ECO-FRIENDLY SYNTHESIS OF 1,2,4-TRIAZINE DERIVATIVES

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Eco-friendly synthesis of (*Z*)-3-alkyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivatives have been developed in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as solvent without catalyst for 20-30 min at 60-65 ^{o}C with good yields.

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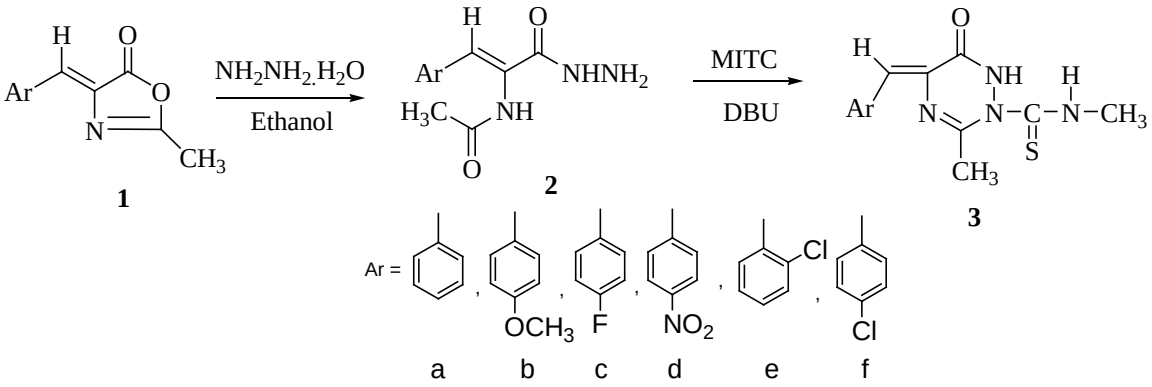
INTRODUCTION

1,2,4-Triazines are well known compounds. A large number of 1,2,4-triazine derivatives including 1,2,4-triazin-6-ones were reported in the literature discussing their special aspects in chemistry and medicine.[1-7] Interest in the biochemical properties of 1,2,4-triazines is high because some 3,5–disubstituted 1,2,4-triazines represent analogues of pyridine nucleobases and a number of antibiotics belong to pyrimido[5,4-*e*]1,2,4-triazine family. 1,2,4-Triazines are reported as both uncondensed and condensed systems. As reported in the literature, there are a large number of 1,2,4-triazines of uncondensed systems having substituent to the carbon atom or nitrogen atom exhibiting profound biological activities. 1,2,4-Triazin-6-ones have exhibited anticancer, antitumor, antibacterial and antifungal, antimicrobial, biological activities of cell lines cytotoxicity, antimalarials, antivirals and herbicides. 1,2,4-Triazine ring system is very significant for its applications as corrosion inhibitors, additives to photographic development baths, UV absorbers for textiles, plastic resins and papers and indicators for volumetric analysis of NH-acids in acetonitriles. The foregoing survey reveals that 1,2,4-triazin-6-ones are characterized by multifarious physiological activities and a scant information regarding synthetic methods is observed. In view of the importance associated with the structural motif, an attempt was made to develop a simple and facile synthesis of substituted 1,2,4-triazin-6-oxo derivatives with high yields, purities and simple processing methods from easily available ecofriendly chemicals. This investigation deals with simple and facile synthesis of (*Z*)-3-alkyl/aryl-5-(benzylidene/substituted benzylidene)-2-N-(carbothioamido)-6-oxo-1,2,5,6-tetrahyd-ro-1(NH)-1,2,4-triazine derivatives possessing different functional groups attached to triazine ring with a sole view to arrive a new heterocyclic system of high antibacterial activity.

