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A facile one-pot synthesis of 3-(1-Benzyl-2-phenyl-1*H*-imidazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one derivatives *via* multi-component approach

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Abstract: A one pot, four component synthesis of 1, 2, 4-trisubstituted imidazoles is described by reacting a mixture of bromo dehydroacetic acid, aromatic aldehyde, benzyl amine, and ammonium acetate in dry alcohol. All the synthesized compounds were characterized by their analytical and spectral data.

Keywords: bromo dehydroacetic acid; aromatic aldehyde; benzyl amine; ammonium acetate; imidazole; one-pot; multi component reactions. © 2014 ACG Publications. All rights reserved.

1. Introduction

Multi Component Reactions (MCRs) are well known to be selective, efficient, and easy to perform requiring readily available starting materials[1]. Multi component reactions involve sequential transformations between three or more compounds existing simultaneously within a reaction mixture, resulting in a product that contains all or segments of each participant[2]. 3-Acetyl-4-hydroxy-6-methyl-2*H*-pyran-2-one (dehydroacetic acid), is an important starting material, and its derivatives find wider applications in the synthesis of heterocyclic compounds. Dehydroacetic acid can be readily converted into the other heterocyclic systems, e.g., pyrazoles[3, 4]. It possesses interesting biological properties such as fungicidal and antibacterial activities. It can also act as a complexing ligand[5, 6]. Imidazole is the constituent of several natural compounds like histamine, histidine, biotin, alkaloids and nucleic acids. It is very important substance among the medicinal compounds[7]. Several imidazole derivatives have been reported to possess anti-inflammatory[8], analgesic[9], and antipyretic[10], activities. Imidazole derivatives are used for the treatment of denture stomatitis[11]. Appropriately substituted imidazoles are extensively used as glucagon receptors[12], and CB1 cannabinoid receptor antagonists[13]. 2-Substituted imidazolines are important due to their use as synthetic intermediates[14], catalysts[15], chiral auxiliaries[16], chiral catalysts[17] and ligands for asymmetric catalysis[18], in various synthetic reactions.

A number of methods have been reported for the synthesis of imidazoles involving a variety of conditions. In this article, as a part of our ongoing studies on the multi component reaction and on the synthesis of novel heterocyclic systems[19–22] , we present herein our results in the synthesis of imidazole derivatives, using commercially available starting materials in excellent yields. We have developed a facile one-pot multi component synthesis of 1, 2, 4-tri substituted imidazole derivatives via a four-component reaction.

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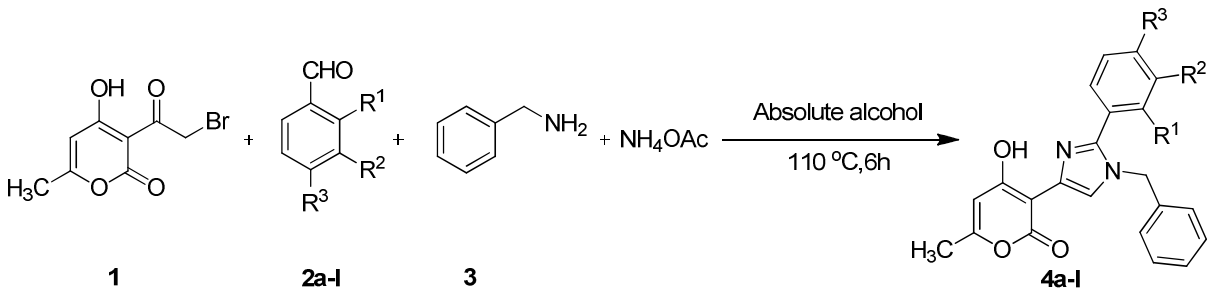
2. Results and discussion

Condensation of equimolar mixture of 3-(2-bromo acetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one **(1)**, various aromatic aldehydes **(2)**, benzyl amine **(3)** and ammonium acetate resulted in the formation of 3-(1-benzyl-2-phenyl-1*H*-imidazol-4-yl)-4-hydroxy-6-methyl-2*H*-pyran-2-one derivatives **(4a-l)** in good yields.



