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Silica-zinc chloride (SiO_2-$ZnCl_2$) catalyzed Michael addition reaction of active methylene compounds to *β*-nitrostyrenes: Synthesis of functionalized pyrazole derivatives

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Under solvent-free conditions, a simple and efficient procedure has been developed for the Michael addition reaction of active methylene compounds to β-nitrostyrenes. The resulting Michael adducts are efficiently converted into functionalized pyrazole derivatives with hydrazine hydrate in excellent yields. All the compounds were well characterized by spectroscopic techniques.

1. Introduction

Solid support catalysts have received considerably much more attention recently by organic synthetic chemists due to their numerous beneficial qualities, including chemical and thermal stability, selectivity, high surface area, reusable, cheap cost, commercial availability, cost minimization, and catalyst reuse. In recent years, numerous solid supported reagents, including SiO_2-$FeCl_3$, SiO_2-$HClO_4$, SiO_2-$KHSO_4$, SiO_2-$ZnCl_2$, SiO_2-SO_3H, and SiO_2-PPA, have been developed. These reagents have been employed in numerous chemical processes. [1-3].

The most prevalent and important motif is pyrazoles, which is found in a wide range of natural products, pharmaceuticals, medicinal chemistry libraries, and agrochemicals. Pyrazole derivatives were found with wide range of biological activities including antimicrobial agent[4], tyrosine kinase-2 inhibitors[5], insulin-like growth factor−1 receptor (IGF-1R)[6], ataxia telangiectasia mutated (ATM) kinase inhibitors[7], T−type calcium channel blockers[8], p21-activated kinase inhibitors[9], etc.

Biological properties of pyrazole derivatives have inspired chemists to develop various synthetic methods that have been reported for the synthesis of pyrazole derivatives[10-15] but still there is a requirement for the new derivatives of pyrazoles to address the new challenging tasks.

In the process of making different complex organic molecules, C-C bond formation processes are crucial. Due to its numerous uses in the synthesis of biologically important natural chemicals, the Michael addition reaction rises to a prominent position among the several C-C bond forming reactions[16-18]. One of the most significant transformations is the

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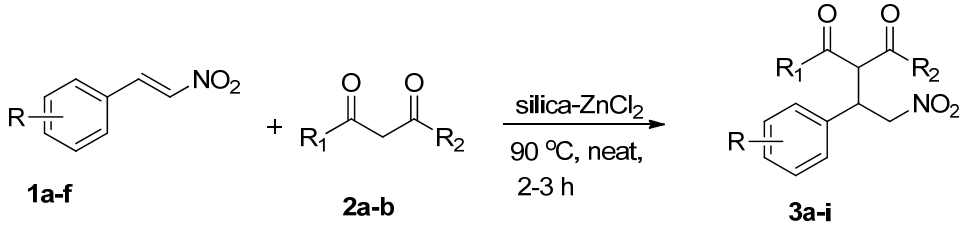
Michael addition reaction of carbon nucleophiles to *β*-nitrostyrenes because the resulting Michael adducts contain a variety of functional groups in close proximity which can be modified synthetically to produce a variety of functionalized carbocyclic and heterocyclic compounds[19]. Various methods have been developed for the synthesis of these Michael adducts [20-23], but still there is a need to develop simple, cost effective and environment friendly methodologies. *β*-nitrostyrenes were also involved in 1,3-dipolar cycloaddition reaction with C-Phenyl-N-phenyl-nitrones[24], diazafluorenes[25], C-(9-anthryl)-N-phenyl-nitrones[26] to form cyclic compounds.

In this article, we describe a straightforward and effective methodology for the pyrazole synthesis, which can be easily obtained from the Michael addition of carbon nucleophiles to the *β*-nitrostyrenes by silica supported $ZnCl_2$ under solvent-free conditions. This methodology is part of our ongoing research on effective methodologies[27-29]on heterocyclic compounds. This method has several advantages 1) very mild conditions 2) low catalyst loading 3) short reaction time 4) catalyst recyclability 5) wide range substrate scope 6) high yield. Zinc chloride is an inexpensive and commercially available reagent, which is also used as a Lewis acid in organic synthesis. It has a hygroscopic nature; anhydrous condition should be required for reaction. To overcome this issue, silica supported zinc chloride was found to be the best choice[1].