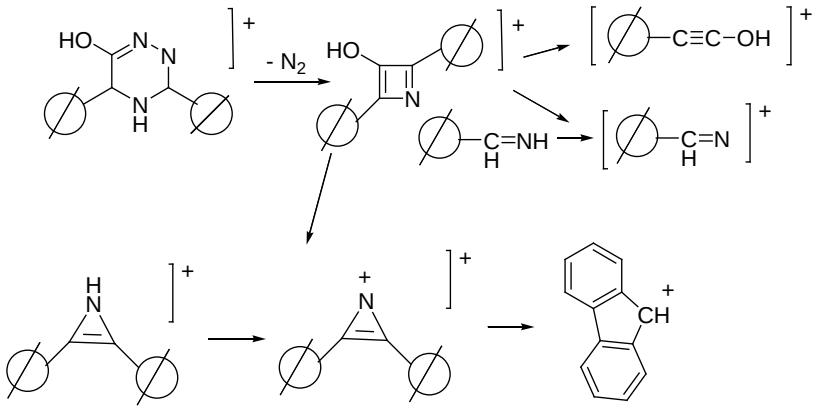
RESULTS AND DISCUSSION

The starting materials, 2-oxazolin-5-one derivatives (**1**) were synthesized from acetylglycine and different aromatic aldehydes in the presence of acetic anhydride and sodium acetate (Erlenmeyer's synthesis). The acetyl glycine is prepared from glycine and acetyl chloride. The corresponding 2-oxazolin-5-ones (**1**) were subjected to ring opening reaction with hydrazine hydrate in ethanol at room temperature to produce (*Z*)-N-[3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamide **(2)**. The title compounds, (*Z*)-3-alkyl/phenyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivatives (**3a-f**) have been synthesized in a one pot reaction by cyclocondensation of (*Z*)-N-[3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamides (**2a-f**) in the presence of methyl isothiocyanate (MITC) in DBU for 20-30 min at 60-65 ^{o}C followed by neutralization with CH_3COOH solution in good yields within a short time (Scheme 1).

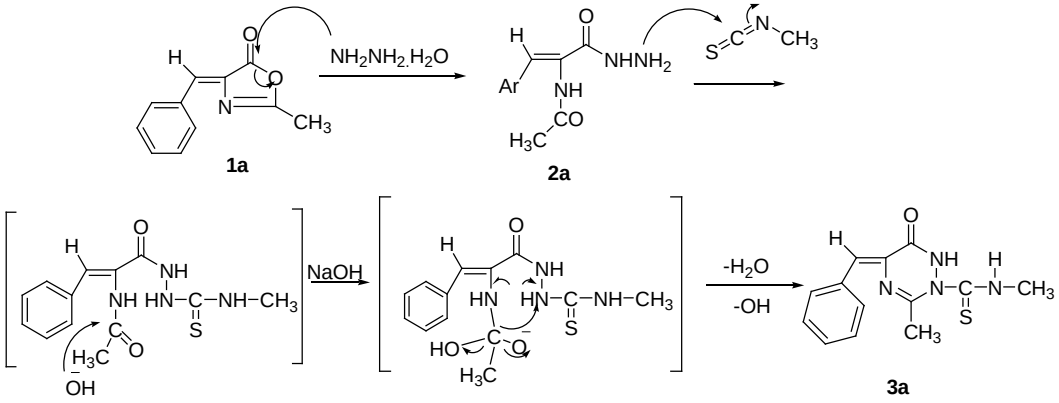
All isolated 1,2,4-triazin-6-one derivatives (**3a-3f)** are stable crystalline solids with high melting points whose structure has been established on the basis of spectral and analytical data. The appearance of NH absorptions at 3471 cm^{-1}, absence of stretching absorption peak for NH_2 at 3248 cm^{-1}, appearance of C=O absorption at 1714 cm^{-1} and C=S absorption at 1270 cm^{-1} in the IR spectrum of the compounds **3a** confirmed cyclocondensation of **2a** to produce 1,2,4-triazine-6-one derivative **3a**. The all 1,2,4-triazin-6-oxo derivatives were synthesized in moderate to good yields. The ^{1}H NMR spectra showed the appearance of signal at δ 2.1 and 2.6 indicate methyl protons of (C-CH_3) and (N-CH_3) groups, two trans olefinic protons were observed at 10.4 along with the signals for aromatic hydrogens at 7.8 and 8.4, signal at 6.8 and 7.4 indicate two –NH group which are D_2O exchangeable. ^{13}C NMR confirms the presence C=S group at δ = 177 and C-N linkage at 164 ppm for the title compound **3a**. The fragmentation of all the compounds follows the pattern as given in Scheme 2. It shows that the fragmentation starts with the loss of nitrogen. The IR, NMR and Mass spectral data of the compounds confirm the proposed structure of all the compounds as per the Scheme 2.



Scheme 1. Synthesis of **3a-3f.**



Scheme 2. Fragmentation pattern of compounds **3**.



Scheme 3. A plausible mechanism for the synthesis of **3a**.

