ONE-POT SYNTHESIS OF 1,2,4-TRIAZINE DERIVATIVES OF 2-SUBSTITUTED BENZAMIDES IN [BMIM][OH]

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One-pot three component synthesis of (Z)-N-5-(benzylidene/substituted benzylidene)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine-2-substituted benzamide derivatives were described by one-pot reaction of (Z)-4-(benzylidene/substituted benzylidene)-2-methyl-oxazol-5(4H)-ones with hydrazine hydrate followed by PhCH=NPh in [BMIM][OH] as ionic liquid for 30 min at 80-85 ºC**.** The importance of this method includes shorter reaction time and high yield.

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INTRODUCTION

Nowadays ionic liquids (ILs) are being used widely as reaction medium for organic reactions. ILs have non-volatile nature at room temperature and are used to develop eco-friendly methods for organic synthesis.[2-4] Multi component reaction (MCR) is a one-pot reaction, which contains three to more components in single reaction vessel to give a final desired product containing substantial components of all the reactants.[5] One of great challenges in modern medicinal chemistry is design and discovery of pharmaceutical active molecules.

Nitrogen containing heterocyclic compounds abounds in nature and their application as pharmaceutical active compounds and agrochemicals are becoming increasingly important.[6] 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, antitumor, antibacterial and antifungal activities, antimicrobial, biological activities of cell line cytotoxicity, antimalarials, antivirals and herbicides.[7-12]

Herein, we now wish to report synthesis of **(***Z***)**-N-5-(benzylidene/substituted benzylidene)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine-2-substituted benzamide derivatives by one-pot three component reaction of (*Z*)-4-(benzylidene/substituted benzylidene)-2-methyl-oxazol-5(4H)-ones (**1a-f**) with hydrazine hydrate (**2**) followed by Schiff base (**3**) in the presence of [BMIM][OH], mediated at 80-85 ºC for 30 min with excellent yields.

EXPERIMENTAL

Melting points were measured in open capillary tubes in sulphuric acid bath and are uncorrected. 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 DMSO-d_6 using TMS as internal standard with a 400 MHZ spectrometer. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q^{+1} value only.

Preparation of (*Z*)-5-(benzylidene/substitutedbenzylidene)-2-N-(benzamide/substituted benzamide)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine 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) followed by Schiff base (**3**) (1 mmol) in 5 equiv. of [BMIM][OH]. The reaction mixture was heated at 80-85 ºC for 30-40 min. the reaction was monitored by TLC (solvent system 1:3 EtOAc:hexane). After completion the reaction mixture was cooled to room temperature and poured into ice-cold water (50 mL). A 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-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives (**4a-f**) (Scheme 1).

4a: M.P. >230 ºC. IR (KBr): 3360 (broad, -NH-N), 3313 (broad, -NH), 1680 (-C=O) cm^{-1}. ^{1}H NMR: δ = 2.9 (s, 3H, N-C**H**$_3$), 3.6 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH) 7.2-8.8 (m, 16H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 219.

4b: M.P. >230 ºC. IR (KBr): 3310 (broad, -NH-N), 3244 (broad, -NH) 1659 (-C=O) cm^{-1}. ^{1}H NMR: 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) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.1 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 249.

4c: M.P. >230 ºC. IR (KBr): 3440 (broad, -NH), 3250 (broad, -NH), 1710 (-C=O) cm^{-1}. ^{1}H NMR: δ = 2.8 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 237.

4d: M.P. >230 ºC. IR (KBr): 3480 (broad, -NH), 3250 (broad, -NH), 1720 (-C=O) cm^{-1}. ^{1}H NMR: δ 2.9 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 5.3 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.1 (s, 1H, **-NH**). MS: $M^{+\cdot}$+1 = 264.

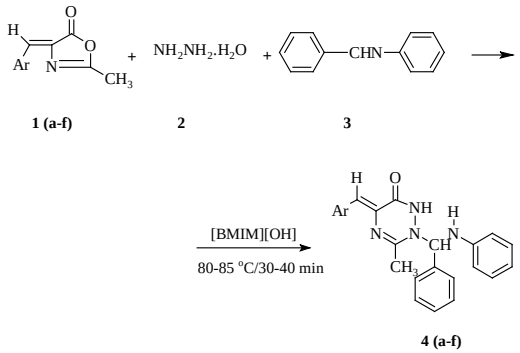
4e: M.P. 180-182 ºC. IR (KBr): 3322 (broad, -NH), 3304 (broad, -NH) 1720 (-C=O) cm^{-1}. ^{1}H- NMR: δ = 2.7 (s, 3H,

N-C**H**$_3$), 3.4 (s, 1H, -C**H**), 5.7 (s, 1H, -N**H**-CH) 7.0-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, -**NH**). MS: $M^{+\cdot}$+1 = 253.