1 **2a-l** **3** **4a-l**

a: R^1=R^2=H, R^3= OCH_3; **b**: R^1=H, R^2=R^3= OCH_3; **c**: R^1=R^2=R^3= H;
d: R^1=R^2=H, R^3= OH; **e**: R^1=OH, R^2=OCH_3, R^3= H; **f**: R^1=OH, R^2=R^3=H;
g: R^1=R^2=H, R^3= Cl; **h**: R^1=R^2=H, R^3= $N(CH_3)_2$; **i**: R^1=R^2=H, R^3= Br;
j: R^1=H, R^2= NO_2, R^3= H; **k**: R^1=H, R^2= OCH_3, R^3=OH; **l**: R^1=OH, R^2=H, R^3= OH.

Figure 1. Synthesis of imidazole derivatives

Table 1. Synthesis of imidazole derivatives **(4a-l)**.

Entry[a]	R^1	R^2	R^3	Product	Time (hr)	Yield[b] (%)
1	H	H	OCH_3	**4a**	6	85
2	H	OCH_3	OCH_3	**4b**	6	80
3	H	H	H	**4c**	7	75
4	H	H	OH	**4d**	7	80
5	OH	OCH_3	H	**4e**	6	85
6	OH	H	H	**4f**	7	80
7	H	H	Cl	**4g**	6	80
8	H	H	$N(CH_3)_2$	**4h**	6	85
9	H	H	Br	**4i**	6	90
10	H	NO_2	H	**4j**	7	80
11	H	OCH_3	OH	**4k**	7	75
12	OH	H	OH	**4l**	7	70

[a]**Reaction conditions**: 3-(2-bromo acetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol), aromatic aldehydes (1 mmol), benzyl amine (1 mmol), ammonium acetate(1.5 mmol), Absolute alcohol (5 mL), reflux.[b]Isolated yields.

A plausible reaction mechanism for this reaction resulting in the formation of imidazole derivative can be explained. First step could involve the condensation of the amine and aldehyde resulting in the

formation of imine (**5)**. Nucleophilic addition of the imine to the bromo dehydroacetic acid leads to the formation of the iminium intermediate (**6),** which may undergo addition of ammonia resulting in the another intermediate (**7)**. Intramolecular condensation of amino functionality of (**7)** with the adjacent carbonyl would give dihydroimidazole intermediate **(8)**, which could undergo aerial oxidation under the reaction conditions to yield the imidazole derivatives (**4a-l)**.

