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RESEARCH ARTICLE

Microwave-assisted neat reaction technology for the synthesis of s-triazolo[3,4-b]-1,3,4-thiadiazines

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An expeditious, solvent-free, and high yielding synthesis of nitrogen containing heterocycles from 1,2,4-s-triazole, benzoin, chloroacetic acid or phenacyl bromide under microwave irradiation is described. This improved greener synthetic methodology provides a simple and straightforward one-pot approach for the synthesis of a variety of heterocycles.

Keywords: 1,2,4-s-Triazole; Benzoin; Chloroacetic acid; Phenacyl bromide; Microwave

1. Introduction

The concept of green chemistry is widely adopted to meet the fundamental scientific challenges of protecting human health and environment while simultaneously achieving commercial viability [1]. The emerging area of green chemistry demands minimum hazard as the performance criteria while designing new chemical processes. The target is to explore alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimum byproducts or waste generation, as well as to eliminate the use of conventional organic solvents. The use of alternative energy sources and alternate reaction media is gaining increasing popularity as well. Neat reaction technology is a lucrative research area [2, 3] considering its cost, effective safety, and environmentally benign process parameters. These approaches need to be considered for assembly of heterocyclic compounds.

Organic reactions assisted by microwave (MW) irradiation have attracted considerable attention in the past decade for the efficient and ecofriendly synthesis of a variety of organic compounds [4]. Nitrogen-containing heterocycles are known subunits in many natural products and biologically active pharmaceuticals. Substituted 1,2,4-*s*-triazoles and the N-bridged heterocycles derived from them are amongst the various heterocycles that have received considerable attention as potential antimicrobial agents during the last two decades [5–7]. Diverse biological activities of various thiadiazines fused with an *s*-triazole ring have been extensively studied [8–10], and especially, *s*-triazolo[3,4-b][1,3,4]thiadiazines have been shown to possess a wide spectrum of bioactivities [11] viz anti-inflammatory, analgesic, and

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anti-fungal activities [12]. In view of the potential biological activity of the bridgehead nitrogen heterocycles and substantial benefits of neat reaction technology under MW in terms of green chemistry, it was of interest to us to prepare the title compounds.

2. Results and discussion

Thiadiazines are generally prepared by refluxing *s*-triazoles **1** with chloroacetic acid, α-halo ketones or benzoin in the presence of hazardous base like pyridine or piperidine in organic solvents like ethanol and benzene for several hours [13, 14]. These classical procedures although conventional yet suffer from some setbacks such as long reaction times, excessive solvents, tedious workup procedures and sometimes low yield [15, 16].

Reports on solvent-free reactions are increasingly frequent and neat reaction technology is one step ahead as it obviates the requirement of solvent for the adsorption of reactant and elution of product in pre and post reaction stages as required in solid supported reaction stages. Therefore, neat reaction technology is the only technology which fulfills the criteria for solvent-free reaction. To broaden the scope of this microwave assisted neat reaction technology, the assembly of 4-amino-5-mercapto-3-substituted-*s*-triazoles (**1a–c**) with chloroacetic acid, benzoin and α-halo ketones was investigated as shown in scheme 1.

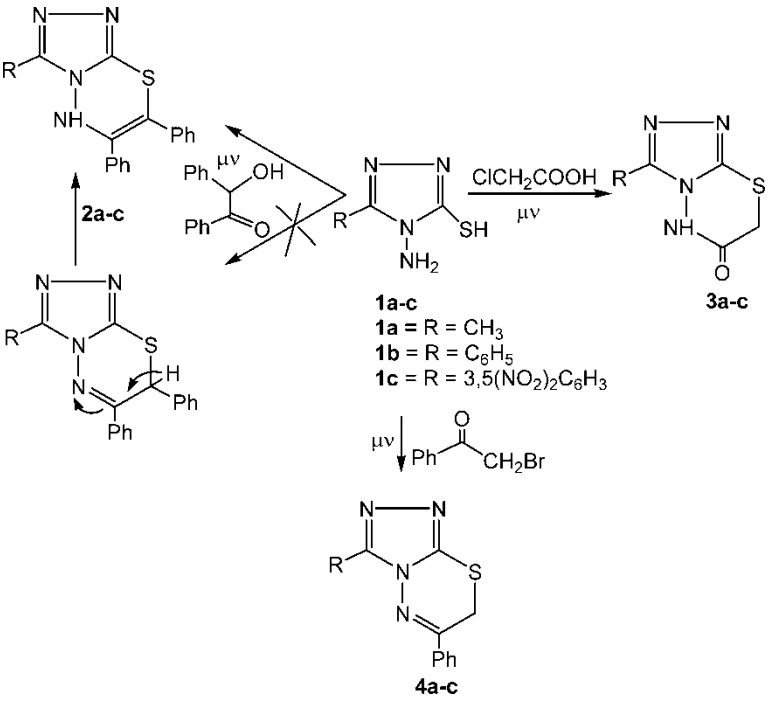
The literature also reveals that anhydrous conditions were required and this MW assisted technology provides anhydrous condition by evaporating polar molecules of water formed during reaction as MW interact with them. This evaporation of side products also directs the equilibrium in a forward direction and hence high yields were obtained with in 3–4 min of irradiation. As can be seen from the results (table 1), neat reaction technology under MW irradiation exhibits several advantages over the conventional heating like simple workup procedure, reduction in reaction time and dramatic improvement in yields.

