GREEN SYNTHESIS OF 1, 2, 4-TRIAZINE-2-SUBSTITUTED BENZAMIDE DERIVATIVES

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Abstract
Green synthesis of (Z)-N-5-(benzylidene/substituted benzylidene)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine-2-substituted benzamide derivatives have been developed by reaction of (Z)-4-(benzylidene / substituted benzylidene)-2-(methyl/phenyl)-oxazol-5(4H)-ones **3(a-l)** with hydrazine hydrate to form (Z)-N-(3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl)acetamides or benzamides **4(a-l)**. Then, **4** was reacted with Schiff base **5** in the presence of L-tyrosine in ethanol for 1 h under reflux condition**.**

Keywords: Green synthesis, Schiff bases, L-tyrosine and 1, 2, 4-triazine

Introduction
1,2,4-Triazinones constitute valuable heterocycles as scaffolds for combinatorial chemistry. Among the different 1,2,4-triazinones described in the literature, only a few are substituted 1,2,4-triazin-6-ones **(1).** An efficient control of different substituent's within the heterocycle is needed to generate the largest molecular diversity.
1,2,4-triazin-6-ones are a very important class of heterocyclic compounds that show a wide variety of applications in both pharmaceutical and agrochemical fields. 1,2,4-Triazin-6-ones have exhibited anticancer[I], antitumour[II], antibacterial and antifungal activities[III], antimicrobial[IV], biological activities of cell line cytotoxicity[V], antimalarials[VI], antivirals[VII] and herbicides[VIII].
 1,2,4-triazine ring system is very significant for its applications as corrosion inhibitors,[IX] additives to photographic development baths uv absorbers for textiles, plastic resins and papers[X] and indicators for volumetric analysis of aminoacids in acetonitriles[XI].
        1,2,4-Triazine-6-ones are less known monohydroxy 1,2,4-triazines. Only three approaches as mentioned in chapter-2 for the synthesis of 1,2,4-triazine-6-ones have been published so far. The first approach was achieved by condensation of hydrazine, considered as 1,2-dinucleophile on a 1,4-dielectrophile[XII]. The second approach is cyclocondensation of an α-aminohydrazide (1,5-dinucleophile) and an orthoester as 1,1-dielectrophile[XIII]. Recently

sanjere et al[XIV] reported the use of N-thioacyclopthalimide as 1,1-electrophile in a reaction with α-amino hydrazides. The third approach[XV] is cyclocondensation of nitrilimines as 1,3-dinucleophiles on α-aminoesters as 1,3-dielectrophiles.

This prompted us to synthesize derivatives of (Z)-N-5-(benzylidene/substituted benzylidene)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine-2-substituted benzamide derivatives.

Results and Discussion

As far as the literature survey is concerned there is no report that describes the synthesis of (Z)-N-5-(benzylidene/substituted benzylidene)-2-N-(benzamide/substituted benzamide)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine derivatives **4(a-l)** from (Z)-N-(3-hydrazinyl-3-oxo-1-(phenyl/substituted phenyl)prop-1-en-2-yl acetamides or benzamides **2(a-l)** and schiff base **3** in ethanol in the presence of L-Tyrosine as catalyst. (Z)-N-5-(benzylidene/substituted benzylidene)-2-N-(benzamide/substituted benzamide)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine derivatives **4(a-l)** have been synthesized by one-pot synthesis through synthetic sequence **(Scheme-1)**. Initially oxazolin-5-ones **1(a-l)** were subjected to ring opening reaction with hydrazine hydrate in ethanol medium at RT for 30 min to produce (Z)-N-(3-hydrazinyl-3-oxo-1-(phenyl/substituted phenyl) prop-1-en-2-yl- acetamides/benzamides **2(a-l)**. Finally, **2(a-l)** were made to react with schiff base **(3)** in the presence of L-tyrosine in ethanol medium for 1 h under reflux condition to yield **4(a-l)** with 85% yield, whose structure has been established on the basis of spectral data. The IR spectrum of the compound **4(a)** confirms the formation of 1, 2, 4-triazine-6-one derivatives by the appearance of absorptions at 3360 cm^{-1} (NH), 2197 cm[-1](Ar) and 1681 cm[-1](C=O). The ^{1}H-NMR spectra showed the signals at δ 2.9 indicating methyl protons, along with trans olefinic proton observed at δ 11 and aromatic protons at δ7.1-8.8.Signals at δ 3.8 and δ 5.2 indicate two –NH protons which were D_2O exchangeable . ^{13}C NMR spectrum showed signals at δ20 (CH_3) , δ115 (CH=C), δ127 (Ar C=C), δ130 (HC=C), δ137 (CH-Ar), δ139 (=CH-Ar), δ140(-C(CH_3)),δ159 (-CO NH),δ164(N-C (Ar)-N). Further the mass spectrum of the compound **4(a)** showed the molecular ion peak at m/z 382 corresponding to molecular weight of the compound **4(a)**. To test its generality the method has been extended to twelve other derivatives and in the all cases the corresponding (Z)-N-5- (benzylidene/ substituted benzylidene)-2-N-(benzamide /substituted benzamide)-3--(methyl/ phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine derivatives **4(a-l)** were isolated in good yields. The synthesis of **4(a-l)** in presence of L-tyrosine produced high yields, purities and less time consuming.

