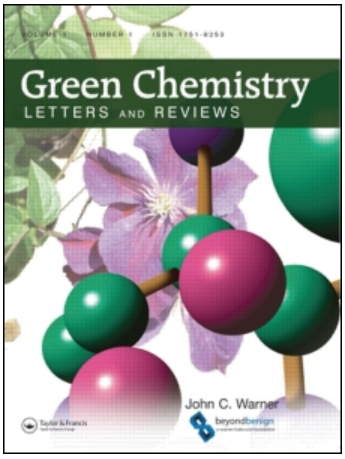

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Novel one-pot synthesis of 1,2,4-triazolidin-3-thiones comprising piperidine moiety

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ORIGINAL ARTICLE

Novel one-pot synthesis of 1,2,4-triazolidin-3-thiones comprising piperidine moiety

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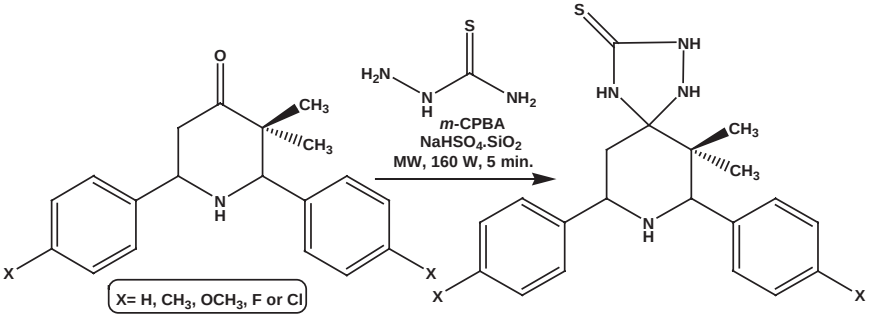
A simple synthetic strategy for the synthesis of piperidinyl spiro-1,2,4-triazolidin-3-thiones **11–15** is proposed, exploiting microwave activation coupled with solvent-free reaction conditions catalyzed by $NaHSO_4.SiO_2$ heterogeneous catalyst is described.



Keywords: 1,2,4-triazolidin-3-thiones; piperidine; *m*-chloroperbenzoic acid; oxidative cyclization; $NaHSO_4.SiO_2$

Introduction

1,2,4-Triazolidin-3-thiones are typically prepared from ketone thiosemicarbazones by oxidative cyclization. Previously, MnO_2, (*1,2*) $FeCl_3.6H_2O$, (*1,3,4*) H_2O_2, (*5*) *m*-chloroperbenzoic acid (*6*) had been used for synthesizing 1,2,4-triazolidin-4-ones from steroidal and non-steroidal homocyclic ketone thiosemicarbazones. The synthetic pathways of 1,2,4-triazolidin-3-thiones derivatives represent an interesting topic since the 1,2,4-triazole moiety has been incorporated in a wide variety of therapeutically interesting drugs (*7–10*) including H1/H2 histamine receptor blockers, cholinesterase active agents, central nervous system (CNS) stimulants, antianxiety agents, sedatives, analgesics, and anticonvulsants. Some examples of 1,2,4-triazole based antibacterial and antifungal drugs are estazolam, (*11*) alprazolam (*12*) and rizatriptan (*13*).

Bioactive heterocyclic ring systems having 2,6-diaryl-piperidin-4-one nucleus with different substituents at 3- and 5-positions of the ring have aroused great interest due to their wide variety of biological properties such as antiviral, antitumor (*14,15*), central nervous system (*16*), local anesthetic (*17*), anticancer (*18*), antimicrobial activity (*19*) and their derivative piperidine are also biologically important and act as neurokinin receptor antagonists (*20*), analgesic and antihypertensive agents (*21*).

The coupling of dry media synthesis with microwave activation is one of the novel approaches to eco-friendly chemistry. Chemical reactions are accelerated essentially because of selective absorption of microwave energy by polar molecules, which are inert to the microwave dielectric loss. Three types of solvent-free procedures can be coupled with dielectric heating provided by a microwave source: reactions among neat reagents, reactions among supported reagents on mineral solid supports and phase transfer catalysis reactions. The procedure using neat reagents has the advantage of easy work-up and the use of a minimal amount of solvent for purification and separation of products. One of the most novel applications in the field of Microwave Assisted Organic Synthesis (MAOS) is heterocyclic chemistry (*22*).

