Synthesis of triazolo[4,3-*b*][1,2,4,5]tetrazines and triazolo[3,4-*b*][1,3,4]thiadiazines using chitosan as ecofriendly catalyst under microwave irradiation

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Abstract

A novel approach to the synthesis of triazolo[4,3-*b*][1,2,4,5]tetrazines **5a-f** and triazolo[3,4-*b*][1,3,4]thiadiazines **10a-g** has been developed *via* reactions of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione **1** with hydrazonoyl halides **2a-f** and **8a-g**, respectively using chitosan as a basic catalyst under microwave irradiation. The structure of the products was established based on elemental and spectral analyses. Further evidence for the assigned structure of the products is based on alternative synthesis. Also the mechanism of the studied reactions was discussed.

Keywords: Chitosan, microwave irradiation, hydrazonoyl halides, triazolotetrazines; triazolothiadiazines

Introduction

Chitosan, the naturally occurring polysaccharides, can be used as heterogeneous phase transfer catalyst in heterocyclic synthesis,[1] as well as transition metal support for the preparation of heterogeneous catalysts.[2] Chitosan is a copolymer containing both glucoseamine units and acetylglucoseamine units. The presence of amino groups is responsible for the basic nature of chitosan (Figure 1).

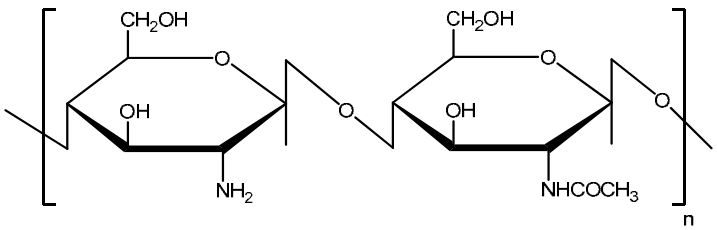


Figure 1

Microwave irradiation, as energy source, can enhance the reaction rates and improve the regioselectivity.[3-10] The utility of microwave irradiation in reactions of hydrazonoyl halides has received limited study.[11,12]

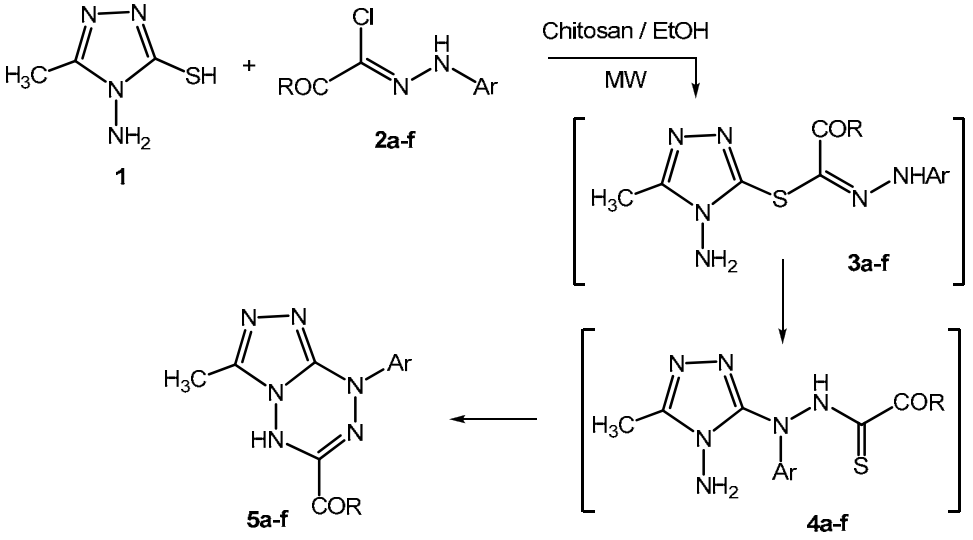
Fused tetrazines have received much attention owing to the reported antimicrobial activity.[13]

Moreover, several triazolo[3,4-*b*][1,3,4]thiadiazines have attracted a great deal of interest due to their biological activities such as antimicrobial,[14-16] anti-inflammatory,[14] and potent chemotype[17] for selective inhibition of PDE4. With these facts in mind, we decided to investigate the reactivity of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione as a valuable synthon towards hydrazonoyl halides using chitosan as ecofriendly catalyst under microwave irradiation.