Scheme-1
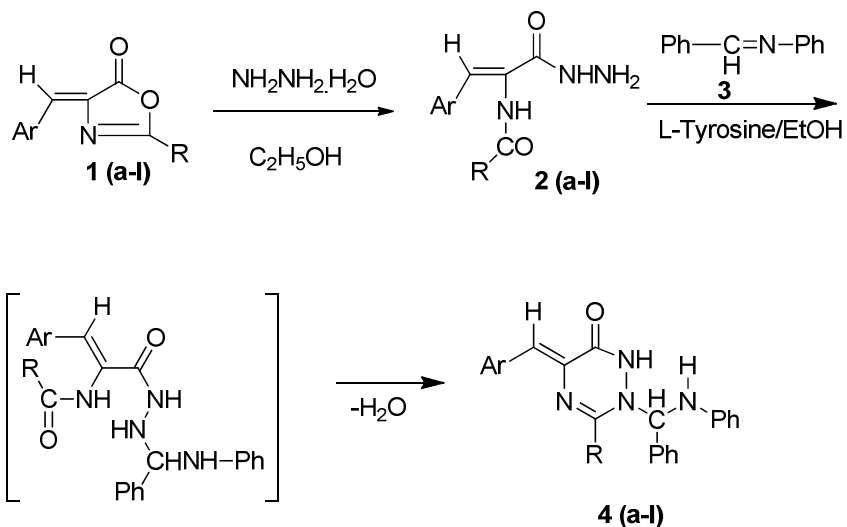
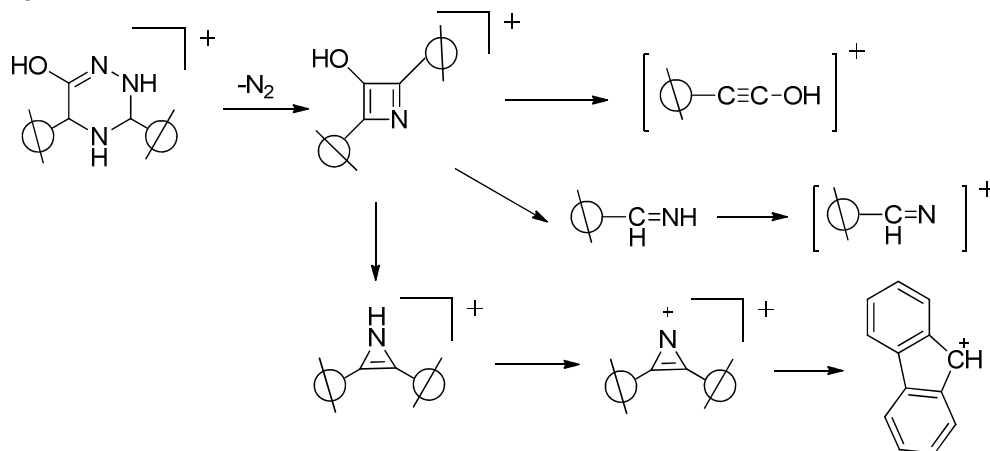Ph = C_6H_5

The fragmentation of all compounds follow the pattern as given in the **scheme-2**, where the fragmentation starts with the loss of nitrogen. Thus the structure of all 1, 2, 4-triazine-6-ones **4(a-l)** were confirmed.

