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Simple and efficient protocol for the synthesis of novel dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-ones via a one-pot four-component reaction

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ABSTRACT

$Ba(OH)_2$ catalyzed simple and efficient one-pot four-component reaction of Meldrums acid, ethyl acetoacetate, hydrazine hydrate, and aromatic aldehydes to give 3-methyl-4-aryl-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-ones in refluxing water is reported. The yields are high and the reactions go to completion in 1–2 h.

Multicomponent reaction (MCR) is a process in which three or more accessible components are combined together in one-pot to produce a final product which shows the features of all the input reactants and therefore, offers the greatest possibilities for molecular diversity in one step with minimum synthetic time and effort.[1] As MCRs are one-pot reactions, they are easier to carry out than the multistep syntheses. This strategy is an important development in the drug discovery in the context of rapid identification and optimization of biologically active lead compounds.[2] In addition, MCRs are environmentally friendly, and often proceed with excellent chemoselectivities.[3] There are three wings (techniques) of green chemistry which, if combined, would result in an excellent green chemistry protocol.[4] These techniques are: the efficient use of solvent-free reactions,[5] reusability of heterogeneous catalysts,[6] and use of multicomponent reactions.[6a]

One of the most challenging aspects in the medicinal chemistry is the design and synthesis of biologically active compounds,[7] and dihydro-1*H*-pyrano[2,3-*c*]pyrazoles represent an interesting template for medicinal chemistry and play an essential role as biologically active molecules.[8] Many of the pyrano[2,3-*c*]pyrazoles are known for their antimicrobial,[9] insecticidal,[10] anti-inflammatory,[11] anticancer,[12] and molluscicidal activities.[13]

During the last few years, synthesis of dihydropyrano[2,3-*c*]pyrazoles has received great interest.[14] Pyranopyrazoles are also used as pharmaceutical ingredients and biodegradable agrochemicals.[15] The first reported pyranopyrazole was synthesized by the reaction between 3-methyl-1-phenyl-pyrazolin-5-one and tetracyanoethylene.[15]

Another attractive area in green chemistry is designing organic reactions in aqueous media.[16] Water offers several benefits such as control over exothermic reactions, salting out, and salting in, as well as variation of pH.[17] We have earlier reported the synthesis of 6-amino-3-methyl-4aryl-1,4-dihydropyrano[2,3-*c*]pyrazol-5-carbonitriles using glycine,[18] iodine,[19] and imidazole[20] as catalysts in water. In continuation of our efforts to develop methods for the synthesis of novel heterocyclic compounds using readily available, inexpensive, and environmentally friendly catalysts,[21–27] herein, we report a rapid and efficient one-pot four-component synthesis of some novel 3-methyl-4-aryl-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-ones[28] by the reaction of aromatic aldehydes, Meldrums acid, hydrazine hydrate, and ethyl acetoacetate in the presence of readily available, inexpensive, mild, green, and common laboratory chemical $Ba(OH)_2$ as a basic catalyst in water (Scheme 1).

In order to optimize the reaction conditions, we carried out the reaction between 3,4,5-trimethoxybenzaldehyde, ethyl acetoacetate, Meldrums acid, and hydrazine hydrate in the presence of 10 mol % of $Ba(OH)_2$ at reflux in different solvents such as EtOH, MeOH, H_2O, and CH_3CN; among all these solvents, H_2O was found to be the best in terms of the yield of the product and time of completion compared to common organic solvents. The results of this study are presented in Table 1.

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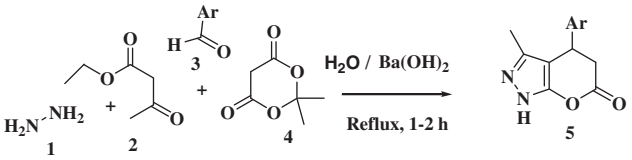


Scheme 1. Synthesis of 3-methyl-4-aryl-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-ones

Table 1
Effect of solvent on the synthesis of 3-methyl-4-(3′,4′,5′-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-one (**5a**)[a]

Entry	Solvent	Time (h)	Yield (%)
1	Ethanol	5	90
2	Methanol	6	87
3	CH_3CN	4	85
4	H_2O	1.5	93

[a] Reactions are performed on a 1 mmol scale of the reactants.

