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VISIBLE LIGHT PROMOTED CATALYST-FREE GREEN SYNTHESIS OF 1,3,5-TRIARYLPYRAZOLES IN AQUEOUS MEDIUM

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ABSTRACT: Herein, an efficient, eco-friendly 1,3,5-Triaryl pyrazole skeleton synthesis is reported incorporating the one-pot multi-component reaction (MCR) of aldehydes, phenyl hydrazines and phenyl acetylene in the presence of visible light through an environment friendly and pragmatic method in green aqueous medium. The current protocol is the first known visible-light mediated synthesis of 1,3,5-triaryl pyrazoles. The key attributes of the disclosed method are the use of visible light as an energy source cum promoter, and water as the reaction medium. Other important attributes of the aforementioned-method are the involvement of readily available reactant moieties, suitable reaction conditions, functional simplicity, broad substrate availability, short reaction times as well as excellent yields, making the present reaction procedure a true green protocol, superior to the previously reported methods.

KEYWORDS: Visible light, Green-synthesis, Multi component reaction, Catalyst free, Aqueous media.

INTRODUCTION

With the current focus on the development of novel chemical procedures that cause least harm to the environment, organic chemists are directing their endeavours towards the designing of innovative new protocols that are eco-friendly as well as sustainable.[i] In this backdrop visible light can serve as a universally available, sustainable, and eco-friendly promoter for organic reactions.[ii]

Consequently, the use of visible-light-initiated chemical reactions have emerged as an impressive synthetic strategy for accomplishing the synthesis of a variety of important organic molecules and intermediates. Recently, several researchers are conducting experiments with visible-light mediated organic synthesis as an efficient and cost effective, energetically potent eco-friendly method for synthesis of the target heterocyclic motifs.[iii-v] Especially interesting are the catalyst-free visible-light-driven organic reactions.[iiia,vi]

Over the past two decades, multi-component reactions have become increasingly popular owing to their ability to quickly synthesize a wide range of organic compounds in a single step.[vii]

The significance of MCR has increased manifold with the advent of green chemistry due to their procedural feasibility, minimal by-product, easy isolation process[vii] in connection to the enormously limited amount of chemicals utilized and aiding in conservation of energy.[viii]

Replacement of toxic volatile organic compound (VOC) based conventional solvents with water remains an important goal in green synthesis.[ix,x]

Water, in additional to being abundantly available, inexpensive, and environmentally benign, possesses some special properties such as hydrogen bonding, high dielectric capacity, high heat capacity and hydrophobic effect, which provides with unique advantages as an eco-friendly solvent in organic synthesis.[x]

Intriguingly, despite the enormous potential of MCRs in water as solvent, it has least attracted chemists for the development of biologically important organic molecules.[xi] Pyrazoles are N-heterocycles exhibiting an extensive range of interesting biological and medicinal properties.[xii](Figure 1).

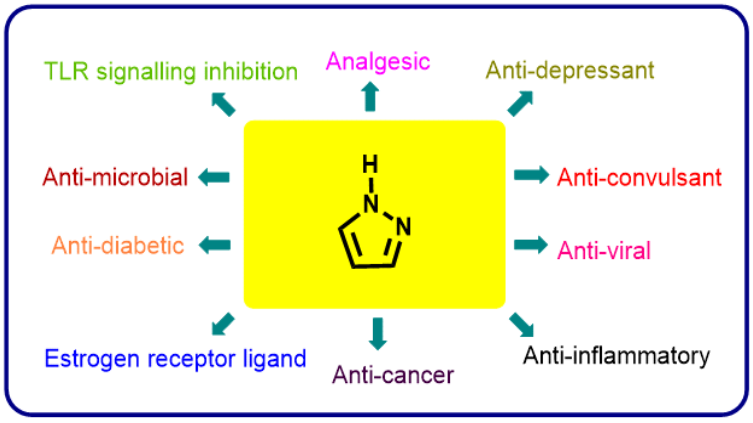


Fig 1. Pyrazole moiety in medicinal chemistry

Among pyrazoles, 1,3,5-trisubstituted pyrazoles, including 1,3,5-triaryl substituted pyrazoles, form a special sub-class within pyrazoles, which display a broad range of biological activities, incorporating but not restricted to anti-inflammatory,[xiii] anti-cancer,[xiv] anti-diabetic,[xv] anti-tubercular,[xvi] anti-microbial,[xvii] toll like receptor signaling inhibition activity,[xviii] estrogen ligand receptorsetc.[xix] (Figure 2)