Scheme-2

Mechanism
The mechanism of the formation of (Z)-N-5-(benzylidene/substituted benzylidene) -2-N-(benzamide /substituted benzamide)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine derivatives **4(a-l)** can be assigned as follows. Initially when (Z)N-(3-hydrazinyl-3-oxo-1-(phenyl/substituted phenyl) prop-1-en-2-yl-acetamides **2(a-l)** were treated with the schiff base which is a proton acceptor, accepts proton from NH_2 group of **2(a-l)** to produce an unstable intermediate, which in presence of a base undergoes enolisation followed by cyclocondensation and eliminates water molecule to produce the title compounds (Z)-N-5-(benzylidene/substituted benzylidene)-2-N-(benzamide/ substituted benzamide)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine derivatives **4(a-l) scheme-3**.The natural aminoacid L-Tyrosine acted as a catalyst in the reaction.

Scheme-3

4 (a-l)
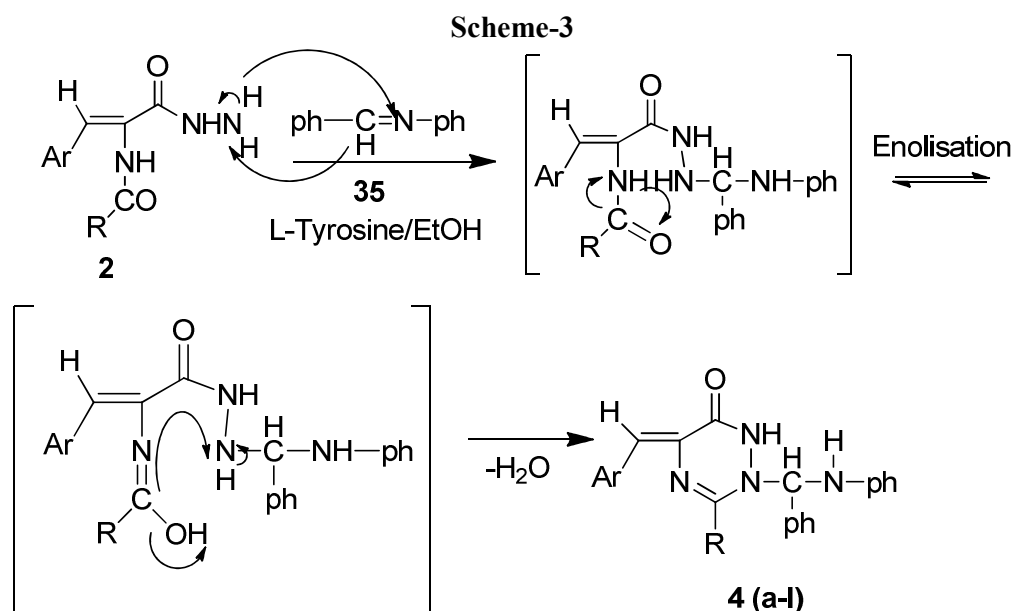
The convertion of **2(a-l)** to produce 1,2,4-triazin-6-ones **4(a-l)** in presence of schiff base and L-tyrosine as a catalyst is confirmed by IR spectra showing the absence of N-H stretching absorptions of the amino group of hydrazine and presence of N-H stretching of amide group which are D_2O exchangeable. The ^{1}HNMR spectra showed the disappearance of signals for NH_2 protons and appearance signals for N-NH,NH-Ph protons which are D_2O exchangeable along with signals for CH-Ph.^{13}C NMR spectra of the compounds **4(a-l)** shows signals for the presence of Ar, C=C, C=O, N-CH₃, C-N and O=C in the structure. Finally the mass spectrum of all the compound confirms the molecular weight of the compound supporting the structure of 1, 2, 4-triazin-6-one derivatives **4(a-l)**.