Table 2
Influence of various catalysts on the synthesis of 3-methyl-4-(3′,4′,5′-trimethoxyphenyl)-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-one (**5a**)[a]

Entry	Catalyst (10 mol %)	Time (h)	Yield (%)
1	K_2CO_3	8	30
2	Piperidine	7	40
3	NaOH	3	65
4	$Ba(OH)_2$	1.5	93

[a] Reactions are performed on a 1 mmol scale of the reactants.

Table 3
Effect of the amount of $Ba(OH)_2$ on the synthesis of (**5a**)[a]

Entry	$Ba(OH)_2$ (mol %)	Yield (%)
1	5	50
2	7	65
3	10	93
4	12	93

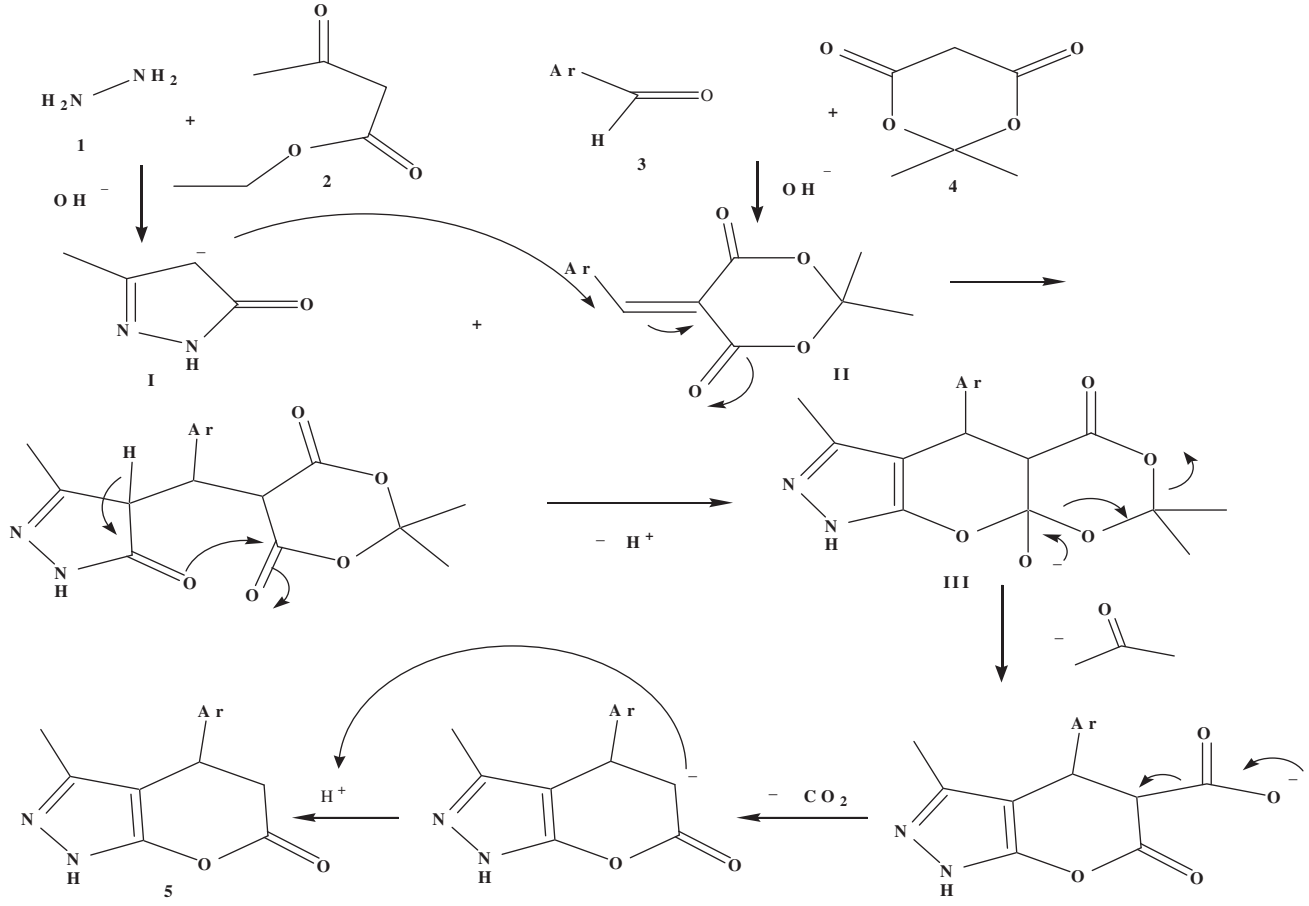
[a] Reactions are performed on a 1 mmol scale of the reactants.