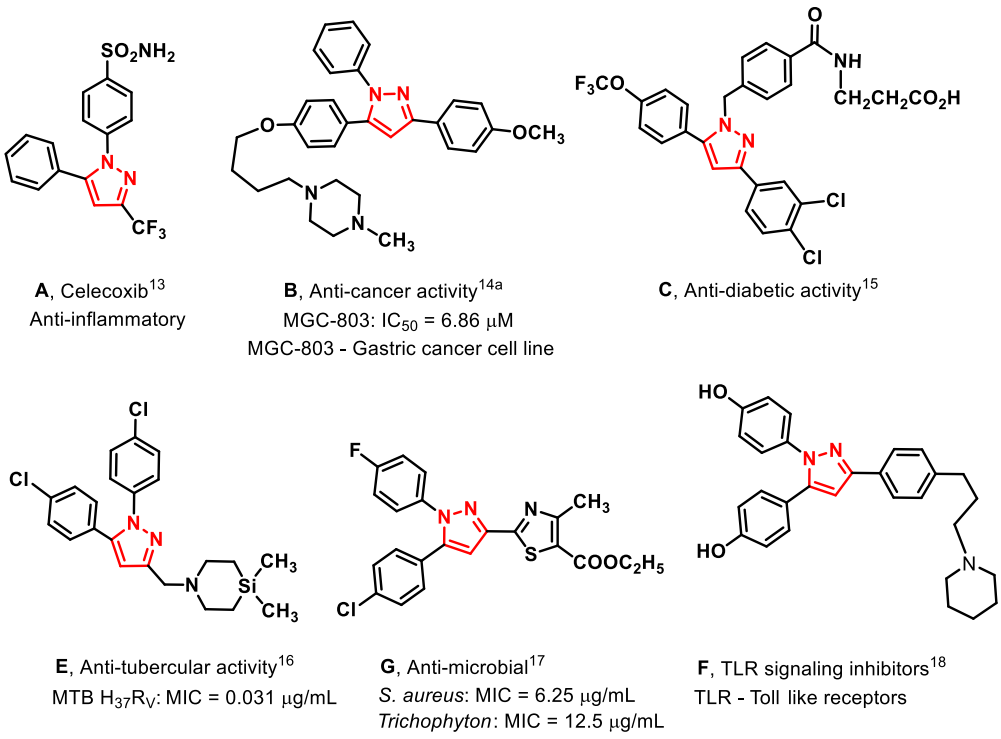


Figure 2. 1,3,5-Triaryl substituted pyrazoles based bioactive molecules and drugs

In this backdrop, here we discuss a novel as well as effective, visible light promoted green synthesis of 1,3,5-triarylsubstituted pyrazole without using catalyst via a one-pot MCR reaction of benzaldehydes, phenylhydrazines, and alkynes, in water as a solvent.

EXPERIMENTAL SECTION:

The chemicals were all reagent grade and were purchased from Fischer Scientific and Aldrich and used as such. Melting points were obtained using an uncorrected open glass capillary technique.

Using $CDCl_3$ as the solvent and TMS as the internal reference, NMR spectra were acquired on a BRUKER AVANCE II- 400FT spectrometer (400 MHz for 1H NMR and 100 MHz for 13C NMR). At 70 eV, mass spectra was analysed on the JEOL SX-102 (FAB) mass spectra. Twenty silica gel G/UV-254 pre-coated TLC sheets with a 0.25 mm thickness were used to monitor the experiments (Merck 60F254).

GENERAL PROCEDURE FOR THE PREPARATION OF 1,3,5-TRIARYLSUBSTITUTED PYRAZOLE:

In a 50 ml round bottom flask with 5 mL of water, a combination of benzalaldehyde 1a (1 mmol), hydrazine 2a (1 mmol), and phenyl acetylene 3a (1 mmol) was added in the presence of visible light. For three to four hours at room temperature, the reaction was agitated until it was finished (TLC control). The pure 1,3,5 triarylsubstituted pyrazoles were obtained by filtering the precipitate and recrystallizing it with ethanol.