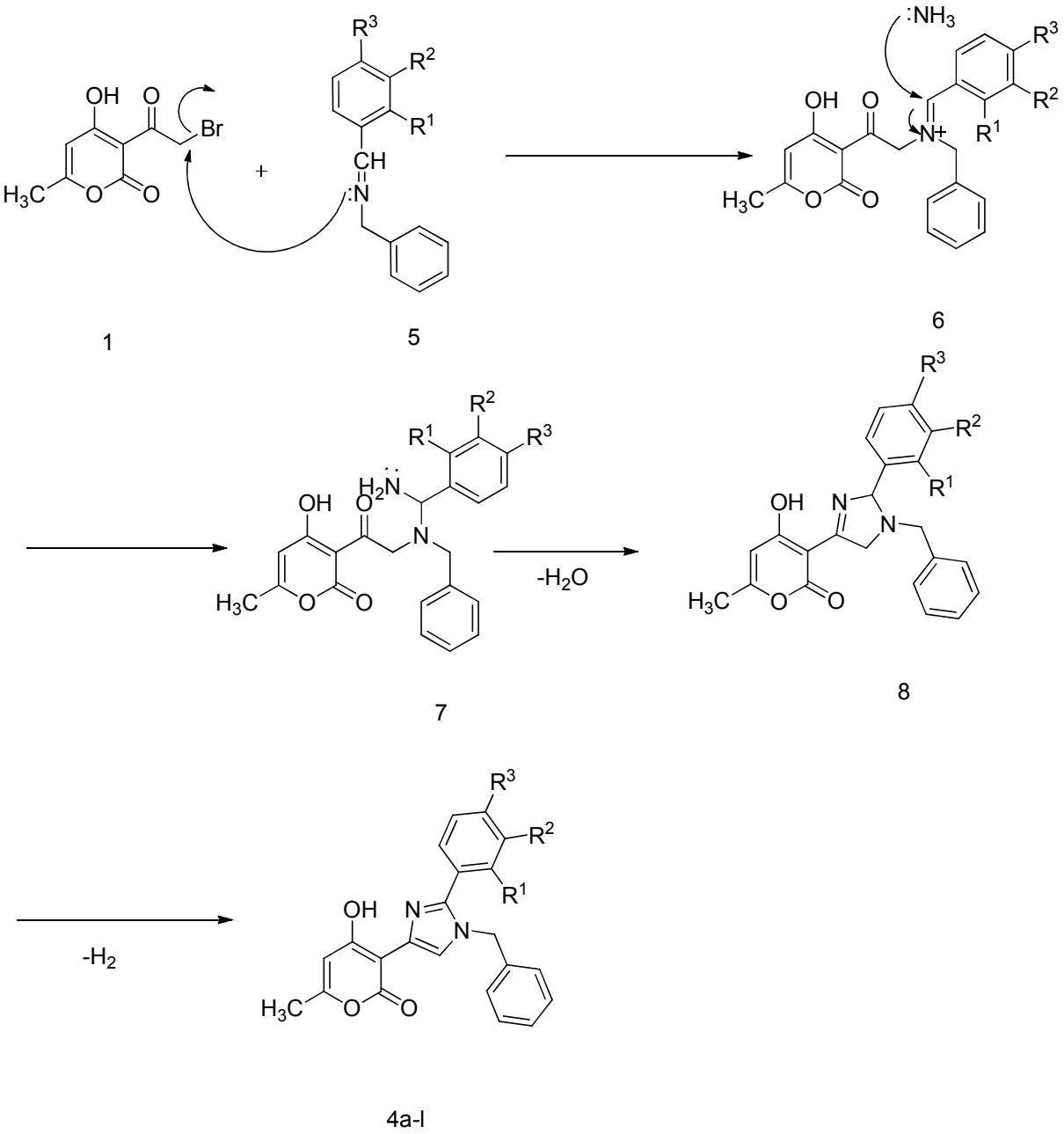


Figure 2. Proposed reaction mechanism

The infrared (IR) spectrum of compound (**4a)** showed prominent peaks at 1740 cm^{-1} for –C=O of lactone, 3464 cm^{-1} for –OH, whereas the ^{1}H NMR spectrum of compound (**4a)** showed characteristic singlets for -CH_3 of pyran proton at δ 2.27, -CH_2 of benzyl proton at δ 4.53, -CH of imidazole proton at δ 8.09 ppm. The ^{13}C NMR spectrum of compound (**4a)** also shows the peaks at δ 22.5 for methyl carbon, 47.5 for benzyl carbon, 55.3 for methoxy carbon, and 165.7 for–C=O of lactone. All the above spectral data clearly confirm the formation of title products.

3. Experimental Section

All the chemicals used in this work were purchased from commercial sources, and were used without further purification. Melting points were determined an Electrothermal-9100 apparatus. The purity of the compounds was checked by TLC plates (E. Merck Mumbai, India). CHNS analysis was done by Carlo Erba EA 1108 automatic elemental analyser. IR spectra (KBr) were recorded on a Bruker WM4(X) spectrometer (577 model). ^{1}H NMR spectra were recorded on a Bruker WM-400 spectrometer in δ ppm using TMS as the standard. ^{1}H, and ^{13}C NMR spectra were obtained for solutions in DMSO using TMS as external standard.; δ in parts per million, J in hertz. Electron ionization mass spectra (EI-MS) were determined on Perkin Elmer (SCIEX API-2000, ESI) at 12.5 eV.

3.1. General procedure for the preparation of title compounds (4a-l):

A mixture of aromatic aldehydes (1 mmol), benzyl amine (1 mmol), 3-(2-bromo acetyl)-4-hydroxy-6-methyl-2*H*-pyran-2-one (1 mmol) and ammonium acetate (1.5 mmol) was taken in anhydrous ethanol (4-6 ml), stirred at 110°C for 6-7h. After completion of the reaction mixture (as indicated by TLC ethyl acetate/n-hexane, 3:7) the reaction mixture was cooled to r.t. and the product precipitated from water and then recrystallised from ethanol.