Table 4
Synthesis of 3-methyl-4-aryl-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-ones

Entry	Aldehyde (3)	Product[a]	Time (h)	Yield[b] (%)	MP (°C)
1	3,4,5-$(MeO)_3C_6H_2CHO$	**5a**	1.5	93	205
2	4-$MeOC_6H_4CHO$	**5b**	1	93	157–160
3	3-$MeOC_6H_4CHO$	**5c**	1.5	93	133–135
4	2-ClC_6H_4CHO	**5d**	2	90	142–145
5	2-HOC_6H_4CHO	**5e**	2	92	235–237
6	4-FC_6H_4CHO	**5f**	2	90	178–180
7	3-$NO_2C_6H_4CHO$	**5g**	2	91	212
8	HCHO	**5h**	10	ND	—
9	CH_3CHO	**5i**	10	ND	—
10	CH_3CH_2CHO	**5j**	10	ND	—
11	$CH_3CH_2CH_2CHO$	**5k**	10	ND	—

ND-not detected.
[a] All isolated products are new and were characterized by IR, ^1H NMR, and ^{13}C NMR spectral analyses and CHN analysis.
[b] Isolated yields.

To select the best catalyst, we carried out the reaction between 3,4,5-trimethoxybenzaldehyde, ethyl acetoacetate, Meldrums acid,



Scheme 2. Mechanism of formation of 3-methyl-4-aryl-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-ones.

and hydrazine hydrate in the presence of 10 mol % of different basic catalysts such as $Ba(OH)_2$, K_2CO_3, piperidine, and NaOH. We found that, K_2CO_3 did not afford the product in good yield and reaction time was very long, similar results were obtained with piperidine. The yield of the desired product improved to a very less extent when NaOH was used as a basic catalyst and the product was a mixture and a sticky mass. When the same reaction was carried out in the presence of $Ba(OH)_2$, the product was obtained in very high yield (93%) within 1.5 h (Table 2, entry 4). The results of this study are presented in Table 2.

We have also varied the amount of $Ba(OH)_2$ from 5, 7, and 10 to 12 mol % and the results revealed that, 10 mol % gives excellent yield of the product in a short duration as shown in Table 3.

After optimizing the conditions, the generality of this method was examined by the reaction of different substituted aldehydes with ethyl acetoacetate, Meldrums acid, and hydrazine hydrate in the presence of 10 mol % $Ba(OH)_2$ in water under reflux. We also examined the use of aliphatic aldehydes to get the corresponding products (Table 4 entries 8–11) but there was no product formation even after 10 h under the optimized reaction conditions, and the results of this study are shown in Table 4.

It is found that, various aromatic aldehydes containing electron-donating or electron-withdrawing functional groups at different positions did show a difference in the reaction time but the yields of products were almost same (Table 4).

The formation of the product in the present reaction is expected to involve the following tandem reaction mechanism:

Formation of pyrazolone I by the reaction between **1** and **2** and Knoevenagel condensation between **3** and **4** to give **II**. Michael addition of **I** with **II** followed by cyclization is expected to give a tricyclic intermediate **III** which may lose a molecule of acetone and a molecule of CO_2 in subsequent steps to give the final product **5** as shown in Scheme 2. In order to establish the mechanism of the reaction, the intermediates-pyrazolone[29] and the Knoevenagel adduct[30] were prepared separately (characterized by the ^1H NMR and ^{13}C NMR spectral analysis) and were treated with each other to get the product **5a** under the standardized reaction condition, which clearly indicates that the intermediates I and II are formed during the course of the present reaction.