Supposed mechanism

Though we have not done any investigation regarding the mechanism of the reaction, a speculative mechanism of the formation of 1,2,4-triazin-6-oxo-derivatives **3a-3f** has been postulated. Initially, nucleophilic addition of hydrazine hydrate to 4-(benzylidene-2-methyloxazolin-5-one (**1a)** produced (*Z*)-N-[3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamide (**2a).** Treatment of **(2a)** with methyl isothiocyanate (MITC) yielded an unstable intermediate (Z)-N-[N^2–[thiouredo-3-hydrazinyl-3-oxo-1-phenylprop-1-en-2-yl]acetamide, which base hydrolysis produces the title compound (Z)-3-alkyl/phenyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivative **(3a)**. The hydroxyl ion of the base is nucleophilic and attacks the carbonyl carbon. The electron rich oxygen abstracts the protons from acidic amide groups resulting in elimination of water, followed by cyclisation as depicted in the Scheme 3.

The conversation of 4-(benzylidene-2-methyloxazolin-5-ones to the corresponding acetamides **2** is confirmed by spectral data. The IR spectra of **2a** showed the presence of NH-stretching absorptions for NH_2 and NH at 3574 and 3249 cm^{-1} and absence of stretching absorptions of lactone ring at 3444 $cm^{-1.}$ The ^1H NMR data showed doublet signal for NH_2 at δ 4.0, a singlet at δ 7.0 for NHCO, a triplet for NH-NH_2 at δ 8.4, and a singlet for NH-CO at δ 8.4 ppm

which are D_2O exchangeable. The mass spectrum of the compound confirms the molecular weight by appearance of M+ peak at *m/z* 119.

The cyclocondensation of **2** to **3** 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. The ^{1}H NMR spectra showed the disappearance of signals for NH_2 protons and appearance of D_2O exchangeable signals for NH-CH_3 and NH-N at δ 6.8 and 7.2 ppm, respectively. The ^{13}C NMR spectra of the compound **3a** showed signals for the presence of Ar, C=O, C=C, C-N, C=S and O-C at δ 24, 42, 149, 164 and 177 ppm, respectively. Finally, the mass spectrum of the compound **3a** confirms the molecular weight of the compound and the mass fragmentation pattern supports the structure of the title compound. All the 1,2,4-triazin-6-ones were synthesized with good yields and the structure was confirmed by elemental analysis, IR, ^{1}H NMR, ^{13}C NMR and MS data.

Table 1. Synthesis of **2a-2f** from **1a** and hydrazine hydrate.

No.	Starting material	Product obtained	Time, min	Yield, %*	M.P., ^{0}C
1	**1a**	**2a**	60	80	154-156
2	**1b**	**2b**	60	80	175-179
3	**1c**	**2c**	65	78	208-210
4	**1d**	**2d**	60	80	220-222
5	**1e**	**2e**	70	75	212-214
6	**1f**	**2f**	60	80	> 220

***** Refers to yields of crude products only.

Table 2. Synthesis of **3a-3f** from **2a-2f** and MITC in DBU.

No.	Starting material	Product obtained	Time, min	Yield %,*	M.P., ^{0}C
1	**2a**	**3a**	20	84	> 220
2	**2b**	**3b**	25	84	> 220
3	**2c**	**3c**	23	80	> 220
4	**2d**	**3d**	24	84	212-214
5	**2e**	**3e**	25	79	> 220
6	**2f**	**3f**	30	85	191-193

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 and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent using TMS as an internal standard with Bruker AM-400 spectrometer at 400 and 100 MHz respectively. Mass spectra were recorded on Agilent-LCMS instrument under CI conditions and given by Q+1 values only.

Preparation of 2a-2f

Starting compound **(1a-1l,** 10 mM) was added to hydrazine hydrate (15 mM) in EOH and stirred at room temperature for 30 min. The deep yellow colour of the solution changed to light yellow. Solid was separated, washed with H_2O (10 mL), dried and recrystallised from EtOH to afford **2a-2f.**

Preparation of 3a-3f

Equimolar quantities of **2a-2f** (10mM) and MITC (10mM) were mixed together in DBU (20 mL). The mixture was heated at 60-65 ^{o}C for 20-30 min. The completion of the reaction was checked by TLC. Om completion the reaction mixture was cooled to 20-30 ^{o}C 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 **3a-3f**.

