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ONE-POT THREE COMPONENT SYNTHESIS OF BENZYLIDENE CONJUGATED-1, 2, 4-TRIAZINES IN GLYCEROL

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ABSTRACT
One-pot three component reaction for the synthesis of Benzylidene conjugated-1, 2, 4-triazines **4a-4f** were depicted by the combination of (Z)- 4-(benzylidene)-2-methyl-oxazol-5(4H)- ones **1a-1f** with hydrazine hydrate **2** followed by Schiff base **3** in Glycerol as solvent in the presence of DBU as base catalyst for 30-40 min at 80-85 ^{o}C. The significance of this reaction incorporates more limited response time and excellent yield.

KEYWORDS: Green synthesis, One-pot synthesis, Schiff bases, DBU and 1, 2, 4-triazine

INTRODUCTION
Nitrogen-containing heterocycles are omnipresent all through Nature, viewed as in each living being in the Plant and Animal realms. The horde organic capacities incited from these heterocycles range from neurological second couriers (serotonin/melatonin), to giving the key hydrogen holding framework that makes up the premise of life, i.e., nucleotide base blending in the DNA and RNA macromolecules. In this manner, it isn't is actually to be expected that novel congeners of normally happening consolidated nitrogen heterocycles, for example, indoles and purines have tracked down utility all through the drug and agrichemical industry. Of exceptional interest are heterocycles that contain a nitrogen-nitrogen bond with one of the nitrogens arranged at the bridgehead of a bicyclic framework. Of the modest number of variations that fall inside this scope, one such heterocycle, the pyrrolo[2,1-f][1,2,4]triazine has given a stage from which an assorted and huge collection of drug work has advanced. Delegate models in both the essential and patent writing have shown that this ring framework can go about as a bioisosteric substitution to quinazoline, pyrimidine, and adenine frameworks just as a special platform that has been found in clinical-level medication applicants [i].
MCR's are one-pot reaction which contains three to more parts in single response vessel to give a last wanted item containing considerable parts of all the reactants [ii]. One of

extraordinary difficulties in present day restorative science is plan and revelation of drug dynamic molecules. Heterocyclic items which have nitrogen particle stretch out over a wide region on the planet, and their demonstration of applying to drug dynamic mixtures and agrochemicals are expanding degree important 6. 1,2,4-triazin-6-ones are a vital class of heterocyclic mixtures that show a wide assortment of utilizations in both drug and agrochemical fields. 1,2,4-triazin-6-ones have displayed anticancer, antitumour, hostile to bacterial and antifungal exercises, antimicrobial, organic exercises of cell line cytotoxicity, antimalarials, antivirals and herbicides [iii-viii] .

2-((5,6-diphenyl-1,2,4-triazin-3-yl)thio)- N-arylacetamide subsidiary **1** with strong electron-pulling out nitro group on the arylacetamide moiety showed intense α-glucosidase inhibitory movement (IC50 = 12.46 ± 0.13 μM)[ix]. 5,6-diaryl-1,2,4-triazine bearing 3-morpholinoethylamine moiety **2** showed a promising antithrombotic profile in vivo, which exhibited less ulcerogenicity in rodents when contrasted with ibuprofen[x]. 1,2,4-triazine subordinate **3** was orchestrated and evaluated for restraint of cyclooxygenases (COX1 and COX-2) with against oxidant movement in light of a cell examine utilizing human entire blood and lipoxygenase [xi]. In any case, not many examinations researched 5,6-diaryl-1,2,4-triazine moiety as a promising anticancer platform (Fig. 1).