In summary, we have demonstrated a simple, efficient, and a novel one-pot four-component protocol for the synthesis of some new pyranopyrazol-6-one derivatives in water using $Ba(OH)_2$ as a readily available, inexpensive, and efficient catalyst. The advantages offered by this method are: simple reaction condition, short reaction time, ease of product isolation, and excellent yields. We wish to state that this method involves environmentally friendly procedure, and is the first procedure for the synthesis of novel 3-methyl-4-aryl-4,5-dihydro-1*H*-pyrano[2,3-*c*]pyrazol-6-one derivatives.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.025.

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28. *General procedure for the synthesis of 3-methyl-4-aryl-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-ones*: In a 50 mL round bottom flask, a mixture of hydrazine hydrate (2 mmol), ethyl acetoacetate (2 mmol), and $Ba(OH)_2$ (10 mol %) were taken, 10 mL water was added to the mixture and stirred in an oil bath at reflux for 15 min; aromatic aldehyde (2 mmol) and Meldrums acid (2 mmol) were then added and refluxing was continued for the remaining time (Table 4). The crude product thus separated was filtered, washed with water, the solid was dried, and subjected to silica gel column chromatography [silica gel G; 100–200 mesh, using EtOAc–hexane (1: 9) as eluent] to get the pure products. The structures of all the products were established by IR, ^1H NMR, ^{13}C NMR spectral, and elemental analyses. *Spectral data: 3-methyl-4-(3′,4′,5′-trimethoxyphenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (**5a**): Yellow crystalline solid (93%, 0.590 g); mp 205 °C: IR (KBr) ν: 3387 (br), 2968 (s), 1734 (vs), 1694 (s), 1622 (s), 1569 (vs), 1498 (s), 1448 (s), 1375 (s), 1236 (s), 1173 (vs), 1033 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.88 (d, J = 8.0 Hz, 2H, CH_2), 3.43 (s, 3H, Me), 3.59 (s, 3H, OCH_3), 3.62 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.81 (t, J = 8.0 Hz, 1H, CH), 6.61 (s, 2H, Ph), 10.85 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.8 (O–C═O), 154.6, 147.3, 132.8, 128.8, 114.8, 108.1 (all ArCs), 145.0 (C–*C*═N pyrazole), 136.8 (O–*C*═C pyrazole), 117.8 (C═*C* pyrazole), 60.1 (2 × OCH_3), 56.5 (OCH_3), 54.7 (CH_2),29.7 (*C*H), 14.7 (**C**H_3); Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80%. Found: C, 60.36; H, 5.70; N, 8.80%. *3-methyl-4-(4′-methoxyphenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (***5b***): Orange amorphous solid (93%, 0.474 g); mp 157–160 °C: IR (KBr) ν: 3401 (br), 2939 (s), 1734 (vs), 1704 (s), 1663 (s), 1504 (vs), 1447 (s), 1373 (vs), 1249 (vs), 1173 (s), 1034 (vs) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.19 (d, J = 8.4 Hz, 2H, CH_2), 3.34 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.29 (t, J = 8.0 Hz, 1H, CH), 6.74 (m, 2H, Ph), 7.04–7.21(dd, J_1 = 8.4 Hz, J_2 = 8.8 Hz, 2H, Ph), 11.10 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9 (O–*C*═O), 154.9, 142.9, 129.9, 127.0, 113.9 (all ArCs), 148.9 (C–*C*═N pyrazole), 138.8 O–*C*═C pyrazole), 114.3 (C═*C* pyrazole), 55.8 (OCH_3), 52.0 (CH_2), 29.9 (CH), 13.6 (CH_3); Anal. Calcd for