Mechanistic considerations suggest the formation of **3a–c** as 5-NH tautomer and **4a–c** and **2a–c** as 7-CH tautomers, yet **2a–c** assumes the 5-NH tautomeric form instead of 7-CH tautomer. The reason for the existence of 5-NH isomer in **2a–c** can be attributed to the fact that phenyl group at C-7 position provides extended conjugation and hence leads to the stability of 5-NH isomer in comparison to 7-CH.

6,7-Diphenyl-5H-3-substituted-1,2,4-s-triazolo[3,4-b][1,3,4]thiadiazines **2a–c** were obtained by treating triazoles **1a–c** with benzoin under MWI. The formation of **2a–c** was evident from the complete disappearance of absorption bands in the region 3100–3250 cm^{-1} due to–NH_2 stretching vibration. IR spectra also showed an intense peak around 1660 (C=N) cm^{-1} and their ^1H NMR spectra exhibited the presence of NH group. In addition, the aromatic protons appeared around 7.4 ppm.

Cyclization of triazoles **1a–c** with chloroacetic acid afforded (7H)-3-substituted-1,2,4-s-triazolo[3,4-b][1,3,4]thiadiazine-6(5H)-ones **3a–c**. The IR spectra of this class of compounds displayed bonds in the region 1700 cm^{-1} (C=O) and 3250 cm^{-1} (−NH). The ^1H NMR spectra exhibited singlets at 4.0 ppm due to the $–SCH_2$ unit.

Conventionally, it was claimed that the reaction of s-triazoles **1a-c** with phenacyl bromide and K_2CO_3 gave the uncyclized product. However, neat technology under MW irradiation of triazoles **1a–c** with phenacyl bromide afforded 7H-3-substituted-s-triazolo[3,4-b][1,3,4]thiadiazines **4a–c**. The IR spectra of compounds were devoid of the characteristic stretching frequencies of the NH_2 and C=O groups. Their ^1H NMR spectra revealed a singlet at δ 4.1–4.27 ppm (2H, CH_2) and lacked the signals for both SH and NH_2 protons indicating that cyclization involving both functional groups took place. Elemental analysis also supports the formation of products.



SCHEME 1 Synthesis of library of s-triazolo[3,4-b][1,3,4]thiadiazine/thiadiazine-6(5H)-ones.

Table 1. Microwave assisted neat synthesis of library of s-triazolo[3,4-b][1,3,4] thiadiazine/thiadiazine-6-one.

Comp d[a]	R	Time (min)	Yield (%)[b]	m.p. exp (lit.)	C Calcd (Found)	H Calcd (Found)	N Calcd (Found)	S Calcd (Found)
2a	CH_3	2 min	89	164–165 °C (163 °C)[13]	66.64 (66.47)	4.61 (4.29)	18.29 (18.37)	10.47 (10.42)
2b	C_6H_5	2.5	92	124–126 °C (127 °C)[16]	71.71 (71.90)	4.38 (4.27)	15.21 (15.28)	8.70 (8.63)
2c	$3,5(NO_2)2C_6H_3$	3	93	152–154 °C	57.64 (57.84)	3.08 (3.03)	18.33 (17.96)	6.99 (6.75)
3a	CH_3	2.5	97	184–185 °C (186–187 °C)[14]	35.29 (36.02)	3.55 (3.53)	32.92 (33.07)	18.84 (18.44)
3b	C_6H_5	3	94	185–186 °C (185–186 °C)[15]	51.71 (51.93)	3.47 (3.49)	24.12 (24.37)	13.81 (13.45)
3c	$3,5(NO_2)C_6H_3$	2.5	89	182–184 °C	37.27 (37.33)	1.88 (1.91)	26.08 (26.53)	9.95 (9.87)
4a	CH_3	2	87	182–183 °C (183–184 °C)[14]	57.37 (57.83)	4.38 (4.33)	24.33 (24.17)	13.92 (13.55)
4b	C_6H_5	2.5	91	212–213 °C (212–213 °C)[17]	65.73 (65.64)	4.14 (4.19)	19.16 (19.21)	10.97 (11.03)
4c	$3,5(NO_2)C_6H_3$	2.5	91	158–160 °C	50.26 (50.01)	2.64 (2.56)	21.98 (21.79)	8.39 (8.59)

[a]Products were characterized by ^{1}H NMR, IR, and Elemental analysis.
[b]Isolated and unoptimized yields.

3. Conclusion

In conclusion, we have described the thiadiazine ring formation starting from s-triazole **1a–c** derivatives. A novel, facile and highly efficient MW assisted neat reaction technology is developed, which allow the rapid assembly of triazoles. The advantage of this ecofriendly and safe is that it includes a simple reaction set up, higher yield, shorter reaction time and devoid of solvent.