Results and Discussion

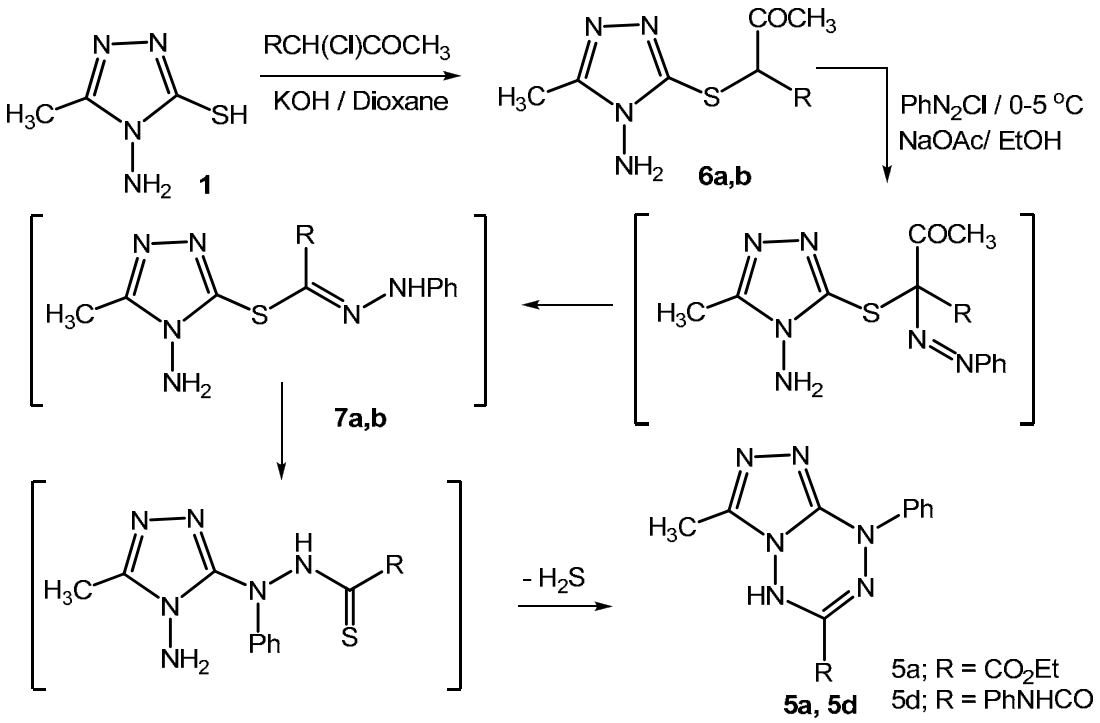
The conventional routes for reactions of hydrazonoyl halides with heterocyclic thiones were used triethylamine[18-20] or sodium ethoxide[21] as basic catalysts to generate, *in situ*, nitrilimine from the corresponding hydrazonoyl halides. In this context, we used chitosan as novel ecofriendly basic catalyst in these reactions under microwave irradiation to afford a new environmentally benign route for synthesis of fused heterocyclic compounds.

We began our studies with the reactions of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione **1** with ethyl arylhydrazonochloroacetate **2a-c** and *N*-aryl 2-oxo-2-phenylaminoethanehydrazonoyl chloride **2d-f** in absolute ethanol in the presence of chitosan under microwave irradiation for 10 minutes as shown in Scheme 1.



