Facile one-pot green chemical synthesis of 1,3,5-tri-(quinazolinyl/benzothiazolyl/benzimidazolyl)-s-triazines in aqueous medium under microwaves[†]

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Reasonable pure 1,3,5-tri-(quinazolinyl/benzothiazolyl/benzimidazolyl)-s-triazines were synthesized in quantitative yield (94–96%) in 3–6 min in aqueous medium under microwaves, by reaction of various heterocyclic amines with aqueous formaldehyde. Results were also compared with conventional synthesis involving prolonged refluxing in dry toluene giving lower yields of required product.

A number of triazine derivatives containing pharmacophoric groups have been reported to possess antiviral activity¹ against *Encephalomyocarditis virus* (EMCV) and *Japanese encephalitis virus* (JEV) both *in vivo* and *in vitro*. Amongst various triazine derivatives trisubstituted 1,3,5-triazines have been the focus of attention for biologist and chemist for long time due to wide variety of biological activities associated with them such as antibacterial², antimicrobial³, antitumor⁴, etc. and most of references are patent showing anti-HIV⁵, herbicidal⁶ and fungicidal⁷ activities.

The compounds incorporating quinazoline nucleus are endowed with various pharmaceutical applications e.g. they are used in treatment of leprosy and mental disorder and also exhibit a wide range of activities⁸. *Methaqualone*, *prazosin* and *quinethazone* are drugs that possess antihypertensive, antidiuretic and anticoagulant activities⁹. Significance is that these compounds possess the potent pharmacodynamic nucleus quinazoline.

Benzothiazole and benzimidazole derivatives have also attracted considerable attention due to their potent diversified bioactivities such as antihelmintic¹⁰, analgesic, anti-inflammatory¹¹, fungicidal¹², etc.

In view of the immense biological activities of these heterocycles, it was thought of interest to construct a system which may combine these heterocyclic biolabile rings in a single molecular framework to see the additive effect towards medicinal power. Therefore, it was planned to synthesize for the first time 1,3,5-tri-(quinazolinyl/benzothiazolyl/benzimidazolyl)-1,3,5-triazines by reacting various heterocyclic amines with formaldehyde.

Conventional syntheses of 1,3,5-trisubstituted-1,3,5-tri-

azines suffer from many disadvantages like multistep procedure^{13,14}, long reaction time, low yield, use of strong acids¹³/base¹⁵/dehydrating agents¹⁶, use of high boiling solvents¹⁷, the use of Dean-Stark apparatus for azeotropic removal of water^{13–15}, etc.

The use of microwaves (MW) for assisting different organic reactions has become very popular in the last few years¹⁸ and recently the use of supported reagents coupled with microwave irradiation has gained special attention due to its ecofriendliness and safety¹⁹. But dry media technique requires an appreciable amount of solvent for adsorption of reactants and elution of products.

Recently, the use of aqueous media for organic reaction is under extensive investigation for synthesis and also to exploit hydrophobic effect. Water has high dielectric constant with a permanent dipole moment, which allows the coupling between the oscillating electric field and the molecular tumbling to occur with high efficient heating. Hence, at elevated temperature it acts as a pseudo-organic solvent and in its use, isolation of products is also facilitated due to decreased solubility of organic material upon post reaction cooling.

In continuation of our earlier interest on the economic and environmentally benign synthesis of biodynamic heterocycles²⁰ and particular interest on use of aqueous medium for heterocyclic synthesis²¹, we report herein for the first time the economic, ecofriendly, facile one-pot synthesis of 1,3,5-triheterocyclyl hexahydro-1,3,5-triazines by the condensation of heterocyclic amines (quinazoline, benzothiazole, benzimidazole) **1a-e** with formaldehyde **2** under microwave irradiation in aqueous medium (Scheme 1).

[†]Dedicated to Professor S. M. Mukherji.

Scheme 1

Table 1. Physical data of synthesized compounds **3a-f**

Entry	Product no.	Amines (1a-e)	Temp. (°C)	Time (min)	Yield ^a (%)	M.P. (°C)
1	3a		101	6.0	96	108
2	3b		101	4.0	95	89
3	3c		101	3.0	94	105
4	3d		102	4.5	94	125
5	3e		101	6.0	95	142

^aIsolated yield of purified compounds that exhibited physical and spectral properties in accordance with the assigned structure.