2. Results and Discussion

To optimize the reaction conditions (**Scheme 1**), we first performed a reaction using a mixture of β-nitrostyrene, acetylacetone, and various catalysts. Our first attempts with silica gel (100-200 mesh) under solvent-free conditions yielded 20% conversion. However, under the same conditions, we tried different silica-supported catalysts such as SiO_2-$KHSO_4$, SiO_2-$FeCl_3$, SiO_2-$HClO_4$, SiO_2-$ZnCl_2$, and $ZnCl_2$ catalyst which yielded 3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**3a**) in 50%, 72%, 48%, 89%, and 0%, respectively (Table 1, entries 2-6). Based on these results, SiO_2-$ZnCl_2$ is found to be a suitable catalyst, then conducted other experiments with different quantities of SiO_2-$ZnCl_2$ catalyst to optimize the reaction conditions (**Table-1,** entries 5, 7-8), and best conversion observed with 10% of catalyst.



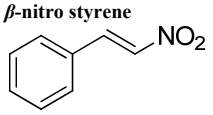
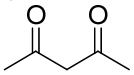
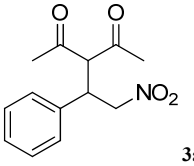
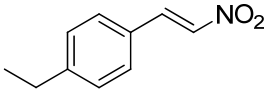
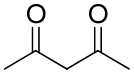
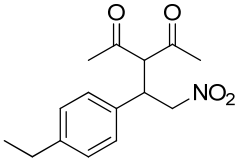
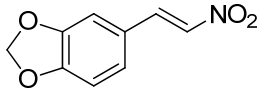
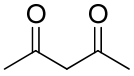
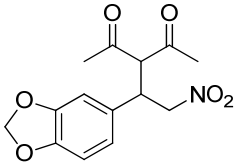
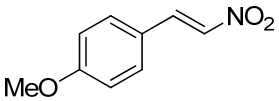
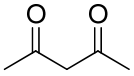
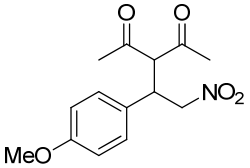
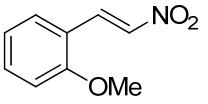
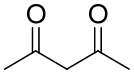
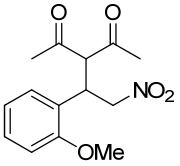
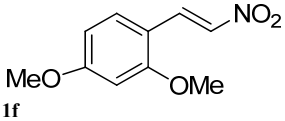
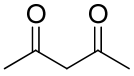
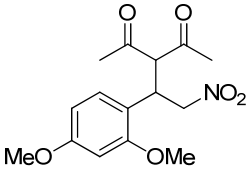
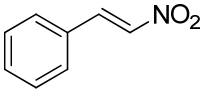
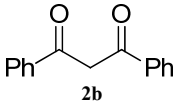
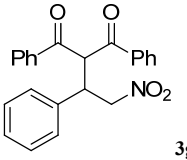
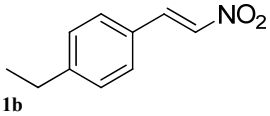
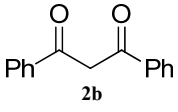
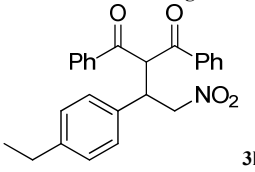
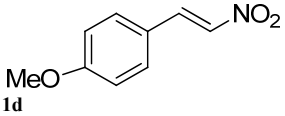
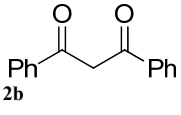
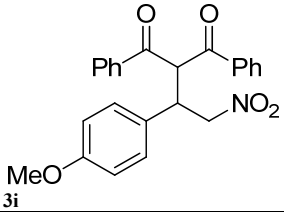
Scheme 1. Development of optimized conditions for Michael adducts

Table 1. Optimization of Michael addition reaction of carbon nucleophiles to β-nitrostyrenes.[a,b]