4(a) 3-(4-Nitrophenyl)-1,5-Diphenyl–1H-pyrazole: orange red solid, M.P. 162-165°C. KBr, IR (cm^{-1}): 1638, 1628, 1537, 1525, 1492, 1421. ^{1}HNMR ($CDCl_3$): δ 7.97-7.92 (m,2H), 7.85-7.56 (m,3H), 7.25-7.13 (m,4H), 7.01-6.85 (m,5H); 6.45 (s,1H); ^{13}CNMR ($CDCl_3$): δ 152.1, 147.07, 141.87, 133.89, 129.34, 128.95, 128.55, 128.02, 127.17, 126.60, 126.29, 125.75, 124.17, 121.32, 118.22, 112.86., Anal. Data for $C_{21}H_{15}N_3O_2$ (343): Calcd C 252, H 15, N 42,

O 32, Found C 252.5, H 15.4, N 42.6, O 32.5.

4 (b) 1,3,5-triphenyl-1H-pyrazole: pale yellow solid, M.P. 136-140°C. KBr, IR (cm^{-1}) 1680, 1640, 1620, 1530, 1490, 1420. ^{1}H NMR ($CDCl_3$): δ 7.97-7.92 (m, 2H), 7.47-7.42 (m, 2H), 7.39-7.28 (m, 11H), 6.83 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$): δ 152.1, 147.07, 141.87, 133.89, 129.34, 128.02, 126.6, 128.55, 126.6, 124.17, 125.75, 121.32, 126.29, 127.17, 128.95, 118.22 112.86, 113.44 ppm; Anal. Data for $C_{21}H_{16}N_2$ (297): Calcd C 252, H 16, N 28, Found C 252.3, H 16.6, N 28.7.

4 (c) 3-(4-Chlorophenyl)-1,5-diphenyl-1H-pyrazole: brown solid, M.P. 144-145°C. KBr, IR (cm^{-1}) 1599, 1517, 1490, 1257, 1122, 742. ^{1}H NMR ($CDCl_3$): δ 7.55-7.51 (d, J = 8.4 Hz, 2H), 7.29-7.25 (m,12H), 6.88 (s,1H) ppm; ^{13}C NMR ($CDCl_3$): δ 144.46, 135.92, 133.96, 133.92, 129.41, 129.31, 129.13, 129.09, 128.86, 127.32, 120.37, 113.60, 113.04, 112.85, 112.62 ppm; Anal. Data for $C_{21}H_{15}N_2Cl$ (332): Calcd. C 252, H 15, N 28, Cl 35.5, Found C 252.4, H 15.4, N 28.3, Cl 35.7.

4 (d) 1-Phenyl-3-(4-nitrophenyl)-5-(4-methoxyphenyl)-1H-pyrazole: reddish brown solid, M.P.175- 180 °C. KBr, IR (cm^{-1}) 3299, 1595.65, 1532.18, 1557.80, 1493.80, 1324.40, 1288.63, 1267.85, ^{1}H NMR ($CDCl_3$) : δ 8.21-8.20 (m,2H), 7.76-7.74 (m,2H), 7.67-7.32 (m,2H), 7.31-7.25 (m,3H), 7.15,7.14 (m,2H), 6.95 (s,1H), 3.78 (s,3H) ppm; ^{13}CNMR ($CDCl_3$) : δ 147, 143.62, 141.80, 133.81, 130.17, 129.47, 129.09, 128.68, 126.54, 126.24, 124.12, 123.64, 121.26, 113.36, 113.14, 55.21ppm;Anal. Data for $C_{22}H_{17}N_3O_3$ (373): Calcd. C 264, H 17, N 42, O 48, Found C 264.3, H 17.4, N 42.6, O 48.5.

4(e). 3-(4-Methoxyphenyl)-1,5-diphenyl-1H-pyrazole: brown solid, M.P. 130-132 °C. KBr, IR (cm^{-1}); 2840, 1690, 1644, 1622, 1531, 1500, 1421. ^{1}H NMR ($CDCl_3$): δ 7.86 (d, J = 8.9 Hz, 2H) 7.38- 7.32 (m, 10H), 6.97 (d, J = 8.9 Hz, 2H), 6.67(s, 1H), 3,86 (s, 3H) ppm; ^{13}CNMR ($CDCl_3$): δ 158.9, 152.0, 144.4, 138.9, 129.7, 128.9, 128.7, 128.6, 128.3, 127.2, 127.3, 125.7, 125.2, 113.8, 104.5, 55.1 ppm; Anal. Data for $C_{22}H_{18}N_2O$ (327.0): Calcd. C 264, H 18, N 28, O 16, Found C 264.2, H 18.4, N 28.1, O 16.3.