3.1.1.3-(1-Benzyl-2-(4-methoxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4a): Light yellow solid; mp. 211-213 ºC; IR (KBr, cm^{-1}) υ_{max}: 3464, 1740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 3.81 (s, 3H), 4.53 (s, 2H), 6.22 (s, 1H), 7.05 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.5 Hz, 5H), 7.81 (d, J = 8.8 Hz, 2H), 8.09 (s, 1H), 12.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.5, 47.5, 55.3, 83.4, 97.7, 114.5, 124.2, 127.5, 127.7, 127.9, 128.1, 128.6, 128.7, 132.2, 135.7, 163.1, 165.7, 175.2, 181.0; MS (ESI) *m/z*: 388 (M+1); Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.15, H, 05.20, N, 07.21. Found: C, 71.10; H, 05.13; N, 07.16.

3.1.2.3-(1-Benzyl-2-(3,4-dimethoxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4b): Light yellow solid; mp. 215-217 ºC; IR (KBr, cm^{-1}) υ_{max}: 3463, 1738; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.21 (s, 3H), 3.79 (s, 3H), 3.81 (s, 3H), 4.53 (s, 2H), 6.14 (s, 1H), 7.07 (d, J = 8.8 Hz, 1H), 7.39-7.42 (m, 8H), 12.38 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.6, 47.4, 55.2, 55.5, 83.4, 95.0, 109.5, 111.9, 119.7, 124.8, 127.7, 128.0, 128.6, 135.7, 137.5, 146.8, 150.3, 153.6, 162.9, 163.1, 170.9, 171.7; Anal. Calcd. for $C_{24}H_{22}N_2O_5$: C, 68.90, H, 05.32, N, 06.70. Found: C, 68.85; H, 05.38; N, 06.75.

3.1.3.3-(1-Benzyl-2-phenyl-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4c): Light yellow solid; mp. 117-119 ºC; IR (KBr, cm^{-1}) υ_{max}: 3233, 1707; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 4.55 (s, 2H), 6.14 (s, 1H), 7.42-7.59 (m, 6H), 7.90-7.93 (m, 5H), 12.27 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.5, 47.6, 83.6, 105.4, 112.0, 117.5, 127.7, 128.1, 128.6, 128.9, 129.3, 130.3, 131.8, 135.7, 153.3, 163.0, 166.2, 180.8; Anal. Calcd. for $C_{22}H_{18}N_2O_3$: C, 73.70, H, 05.06, N, 07.84. Found: C, 73.75; H, 05.12; N, 07.88.

3.1.4.3-(1-Benzyl-2-(4-hydroxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4d): Light yellow solid; mp. 118-120 ºC; IR (KBr, cm^{-1}) υ_{max}: 3434, 1738; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.27 (s, 3H), 4.51 (s, 2H), 6.18 (s, 1H), 6.92 (d, J = 8.4 Hz, 2H), 7.31-7.44 (m, 6H), 7.76 (d, J = 8.8 Hz, 2H), 11.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.2, 47.0, 94.4, 106.1, 114.6, 115.4, 115.8, 127.6, 128.2, 128.3, 128.6, 128.7, 129.6, 132.0, 159.8, 161.5, 176.2, 176.9; Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.65, H, 04.89, N, 07.43. Found: C, 70.60; H, 04.85; N, 07.48.

3.1.5.3-(1-Benzyl-2-(2-hydroxy-3-methoxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4e): Light yellow solid; mp. 204-206 ºC; IR (KBr, cm^{-1}) υ_{max}: 3490, 1741; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H), 3.83 (m, 3H), 4.53 (s, 2H), 6.13 (s, 1H), 6.87-7.00 (m, 2H), 7.41-7.53 (m, 7H), 12.30 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.3, 47.5, 55.9, 83.5, 97.7,

103.1, 112.9, 118.9, 119.2, 121.5, 127.7, 128.0, 128.6, 135.7, 139.5, 146.1, 147.7, 163.0, 165.9, 175.3, 181.0; Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31, H, 05.00, N, 06.95. Found: C, 68.37; H, 05.10; N, 06.89.