Scheme 1

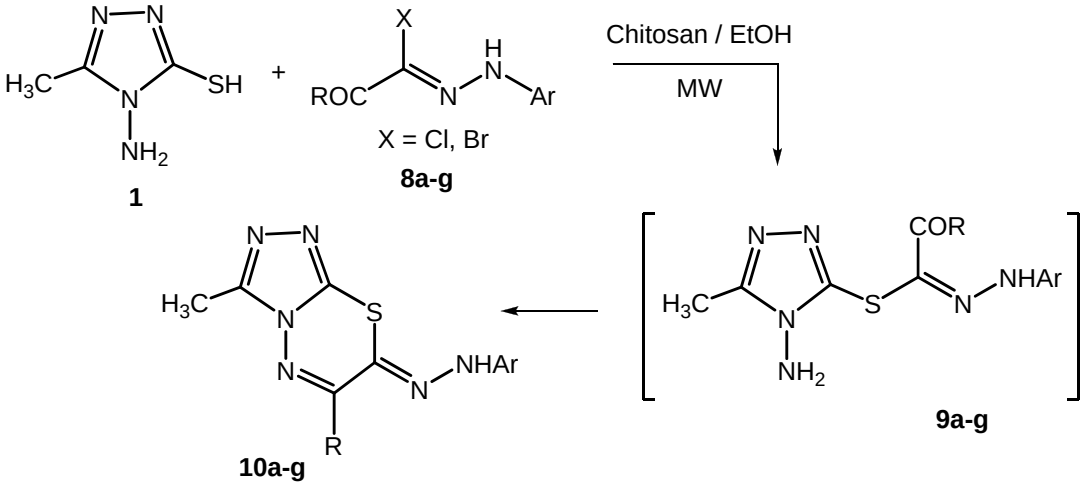
In all cases, we found that the respective triazolo[4,3-b][1,2,4,5]tetrazines **5a-f** were formed *via* *S*-alkylation[22] followed by Smiles rearrangement[23] and finally cyclization of the intermediates **4a-f** *via* elimination of hydrogen sulfide (cf. Scheme 1). The structure of the isolated products was unambiguously established by spectral data (MS, IR, ^{1}H NMR) and its elemental analyses (see experimental). For example, the IR spectrum of **5a** showed two characteristic bands at υ 3222 and 1740 cm^{-1} assignable for NH and COOEt groups respectively and the ^{1}H NMR spectra showed, in each case, one characteristic singlet signal at δ 9.24 ppm[24] assignable to the tetrazine NH. Also ^{1}H NMR spectra revealed the absence of NH_2 signal which appear at δ 4.8 ppm[25] of compound **1**. The assignment for the structure products and reaction mechanism can be manifested by alternate synthesis. Thus, treatment of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione **1** with each of ethyl 2-chloro-3-oxobutanoate and *N*-phenyl 2-chloro-3-oxobutanamide in dioxane in the presence of potassium hydroxide at room temperature yielded the corresponding *S*-alkylated products **6a,b**. Coupling of **6a,b** with benzenediazonium chloride in ethanol in the presence of sodium acetate at low temperature (0-5 ^{o}C) yielded the corresponding thiohydrazonate esters **7a,b** *via* Japp-Klingemann cleavage of the acetyl group.[26] The latter underwent *in situ* Smiles rearrangement[23] followed by elimination of hydrogen sulfide to give products **5a, 5d** (Scheme 2) which are identical in all respect (mp, mixed mp, IR), with that obtained from reactions of **1** with each of hydrazonoyl halides **2a** and **2d** (Scheme 1).



Scheme 2

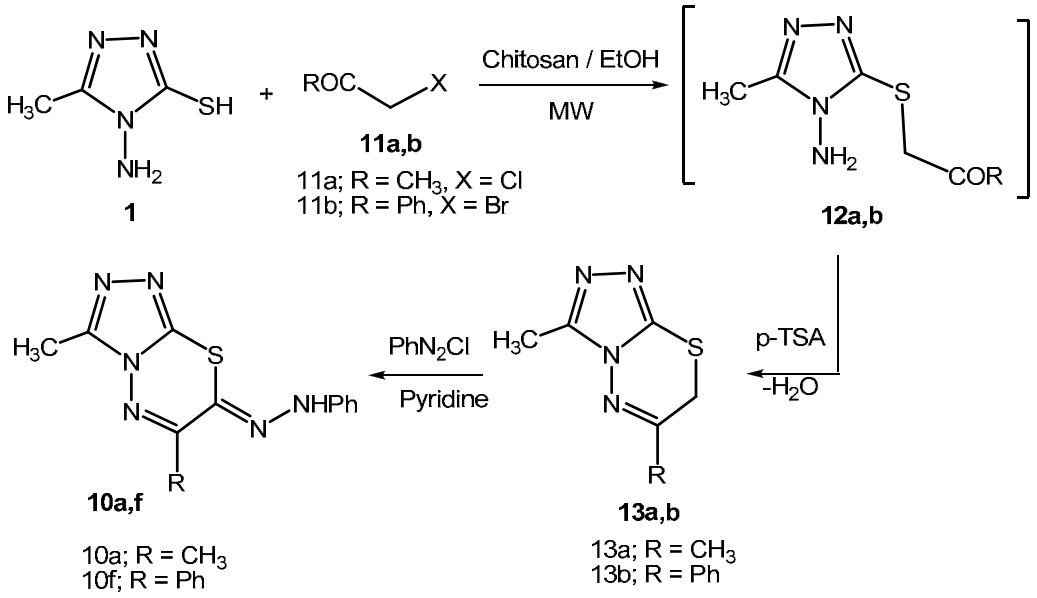
Our interest was extended to study the reactivity of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione **1** towards other hydrazonoyl halides such as *N*-aryl 2-oxopropanehydrazonoyl chlorides **8a-e** and *N*-aryl 2-oxo-2-phenylethanehydrazonoyl bromides **8f,g**. Thus, treatment of **1** with each of **8a-g** in ethanolic solution containing chitosan under microwave irradiation for 10 minutes afforded isolable products which are completely different from compounds **5a-g**. These compounds were assigned as 7-arylhydrazono-3-methyl-6-substituted[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines structure **10a-g.** The isolable products were formed *via in situ* dehydrative cyclization of the initially formed thiohydrazonates **9a-g** (Scheme 3). As previously, the structure of isolable products was rigorously characterized by spectral (IR, ^{1}H NMR, MS) and elemental analyses data (see experimental). IR spectra in each case revealed one band at υ 3178-3166 cm^{-1} assigned to NH group and revealed the absence of the absorption band corresponding to CO group. ^{1}H NMR showed characteristic singlet signal near δ = 10.4 ppm assignable for NH of hydrazone tautomer[27] beside the signals assigned for aliphatic and aromatic protons.