All compounds gave satisfactory elemental analyses (C, H and N) within $\pm 0.25\%$ of theoretical value.

Finally, in order to check the possible intervention of specific (non-thermal) MW effects, the results obtained under MW were compared to conventional heating. The reaction, in the case of compounds **3b** has been carried out using pre-heated oil bath, under the same conditions as under MW (time, temperature, vessel) (Table 2).

In these cases it has been found that reactions proceed with considerable lower yields under similar thermal conditions demonstrating that the effect of MW is evidently not purely thermal²². These specific non-thermal effects, remain noticeable even by extended reaction times up to 5 h, are consistent with the consideration of mechanisms²³ and with the assumption that MW effects are increased when the polarity of a system is enhanced. The first step consists of the nucleophilic addition of heterocyclic amines (**1b**) on the C=O of the formaldehyde (**2**) to give dipolar transition state. One can expect an important specific microwave

Table 2. Comparative results obtained for the synthesis of **3b** by reacting heterocyclic amine (**1b**) with formaldehyde

Entry	Medium	Mode of reaction Δ /MW (Power W)	Temp. ^a (°C)	Time (min)	Yield ^b (%)
3b	Aqueous medium	MW (640)	101	4	94
	Aqueous medium	Δ	101	4	No reaction
	Aqueous medium	Δ	101	300	58*

^aFinal temperature is measured at the end of microwave irradiation.

^bIsolated yield of purified compounds.

*Yields obtained after extension of reaction time up to 300 min at similar temperature (under MWs). TLC indicated complete conversion of reactants but formation of mixture of product causing decrease in yield of required compounds.

effect due to the evolution of polarity of the system during the reaction progress, as the transition state (T.S.) is more polar than the ground state (G.S.) in this reaction. The most important stabilization of the transition state is, therefore, responsible for an enhancement of reactivity by a decrease of the activation energy (Scheme 2).

Scheme 2

The first step is followed by trimersation of aldimines under similar conditions to yield 1,3,5-trisubstituted hexahydro-1,3,5-triazines in one step efficiently, which also involves the formation of dipolar transition state.

Results and discussion

IR spectra of the products (**3a-e**) displayed characteristic absorptions in the region 2820–2980 (aliphatic CH), 1605–1620 (C=N). The ¹H NMR spectra of all products (**3a-e**) showed characteristic methylene proton signal of s-triazine at δ 4.26–4.35 (6H, s, CH₂) along with signals for aromatic protons at 6.93–7.42 (m, Ar-H). Disappearance of C=O (formaldehyde) at 1740 cm⁻¹ and primary amino group absorption at 3450–3330 cm⁻¹ further confirmed the structure of **3**. ¹³C NMR of **3a, b, e** showed a sharp signal

Table 3. Spectral data of synthesized compounds **3a-e**

Compd.	IR (cm ⁻¹)	¹ H NMR (δ , ppm)	Ar-H	¹³ C NMR (δ , ppm)
3a	2970–2830 (ali. CH), 1695 (C=O), 1620 (C=N), 1180–1150 (C–N)	3.96 (6H, s, CH ₂ Ph), 4.26 (6H, s, CH ₂)	6.95–7.32 (22H, m)	38.2 (C–CH ₂ –Ph), 78.3 (N–CH ₂ –N), 120.8–138.2 (aromatic carbons), 145.2 (C–N), 164.02 (C=N), 169 (C=O)
3b	2980–2840 (ali. CH), 1610 (C=N), 1180–1150 (C–N)	2.15 (3H, s, CH ₃), 4.32 (6H, s, CH ₂)	6.93–7.95 (9H, m)	20.5 (CH ₃), 78.8 (N–CH ₂ –N), 119.2–135.2 (aromatic carbons), 146.5 (C–N), 164.08 (C=N), 174.2 (C–S)
3c	2970–2850 (ali. CH), 1615 (C=N), 1180–1160 (C–N), 1120–1090 (C–O–C)	3.78 (3H, s, OCH ₃), 4.28 (6H, s, CH ₂)	6.98–7.25 (9H, m)	–
3d	2975–2860 (ali. CH), 1620 (C=N), 1170–1150 (C–N), 1110–1080 (C–O–C)	1.34 (2H, q, CH ₂), 3.93 (3H, t, CH ₃), 4.34 (6H, s, CH ₂)	6.95–7.42 (9H, m)	–
3e	3320–3280 (NH), 2980–2830 (ali. CH), 1610 (C=N), 1180–1150 (C–N)	4.35 (6H, s, CH ₂)	6.90–7.35 (12H, m), 8.21 (1H, br, NH, D ₂ O exchange)	79.2 (N–CH ₂ –N), 121–137.2 (aromatic carbons), 146.5 (C–N), 164.07 (C=N)