Entry	Catalyst	Time (h)	Yield (%)
1	Silica	6	20
2	SiO_2-$KHSO_4$	4	50
3	SiO_2-$FeCl_3$	3	72
4	SiO_2-$HClO_4$	4	48
5	SiO_2-$ZnCl_2$ (10 mol%)	2	89
6	$ZnCl_2$	3	NR
7	SiO_2-$ZnCl_2$ (5 mol%)	3	76
8	SiO_2-$ZnCl_2$ (15 mol%)	3	88

The Michael addition reaction involving acetylacetone electrophile attack on the beta-position of nitroalkenes to yield addition product (or) Michael adduct and the progress of the reaction was monitored by TLC; the crude reaction mixture was purified by column chromatography to afford the expected product 3-(2-nitro-1-phenylethyl)pentane-2,4-dione (**3a**) in 89% isolated yield (**Table 2**). The product thus obtained was also confirmed by ^1H and ^{13}C NMR analysis. Excited with the preliminary result, we proceeded to explore the reactivity of other substrates in the current protocol. Accordingly, we have chosen various substituted *β*-nitrostyrene derivatives (**1a-f**) as shown in **Table 2**. The reaction of **1b** having ethyl substituent in *para* position reacted well with acetylacetone **2a** under similar conditions to afford the desired product **3b** in 86% yield (**Table 2**). The reaction of **1c** with acetylacetone **2a** was also underwent smoothly and provided the anticipated product **3c** in 80% yield. The *β*-nitrostyrenes **1d** having methoxy substituent in *para* position and **1e** having methoxy substituent in *ortho* position reacted effectively with acetylacetone and gave the corresponding products **3d** and **3e** 84% and 75% yields respectively (**Table 2**). The disubstituted *β*-nitrostyrene **1f** having methoxy substituent at 2,4-position also reacted smoothly to provide the Michael adduct **3f** in 72% isolated yield. Further, the reaction of **1a** with 1,3-diphenylpropane-1,3-dione **2b** under the standard reaction conditions provided the product **3g** in 88% yield. The reactions of *β*-nitrostyrene derivatives **1b-d** with1,3-diphenylpropane-1,3-dione **2b** under the similar reaction conditions afforded their respective products **3h**, **3i**, in 82%, and 79% yields (**Table 2**).

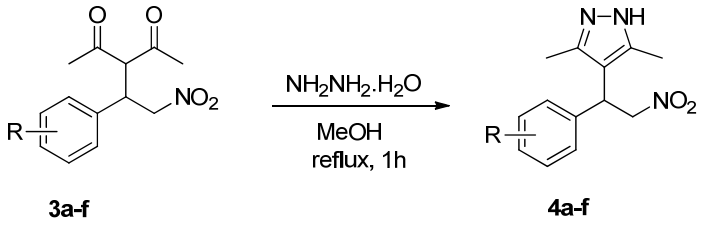
Table 2. Diversity in the synthesis of substituted Michael adducts using SiO_2-$ZnCl_2$ (10 mol%) catalyst

Entry	*β*-nitro styrene	1,3-diketone	Product	Time (h)	Yield (%)
1	 **1a**	 **2a**	 **3a**	2	89
2	 **1b**	 **2a**	 **3b**	2	86
3	 **1c**	 **2a**	 **3c**	2	80
4	 **1d**	 **2a**	 **3d**	2	84
5	 **1e**	 **2a**	 **3e**	3	75
6	 **1f**	 **2a**	 **3f**	3	72
7	 **1a**	 **2b**	 **3g**	3	88
8	 **1b**	 **2b**	 **3h**	2	82
10	 **1d**	 **2b**	 **3i**	3	79

[a]All the reactions were carried out with *β*-nitrostyrene derivative (1.0 mmol) and acetylacetone/1,3-diphenylpropane-1,3-dione (1.2 mmol) in presence of silica gel-$ZnCl_2$ (10 mol%) at 90 °C for 2 h. [b] yields are of pure and isolated compounds.