The structure of the product **10** was further proved *via* an alternative method (Scheme 4). Thus, reaction of compound **1** with each of chloroacetone **11a** and phenacyl bromide **11b** in ethanol in the presence of chitosan under microwave irradiation led to formation of the respective *S*-alkylated products **12a,b**. The latter, nonisolable intermediates, undergo dehydrative cyclization on treatment with *p*-toluenesulphonic acid to give compounds **13a,b**. The structure of compounds **13a,b** was substantiated by spectral (MS, IR, and ^{1}H NMR) and elemental analyses data (see experimental). Coupling of compounds **13a,b** with benzenediazonium chloride at 0-5 °C in pyridine led to formation of products which are identical in all respects (mp, mixed mp and IR) with compounds **10a, 10f**.



10a; R = CH_3, Ar = C_6H_5 10b; R = CH_3, Ar = 4-ClC_6H_4
10c; R = CH_3, Ar = 4-BrC_6H_4 10d; R = CH_3, Ar = 4-$CH_3OC_6H_4$
10e; R = CH_3, Ar = 4-$NO_2C_6H_4$ 10f; R = C_6H_5, Ar = C_6H_5
10g; R = C_6H_5, Ar = 4-ClC_6H_4

Scheme 3



Scheme 4

Conclusions

The outstanding reactivity of aminomercaptotriazole **1** towards hydrazonoyl halides afforded either triazolotetrazines or triazolothiadiazines depending on the type of hydrazonoyl halides. Expanding the scope for utilizing chitosan as basic catalyst was investigated in these reactions.

Experimental Section

General Procedures. All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer and the chemical shifts were related to that of the solvent deuterated chloroform $CDCl_3$. The mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers, the ionizing voltage was 70 eV. Elemental analyses were carried out by the Microanalytical Center of Cairo University, Giza, Egypt. Microwave experiments were carried out using CEM Discover Labmate microwave apparatus (300 W with Chem. Driver Software). 4-Amino-5-methyl-1,2,4-triazole-3(2*H*)-thione **1**,[25] hydrazonoyl halides **2a-f** and **8a-g** were prepared following literature methods.[28-33]

Synthesis of [1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazines 5a-f under microwave irradiation

To a solution of **1** (0.13 g, 1 mmol) and the appropriate hydrazonoyl halides **2a-f** (1 mmol of each) in absolute ethanol (10 ml) was added chitosan (0.1 g) at room temperature. The reaction mixture was irradiated under constant pressure (11.2 Bar, 80 ^{o}C) for 10 min. at a power of 300 W. The hot solution was filtered to remove chitosan. After cooling, dil. HCl was added till pH became acidic, and the solid product was collected and recrystallized from ethanol to give products **5a-f**. The physical constants together with the spectral data of **5a-f** are listed below.