Experimental:
Melting points are uncorrected and taken in open capillary tubes in sulphuric acid bath. TLC was run on silica gel – G and visualization was done using UV light. IR spectra were recorded using Perkin – Elmer 1000 instrument in KBr pellets. ^{1}H NMR spectra were recorded in CDCl₃ using TMS as internal standard with 400 MHZ spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 value only. Compound **1** was prepared by literature method[XIII].

General procedure for the Preparation of (Z)-N-(3-hydrazinyl-3-oxo-1-(Phenyl/substituted phenyl) prop-1-en-2-yl acetamides 2 (a-l):

0.1 mol of 4-(benzylidene/substituted benzylidene) -2-methyl oxazolin -5-ones **1(a-l)** were dissolved in 50ml of ethanol and treated with 10ml (0.2M) of hydrazine hydrate (99%) in 10ml of ethanol. The mixture was stirred well till the deep yellow colour of the reaction mixture turned light yellow.The compounds (Z)-N-(3-hydrazinyl-3-oxo-1-(phenyl/substituted phenyl) prop-1-en-2-yl-acetamides **2(a-l)** separated were filtered and recrystallized from methanol.

Preparation of (Z)-5-(benzylidene/substituted benzylidene)-2-N-(benzamide/substituted benzamide)-3-(methyl/phenyl)-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives 4 (a-l).
Equimolar quantities of (Z)-N-(3-hydrazinyl-3-oxo-1-(phenyl/substituted phenyl)prop-1-en-2-yl acetamides or benzamides **2(a-l)** (10mM) and N-benzylideneaniline **3** (10mM) were mixed together in 20 ml of ethanol and L-Tyrosine which acts as a catalyst. The mixture was refluxed for 1 h. The path and completion of the reaction was monitored by TLC (solvent system 1:3 EtOAc: Hexane).The reaction mixture was cooled to room temperature and poured into ice-cold water (50 ml).The solid separated out which was collected, washed with water (10 ml) and dried. The product was recrystallised from ethanol to obtain (Z)5-(benzylidene/substituted benzylidene)-2-N-(benzamide/substituted benzamide)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine derivatives **4(a-l)**.

Table-1
Synthesis of **2(a-l)** from **1(a-l)}** and **Hydrazine hydrate.**

Entry	Starting material	Product	Time (min)	Yield*	M.P(^{0}C) [lit. M.P ^{o}C]	M. Wt
1	**1a**	**2a**	60	80	154-156 [156-158][15]	219
2	**1b**	**2b**	60	80	175-179 [176-180][16]	249
3	**1c**	**2c**	65	78	208-210	237
4	**1d**	**2d**	60	80	220-222	264
5	**1e**	**2e**	70	75	212-214	253
6	**1f**	**2f**	60	80	> 220	253
7	**1g**	**2g**	65	81	> 220	281
8	**1h**	**2h**	70	80	192-196	311
9	**1i**	**2i**	65	82	210-212	299
10	**1j**	**2j**	70	82	> 220	326

| 11 | **1k** | **2k** | 60 | 81 | 220-222 | 315 |
| 12 | **1l** | **2l** | 70 | 80 | > 220 | 315 |

* Refers to yields of crude products only.

Table-2

Synthesis of **4(a-l)** from **2(a-l)}** and **3.**

entry	Starting material	Product	Time (min)	Yield*	M.P(^{0}C)	M. Wt
1	**2a**	**4a**	90	85	> 230	382
2	**2b**	**4b**	90	84	> 230	412
3	**2c**	**4c**	95	80	> 230	400
4	**2d**	**4d**	100	85	.>230	427
5	**2e**	**4e**	85	85	180-182	416
6	**2f**	**4f**	100	80	170-172	416
7	**2g**	**4g**	90	85	192-194	478
8	**2h**	**4h**	90	83	> 230	474
9	**2i**	**4i**	90	85	>230	462
10	**2j**	**4j**	85	84	>230	489
11	**2k**	**4k**	90	85	225-227	478
12	**2l**	**4l**	90	85	192-194	478

* Refers to yields of crude products only

(Z)-N-5-(benzylidene/substituted benzylidene)-3-(methyl/phenyl)-6-oxo-1, 2, 5, 6-tetrahydro-1, 2, 4-triazine-2-substituted benzamide derivatives {4(a-l)}:

4a: 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-C**H$_3$**), 3.6 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH**, D$_2$O exchangeable**) 7.2-8.8 (m, 16H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.2 (s, 1H, **-NH, D$_2$O exchangeable)**.