After successfully developing a new methodology for the synthesis of Michael adducts by reacting carbon nucleophiles with *β*-nitrostyrenes in the presence of silica-$ZnCl_2$ under solvent free conditions, the Michael adducts were planned to

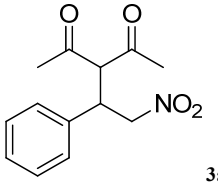
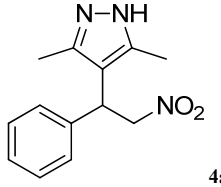
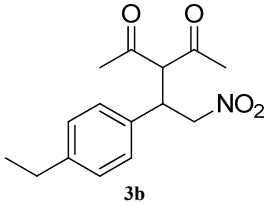
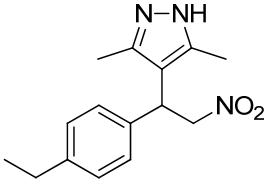
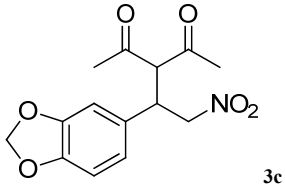
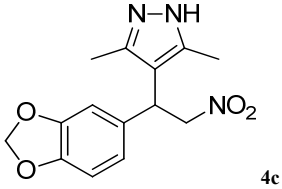
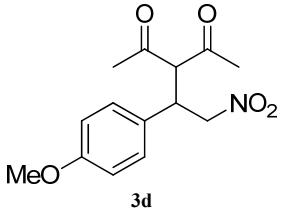
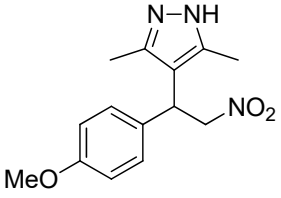
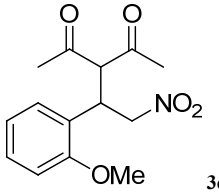
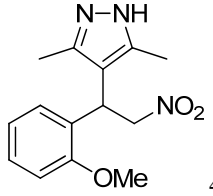
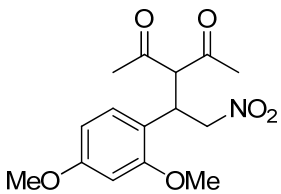
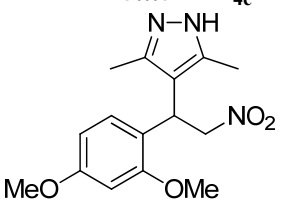
transform into functionalized pyrazole compounds by reacting with hydrazine hydrate as shown in **Scheme 2**. In the preliminary reaction the Michael adduct **3a** and hydrazine hydrate were reacted in methanol at reflux temperature for 1 h. The reaction progress was monitored by TLC, and after completion of the reaction the desired pyrazole derivative 3,5-dimethyl-4-(2-nitro-1-phenylethyl)-1H-pyrazole (**4a**) was isolated with good yield (97%) without the necessity of purification by column chromatography (**Table 3**).



3a-f **4a-f**

Scheme 2. Synthesis of pyrazole derivatives by employing the Michael adducts

Table 3. Synthesis of functionalized pyrazole derivatives from Michael adducts.[a,b]

Entry	Michael adduct	Functionalized Pyrazole	Time (h)	Yield (%)
1	 **3a**	 **4a**	1	97
2	 **3b**	 **4b**	1	94
3	 **3c**	 **4c**	1	91
4	 **3d**	 **4d**	1	96
5	 **3e**	 **4e**	1.5	92
6	 **3f**	 **4f**	1.5	89

[a)] All the reactions were carried out with Michael adduct **2a** (1.0 mmol) and hydrazine hydrate (1.5 mmol) in methanol (4 mL) at reflux temperature for 1 h. [b)] yields are of pure and isolated products.

The product **4a** was also confirmed by the ^{1}H and ^{13}C NMR analysis. Encouraged with the result obtained we proceeded further to extend the current protocol to other Michael adducts. The reaction of **3b** with hydrazine hydrate under the standard conditions provided the pyrazole derivative **4b** in 94% yield. Similarly, the reaction of **3c** with hydrazine hydrate also underwent smoothly and afforded the desired product in 91% yield. The reactions of **3d, 3e** and **3f** reacted with hydrazine hydrate reacted effectively to provide the corresponding products in 96%, 92% and 89% respectively (**Table 3**). All the products were also well characterized by using the modern analytical tools.