Ethyl 6-methyl-1-phenyl-1,4-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine-3-carboxylate (5a). 0.24 g (85% yield), mp 148-150 ^{o}C; IR (KBr) υ = 3222 (NH), 1740 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.77 (t, 3H, *J* = 7 *Hz*, CH_3), 1.96 (s, 3H, CH_3), 4.25 (q, 2H, *J* = 7 *Hz*, CH_2), 7.21-7.37 (m, 5H, Ar-H), 9.24 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ= 9.6, 14.7, 58.4, 116.7, 120.6, 123.2, 124.2, 128.4, 138.1, 138.4, 158.9 ppm; MS, *m/z* (%) 286 (M^+, 100), 213 (50), 77 (80). *Anal*. Calcd. for $C_{13}H_{14}N_6O_2$ (286.12): C, 54.54; H, 4.93; N, 29.35. Found: C, 54.31; H, 4.84; N, 29.42%.

Ethyl 6-methyl-1-(4-chlorophenyl)-1,4-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine-3-carboxylate (5b). 0.28 g (88% yield), mp 164-166 ^{o}C; IR (KBr) υ = 3214 (NH), 1737 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ= 1.78 (t, 3H, *J* = 7 *Hz*, CH_3), 1.92 (s, 3H, CH_3), 4.35 (q, 2H, *J* = 7 *Hz*, CH_2), 7.31-7.57 (m, 4H, Ar-H), 9.44 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ= 9.7, 14.8, 58.8, 116.8, 120.9, 123.7, 125.2, 128.8, 138.7, 139.2, 160.4 ppm; MS, *m/z* (%) 322 (M^++2, 30), 320 (M^+, 100), 248 (10), 246 (35), 111 (40). *Anal*. Calcd. for $C_{13}H_{13}ClN_6O_2$ (320.08): C, 48.68; H, 4.09; N, 26.20. Found: C, 48.61; H, 4.14; N, 26.43%.

Ethyl 6-methyl-1-(4-methylphenyl)-1,4-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine-3-carboxylate (5c). 0.24 g (80% yield), mp 156-158 ^{o}C; IR (KBr) υ = 3213 (NH), 1738 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.79 (t, 3H, *J* = 7 *Hz*, CH_3), 1.95 (s, 3H, CH_3), 2.52 (s, 3H, Ar-CH_3), 4.21 (q, 2H, *J* = 7 *Hz*, CH_2), 7.21-7.39 (m, 4H, Ar-H), 9.14 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 14.7, 15.3, 58.2, 116.2, 119.8, 122.7, 124.1, 127.8, 137.4, 138.1, 158.2 ppm; MS, *m/z* (%) 300 (M^+, 100), 227 (35), 91 (50). *Anal*. Calcd. for $C_{14}H_{16}N_6O_2$ (300.13): C, 55.99; H, 5.37; N, 27.98. Found: C, 55.81; H, 5.44; N, 27.78%.

***N*,1-Diphenyl- 6-methyl-1,4-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4,5]tetrazine-3-carboxamide (5d).** 0.29 g (88% yield), mp 250-252 ^{o}C; IR (KBr) υ = 3383, 3300 (2NH), 1667 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.95 (s, 3H, CH_3), 7.25-7.81 (m, 10H, Ar-H), 9.24 (s, 1H, NH), 10.87 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.3, 114.6, 115.1, 120.3, 122.8, 123.9, 124.4, 128.4, 129.1, 137.4, 142.1, 158.4, 162.5 ppm; MS, *m/z* (%) 333 (M^+, 100), 213 (40), 77 (65). *Anal*. Calcd. for $C_{17}H_{15}N_7O$ (333.13): C, 61.25; H, 4.54; N, 29.41. Found: C, 61.31; H, 4.64; N, 29.49%.

***N*-Phenyl-1-(4-chlorophenyl)-6-methyl-1,4-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4,5] tetrazine-3-carboxamide (5e).** 0.29 g (80% yield), mp 274-276 ^{o}C; IR (KBr) υ = 3377, 3288 (2NH), 1668 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.99 (s, 3H, CH_3), 7.25-7.81 (m, 9H, Ar-H), 9.31 (s, 1H, NH), 10.89 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.6, 115.3, 115.8, 121.2, 123.5, 124.5, 125.9, 128.9, 129.8, 138.1, 143.4, 159.5, 163.5 ppm; MS, *m/z* (%) 369 (M^++2, 30), 367

(M^+, 100), 249 (20), 247 (45), 111 (80). *Anal*. Calcd. for $C_{17}H_{14}ClN_7O$ (367.09): C, 55.52; H, 3.84; N, 26.66. Found: C, 55.32; H, 4.04; N, 26.49%.

