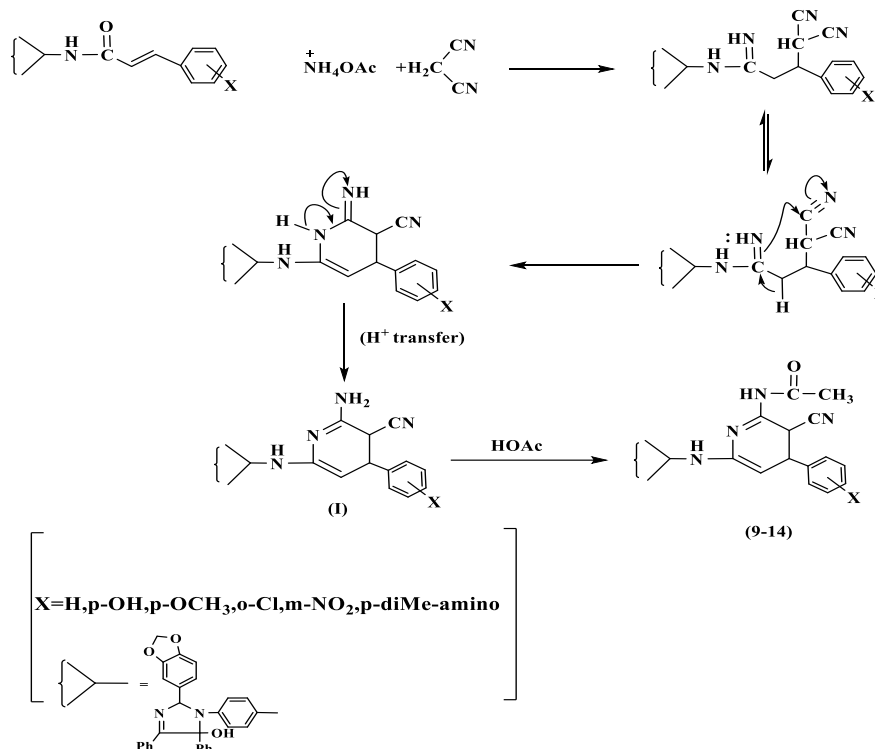
These chalcones shown in FT-IR spectroscopy the appearance of C=C (a cyclic) absorption band at (1597-1601 cm^{-1}). Where as in ¹H-NMR the compound (3-6) shown a significant peak at (2.02-3.03 ppm) as doublet band which a signed to the double bond protons in α - β -unsaturated system of chalcones and actually this supporting the suggested structure in addition to the other peaks listed in the table (4).

Table (5) :Spectral properties NMR for compound (3-6)

Comp No.	¹ H-NMR (δ Ppm)
3	CH=CH (d,2.02-2.60& 2.41-2.42,2H); NH (s 2,61,1H); imidazole-CH (s,4.05,1H); CH ₂ piperonal; CH ₂ (s,6.02,2H); piperonal ring(m,6.85-6,92,3H); 3phenyl ring(m,7.17-7.32,15H,); ph (AB system) (d-d, 7.46-7.53, 4H ; OH(s,10.06,1H).
4	CH=CH (d,2.03,2H); NH (s,5.90,1H);piperonal-CH ₂ (s,6.02,2H); imidazole-CH (s,6.04,1H) piperonal ring (m,6.85-6,91,3H); 2phenyl ring (m,7.17-7.24,OH); m-NO ₂ phenyl (m,7.30-7.32,4H); ph ABsystem (d-d,7.46-7.53,4H) ;OH (s,10.45,1H).
5	2CH ₃ (s,2.03,6H); CH=CH(d,3.01-3.02,2H); NH (s,3.05, 1H); piperonal CH ₂ (s,6.03,2H); imidazole-CH (s,6.04,1H) ;piperonal ring (m,6.87-6,94,3H); 2phenylring (m,7.17-7.24,10H); p-(CH ₃) ₂ N-phenyl (m,7.30-7.31,4H); ph (ABsystem) (d-d,7.46-7.53,4H); OH (s,10.06,1H).
6	CH=CH (d,2.03,2H);NH(s,2.60,1H); piperonal-CH ₂ (s,6.02,2H); imidazole-CH (s,6.03,1H) ;piperonal ring(m,6.87-6,92,3H); 2phenyl ring (m,7.17-7.26,10H); p-OHphenyl (d-d,7.29-7.33,4H); phenyl (AB system) (d-d, 7.46-7.53,4H); OH (s,10.06,1H).