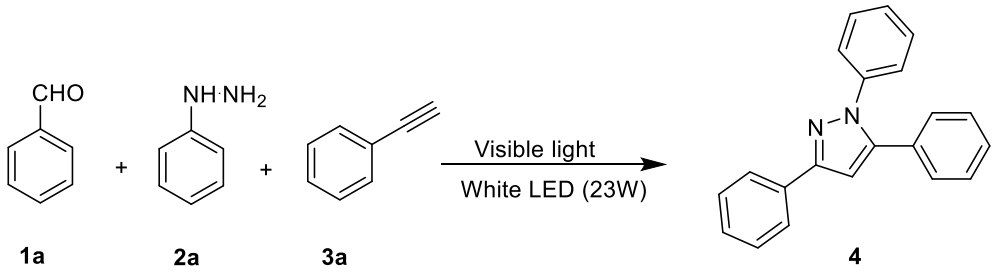
4 (f). 5-(4-Methylphenyl)-1,3-diphenyl-1H-pyrazole: white solid,M.P.114-116°C.**^{1}H (**$CDCl_3$) : δ7.89 (d,J=8.4Hz,2H), 7.37-7.31 (m,12H), 6.77 (s,1H), 2.38 (s,3H) ppm; **^{13}CNMR** ($CDCl_3$) : δ 150.8, 143.2, 140.0, 135.7, 134.8, 132.7, 128.8, 127.8, 127.5, 127.3, 127.2, 126.6, 125.8, 124.9, 124.2, 105.2, 20.1 ppm; Anal. Data for $C_{22}H_{18}N_2$ (311): Calcd. C 264, H 18, N 28, Found C 264.5, H 18.2, N 28.3.

4 (g).5-(4-Fluorophenyl)-1,3-diphenyl-1H-pyrazole: pale yellow solid, M.P.140-142°C. **^{1}H NMR** ($CDCl_3$): δ 8.24 (m,2H), 7.37-7.25 (m,5H), 7.10-6.95 (m,5H), 6.69 (m,2H) ppm; **^{13}CNMR**($CDCl_3$): δ 160.2, 150.9, 143.9, 140.3, 134.7, 130.6, 128.8, 128.7, 128.3, 127.4, 126.2, 125.3, 124.8, 115.5, 105.1 ppm; Anal. Data for $C_{21}H_{15}N_2F$ (315): C 252, H 15, N 28, F 18, Found C 252.3, H 15.2, N 28.3, F 18.2.

4 (h). 5-(4-Bromophenyl)-1,3-diphenyl-1H-pyrazole: pale yellow solid, M.P.125-127°C. **^{1}H NMR** ($CDCl_3$): 7.85 (d,2H, J=8.6Hz), 7.33-7.20 (m,12H), 6.73 (s,1H) ppm; **^{13}C NMR** ($CDCl_3$) δ 151.8, 144.1, 140.1, 133.8, 131.6, 130.7, 129.1, 128.5, 128.2, 127.2, 126.4, 125.1, 124.8, 123.7, 105.1ppm; Anal. Data for $C_{21}H_{15}N_2Br$ (375): Calcd. C 252, H 15, N 28, Br 79, Found C 252.2, H 15.4, N 28.3, Br 79.1.

4 (i) 5-butyl-1,3-diphenyl-1H-pyrazole: colourless solid, M.P.50-51°C. KBr,IR (cm^{-1}) 2842, 1678, 1643, 1621, 1532, 1486, 1423; **^{1}H NMR** ($CDCl_3$) : δ 7.67 (d,J=7.7Hz,2H), 7.47-7.42(m,4H),7.35-7.28 (m,3H), 7.21 (t,J=7.3Hz,1H), 6.36 (s,1H), 2.47 (t,J=7.6Hz,2H), 1.52-1.56 (m,2H), 1.26-1.28 (m,2H) 0.93 (t,J=7.6Hz,3H) ppm; **^{13}C NMR** ($CDCl_3$) : δ 152.0, 146.2, 139.7, 132.2, 129.2, 128.6, 127.8, 127.6, 124.9, 124.8, 102.8, 30.9, 26.0, 22.4, 13.8 ppm; **MS** : m/z = 277 [$M+H^+$].