***N*-Phenyl-1-(4-methylphenyl)-6-methyl-1,4-dihydro[1,2,4]triazolo[4,3-*b*][1,2,4,5] tetrazine-3-carboxamide (5f).** 0.27 g (78% yield), mp 270-272 °C; IR (KBr) υ = 3380, 3289 (2NH), 1662 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.93 (s, 3H, CH_3), 2.22 (s, 3H, Ar-CH_3) 7.29-7.78 (m, 9H, Ar-H), 9.24 (s, 1H, NH), 10.87 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.3, 14.3, 114.2, 115.1, 120.1, 122.4, 123.5, 124.1, 128.1, 128.6, 137.2, 142.1, 158.1, 162.2 ppm; MS, *m/z* (%) 347 (M^+, 100), 227 (30), 91 (55). *Anal*. Calcd. for $C_{18}H_{17}N_7O$ (347.15): C, 62.24; H, 4.93; N, 28.23. Found: C, 62.31; H, 4.84; N, 28.49%.

Reactions of 4-amino-5-methyl-1,2,4-triazole-3(2*H*)-thione (1) with α-halo compounds

To a solution of **1** (0.13 g, 1 mmol) in ethanol was added an aqueous solution of potassium hydroxide (1 mL, 75%), and the mixture was warmed for 10 min at 80 °C and cooled. To the resulting clear solution was added ethyl 2-chloro-3-oxobutanoate or *N*1-phenyl-2-chloro-3-oxobutanamide (1 mmol) dropwise while stirring the reaction mixture. After complete addition, the reaction mixture was stirred for a further 4 h at room temperature. The solid that precipitated was filtered off, washed with water, dried and finally crystallized from ethanol to give the respective products **6a,b**.

Ethyl 2-[(4-amino-5-methyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-3-oxobutanoate (6a). 0.19 g, (75% yield), mp 138-140 °C; IR (KBr) υ = 3406, 3248 (NH_2), 1725, 1707 (2CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.37 (t, 3H, *J* = 7 *Hz*, CH_3), 1.97 (s, 3H, CH_3), 2.46 (s, 3H, $COCH_3$), 4.33 (q, 2H, *J* = 7 *Hz*, CH_2), 4.65, (s, 1H, CH), 5.81 (s, 2H, NH_2) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.3, 14.7, 28.3, 58.2, 68.3, 140.1, 141.3, 161.3, 170.2; MS, *m/z* (%) 258 (M^+, 100), 215 (55), 73 (40); *Anal*. Calcd for $C_9H_{14}N_4O_3S$ (258.08): C, 41.85; H, 5.46; N, 21.69; S, 12.41. Found: C, 41.21; H, 5.44; N, 21.62; S, 12.64%.

***N*-Phenyl 2-[(4-amino-5-methyl-4*H*-1,2,4-triazol-3-yl)sulfanyl]-3-oxobutanamide (6b).** 0.23 g, (75% yield), mp 240-242 °C; IR (KBr) υ = 3406, 3271 (NH_2), 3248 (NH), 1725, 1630 (2CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.92 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 4.35 (s, 1H, CH), 5.92 (s, 2H, NH_2), 7.25-7.81 (m, 5H, Ar-H), 10.31 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 28.6, 68.1, 122.8, 124.3, 127.9, 128.8, 140.2, 140.9, 158.3, 170.1; MS, *m/z* (%) 305 (M^+, 100), 262 (40), 120 (70); *Anal*. Calcd for $C_{13}H_{15}N_5O_2S$ (305.09): C, 51.13; H, 4.95; N, 22.94; S, 10.50. Found: C, 51.21; H, 5.04; N, 22.82; S, 10.64%.

Coupling of 6a,b with benzenediazonium chloride

To a solution of **6a** or **6b** (1 mmol) in ethanol (20 mL) was added sodium acetate trihydrate (0.138 g, 1 mmol), and the mixture was cooled to 0-5 °C in an ice bath. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride [prepared by diazotizing aniline (1 mmol) dissolved in hydrochloric acid (6 M, 1 mL) with a solution of sodium nitrite (0.07 g, 1 mmol) in water (2 mL)]. After complete addition of the diazonium salt, the reaction mixture was stirred for a further 30 min in an ice bath. The solid precipitated was

filtered off, washed with water, dried and crystallized from ethanol to give the respective products identical in all respects with **5a** and **5d**.