$C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85%. Found: C, 65.12; H, 5.47; N, 10.84%. *3-methyl-4-(3'-methoxyphenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (***5c***): White amorphous solid (93%, 0.474 g); mp 133–135 °C: IR (KBr) ν: 3356 (br), 2968 (s), 1733 (vs), 1704 (s), 1668 (s), 1596 (vs), 1508 (s), 1448 (s), 1375 (s), 1283 (vs), 1152 (vs), 1060 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.09 (d, *J* = 8.4 Hz, 2H, CH_2), 3.54 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.36 (t, *J* = 8.0 Hz, 1H, CH), 6.99 (s, 1H, Ph), 7.37–7.42 (m, 2H, Ph), 7.68 (d, *J* = 5.6 Hz, 1H, Ph), 11.13 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7 (O–*C*═O), 153.3, 141.6, 129.7, 122.2, 115.7, 112.6 (all ArCs), 144.5 (C–*C*═N pyrazole), 135.7 (O–*C*═C pyrazole), 116.0 (C═*C* pyrazole), 55.7 (OCH_3), 52.7 (*C*H_2), 32.9 (*C*H), 12.6 (CH_3); Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85%. Found: C, 65.12; H, 5.47; N, 10.84%. *3-methyl-4-(2'-cholorophenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (***5d***): Pale orange crystalline solid (90%, 0.4672 g); mp 142–145 °C: IR (KBr) ν: 3394 (br), 2959 (s), 1734 (vs), 1704 (s), 1666 (vs), 1615 (s), 1508 (s), 1447 (s), 1380 (s), 1276 (vs), 1173 (vs), 1034 (s), 746 (vs) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.19 (d, *J* = 8.4 Hz, 2H, CH_2), 3.54 (s, 3H, CH_3), 4.69 (t, *J* = 8 Hz, 1H, CH), 7.06–7.25 (dd, J_1 = 6.4 Hz, J_2 = 6.4 Hz, 2H, Ph), 7.29 (d, *J* = 7.6 Hz, 1H, Ph), 7.59 (d, *J* = 7.2 Hz, 2H, Ph), 11.15 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1 (O–*C*═O), 141.1, 129.9, 128.9, 126.9, 122.1, 117.1 (all ArCs),, 149.9 (C–*C*═N pyrazole), 135.3 (O–*C*═C pyrazole), 114.1 (C═*C* pyrazole), 52.1 (*C*H_2), 32.1 (*C*H), 10.7 (*C*H_3); Anal. Calcd for $C_{13}H_{11}ClN_2O_2$: C, 59.44; H, 4.22; N, 10.66%. Found: C, 59.12; H, 4.22; N, 10.65%. *3-methyl-4-(2'-hydroxyphenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (***5e***): Pale yellow amorphous solid (92%, 0.444 g); mp 235–237 °C: IR (KBr) ν: 3562 (br), 3362 (s), 2968 (s), 1733 (vs), 1694 (w), 1622 (s), 1508 (w), 1448 (s), 1375 (s), 1269 (s),1163 (s),1033 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.99 (d, *J* = 6.8 Hz, 2H, CH_2), 3.29 (s, 1H, OH), 3.69 (s, 3H, CH_3), 4.29 (t, *J* = 6.8 Hz, 1H, CH), 6.94–6.98 (m, 2H, Ph), 7.39 (d, *J* = 7.2 Hz, 1H, Ph), 7.67 (d, *J* = 8 Hz, 2H, Ph) 11.09 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.7 (O–*C*═O), 159.5, 131.7, 120.5, 119.9, 117.4 (all ArCs), 144.7 (C–*C*═N pyrazole), 134.1(O–*C*═), 114.7 (C═*C* pyrazole), 52.9 (*C*H_2), 32.9 (*C*H), 12.3(*C*H_3); Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47%. Found: C, 63.93; H, 4.95; N, 11.49%. *3-methyl-4-(4'-fluorophenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (***5f***): Pale orange crystalline solid (91%, 0.442 g); mp 178–180 °C: IR (KBr) ν: 3398 (br), 2959 (s), 1734 (vs), 1704 (s), 1681 (s), 1544 (vs), 1504 (s), 1448 (s), 1354 (vs), 1223 (vs), 1152 (vs), 1034 (s) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.17 (d, *J* = 8.0 Hz, 2H, CH_2), 3.64 (s, 3H, CH_3), 4.29 (t, *J* = 6.0 Hz, 1H, CH), 7.00–7.03 (m, 2H, Ph), 7.11–7.28 (m, 2H, Ph), 11.23 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.8 (O–*C*═O), 152.5, 130.1, 130.0, 115.0, 105.0 (all ArCs), 160.1 (C–*C*═N pyrazole), 140.2(O–*C*═C pyrazole), 115.2 (C═*C* pyrazole), 52.3 (*C*H_2), 32.9 (*C*H), 11.2 (*C*H_3); Anal. Calcd for $C_{13}H_{11}FN_2O_2$: C, 63.41; H, 4.50; N, 11.38%. Found: C, 63.39; H, 4.50; N, 11.39%. *3-methyl-4-(3'-nitrophenyl)-4,5-dihydro-1H-pyrano[2,3-c]pyrazol-6-one* (***5g***): Pale orange crystalline solid (90%, 0.486 g); mp 212 °C: IR (KBr) ν: 3389 (br), 2968 (s), 1733 (vs), 1704 (s), 1668 (w), 1596 (s), 1538 (vs), 1448 (s), 1375 (w), 1348 (s), 1256 (s), 1173 (s), 1033 (s) $cm0^{-1}$; ^1H NMR (400 MHz, DMSO-d_6): δ 3.10 (d, *J* = 8.0 Hz, 2H, CH_2), 3.50 (s, 3H, CH_3), 4.29 (t, *J* = 8.0 Hz, 1H, CH), 7.54 (d, *J* = 8.0 Hz, 1H, Ph), 7.79 (d, *J* = 7.6 Hz, 1H, Ph), 8.01 (d, *J* = 8.0 Hz, 1H, Ph), 8.18 (d, *J* = 3.2 Hz, 1H,Ph), 10.99 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.6 (O–*C*═O), 148.6, 147.7, 130.6, 122.7, 122.0, 102.3 (all ArCs),, 152.8 (C–*C*═N pyrazole), 135.2 (O–*C*═C pyrazole), 112.3 (C═*C* pyrazole), 52.2 (*C*H_2), 36.6 (*C*H), 10.8 (*C*H_3); Anal. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38%. Found: C, 57.14; H, 4.06; N, 15.38%.