Silica gel supported sodium hydrogen sulfate ($NaHSO_4.SiO_2$), a non-toxic and inexpensive

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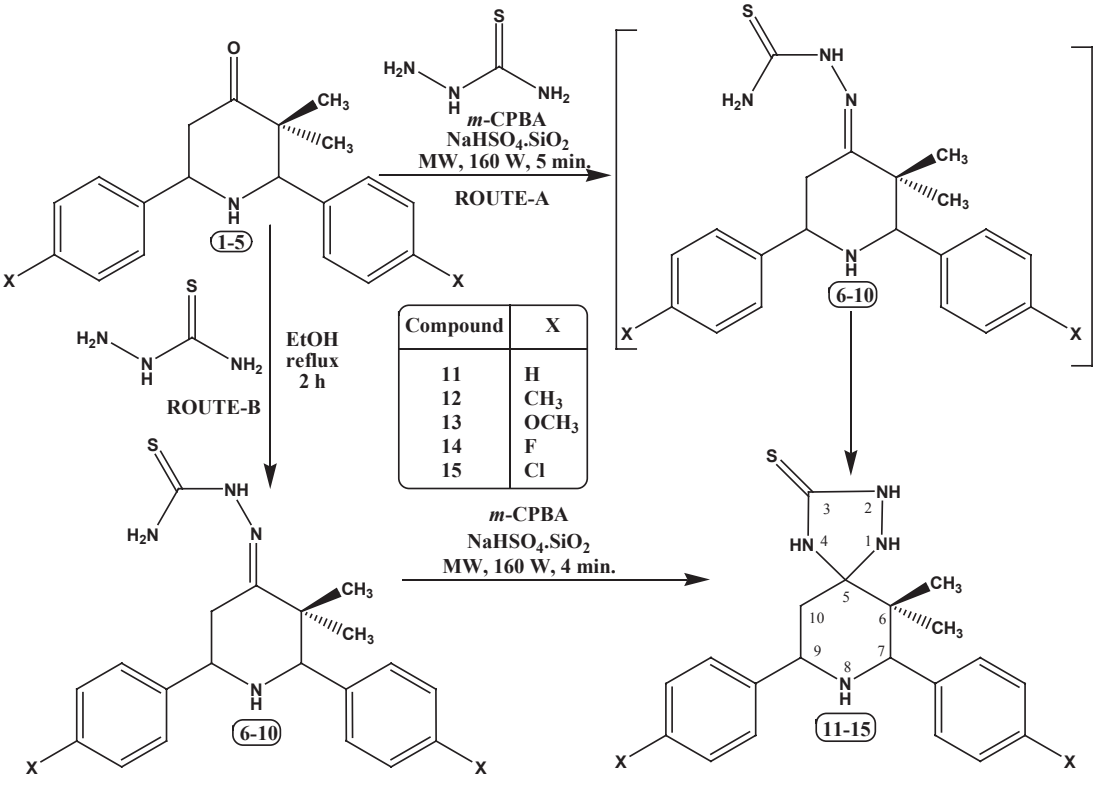
catalyst, has been used for one-pot conversion of ketones to amides, (*23*) synthesis of imines, (*24*) single-step synthesis of 4(3H)-quinazolinones (*25*) and one-pot synthesis of 1,2,3-selenadiazoles (*26*).

Owing to our interest in synthesizing fascinating pharmacological and therapeutic important compounds under solid-state reactions (*27,28*), we attempt and succeed now to use silica gel supported sodium hydrogen sulphate ($NaHSO_4.SiO_2$), as a heterogeneous catalyst for the one-pot conversion of 3,3-dimethyl-2,6-diaryl-piperidin-4-ones **(1–5)** to 6,6-dimethyl-7,9-diaryl-1,2,4,8-tetraazaspiro[4.5]decan-3-thiones **(11–15)** in dry media under microwave irradiation, since coupling of dry media synthesis with microwave activation is one of the novel approaches to eco-friendly chemistry.