Synthesis of 7-arylhydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazines 10a-g under microwave irradiation

To a solution of **1** (0.13 g, 1 mmol) and the appropriate hydrazonoyl halides (1 mmol of each) in absolute ethanol (10 ml) was added chitosan (0.1 g) at room temperature. The reaction mixture was irradiated under constant pressure (11.2 Bar, 80 ^{o}C) for 10 min. at a power of 300 W. The hot solution was filtered to remove chitosan. After cooling, dil. HCl was added till pH became acidic, and the solid product was collected and recrystallized from ethanol to give products **10a-g**.

3,6-Dimethyl-7*H*-7-phenylhydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (10a). 0.22 g, (82% yield), mp 254-256 ^{o}C; IR (KBr) υ = 3173 (NH), 1596 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.97 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 7.21-7.37 (m, 5H, Ar-H), 10.31 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 13.6, 115.8, 120.2, 127.4, 130.2, 136.4, 141.1, 149.5, 151.2 ppm; MS, *m/z* (%) 272 (M^+, 100), 167 (40), 77 (70); *Anal*. Calcd for $C_{12}H_{12}N_6S$ (272.08): C, 52.92; H, 4.44; N, 30.86; S, 11.77. Found: C, 52.81; H, 4.24; N, 30.82; S, 11.64%.

3,6-Dimethyl-7*H*-7-(4-chlorophenyl)hydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (10b). 0.24 g, (81% yield), mp 274-276 ^{o}C; IR (KBr) υ = 3167 (NH), 1599 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.95 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.26-7.47 (m, 4H, Ar-H), 10.41 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 13.8, 115.4, 120.8, 128.1, 132.2, 136.9, 142.3, 149.9, 152.4 ppm; MS, *m/z* (%) 308 (M^++2, 30), 306 (M^+, 100), 167 (40), 111 (80); *Anal*. Calcd for $C_{12}H_{11}ClN_6S$ (306.05): C, 46.98; H, 3.61; N, 27.39; S, 10.45. Found: C, 47.01; H, 3.44; N, 27.52; S, 10.61%.

3,6-Dimethyl-7*H*-7-(4-bromophenyl)hydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (10c). 0.28 g, (80% yield), mp 296-298 ^{o}C; IR (KBr) υ = 3166 (NH), 1595 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.96 (s, 3H, CH_3), 2.58 (s, 3H, CH_3), 7.24-7.44 (m, 4H, Ar-H), 10.40 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 13.7, 115.3, 120.5, 127.9, 132.1, 136.6, 142.1, 149.5, 152.0 ppm; MS, *m/z* (%) 354 (M^++2, 30), 352 (M^+, 35), 167 (40), 155 (80); *Anal*. Calcd for $C_{12}H_{11}BrN_6S$ (349.99): C, 41.04; H, 3.16; N, 23.93; S, 9.13. Found: C, 41.01; H, 3.24; N, 23.82; S, 9.21%.

3,6-Dimethyl-7*H*-7-(4-methoxyphenyl)hydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine (10d). 0.24 g, (80% yield), mp 284-286 ^{o}C; IR (KBr) υ = 3178 (NH), 1593 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 1.96 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 3.82 (s, 3H, OCH_3), 6.91-7.48 (m, 4H, Ar-H), 10.21 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 13.6, 44.3, 115.6, 120.1, 127.1, 130.0, 136.2, 140.7, 149.1, 150.4 ppm; MS, *m/z* (%) 302 (M^+, 40), 167 (40), 122 (80); *Anal*. Calcd for $C_{13}H_{14}N_6OS$ (302.09): C, 51.64; H, 4.67; N, 27.80; S, 10.61. Found: C, 51.41; H, 4.44; N, 27.62; S, 10.52%.

3,6-Dimethyl-7*H*-7-(4-nitrophenyl)hydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (10e). 0.25 g, (78% yield), mp 320-322 ^{o}C; IR (KBr) υ = 3176 (NH), 1610 (C=N) cm^{-1}; ^{1}H NMR

. ($CDCl_3$) δ = 1.95 (s, 3H, CH_3), 2.68 (s, 3H, CH_3), 7.46-7.87 (m, 4H, Ar-H), 10.51 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.7, 13.9, 115.6, 122.4, 129.2, 134.2, 138.7, 143.1, 150.4, 154.5 ppm; MS, *m/z* (%) 317 (M^+, 100), 167 (40), 122 (50); *Anal*. Calcd for $C_{12}H_{11}N_7O_2S$ (317.07): C, 45.42; H, 3.49; N, 30.90; S, 10.10. Found: C, 45.21; H, 3.44; N, 30.72; S, 10.21%.