29. *Synthesis of 5–methyl–2,4–dihydro-pyrazol–3–one* (***I***): A mixture of hydrazine hydrate (10 mmol), ethyl acetoacetate (10 mmol), and $Ba(OH)_2$ (10 mol %) were taken, 5 mL water was added to the mixture and stirred at 26 °C for 45 min (TLC), the crude solid thus separated was filtered, washed with water, and dried to get 5-methyl-2,4-dihydro-pyrazol-3-one in quantitative yield whose structure was established by ^1H NMR and ^{13}C NMR spectral analysis. White solid, mp: 215–216 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.55 (s, 3H, CH_2), 3.14 (s, 2H, CH_2), 6.80 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.1 (NH–*C*═O), 153.9 (–*C*═N), 43.5 (*C*H_2), 20.6 (*C*H_3).
30. *Synthesis of 2,2-dimethyl-5-(3′,4′,5′-trimethoxybenzylidene)-[1,3]-dioxane-4,6-dione* (***II***): A mixture of 3,4,5-trimethoxy benzaldehyde (2 mmol), Meldrum's acid (2 mmol), and $Ba(OH)_2$ (10 mol %) were taken in 5 mL water and stirred at reflux for 15 min (TLC), the solid thus separated was filtered, washed with water, and dried to get 2,2-dimethyl-5-(3′,4′,5′-trimethoxybenzylidene)-[1,3]-dioxane-4,6-dione in almost pure form. The structure was confirmed by ^1HNMR and ^{13}CNMR spectral analysis. Pale green solid, mp: 118 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.76 (s, 6H, 2 × CH_3), 3.10 (s, 6H, OCH_3), 3.98 (s, 3H, OCH_3), 7.61 (s, 2H, AcH), 8.32 (s, 1H, ═CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8 (2 × O–*C*═O), 148.8 (H–*C*═C), 144.9, 131.4, 129.9, 111.1, 108.2, 106.2 (all ArCs), 117.8 (CO–*C*═C), 103.3 (>C–O), 57.8, 55.8, 53.5 (3 × OCH_3), 30.1, 27.8 (2 × *C*H_3).