Finally , these chalcones (3-8) were inserted a one-pot three component reaction with malononitrile and ammonium acetate to afford the tetra substituted pyridines (9-14) as illustrated in the following mechanism⁽²⁰⁾.





While, in ¹H-NMR they shown significant peaks at δ (2.41-3.44 ppm) . Refer to the pyridine protons as well as to the methyl group at δ (2.02 ppm) and secondary amino group at δ(3.32-4.10 ppm), which mean that the pyridine ring involving in it's structure an acetamide group(Table 6).

Tetra substituted pyridines (9-14) were illustrated via spectroscopy methods, so, they shown in FT-IR spectroscopy a significant absorption band at ν (3192-3304 cm⁻¹), (1662-1678 cm⁻¹), (2150-2400 cm⁻¹) refer to the amino, acetyl and nitrite groups respectively , Table (3).

Table (6): Spectral properties NMR of compounds (9,12,13)

Comp. No.	¹ H-NMR (δppm)
9	CH ₃ (s,2.02,3H); H-pyridine(s,2.42,2.60& 3.26,3H);NH- phenyl (s,3.45,1H); CH ₂ -piperonal(s,6.02,2H); CH-imidazole (s,6.03,1H) ; piperonal ring (m,6.87-6, 90,3H); 3ph (m,7.17-7.31,15H); phenyl (AB system) (d-d, 7.46-7.53,4H) ; NH-C=,1H); OH (s,10.07,1H).
12	CH ₃ (s,2.02,3H); H-pyridine(s,2.41,2.42& 2.60,3H);2CH ₃ (s,3.12,6H) ; NH- phenyl (s,3.32,1H); CH ₂ -piperonal(s,6.02,2H);CH-imidazole (s,6.03,1H); NH(s,2.60,1H); piperonal ring (m,6.85-6,92,3H); 2ph(m,7.17-7.32,10H); phenyl (AB system) (d-d,7.46-7.53,4H) ; p-(CH ₃) ₂ N-phenyl (AB system) (d-d, 7.85-7.89,4H) ; NH-C=O (s,8.10,1H);OH (s,10.07,1H).
13	CH ₃ (s,2.02,3H); H-pyridine (s,3.33,2.42 & 3.44,3H); NH- phenyl (s,4.1,1H);CH ₂ -piperonal(s,6.02,2H);H-imidazole (s,6.03,1H); 2CH ₃ (s,3.12,6H);NH- phenyl (s,3.32,1H); piperonal ring (m,6.85-6,92,3H); 3ph(m,7.17-7.31,15H);phenyl AB system (d-d,7.46-7.53,4H) ; p-(CH ₃) ₂ N-phenyl AB system (d-d,7.46-7.53,4H) ; NH-C=O (s,7.60,1H);OH (s,10.07,1H).

Actually , we planning to prepare 2-amino pyridine derivatives but as shown in ¹H-NMR spectroscopy which gave us an acetamide protons and also this formed because of the ammonium

acetate which decomposed during the reaction to ammonia and acetic acid (equation 3) and the form acid react quickly with the amino group to afford the corresponding N-acetyl derivatives.



Conclusion

One-pot multicomponent reaction gave a magnificent yield of imidazole (1)(97%) without any isolated side products, so it intimately associated with the principles of green chemistry as well as, the final products were easily formed with acceptable yields, beside that it could be used later as active synthon in organic synthesis due to the acetyl and cyano functional groups in its structure.

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