at 78.3–79.2 (N–CH₂–N), 119.2–138.2 (aromatic carbons), 145.2–146.5 (C=N), and 164.02–164.08 (C–N) (Table 3). In the mass spectra of **3b** and **3e**, molecular ion peaks were observed at *m/z* 528 (5%) and 435 (9%) corresponding to their molecular formula C₂₇H₂₄N₆S₃ and C₂₇H₂₄N₉ respectively.

Conclusion

In conclusion, we have developed a new economical, safe and environmentally benign solvent free synthesis of 1,3,5-trisubstituted hexahydro-1,3,5-triazines under microwave irradiation using water as aqueous medium. The operational simplicity, avoiding the use of solvent and solid support and high yield in significantly very short reaction times can prove this procedure as a useful and attractive alternative to the currently available methods.

Experimental

Melting points were determined in open glass capillaries and were uncorrected. Thin layer chromatography on silica gel 'G' coated glass plates using benzene, ethanol (8 : 2) as eluent was used for monitoring progress of the reactions. IR spectra (KBr) were recorded on a Magna FT IR-550 spectrophotometer, ¹H and ¹³C NMR spectra [CDCl₃ + (CD₃)₂SO] were taken on a Jeol FX 90Q spectrometer at 89.55 and 22.49 MHz respectively, using TMS as an internal standard for PMR and ¹³C NMR and mass spectra were

recorded on Jeol D-300 spectrometer at an ionisation potential of 70 eV. Microwave assisted reactions were carried out in a household MW oven (Panasonic-NN-781JF) equipped with inverter technology (generating fixed frequency through out the required time) for realistic control of the microwaves operating at 1000 W generating 2450 MHz frequency. 2-Aminobenzimidazole was purchased from Aldrich Chemical Co. and used as received. Formaldehyde was of concentration 37–39% (w/w).

2-Phenylmethyl-3-amino-quinazolin-4(3H)-one²⁴ (**1a**) / 5-methyl/methoxy/ethoxy-2-aminobenzthiazoles²⁵ (**1b-d**) were synthesized according to literature reported methods.

1,3,5-Tri-(quinazolinyl)-hexahydro-1,3,5-triazine (**3a**) was prepared by two different ways :

2-Phenylmethyl-3-amino-quinazolin-4(3H)-one (**1a**) (2.51 g, 10 mmol) was stirred and heated (oil bath temperature slowly raised from 90 to 110°) with para formaldehyde (0.32 g, 10 mmol) in anhydrous toluene (30 mL) with azeotropic removal of water, using Dean and Stark apparatus for 10 h. The remaining toluene was removed under reduced pressure and solid residue was extracted with ether, the ether layer dried (Na₂SO₄) and evaporated under suction to give crude product which was further recrystallized from hexane to give **3a** (m.p. 108°; yield 45%).

Microwave mediated synthesis :

A mixture of **1a** (2.51 g, 10 mmol) and aqueous formaldehyde (4 ml, 12 mmol) in open borosil beaker (100 ml) was irradiated inside a microwave oven at 700 watts till the completion of reaction (TLC) to give an oil which was solidified on standing, which was washed with water and found to be pure by (TLC), with no need of further purification process (m.p. 108°; yield 96%).

Likewise, following the same procedure compounds **3b-f** were prepared under microwaves and their structural characterization was done on the basis of IR, ¹H NMR, ¹³C NMR, mass spectral and elemental analyses (Table 3).

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