3. Conclusions

We developed a clean, cost-effective, and environmentally friendly methodology for the Michael addition of carbon nucleophiles to β-nitrostyrene using silica-$ZnCl_2$. The current methodology is straightforward and allows for the synthesis of a wide range of functionalized Michael adducts. We have also successfully used hydrazine hydrate to cyclize the michael adducts into pyrazole derivatives. It is worth noting that the pyrazole derivatives are obtained in excellent yields following the standard workup without the need for further purification.

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4. Experimental

4.1 Materials and methods

All the reagents used in the synthesis are laboratory grade. The IR spectra were done on the Perkin- Elmer FT-IR instrument. The ^{1}H NMR and ^{13}C NMR spectra were taken in $CDCl_3$ at 300 MHz/ 400MHz and 100 MHz respectively on Varian series (EM-360) NMR instruments. The mass spectra were done on an Agilent 1100 series instrument. The melting points were determined on Meltemp equipment. TLC (E.Merck AL silica gel 60 F254) of Merck manufactures was used for reaction progress and purity checking. Microanalysis were performed on the Perkin Elmer 2400 CHNS analyzer.

4.2 Typical general procedure for β-nitrostyrene derivatives (1a-f): To a mixture of ammonium acetate (12 mmol), nitromethane(10 ml) in acetic acid (20 ml) was added aromatic aldehyde (10 mmol) and the reaction mixture allowed to stir at 90 ºC for 6 h. After completion of the reaction as shown by the TLC, the reaction mixture was quenched with water and extracted with ethylacetate (3x20 mL), dried over sodium sulphate and concentrated under vacuum. The crude was purified by column chromatography using 5-10% of ethylacetate in hexane to yield **1a-f**. The ^{1}H NMR data of known compounds **1a, 1b, 1c, 1d, 1e, 1f** [30-32] were in agreement with those reported in the literature.

4.3 Typical general procedure for Michael adducts (3a-i): To a mixture of β-nitrostyrene derivative (**1a-f**) (1.0 mmol) and acetylacetone (**2a**)/1,3-diphenylpropane-1,3-dione (**2b**) (1.2 mmol) was added silica-$ZnCl_2$[1] (0.1 mmol) and the reaction mixture allowed to stir at 90 ºC for 2 h. After completion of the reaction as shown by the TLC, the crude reaction mixture was purified by column chromatography using 10-20% of ethylacetate in hexanes to yield **3a-i**. The HNMR data of known compounds **3a, 3c 3d, 3e, 3f, 3g, 3i** [33-35] were in agreement with those reported in the literature.

4.4 Typical procedure for synthesis of pyrazole derivatives (4a-f):

To a mixture of Michael adduct **3a-f** (1.0 mmol) and methanol (4 mL) was added hydrazine hydrate (1.5 mmol) and the reaction mixture was allowed to reflux for 1 h. After completion of the reaction, the solvent was evaporated and the reaction mixture was diluted with EtOAc (5 mL). The organic layer was washed twice with water (2X10 mL) and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to obtain the desired product **4a-f**. The ^{1}H NMR data of known compounds **4a-f**[36] were in good agreement with those reported in the literature.

3-(2-nitro-1-phenylethyl)pentane-2,4-dione (3a):

Yield: 89% as pale yellow solid, m.p.: 110-112 °C, IR: *v* 1679, 1592, 1495,1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.34-7.26 (m, 3H), 7.19-7.18 (m, 2H), 4.67-4.58 (m, 2H), 4.37 (d, *J* = 10.8 Hz, 1H), 4.27-4.22 (m, 1H), 2.29 (s, 3H), 1.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.6, 30.5, 42.8, 70.6, 78.2, 127.9, 128.5, 129.3, 136.0, 201.1, 201.8 ppm; Mass (m/z): 250$(M+H)^+$. Anal Calc for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62 %; found: C, 62.58; H, 6.03; N, 5.99%.