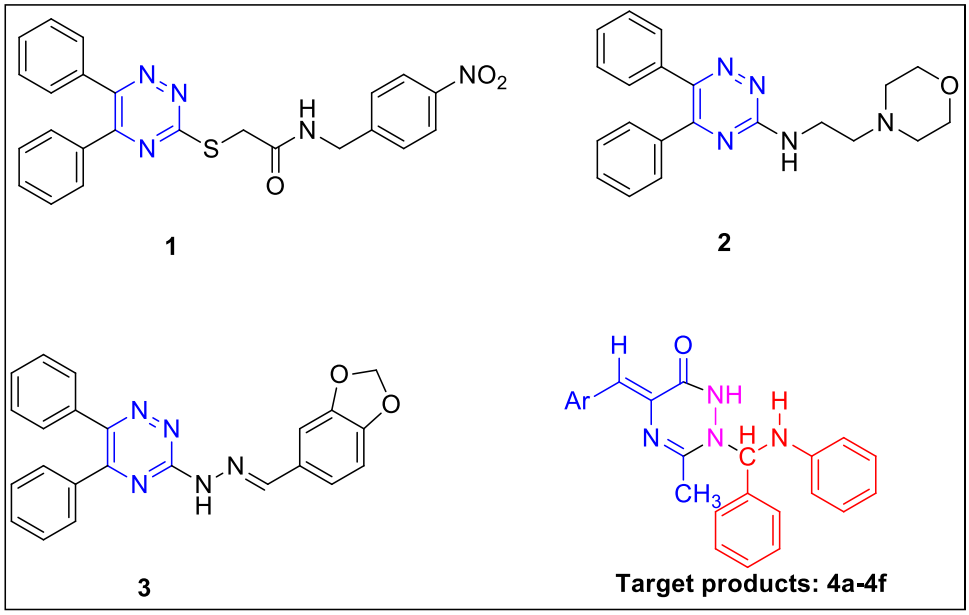


Fig-1: Bioactive 1, 2, 4-triazines

Herein, we now wish to report synthesis of benzylidene conjugated-1, 2, 4-triazines **4a-4f** by using (Z)- 4-(benzylidene)-2-methyl-oxazol-5(4H)- ones **1a-1f** with hydrazine hydrate **2** followed by Schiff base **3** in Glycerol as solvent in the presence of DBU as base catalyst for 30-40 min at 80-85 ^{o}C.

EXPERIMENTAL SECTION

Melting points are uncorrected and taken in open capillary tubes in sulphuric acid. Attention was run on silica gel - G and representation was finished utilizing UV light. IR spectra were recorded involving Perkin - Elmer 1000 instrument in KBr pellets. 1H NMR spectra were recorded in CDCl3 involving TMS as inward norm with 400 MHZ spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 esteem as it were.

Preparation of Benzylidene conjugated-1, 2, 4-triazines derivatives 4 (a-f).

Charged the (Z)- 4-(benzylidene-2-methyl-oxazol-5(4H)- ones **1 (a-f)** (1 mmol) with hydrazine hydrate **2** (1 mmol) trailed by Schiff base **3** (1 mmol) in Glycerol (50 ml) and 2 eq of DBU as base catalyst. Warmed response mass at 80-85 ^{o}C and kept up with for 30-40 min. The way and fulfilment of the response was observed by TLC (dissolvable framework 2:2 EtOAc: Hexane). The response combination was cooled to room temperature and filled super cold water (60 ml). The strong isolated out which was gathered, washed with water (20 ml) and dried. The item was recrystallised from ethanol to acquire (Z)-5-(benzylidene/subbed benzylidene)- 2-N-(benzamide/subbed benzamide)- 3-methyl-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine subsidiaries **4(a-f).**

Benzylidene conjugated 1, 2, 4-triazines derivatives 4(a-f):

4a: M.P: 242-244 ^{o}C; IR (KBr) cm^{-1}: 3360 (broad, -NH-N), 3313 (broad, -NH), 1680 (-C=O); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.9 (s, 3H, N-CH_3), 3.6 (s, 1H, -CH), 5.3 (s, 1H, -NH-CH) 7.2-8.8 (m, 16H, Ar-H and s, 1H, =CH-Ar), 11.2 (s, 1H, -NH); $M^{+\cdot}$+1 = 383.