4f: M.P. 170-172 ^{o}C. IR (KBr): 3334 (broad, -NH), 3283 (broad, -NH), 1712 (-C=O) cm^{-1}. ^{1}H- NMR: δ = 2.8 (s, 3H, N-C**H**$_3$), 3.5 (s, 1H, -C**H**), 5.5 (s, 1H, -N**H**-CH) 7.2-8.4 (m, 15H, Ar-**H** and s, 1H, =C**H**-Ar)**,** 11.2 (s, 1H, -**NH**). MS: $M^{+\cdot}$+1 = 253.

RESULTS AND DISCUSSION

Herein, the one-pot three component synthesis of (Z)-N-5-(benzylidene-3-(methyl/phenyl)-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine derivatives (**4**) has been described.



Scheme 1. One pot three-component synthesis of **4a-4f**.

To optimize the reaction conditions, **1a** (1 mmol) was treated with **2** (1 mmol) followed by Schiff base **3** (1 mmol) in the presence of 5 equiv. of different ionic liquid ([BMIM][OH], [BMIM]Br and [BMIM]BF$_6$) at different temperature (Table 1). However, compound **4a** has formed with excellent yield in [BMIM][OH] as ionic liquid mediated at 80-85 ^{o}C for 30 min with excellent yields 90% (Table 1, entry 4).

Table 1. Effect of Ionic liquid and temperature on the reaction.

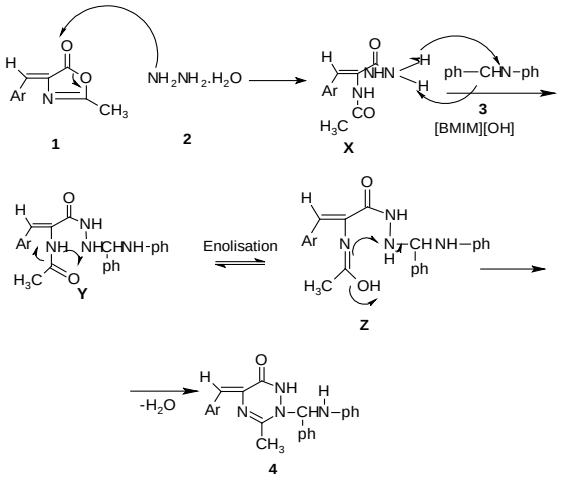
Entry	IL 5eq	Temp., ^{o}C	Time, min	4a, %
1	[BMIM][OH]	70-75	120	85
2	[BMIM] Br	70-75	450	83
3	[BMIM] BF$_6$	70-75	300	82
4	[BMIM][OH]	80-85	30	90
5	[BMIM] Br	80-85	300	85
6	[BMIM] BF$_6$	80-85	240	84
7	[BMIM][OH]	90-95	25	86
8	[BMIM] Br	90-95	120	82
9	[BMIM] BF$_6$	90-95	120	81

The structure of the compound has been confirmed by IR, ^{1}H and ^{13}C-NMR and MS (see in Electronic Supplementary Material). The IR spectrum of the compound **4a** 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(CH3)), δ159(-CONH), δ164(N-C(Ar)-N). Further the mass spectrum of the compound **4a** showed the molecular ion peak at m/z 382 corresponding to molecular weight of the compound **4a**.

Based on the optimised condition and to test its generality the method, extended to six 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 **(4a-4f)** were isolated in excellent yields. The synthesis of **4a-4f** in presence of [BMIM][OH] as ionic liquid at 80-85 ^{o}C for 30-40 min produced high yields, purities and short reaction time.

Mechanism

Though we have not investigated the mechanism, a plausible mechanism is suggested.



Scheme 2. A plausible mechanism of the formation of **4 a**

Initially, the compound (*Z*)-4-(benzylidene-2-methyl-oxazol-5(4H)-ones **1** was reacted with hydrazine hydrate by nucleophilic substitution to form the intermediate (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, accepts proton from NH_2 group of **X** 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-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine **(4a)** (Scheme-2).

CONCLUSION

In summary, we developed the synthesis of (Z)-N-5-(benzylidene/substituted benzylidene)-3-methyl-6-oxo-1,2,5,6-tetrahydro-1,2,4-triazine-2-substituted benzamide derivatives (**4a-4f)** by one-pot reaction in [BMIM][OH] as

ionic. The importance of this method includes shorter reaction time and high yield.

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