3-(1-(4-ethylphenyl)-2-nitroethyl)pentane-2,4-dione (3b):

Yield: 86%, m.p.: 84-86 °C, IR: *v* 1698, 1634, 1512,1448 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.14 (d, *J* = 8.2 Hz, 2H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.62-4.59 (m, 2H), 4.36 (d, *J* = 10.9 Hz, 1H), 4.23-4.20 (m, 1H), 2.60 (q, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 1.94 (s, 3H), 1.20(t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 15.2, 28.4, 29.6, 30.4, 42.5, 70.7, 78.3, 127.9, 128.7, 133.1, 144.5, 201.3, 201.9 ppm; Mass (m/z): 278$(M+H)^+$. Anal Calc for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05 %; found: C, 64.88; H, 6.83; N, 5.01%.

3-(1-(benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)pentane-2,4-dione (3c):

Yield:80%, m.p: 107-109 °C, IR: *v* 1705, 1685, 1496, 1452 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 6.74 (d, *J* = 7.9 Hz, 1H), 6.67-6.62 (m, 2H), 5.96 (s, 2H), 4.59-4.55 (m, 2H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.20-4.13 (m, 1H), 2.29 (s, 3H), 1.99 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.6, 30.4, 42.6, 70.8, 78.4, 101.4, 102.1, 108.1, 108.8, 121.5, 129.5, 147.7, 148.3, 201.0, 201.8 ppm; Mass (m/z): 294$(M+H)^+$. Anal Calc for $C_{14}H_{15}NO_6$: C, 57.34; H, 5.16; N, 4.78 %; found: C, 57.29; H, 5.13; N, 4.75%.

3-(1-(4-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (3d):

Yield: 84%, m.p: 113-114 °C, IR: *v* 1696, 1589, 1481,1463 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.10 (d, *J* = 8.7 Hz, 2H), 6.84 (d, *J* = 8.7 Hz, 2H), 4.59 (d, *J* = 6.4 Hz, 2H), 4.34 (d, *J* = 10.9 Hz, 1H), 4.24-4.16 (m, 1H), 3.76 (s, 3H), 2.28 (s, 3H), 1.94 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 29.7, 30.4, 42.1, 55.2, 70.7, 78.4, 114.6, 127.7, 129.1, 159.4, 201.3, 201.8 ppm; Mass (m/z):280$(M+H)^+$. Anal Calc for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02 %; found: C, 60.18; H, 6.08; N, 4.98%.

3-(1-(2-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione(3e):

Yield: 75% as yellow viscous liquid, IR: *v* 1707, 1692, 1488, 1454 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.28-7.24 (m, 1H), 7.07 (dd, *J* = 1.7, 8.0 Hz, 1H), 6.90-6.87 (m, 2H), 4.78 (dd, *J* = 8.0, 12.2 Hz, 1H), 4.62-4.55 (m, 2H), 4.52-4.44 (m, 1H), 3.88 (s, 3H), 2.27 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 28.9, 30.4, 39.1, 55.4, 68.7, 76.5, 111.2, 121.0, 123.5, 129.7, 130.2, 157.0 ppm; Mass (m/z): 280$(M+H)^+$. Anal Calc for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14; N, 5.02 %; found: C, 60.16; H, 6.06; N, 5.00%.

3-(1-(2,4-dimethoxyphenyl)-2-nitroethyl)pentane-2,4-dione(3f):

Yield: 72% as yellow viscous liquid, IR: *v* 1686, 1597, 1481, 1449 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 6.97 (d, *J* = 8.4 Hz, 1H), 6.44 (d, *J* = 2.4 Hz, 1H), 6.40 (dd, *J* = 2.4, 8.4 Hz, 1H), 4.74 (dd, *J* = 8.1, 12.0 Hz, 1H), 4.59-4.49 (m, 2H), 4.44-4.35 (m, 1H), 3.85 (s, 3H), 3.77 (s, 3H), 2.27 (s, 3H), 1.93 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 28.7, 30.3, 38.7, 55.3, 55.4, 68.9, 76.7, 99.2, 104.6, 115.6, 130.9, 158.1, 160.9 ppm; Mass (m/z): 310$(M+H)^+$. Anal Calc for $C_{15}H_{19}NO_6$: C, 58.25; H, 6.19; N, 4.53 %; found: C, 58.18; H, 6.13; N, 4.48%.