4b: M.P: 253-255 ^{o}C; IR (KBr) cm^{-1} : 3310 (broad, -NH-N), 3244 (broad, -NH) 1659 (-C=O); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.9 (s, 3H, N-CH_3), 3.5 (s, 1H, -CH), 3.9 (s, 3H, -CH_3), 5.3 (s, 1H, -NH-CH) 7.0-8.4 (m, 15H, Ar-H and s, 1H, =CH-Ar), 11.1 (s, 1H, -NH); $M^{+\cdot}$+1 = 413.

4c: M.P: 263-265 ^{o}C; IR (KBr) cm^{-1}: 3440 (broad, -NH), 3250 (broad, -NH), 1710 (-C=O); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.8 (s, 3H, N-CH_3), 3.5 (s, 1H, -CH), 5.3 (s, 1H, -NH-CH) 7.0-8.4 (m, 15H, Ar-H and s, 1H, =CH-Ar), 11.2 (s, 1H, -NH); $M^{+\cdot}$+1 = 401.

4d: M.P: 235-237 ^{o}C; IR (KBr) cm^{-1}: 3480 (broad, -NH), 3250 (broad, -NH), 1720 (-C=O); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.9 (s, 3H, N-CH_3), 3.5 (s, 1H, -CH), 5.3 (s, 1H, -NH-CH) 7.0-8.4 (m, 15H, Ar-H and s, 1H, =CH-Ar), 11.1 (s, 1H, -NH); $M^{+\cdot}$+1 = 428.

4e: M.P: 184-186 ^{o}C; IR (KBr) cm^{-1}: 3322 (broad, -NH), 3304 (broad, -NH) 1720 (-C=O); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.7 (s, 3H, N-CH_3), 3.4 (s, 1H, -CH), 5.7 (s, 1H, -NH-CH) 7.0-8.4 (m, 15H, Ar-H and s, 1H, =CH-Ar), 11.2 (s, 1H, -NH); $M^{+\cdot}$ = 417.

4f: M.P: 173-175 ^{o}C; IR (KBr) cm^{-1}: 3334 (broad, -NH), 3283 (broad, -NH), 1712 (-C=O); ^{1}H- NMR (400MHz, DMSO-d_6/TMS): δ 2.8 (s, 3H, N-CH_3), 3.5 (s, 1H, -CH), 5.5 (s, 1H, -NH-CH) 7.2-8.4 (m, 15H, Ar-H and s, 1H, =CH-Ar), 11.2 (s, 1H, -NH) ; $M^{+\cdot}$ = 417.

RESULTS AND DISCUSSION

As outlined in the scheme-1, Multi-component reaction for preparation of (Z)- N-5-(benzylidene-3-(methyl/phenyl)- 6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine **4a** has been developed by utilizing (Z)- 4-(benzylidene-2-methyl-oxazol-5(4H)- ones **1a** (1 mmol) with hydrazine hydrate **2** (1 mmol) trailed by Schiff base **3** (1 mmol) within the presence of 2 eq of various bases (DBU, Et3N and piperdine) at various temperature (70-75 ^{o}C , 80-85 ^{o}C and 90-95 ^{o}C) in various solvents (Glycerol, PEG-600 and ethyleneglycol) **(Table-1)**. Notwithstanding, compound **4a** has been developed in Glycerol as dissolvable at 80-85 ^{o}C within the presence of 2 eq of DBU as base catalyst for 30 min with brilliant yields 90% (Table-1, S no: **4**). The design of the compound has been affirmed by IR, ^{1}H and ^{13}C-NMR and Mass. The IR range of the compound **4(a)** affirms the development of 1, 2, 4-triazine-6-one subsidiaries by the presence of absorbance at 3360 cm^{-1} (NH), 2197 cm^{-1}(Ar) and 1681 cm^{-1}(C=O). The ^{1}H-NMR spectra showed the signs at δ 2.9 demonstrating methyl protons, alongside trans olefinic proton saw at δ 11 and fragrant protons at δ7.1-8. 8.Signals at δ 3.8 and δ 5.2 show two - NH protons which were D_2O interchangeable . ^{13}C NMR range showed signals at δ 20 (CH_3) , δ 115 (CH=C), δ 127 (Ar C=C), δ 130 (HC=C), δ137 (CH-Ar), δ139 (=CH-Ar), δ140(- C(CH_3),δ159 (- CO NH), δ164 (N-C (Ar)- N). Further the mass range of