4 (j). 3-(4-Methylphenyl)-1,5-diphenyl-1H-pyrazole: white solid, M.P. 125-126°C. **^{1}H NMR** ($CDCl_3$): δ 8.25 (m,2h), 7.41-7.27 (m,6H), 7.02-6.93 (m,6H), 6.87 (s,1H), 2.29 (s,3H) ppm;**^{13}C NMR** ($CDCl_3$): δ 150.0, 143.9, 140.7, 137.6, 131.4, 131.3, 129.9, 128.7, 128.5, 128.1, 127.8, 126.7, 126.0, 124.9, 105.9, 20.9 ppm; Anal. Data for $C_{22}H_{18}N_2$ (311): Calcd. C 264, H 18, N 28, Found 264.3, H 18.5, N 28.2.



Scheme-1

RESULT AND DISCUSSION:

This work was initiated by using benzaldehyde **(1a)**, phenyl hydrazine **(2a)** and phenyl acetylene **(3a)** as the model substrates. In our initial attempt we reacted **1a** (1 mmol), **2a** (1mmol), and acetylene **3a,** under air, at room temperature, under solvent and catalyst free conditions in the presence of a simple white LED bulb (23W) as the visible light source.

But after 12 hours of stirring, the product was barely detected in tiny levels (Entry 1, Table 1).

We now replicated the model reaction with EtOH as the solvent. Remarkably, the reaction in this instance proceeded without any problems, resulting in the synthesis of a single product that was separated, refined, and identified as the intended 1, 3, 5 trisubstituted pyrazole 4 (75%) (Entry 1, Table 1). We now tested with various ratios of EtOH and water (1:1) & (1:4), respectively, as solvents in an attempt to increase the product yield and shorten the reaction time (Entries 3, 4, Table 1). In the latter instance, a notable increase in yield was noted. Nonetheless, a little increase in reaction time was noted in both situations.

Use of exclusively water as solvent led to further increase in yield of the desired product **4** (87%) (Entry 5, Table 1). To further improve yield of the reaction we now performed a group of experiments utilizing various solvents (Entries 6-9, Table 1). However, these experiments did not yield better result. When this reaction was conducted in absence of visible light, formation of the desired product moeity was not seen.

Table 1: Optimization of chemical reactions[a]

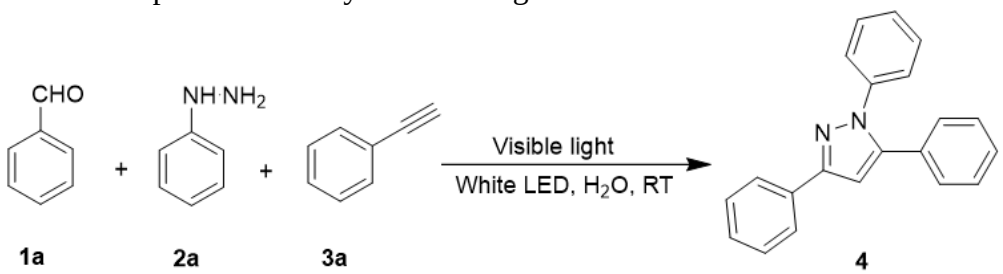
Entry	**Solvent**	**Time(h)**	**Yield (%)** [b]
1	Solvent free	12	Trace
2	C_2H_5OH	5.0	75
3	C_2H_5OH+ H_2O (1:1)	5.5	80
4	C_2H_5OH+ H_2O (1:4)	6	85
5	**H2O**	**6**	**87**
6	CH3OH	5	78
7	*i*PrOH+H_2O (1:1)	5.5	74
8	THF	7	62
9	CH_3CN	5	70
10[c]	H_2O	12	Not formed[d]

[a]Reaction condition: Benzaldehyde **1a** (1 mmol), phenyl hydrazine **2a** (1 mmol), and

phenylhydrazine **3a** (1mmol) were reacted in different solvents (4mL), under stirring at room temperature, under air. [b]Isolated yield of products.[c]Reaction conducted in absence of visible light.[d]Formation of hydrazone between the benzaldehyde **1a** and phenylhydrazine **2a** was observed.

We now turned our attention towards investigating the impact of the intensity of light on the reaction course. White LED bulbs of 12 W, 15 W, 23W and 32 W were used to promote the reaction. An increase of yield and faster reaction rates were observed as intensity of light was increased from 12W to 23 W (Entries 1-3, Table 2). However, when 32 W LED was used, although no further increment in yield was observed, the reaction reached completion in just 3 hours (Entry 4, Table 2).