Results and discussion

1,2,4-triazolidin-3-thiones and their derivatives can be conveniently synthesized from aldehyde/ketone thiosemicarbazones and also from substituted thiosemicarbazide by cyclization using suitable reagents (*29*) such as MnO_2, $FeCl_3.6H_2O$, H_2O_2, and *m*-chloroperbenzoic acid. There are some problems associated with above synthesis, such as severe conditions, low to moderate yields for the reaction and difficulty in separating the products from the system. Cyclocondensation reaction of respective ketone, aldehyde and ammonium acetate in the ratio of 1:2:1, respectively afforded the formation of 2,6-diaryl-3,3-dimethyl-piperidin-4-ones **1–5**. In the present procedure, treatment of 0.01 mol of **1–5**, 0.01 mol of thiosemicarbazide and 0.02 mol of *m*-chloroperbenzoic acid along with 0.56 mmol of $NaHSO_4.SiO_2$ afford the corresponding 7,9-diaryl-6,6-dimethyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thi ones **(11–15)** (Scheme 1) in high yields with shorter time period in dry media under MW irradiation than the classical method and the results are shown in Table 1. In the intramolecular cyclization of thiosemicarbazones **6–10**, 2.0 equivalent of *m*-CPBA is used for the reaction Apart from the intramolecular cyclization, N-hydroxy substituted cyclized products are also expected. But the secondary amine in piperidone moiety is not hydroxylated by the addition of *m*-CPBA. Only 7,9-diaryl-6,6-dimethyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thiones **(11–15)** are exclusively formed. Free radical generated from *m*-CPBA is responsible for the intra molecular cyclization and the free radical mechanism is proposed in Scheme 2.



Scheme 1. Synthesis of novel piperidinyl spiro-1,2,4-triazolidin-3-thiones in "dry media."

Table 1. Physical and analytical data of piperidinyl spiro-1,2,4-triazolidin-3-thiones **11–15**.

Compound	X	MW time (min.)	MW yield (%)	m.p°C	Elemental analysis (%)			m/z ($M^{+\cdot}$)
					C found (calculated)	H found (calculated)	N found (calculated)	Molecular formula
11	H	4 (60)	85 (55)	118–120	68.10 (68.15)	6.82 (6.86)	15.85 (15.89)	353 $C_{20}H_{24}N_4S$
12	CH_3	4 (70)	78 (45)	108–110	69.39 (69.44)	7.36 (7.42)	14.68 (14.72)	381 $C_{22}H_{28}N_4S$
13	OCH_3	4 (60)	75 (50)	112–114	64.01 (64.05)	6.80 (6.84)	13.54 (13.58)	413 $C_{22}H_{28}N_4O_2S$
14	F	3 (45)	80 (60)	126–128	61.78 (61.83)	5.66 (5.71)	14.38 (14.42)	389 $C_{20}H_{22}F_2N_4S$
15	Cl	5 (60)	75 (50)	121–123	56.97 (57.01)	5.21 (5.26)	13.25 (13.30)	421 $C_{20}H_{22}Cl_2N_4S$

Note: The values in parentheses are the results obtained by conventional reaction method.

$NaHSO_4.SiO_2$ catalyst was shown to be one of the most efficient MW absorber with a very high specificity to MW heating. It was able to reach a temperature of 110°C after 3 min. of irradiation in a domestic oven (320 W). Mere 0.56 mmol of $NaHSO_4.SiO_2$ catalyst to 0.01 mol of substrates is the most acceptable ratio in terms of efficiency and safety; a power level of 160 watts is the most suitable one. In order to perform a model reaction to evaluate the amount of $NaHSO_4.SiO_2$ catalyst required for the synthesis of 6,6-dimethyl-7,9-diphenyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thione **11** from the respective 3,3-dimethyl-2,6-diphenylpiperidin-4-one **1**, several experiments were tried with different concentrations of catalyst such as 0.28, 0.84 and 1.12 mmol. and the yields are 20, 70, 50%, respectively (Table 2). Hence 0.56 mmol. is the optimum amount of catalyst to be used for the reaction in high yields (85%). In addition, the present dry media procedure eliminates the usage of chloroform (*6*) for the formation of respective 1,2,4-triazolidin-3-thiones.