the compound **4(a)** showed the molecular ion peak at m/z 382 corresponding to molecular weight of the compound **4(a).**

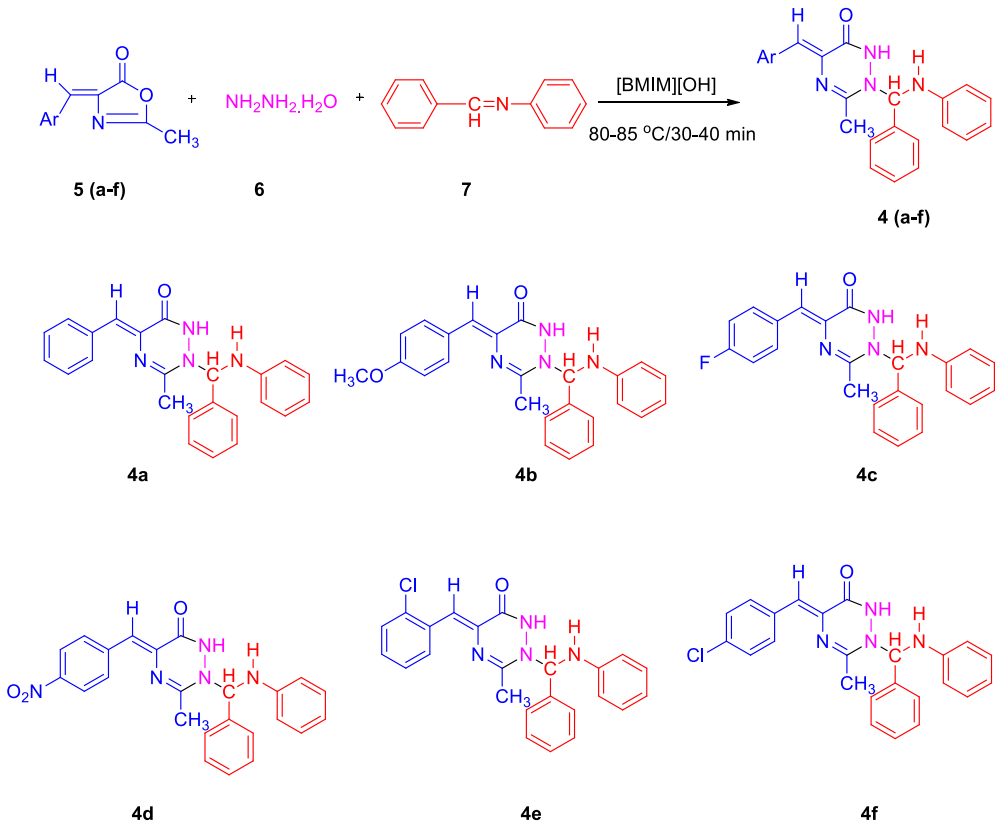
In light of the upgraded condition and to test its over-simplification the strategy, reached out to six other Benzylidene formed 1, 2, 4-triazines subordinates and in the all cases the comparing subsidiaries **4(a-f)** were separated in amazing yields. The combination of **4(a-f)** in presence of DBU in Glycerol as dissolvable at 80-85 ^{o}C for 30-40 min delivered exceptional returns, purities and with less time.