(*Z*)-3-alkyl-5-(benzylidene/substituted benzylidene)-2N-(carbothioamido)-6-oxo-1,2,5,6-tetrahydro-1-NH-1,2,4-triazine derivatives (3a-3f)

3a: IR (KBr): 3471 (broad, -NH-N), 3084 (broad, -NH), 1714 (-C=O), 1270 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, CDCl3/TMS) δ = 2.1 (s, 3H, C-CH_3), δ 2.6 (s, 3H, N-CH_3), δ 6.8 (s, 1H, -NH-CH_3) 7.4-8.4 (m, 6H, Ar-H and s, 2H, =CH-Ar), 10.6 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 24.66 (C-CH_3), 42.94 (N-CH_3), 116.79 (Ar-C=C), 120.14-137.69 (Ar), 147.79 (N-C-CH_3), 149.96 (Ar-C=C), 164.01 (C=S), 177. 70 (O=C-N). MS: *m/z* 239 (20 %), 260 (10 %), $M^{+\cdot}1$ = 275.

3b: IR (KBr): 3313 (broad, -NH-N), 3249 (broad, -NH) 1656 (-C=O), 1263 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 2.2 (s, 3H, C-CH_3), δ 2.6 (s, 3H, N-CH_3), δ 3.0 (s, 3H, -CH_3), δ 6.8 (s, 1H, -NH) 7.2-8.3 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.6 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.62 (C-CH_3), 43.93 (N-CH_3), 53.93 (-OCH_3), 114.29 (Ar-C=C), 124.13-133.65 (Ar), 146.73 (N-C-CH_3), 149.94 (Ar-C=C), 163.31 (C=S), 176. 30 (O=C-N). MS: *m/z* 273 (10 %), $M^{+\cdot}1$ = 305.

3c: IR (KBr): 3445 (broad, -NH), 3051 (broad, -NH), 1724 (-C=O), 1280 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 2.4 (s, 3H, C-CH_3), δ 2.8 (s, 3H, N-CH_3), δ 6.6 (s, 1H, -NH) 7.4-8.4 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.4 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.26 (C-CH_3), 42.24 (N-CH_3), 116.59 (Ar-C=C), 123.15-136. 69 (Ar), 144.49 (N-C-CH_3), 148.96 (Ar-C=C), 163.04 (C=S), 174. 60 (O=C-N). MS: *m/z* 239 (20 %), $M^{+\cdot}1$ = 293.

3d: IR (KBr): 3283 (broad, -NH), 3251 (broad, -NH), 1726 (-C=O), 1257 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.8 (s, 3H, C-CH_3), δ 2.3 (s, 3H, N-CH_3), δ 6.6 (s, 1H, -NH) 7.4-8.4 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.2 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.63 (C-CH_3), 41.93 (N-CH_3), 115.39 (Ar-C=C), 121.13-136.62 (Ar), 146.74 (N-C-CH_3), 148.93 (Ar-C=C), 163.04 (C=S), 179.78 (O=C-N). MS: *m/z* 273 (10 %), $M^{+\cdot}1$ = 320

3e: IR (KBr): 3307 (broad, -NH), 3198 (broad, -NH) 1729 (-C=O), 1255 (C=S) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$/TMS) δ = 1.8 (s, 3H, C-CH_3), δ 2.4 (s, 3H, N-CH_3), δ 6.6 (s, 1H, -NH) 7.4-8.4 (m, 5H, Ar-H and s, 2H, =CH-Ar), 10.2 (s, 1H, -NH). ^{13}C NMR ($CDCl_3$) δ = 23.26 (C-CH_3), 41.93 (N-CH_3), 113.29 (Ar-C=C), 121.24-135.66 (Ar), 146.76 (N-C-CH_3), 148.94 (Ar-C=C), 163.05 (C=S), 174. 60 (O=C-N). MS: $M^{+\cdot}1$ = 309

3f: IR (KBr): 3300 (broad, -NH), 3280 (broad, -NH), 1710 (-C=O), 1280 (C=S) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$/TMS) δ = 2.4 (s, 3H, C-CH_3), δ 2.6 (s, 3H, N-CH_3), δ 6.8 (s, 1H, -NH) 7.4-8.4 (m, 6H, Ar-H and s, 2H, =CH-Ar), 10.6 (s, 1H, -NH). ^{13}C NMR (CDCl3) δ = 23.56 (C-CH_3), 41.54 (N-CH_3), 114.69 (Ar-C=C), 122.24-137.65 (Ar), 146.69 (N-C-CH_3), 148.76 (Ar-C=C), 163.21 (C=S), 176. 40 (O=C-N). MS: $M^{+\cdot}1$ = 309.

CONCLUSION

Eco-friendly synthesis of compounds **3a-3f** has been developed with excellent yields, short time and easy work up process in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as solvent without catalyst for 20-30 min at 60-65 ºC.

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