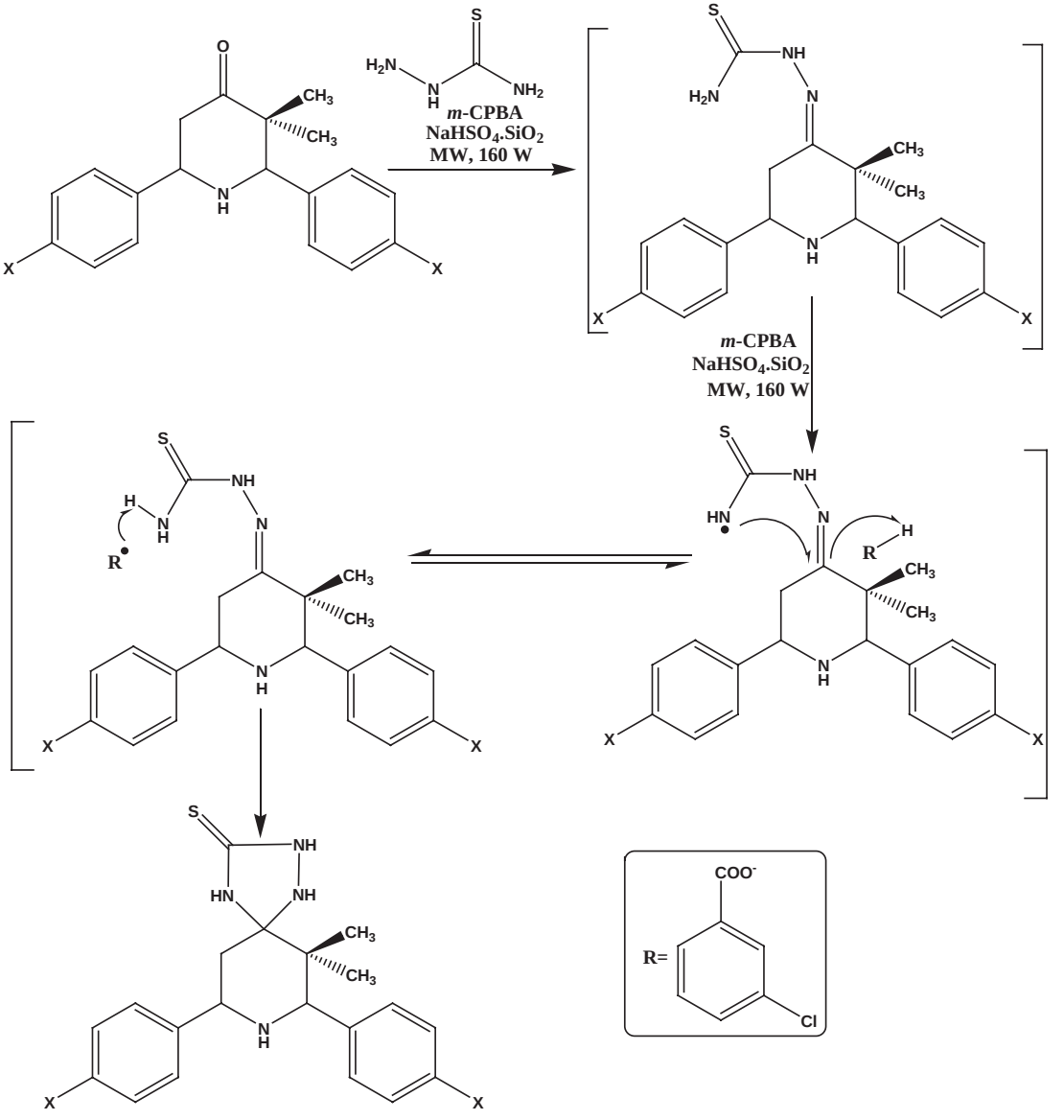
The respective thiosemicarbazones **6–10** are believed to be the intermediates in the reaction, but we are unable to isolate the respective thiosemicarbazones. To confirm the formation of thiosemicarbazones as intermediates, we ran the reaction with respective thiosemicarbazones, *m*-CPBA and $NaHSO_4.SiO_2$ heterogeneous catalyst under microwave irradiation at $P = 160$ W. As we expected, the thiosemicarbazones gave the 7,9-diaryl-6,6-dimethyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thiones **11–15**, quantitatively.

The structure of the newly synthesized compounds **11–15** is confirmed by melting point, elemental analysis, MS, FT-IR, one-dimensional NMR (^1H & ^{13}C) spectroscopic data. A free radical mechanism, assisted by microwaves (Scheme 2) has been proposed for the conversion of thiosemicarbazones generated *in situ* from their carbonyl precursors to the piperidinyl spiro-1,2,4-triazolidin-3-thiones in the presence of $NaHSO_4.SiO_2$ heterogeneous catalyst.

A major role is played by $NaHSO_4.SiO_2$ heterogeneous catalyst, which can be recovered and re-used (Figure 1) by simple washing with ethyl acetate after each use and activated in an oven at 120°C for 1 h prior to use, rendering thus the process more economic and green. In total, eight successive re-use runs were possible. However, little palpable decrease in the reaction yield was noted up to five runs. All these constitute a green and efficient alternative to the classical method using chloroform (*6*) as solvent.