2-(2-nitro-1-phenylethyl)-1,3-diphenylpropane-1,3-dione (3g):

Yield: 88%, m.p: 156-157 °C, IR: *v* 1688, 1596, 1508, 1466 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.86 (dd, *J* = 1.0, 8.3 Hz, 2H), 7.78 (dd, *J* = 1.1, 8.3 Hz, 2H), 7.57-7.48 (m, 2H), 7.42-7.33 (m, 4H), 7.25-7.14 (m, 5H), 5.84 (d, *J* = 8.0 Hz, 1H), 5.00 (d, *J* = 6.9 Hz, 2H), 4.62 (dd, *J* = 6.9, 14.7 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 44.1, 59.8, 77.3, 128.2, 128.3, 128.6, 128.8, 128.9, 129.0, 133.8, 134.1, 135.8, 136.2, 136.8, 193.6, 194.3 ppm; Mass (m/z): 374$(M+H)^+$. Anal Calc for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75 %; found: C, 73.89; H,5.03; N, 3.69%.

2-(1-(4-ethylphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3h):

Yield: 82%, m.p: 129-130 °C, IR: *v* 1702, 1658, 1548, 1444 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.88-7.82 (m, 2H), 7.80-7.74 (m, 2H), 7.54-7.43 (m, 2H), 7.39-7.28 (m, 4H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.00 (d, *J* = 8.1 Hz, 2H), 5.84 (d, *J* = 7.9 Hz, 1H), 4.98 (d, *J* = 7.0 Hz, 2H), 4.59 (q, *J* = 7.1 Hz, 1H), 2.49 (q, *J* = 7.6 Hz, 2H), 1.10 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 15.4, 28.4, 43.8, 59.9, 77.4, 128.2, 128.4, 128.6, 128.8, 128.8, 128.9, 133.7, 133.9, 134.0, 135.9, 136.2, 144.2, 193.9, 194.4 ppm; Mass (m/z): 402$(M+H)^+$. Anal Calc for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49 %; found: C, 74.71; H, 5.73; N, 3.35%.

2-(1-(4-methoxyphenyl)-2-nitroethyl)-1,3-diphenylpropane-1,3-dione (3i):

Yield: 79%, m.p.: 136-138 °C, IR: *v* 1697, 1591, 1483, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.92-7.86 (m, 2H), 7.81-7.73 (m, 2H), 7.56-7.48 (m, 2H), 7.41-7.33 (m, 4H), 7.14 (d, *J* = 8.7 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 2H), 5.81 (d, *J* = 10.0 Hz, 1H), 4.99-4.89 (m, 2H), 4.58 (dd, *J* = 7.5, 14.4 Hz, 1H), 3.70 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 37.4, 49.1, 54.0, 71.6, 108.3, 122.4, 122.6, 122.7, 122.7, 122.9,123.4,127.7, 127.9, 129.8, 130.1, 153.2, 187.7, 188.3 ppm; Mass (m/z): 404$(M+H)^+$. Anal Calc for $C_{24}H_{21}NO_5$: C, 71.45; H, 5.25; N, 3.47 %; found: C, 71.41; H, 5.18; N, 3.41%.

3,5-dimethyl-4-(2-nitro-1-phenylethyl)-1H-pyrazole(4a):

Yield: 97% as yellow viscous liquid, IR: *v* 3425, 1506, 1470 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ= 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 7.17-7.15 (m, 2H), 5.08-5.01 (m, 1H), 4.91-4.85 (m, 2H), 2.18 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.6, 38.8, 78.1, 112.7, 127.1, 127.3, 128.9, 138.7, 142.6 ppm; Mass (m/z): 246$(M+H)^+$. Anal Calc for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13 %; found: C, 63.58; H, 6.09; N, 17.09%.