4. Experimental

Melting points were taken on a Thomas Hoover melting point apparatus and were uncorrected. IR (nujol) spectra (ν in cm^{-1}) were obtained on a Perkin Elmer 1710 Spectrophotometer. ^1H NMR spectra were recorded in $CDCl_3$ on FTNMR Hitachi R-600 spectrometer operating at 60 MHz using TMS as internal standard (chemical shift in δ ppm). Elemental analyses were performed on Heraeus CHN rapid analyzer. A Kenstar (model no. OM9925E) microwave oven (2450 MHz, 850 W) was used for the experiment. The purity of compounds was checked on silica gel coated aluminium plates (Merck).

4.1 *General procedure for the synthesis of s-triazolo[3,4-b][1,3,4]thiadiazines (2a–c)/(3a–c)/(4a–c)*

A mixture of 1,2,4-s-triazole (**1a–c)** (0.01 mol), benzoin/chloroacetic acid/phenacylbromide (0.01 mol) and almost one equivalent of solid K_2CO_3 was mixed using piston grinder and then taken in an Erlenmeyer flask. This was subjected to microwave irradiation intermittently for a sufficient interval of time using resting intervals of 1 min after every 30 s of irradiation. Temperature of reaction mixture raises up to 130 °C ≈ 150 °C, as measured by AZ, Mini Non-contact Infrared Thermometer model no. 8868. Reaction progress was monitored by TLC. Upon completion of reaction, the reaction mixture was cooled and potassium carbonate was triturated into water. The solid product was filtered from the water and recrystallized from ethanol.

4.2 *Data for compounds 2a–c, 3a–c and 4a–c*

4.2.1 3-Methyl-6,7-diphenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2a). ^1H-NMR 60 MHz (DMSO-d_6): δ 2.36 (3H, s), 5.89 (s, br, NH), 7.29–7.82 (m, 10H, ArH). IR (ν_{max} cm^{-1}, Nujol): 1563 (C−N), 1661 (C=N), 3340 (NH).

4.2.2 3,6,7-Triphenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (2b). ^1H-NMR 60 MHz (DMSO-d_6): δ 5.97 (s, br, NH), 7.32–7.93 (m, 15H, Ar−H). IR (ν_{max} cm^{-1}, Nujol): 1560 (C−N), 1665 (C=N), 3347 (NH).

4.2.3 3-(3,5-Dinitrophenyl)-6,7-diphenyl-5*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine (2c). ^1H-NMR 60 MHz (DMSO-d_6): δ 5.93 (s, br, NH), 7.42–7.69 (m, 13H, ArH). IR (ν_{max} cm^{-1}, Nujol): 1565 (C−N), 1660 (C=N), 3337 (NH).

4.2.4 3-Methyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-6-one (3a). ^{1}H-NMR 60 MHz (DMSO-d_6): δ 2.34 (3H, s), 4.12 (s, 2H, SCH_2), 6.23 (s, br, NH). IR (ν_{max} cm^{-1}, Nujol): 1698 (C=O), 3221 (NH).

4.2.5 3-Phenyl[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-6-one (3b). ^{1}H-NMR 60 MHz (DMSO-d_6): δ 4.16 (s, 2H, SCH_2), 6.19 (s, br, NH), 7.37–7.83 (m, 5H, Ar−H). IR (ν_{max} cm^{-1}, Nujol): 1701 (C=O), 3239 (NH).

4.2.6 3-(3,5-Dinitrophenyl)[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine-6-one (3c). ^{1}H-NMR 60 MHz (DMSO-d_6): δ 4.16 (s, 2H, SCH_2), 6.21 (s, br, NH), 7.41–7.76 (m, 3H, Ar−H). IR (ν_{max} cm^{-1}, Nujol): 1705 (C=O), 3226 (NH).

4.2.7 3-Methyl-6-phenyl-7-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (4a). ^{1}H-NMR 60 MHz (DMSO-d_6): δ 2.85 (s, 3H, CH_3), 4.13 (2H, s, SCH_2), 7.14 (m, 5H, ArH). IR (ν_{max} cm^{-1}, Nujol): 1547 (C−N), 1652 (C=N).

4.2.8 3,6-Diphenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (4b). ^{1}H-NMR 60 MHz (DMSO-d_6): δ 4.10 (2H, s, SCH_2), 7.21–7.59 (m, 10H, Ar−H). IR (ν_{max} cm^{-1}, Nujol): 1551 (C−N), 1653 (C=N).

4.2.9 3-(3,5-Dinitrophenyl)-6-phenyl-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4] thiadiazine (4c). ^{1}H-NMR 60 MHz (DMSO-d_6): δ 4.14 (2H, s, SCH_2), 7.39–7.81 (m, 10H, Ar−H). IR (ν_{max} cm^{-1}, Nujol): 1545 (C−N), 1661 (C=N).

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