3.1.6.3-(1-Benzyl-2-(2-hydroxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4f): Light yellow solid; mp. 116-118 ºC; IR (KBr, cm^{-1}) υ_{max}: 3272, 1740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H), 4.42 (s, 2H), 6.18 (s, 1H), 6.86-6.93 (m, 4H), 7.29-7.49 (m, 6H), 12.32 (s, 1H), 12.85 (s, 1H); Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58, H, 04.85, N, 07.48. Found: C, 70.53; H, 04.89; N, 07.42.

3.1.7.3-(1-Benzyl-2-(4-chlorophenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4g): Light yellow solid; mp. 212-214 ºC; IR (KBr, cm^{-1}) υ_{max}: 3490, 1741; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 4.52 (s, 2H), 6.12 (s, 1H), 7.36-7.42 (m, 6H), 8.00 (d, *J* = 8.4 Hz, 2H), 8.52 (d, *J* = 8.4 Hz, 2H), 12.64 (s, 1H); MS (ESI) *m/z*: 392 $(M)^+$; Anal. Calcd. for $C_{22}H_{17}ClN_2O_3$: C, 67.26, H, 04.36, N, 07.13. Found: C, 67.22; H, 04.39; N, 07.17.

3.1.8.3-(1-Benzyl-2-(4-(dimethylamino)phenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4h): Light yellow solid; mp. 222-224 ºC; IR (KBr, cm^{-1}) υ_{max}: 3464, 1741; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.23 (s, 3H), 3.00 (s, 3H), 3.04 (s, 3H), 4.51 (s, 2H), 6.15 (s, 1H), 7.31-7.43 (m, 8H), 7.78 (d, *J* = 8.8 Hz, 2H), 12.41 (s, 1H); Anal. Calcd. for $C_{24}H_{23}N_3O_3$: C, 71.80, H, 05.77, N, 10.47. Found: C, 71.85; H, 05.72; N, 10.42.

3.1.9.3-(1-Benzyl-2-(4-bromophenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4i): Light yellow solid; mp. 221-223 ºC; IR (KBr, cm^{-1}) υ_{max}: 3434, 1739; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H), 4.55 (s, 2H), 6.15 (s, 1H), 7.32-7.41 (m, 6H), 7.66 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 12.0 Hz, 2H), 12.43 (s, 1H); Anal. Calcd. for $C_{22}H_{17}BrN_2O_3$: C, 66.43, H, 03.92, N, 06.40. Found: C, 66.48; H, 03.97; N, 06.44.

3.1.10.3-(1-Benzyl-2-(3-nitrophenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4j): Light yellow solid; mp. 115-117 ºC; IR (KBr, cm^{-1}) υ_{max}: 3435, 1740; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H), 4.43 (s, 2H), 6.18 (s, 1H), 7.32-7.53 (m, 5H), 7.55-7.67 (m, 4H) 7.97 (s, 1H), 12.36 (s, 1H); Anal. Calcd. for $C_{22}H_{17}N_3O_5$: C, 65.50, H, 04.25, N, 10.42. Found: C, 65.57; H, 04.29; N, 10.48.

3.1.11.3-(1-Benzyl-2-(4-hydroxy-3-methoxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4k): Light yellow solid; mp. 111-113 ºC; IR (KBr, cm^{-1}) υ_{max}: 3690, 1738; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H), 3.83 (s, 3H), 4.43 (s, 2H) 6.18 (s, 1H), 6.82 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 7.14-7.16 (m, 1H), 7.25-7.31 (m, 2H), 7.32-7.38 (m, 4H), 12.76 (s, 1H); Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31, H, 05.00, N, 06.95. Found: C, 68.27; H, 05.21; N, 06.99.

3.1.12.3-(1-Benzyl-2-(2,4-dihydroxyphenyl)-1H-imidazol-4-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4l): Light yellow solid; mp. 110-112 ºC; IR (KBr, cm^{-1}) υ_{max}: 3468, 1738; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.22 (s, 3H), 4.44 (s, 2H), 6.12 (s, 1H), 7.32-7.40 (m, 8H), 7.95 (s, 1H), 12.33 (s, 1H); Anal. Calcd. for $C_{22}H_{18}N_2O_5$: C, 67.69, H, 04.65, N, 07.18. Found: C, 67.62; H, 04.61; N, 07.23.

4. Conclusion

In conclusion, a facile one-pot reaction has been described for the synthesis of tri-substituted imidazole derivatives via multi-component approach using readily available starting materials.

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