4b: 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-C**H$_3$**), 3.5 (s, 1H, -C**H**), 3.9 (s, 3H, -C**H$_3$**), 5.3 (s, 1H, -N**H**-CH**, D$_2$O exchangeable**) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.1 (s, 1H, **-NH, D$_2$O exchangeable).**

4c: 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-C**H$_3$**), 3.5 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH**, D$_2$O exchangeable**) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.2 (s, 1H, **-NH, D$_2$O exchangeable).**

4d: 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-C**H$_3$**), 3.5 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.1 (s, 1H, **-NH, D$_2$O exchangeable).**

4e: 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-C**H$_3$**), 3.4 (s, 1H, -C**H**), 5.7 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.2 (s, 1H, **-NH, D$_2$O exchangeable).**

4f: 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-C**H$_3$**), 3.5 (s, 1H, -C**H**), 5.5 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.2-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.2 (s, 1H, **-NH, D$_2$O exchangeable).**

4g: IR (KBr) cm^{-1} : 3380 (broad, -NH), 3360 (broad, -NH), 1710 (-C=O); ^{1}H- NMR (400MHz, DMSO-d$_6$/TMS): δ 3.5 (s, 1H, -C**H**), 5.4 (s, 1H, -N**H**-C**H$_3$, D$_2$O exchangeable**) 7.2-8.6 (m, 21H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.1 (s, 1H, **-NH, D$_2$O exchangeable).**

4h: IR (KBr) cm^{-1} : 3313 (broad, -NH), 3302 (broad, -NH), 1700 (-C=O); ^{1}H- NMR (400MHz, DMSO-d$_6$/TMS): δ 3.5 (s, 1H, -C**H**), 3.9 (s, 3H, -C**H$_3$**), 5.7 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.0-8.4 (m, 20H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.0 (s, 1H, **-NH, D$_2$O exchangeable).**

4i: IR (KBr) cm^{-1}: 3342 (broad, -NH), 3330 (broad, -NH), 1722 (-C=O); ^{1}H- NMR (400MHz, DMSO-d$_6$/TMS): δ 3.5 (s, 1H, -C**H**), 5.0 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.2-8.4 (m, 20H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.2 (s, 1H, **-NH, D$_2$O exchangeable).**

4j: IR (KBr) cm^{-1}: 3340 (broad, -NH), 3320 (broad, -NH), 1700 (-C=O); ^{1}H- NMR (400MHz, DMSO-d$_6$/TMS): δ 3.2 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.1-8.4 (m, 20H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.1 (s, 1H, **-NH, D$_2$O exchangeable).**

4k: IR (KBr) cm^{-1} : 3413 (broad, -NH), 3352 (broad, -NH), 1722 (-C=O); ^{1}H- NMR (400MHz, DMSO-d$_6$/TMS): δ 3.3 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.2-8.4 (m, 20H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.1 (s, 1H, **-NH, D$_2$O exchangeable).**

4l: IR (KBr) cm^{-1} : 3402 (broad, -NH), 3352 (broad, -NH) 1702 (-C=O); ^{1}H- NMR (400MHz, DMSO-d$_6$/TMS): δ 3.4 (s, 1H, -C**H**), 5.5 (s, 1H, -N**H**-C**H, D$_2$O exchangeable**) 7.0-8.4 (m, 20H, Ar-**H** and s, 1H, =C**H**-Ar **),** 11.1 (s, 1H, **-NH, D$_2$O exchangeable).**

Conclusion

Green process for the preparation of moderate anti-biological compounds **4(a-l)** has been developed with excellent yields and the evaluation of their anti-microbiological acitivity is encouraging.

Acknowledgement

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