Experimental

Performing thin layer chromatography (TLC) assessed the reactions and the purity of the products. All the



Scheme 2. Microwave assisted *in situ* formed piperidinyl thiosemicarbazones followed by an oxidative free radical mechanism catalyzed by heterogeneous $NaHSO_4.SiO_2$.

reported melting points were taken in open capillaries and were uncorrected. Infrared (IR) spectra were recorded in KBr (pellet forms) on a Nicolet-Avatar–330 FT-IR spectrophotometer and note worthy absorption values (cm^{-1}) alone are listed. ^1H and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively on Bruker AMX 400 NMR spectrometer using DMSO-*d* as solvent. The ESI +ve MS spectra were recorded on a Bruker Daltonics LC-MS spectrometer. Satisfactory microanalysis was obtained on Carlo Erba 1106 CHN analyzer. A conventional (*unmodified*) domestic microwave oven equipped with a turntable (LG, MG-395 WA, 230V ~ 50Hz, 760 W) was used for the irradiation.

By adopting the literature precedent (*30*), 3,3-dimethyl-2,6-diarylpiperidin-4-ones **1–5** and their thiosemicarbazones **6–10** were prepared.

Table 2. Optimization of $NaHSO_4.SiO_2$ catalyst requirement for the formation of 6,6-dimethyl-7,9-diphenyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thione **11.**

Entry	Amount of $NaHSO_4.SiO_2$ used (mmol.)	Yield[a] (%)
1	0.28	20
2	0.56	85
3	0.84	70
4	1.12	50

[a]Isolated yield.

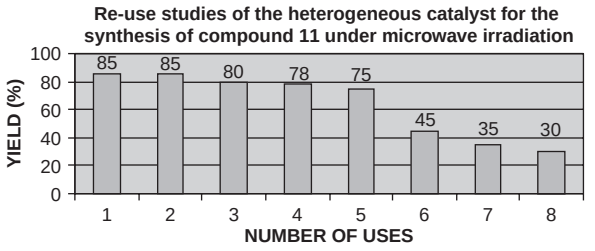


Figure 1. Re-use studies of the heterogeneous catalyst for the synthesis of compound 11 under microwave irradiation.

Typical procedure for the synthesis of 6,6-dimethyl-7,9-diphenyl-1,2,4,8-tetraazaspiro[4.5]decan-3-thione 11

A mixture containing 0.01 mol of 3,3-dimethyl-2,6-diphenylpiperidin-4-one **1**, 0.01 mol of thiosemicarbazide, 0.02 mol of *m*-chloroperbenzoic acid and $NaHSO_4.SiO_2$ (0.56 mmol) was added in an alumina bath and mixed properly with the aid of glass rod (10s) and then irradiated in a microwave oven for 4 min. at 160W (monitored by TLC). After completion of the reaction, the reaction mixture was extracted with ethyl acetate (3×5 mL). The catalyst and other solid wastes were removed by filtration. The combined organic layer was washed with water three times and then dried over anhydrous $MgSO_4$. The organic layer was concentrated *in vacuo* to furnish the products, which were purified by column chromatography using silica gel (100–200 mesh), with ethyl acetate – Petroleum ether (bp 40–60) in the ratio (3:7) as eluent. IR (KBr) (cm^{-1}): 3424, 3366, 3146, 3030, 2971, 2928, 1289, 764, 701; ^{1}H NMR (δppm): 0.94 (s, 3H, CH_3 at C-6), 1.15 (s, 3H, CH_3 at C-6), 2.63 (s, 1H, H_8), 2.13–2.19 (dd, 1H, H_{10a}), 3.22–3.29 (dd, 1H, H_{10e}), 3.66 (s, 1H, H_2) 3.77–3.83 (dd, 1H, H_{9a}, $J_{9a,10e} = 2.92$, $J_{9a,10a} = 17.12$), 7.13 (s, 1H, H_1), 7.26–7.58 (m, 10H, H_{arom}), 8.32 (s, 1H, H_4); ^{13}C NMR (δppm): 20.8, CH_3 at C-6, 21.3 CH_3 at C-6, 32.6, C-10, 42.4, C-6, 59.9, C-9, 69.7, C-7, 79.1, C-5, 126.7–128.9 $-C_{arom}$,140.4, 144.1 *ipso*-C, 179.0 C-3.