4-(1-(4-ethylphenyl)-2-nitroethyl)-3,5-dimethyl-1H-pyrazole (4b):

Yield: 94% as yellow viscous liquid, IR: *v* 3360 1500, 1449 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ= 7.14 (d, *J* = 8.1 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.02 (dd, *J* = 11.3, 16.4 Hz, 1H), 4.87-4.86 (m, 2H), 2.61 (q, *J* = 7.6 Hz, 2H), 2.19 (s, 6H), 1.21 (t, *J* = 7.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.6, 15.4, 28.3, 29.7, 38.6, 78.3, 112.8, 127.0, 128.3, 135.8, 142.5, 143.3 ppm; Mass (m/z): 274$(M+H)^+$. Anal Calc for $C_{15}H_{19}N_3O_2$: C, 65.91; H, 7.01; N, 15.37 %; found: C, 65.88; H, 6.98; N, 15.35%.

4-(1-(benzo[d][1,3]dioxol-5-yl)-2-nitroethyl)-3,5-dimethyl-1H-pyrazole (4c):

Yield: 91% as yellow viscous liquid, IR: *v* 3481, 1493, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 6.72 (d, *J* = 8.5 Hz, 1H), 6.63-6.61 (m, 2H), 5.91 (s, 2H), 4.97 (dd, *J* = 6.2, 10.9 Hz, 1H), 4.85-4.76 (m, 2H), 2.18 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.6, 38.7, 78.3, 101.2, 107.9, 108.3, 112.7, 119.9, 132.6, 146.7, 148.1 ppm; Mass (m/z): 290$(M+H)^+$. Anal Calc for $C_{14}H_{15}N_3O_4$: C, 58.13; H, 5.23; N, 14.53 %; found: C, 58.08; H, 5.15; N, 14.45%.

4-(1-(4-methoxyphenyl)-2-nitroethyl)-3,5-dimethyl-1H-pyrazole (4d):

Yield: 96% as yellow viscous liquid, IR: *v* 3430, 1488, 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.06 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.02-4.95 (m, 1H), 4.85-4.79 (m, 2H), 3.74 (s, 3H), 2.16 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.5, 38.1, 55.1, 78.2, 112.7, 114.1, 128.1, 130.6, 142.3, 158.5 ppm; Mass (m/z): 276$(M+H)^+$. Anal Calc for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26 %; found: C, 61.01; H, 6.15; N, 15.21%.

4-(1-(2-methoxyphenyl)-2-nitroethyl)-3,5-dimethyl-1H-pyrazole (4e):

Yield: 92% as white solid, m.p: 82-84ºC, IR: *v* 3398, 1496, 1468 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 7.25(dt, *J* = 1.7, 7.9 Hz, 1H), 7.06 (dd, *J* = 1.4, 7.6 Hz, 1H), 6.95-6.88 (m, 2H), 5.14 (dd, *J* = 6.3, 10.0 Hz, 1H), 5.08 (dd, *J* = 6.4, 12.3 Hz, 1H), 4.83 (dd, *J* = 10.0, 12.3 Hz, 1H), 3.85 (s, 3H), 2.25 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 5.7, 28.1, 49.3, 70.9, 104.7, 105.7, 114.3, 120.3. 121.7, 122.5, 150.8 ppm; Mass (m/z): 276$(M+H)^+$. Anal Calc for $C_{14}H_{17}N_3O_3$: C, 61.08; H, 6.22; N, 15.26 %; found: C, 61.03; H, 6.09; N, 15.19%.

4-(1-(2,4-dimethoxyphenyl)-2-nitroethyl)-3,5-dimethyl-1H-pyrazole (4f):

Yield: 89% as yellow viscous liquid, IR: *v* 3431, 1494, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 6.94 (d, *J* = 8.5 Hz, 1H), 6.46 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 2.4, 8.5 Hz, 1H), 5.07-5.01 (m, 2H), 4.79 (dd, *J* = 12.0, 14.1 Hz, 1H), 3.82 (s, 3H), 3.78 (s, 3H), 2.24 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 11.71, 33.81, 55.34, 55.37, 77.14, 98.86, 103.81, 111.94, 118.74, 128.36, 142.72, 157.83, 160.16 ppm; Mass (m/z): 306$(M+H)^+$. Anal Calc for $C_{15}H_{19}N_3O_4$: C, 59.01; H, 6.27; N, 13.76 %; found: C, 58.98; H, 6.03; N, 13.55%.

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