Table 2. Impact of intensity of visible light on reactions



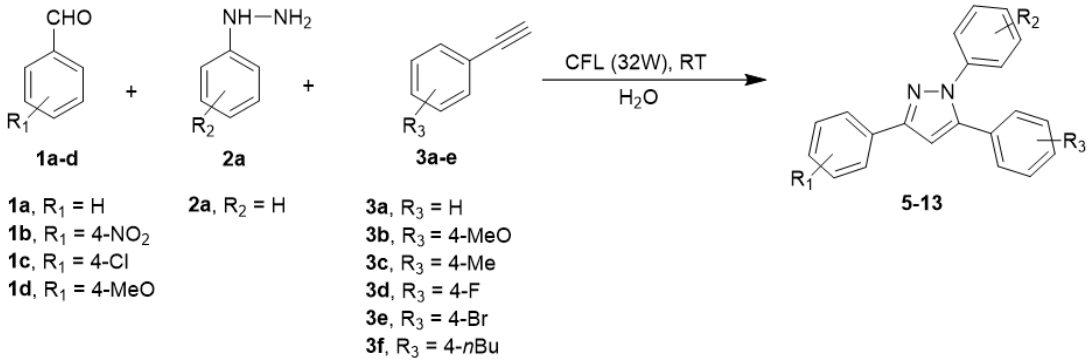
Entry	Visible light intensity	Time (h)	Yield (%) [b]
1	LED 12 W	10	72
2	LED 15 W	9	79
3	LED 23 W	6	87
4	LED 32 W	5	87

[a]Reaction condition: Benzaldehyde **1a** (1mmol), phenyl hydrazine **2a** (1mmol), and phenyl hydrazine **3a** (1mmol) were stirred under air. [b]Isolated yield of products.

The above set of experiments led us to the conclude that the best condition for carrying out this one-pot reaction of benzaldehyde (**1a**) (1 mmol), phenyl hydrazine (**2a**) (1 mmol), and phenyl acetylene (**3a**) (1 mmol) involving white LED of 32 W, at room temperature, using water as solvent.

Once optimized reaction conditions have been obtained for carrying out reaction, we set out to explore its generality and scope. The reaction was evaluated using a several benzaldehydes and phenyl acetylenes possessing electron withdrawing and electron releasing groups. In all the cases the reaction advanced feasibly with the synthesis of necessary 1,3,5-triarylsubstituted pyrazoles in 94-75%. We observed that benzaldehydes with an electron withdrawing substituent on the phenyl ring gave better yields as compared to benzaldehydes (Entries 1 & 2, Table 3), while benzaldehydes with electron releasing substituent on the phenyl ring gave reduced yields as compared to benzaldehydes (Entry 3, Table 3). However, in the case of phenyl acetylenes, while involvement of electron releasing substituents on the aromatic ring led to better yields (Entries 4, 5 & 8, Table 3), substituents present on the aromatic ring of electron withdrawing nature gave reduced lead (Entries 6 & 7, Table 3).

Table3. Substrate scope[a]



Entry	Benzaldehydes	Phenyl hydrazines	Alkynes	Time(h)	Product	Yield (%) [b]
1	**1b**	**2a**	**3a**	3	**6**	92
2	**1c**	**2a**	**3a**	4	**7**	87
3	**1d**	**2a**	**3a**	4	**9**	75
4	**1b**	**2a**	**3b**	3	**10**	94
5	**1a**	**2a**	**3c**	5	**11**	90
6	**1a**	**2a**	**3d**	5	**12**	78
7	**1a**	**2a**	**3e**	5	**13**	83
8	**1a**	**2a**	**3f**	6	**14**	88

[a]Reaction conditions: Benzaldehydes **1a-d** (1 mmol), phenyl hydrazines **2a** (1 mmol), and phenyl acetylenes **3a-e** (1mmol) were refluxed in water (4mL), under air. [b] Isolated yield of pure product.

CONCLUSION:

To conclude, we have elaborated a visible light-promoted, environmentally benign, catalyst-free one-pot MCR technique that creates 1,3,5-triarylsubstituted pyrazoles by an alkyne-phenyl hydrazine-benzaldehyde one-pot reaction.

The main attributes of the discussed method is the utilization of visible light as an activating agent and water as a reaction medium. The other merits of the present method are the use of cheap, easily available synthons, fast reaction times etc. The green attributes of this method along with the other advantages that it has over previous methods makes it a protocol of choice for synthesizing the pyrazoles.

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