3-Methyl-6-phenyl-7*H*-7-phenylhydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (10f). 0.26 g, (78% yield), mp 242-244 °C; IR (KBr) υ = 3166 (NH), 1596 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.97 (s, 3H, CH_3), 7.21-7.87 (m, 10H, Ar-H), 10.21 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 115.5, 117.7, 120.8, 125.7, 127.8, 128.9, 129.6, 130.2, 134.4, 142.4, 150.6, 151.7 ppm; MS, *m/z* (%) 334 (M^+, 100), 232 (40), 77 (70); *Anal*. Calcd for $C_{17}H_{14}N_6S$ (344.10): C, 61.06; H, 4.22; N, 25.13; S, 9.59. Found: C, 60.91; H, 4.24; N, 25.32; S, 9.64%.

3-Methyl-6-phenyl-7*H*-7-(4-chlorophenyl)hydrazono-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine (10g). 0.29 g, (80% yield), mp 278-280 °C; IR (KBr) υ = 3168 (NH), 1599 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.99 (s, 3H, CH_3), 7.29-7.88 (m, 9H, Ar-H), 10.51 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.6, 115.8, 117.9, 121.4, 125.9, 128.6, 128.9, 130.1, 130.8, 134.64, 142.8, 150.6, 151.9 ppm; MS, *m/z* (%) 370 (M^++2, 30), 368 (M^+, 100), 234 (15), 232 (40), 111 (70); *Anal*. Calcd for $C_{17}H_{13}ClN_6S$ (368.06): C, 55.36; H, 3.55; N, 22.78; S, 8.69. Found: C, 55.41; H, 3.34; N, 22.62; S, 8.64%.

Synthesis of 3-methyl-6-substituted-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (13a,b)

To an equimolecular amounts (1 mmol) of compound **1** and chloroacetone or phenacyl bromide **11a,b** in absolute ethanol, chitosan (0.1 g) was added. The reaction mixture was irradiated under constant pressure (11.2 Bar, 80 °C) for 10 min. at a power of 300 W. The hot solution was filtered to remove chitosan. *p*-Toluenesulphonic acid (0.17 g, 1 mmol) was then added and the reaction mixture was further irradiated for 5 minutes. The precipitate formed was collected by filtration, dried and recrystallized from acetic acid to give products **13a,b**.

3,6-Dimethyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (13a). 0.13 g, (78% yield), mp 236-238 °C; IR (KBr) υ = 1605 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.95 (s, 3H, CH_3), 2.79 (s, 3H, CH_3), 3.91 (s, 2H, CH_2) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.4, 13.6, 32.1, 141.3, 149.4, 151.2 ppm; MS, *m/z* (%) 168 (M^+, 30), 127 (100); *Anal*. Calcd for $C_6H_8N_4S$ (160.05): C, 42.84; H, 4.79; N, 33.31; S, 19.06. Found: C, 42.61; H, 4.64; N, 33.52; S, 19.14%.

3-Methyl-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (13b). 0.18 g, (80% yield), mp 192-194 °C; IR (KBr) υ = 1591 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.91 (s, 3H, CH_3), 3.98 (s, 2H, CH_2), 7.27-7.92 (m, 5H, Ar-H) ppm; ^{13}C NMR ($CDCl_3$) δ = 9.5, 13.8, 32.4, 122.4, 129.2, 134.2, 138.7, 141.6, 149.7, 151.6 ppm MS, *m/z* (%) 230 (M^+, 30), 104 (70), 77 (100); *Anal*. Calcd for $C_{11}H_{10}N_4S$ (230.06): C, 57.37; H, 4.38; N, 24.33; S, 13.92. Found: C, 57.61; H, 4.62; N, 24.51; S, 14.14%.

Coupling of 3-methyl-6-substituted-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine 13a,b with benzenediazonium chloride

To a solution of each of compounds **13a,b** (1 mmol) in pyridine (10 ml) was added benzenediazonium chloride solution, [prepared as usual by diazotizing aniline (1 mmol) in hydrochloric acid (1 ml, 6 M) with sodium nitrite (0.07 g, 1 mmol) in 10 ml water] portionwise with stirring and cooling. After complete addition, the reaction mixture was left for 12 hrs in the refrigerator. The precipitate formed was collected by filtration, washed with water, dried and then recrystallized from ethanol to give pure **10a, 10f,** respectively.

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