TABLE 1

Effect of solvent /2eq of base and temperature on one-pot three component reaction of **1a**, **2, & 3** to from **4a.**

Entry	**Solvent/Base**	**Temperature(^{o}C)**	**Time (min)**	**4a (%)**
1	Glycerol/ DBU	70-75	150	86
2	PEG-600/ DBU	70-75	180	84
3	Ethylene glycol/ DBU	70-75	180	84
4	**Glycerol/ DBU**	**80-85**	**30**	**86**
5	PEG-600/ DBU	80-85	35	84
6	Ethylene glycol/ DBU	80-85	40	84
7	Glycerol/ DBU	90-95	30	86
8	PEG-600/ DBU	90-95	38	85
9	Ethylene glycol/ DBU	90-95	42	86

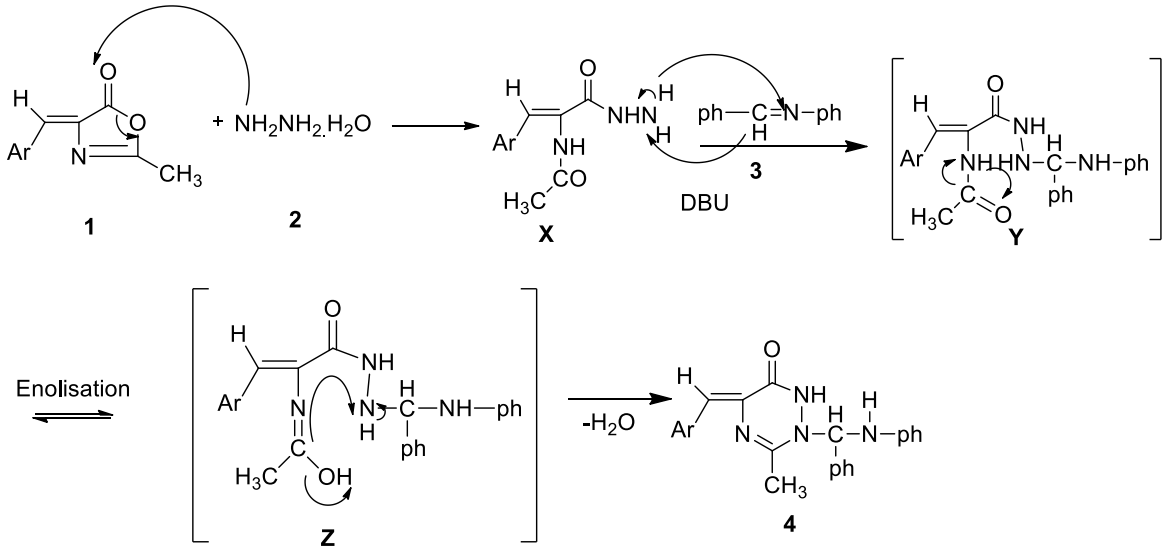
Scheme-1



Mechanism

At first, the compound (Z)- 4-(benzylidene-2-methyl-oxazol-5(4H)- ones **1** was responded with hydrazine hydrate by nucleophilic replacement to frame the halfway (Z)- N-(3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl-acetamides **X** which was treated with the schiff base which is a proton acceptor, acknowledges proton from NH_2 gathering of **X** to create an unsound middle, which in presence of a base goes through enolisation followed by cyclocondensation and wipes out water particle to deliver the title intensifies title 1, 2, 4-triazines **4** (Scheme-2).

Scheme-2



CONCLUSION

In summary, we developed the one-pot three component reaction for the synthesis of Benzylidene conjugated-1, 2, 4-triazines **4a-4f** were depicted by the combination of (Z)- 4-(benzylidene)-2-methyl-oxazol-5(4H)- ones **1a-1f** with hydrazine hydrate **2** followed by Schiff base **3** in Glycerol as solvent in the presence of DBU as base catalyst for 30-40 min at 80-85 ^{o}C. The importance of this method includes shorter reaction time and high yield.

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