The compounds **12–15** were synthesized correspondingly.

6,6-dimethyl-7,9-bis(4-methyphenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione 12

IR (KBr) (cm^{-1}): 3429, 3315, 3102, 3022, 2972, 2924, 1246, 817, 745; ^{1}H NMR (δppm): 1.02 (s, 3H, CH_3 at C-6), 1.08 (s, 3H, CH_3 at C-6), 2.07 (s, 6H, CH_3 at arom. ring) 2.49 (s, 1H, H_8), 2.18–2.27 (dd, 1H, H_{10a}), 2.94–3.10 (dd, 1H, H_{10e}), 3.61 (s, 1H, H_2) 3.67–3.71 (dd, 1H, H_{9a}, $J_{9a,10e} = 2.12$, $J_{9a,10a} = 15.52$), 7.08 (s, 1H, H_1), 7.10–1.42 (m, 8H, H_{arom}), 8.50 (s, 1H, H_4); ^{13}C NMR (δppm): 20.6, CH_3 at C-6, 21.1 CH_3 at C-6, 22.7, CH_3 at arom. ring 32.3, C-10, 42.2, C-6, 59.8, C-9, 69.5, C-7, 79.0, C-5, 126.5–128.7 $-C_{arom}$, 136.1, 137.5, 141.1, 159.7 *ipso*-C, 180.0 C-3.

6,6-dimethyl-7,9-bis(4-methoxyphenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione 13

IR (KBr) (cm^{-1}): 3427, 3314, 3246, 3158, 2969, 2929, 1246, 832, 750; ^{1}H NMR (δppm): 0.92 (s, 3H, CH_3 at C-6), 1.16 (s, 3H, CH_3 at C-6), 2.49 (s, 1H, H_8), 2.13–2.31 (dd, 1H, H_{10a}), 3.47–3.51 (dd, 1H, H_{10e}), 3.59 (s, 1H, H_2) 3.69–3.74 (dd, 1H, H_{9a}, $J_{9a,10e} = 2.16$, $J_{9a,10a} = 16.04$), 3.87 (s, 6H, OCH_3 at arom. ring), 7.13 (s, 1H, H_1), 7.33–7.97 (m, 8H, H_{arom}), 8.30 (s, 1H, H_4); ^{13}C NMR (δppm): 20.8, CH_3 at C-6, 22.7 CH_3 at C-6, 32.7, C-10, 42.6, C-6, 55.0, 54.9, OCH_3 at arom. ring, 59.7, C-9, 69.1, C-7, 79.0, C-5, 126.6–129.8 $-C_{arom}$, 132.5, 136.2, 158.4, 159.9 *ipso*-C, 179.0 C-3.

6,6-dimethyl-7,9-bis(4-fluorophenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione 14

IR (KBr) (cm^{-1}): 3427, 3369, 3254, 3149, 2975, 2931, 1291, 823, 748; ^{1}H NMR (δppm): 1.12, (s, 3H, CH_3 at C-6), 1.17 (s, 3H, CH_3 at C-6), 2.60 (s, 1H, H_8), 2.31–2.39 (dd, 1H, H_{10a}), 3.53–3.58 (dd, 1H, H_{10e}), 3.68–3.76 (dd, 1H, H_{9a}, $J_{9a,10e} = 2.15$, $J_{9a,10a} = 16.38$), 7.18 (s, 1H, H_1), 7.37–7.81 (m, 8H, H_{arom}), 8.37 (s, 1H, H_4); ^{13}C NMR (δppm): 21.5, CH_3 at C-6, 22.3 CH_3 at C-6, 32.8, C-10, 42.8, C-6, 60.1, C-9, 69.9, C-7, 80.6, C-5, 127.8–129.3 $-C_{arom}$, 137.9, 141.6, 158.3, 158.74 *ipso*-C, 180.2 C-3.

6,6-dimethyl-7,9-bis(4-chlorophenyl)-1,2,4,8-tetraazaspiro[4.5]decan-3-thione 15

IR (KBr) (cm^{-1}): 3425, 3368, 3251, 3147, 2972, 2929, 1289, 824, 745; ^{1}H NMR (δppm): 1.16, (s, 3H, CH_3 at C-6), 1.19 (s, 3H, CH_3 at C-6), 2.61 (s, 1H, H_8), 2.30–2.38 (dd, 1H, H_{10a}), 3.51–3.57 (dd, 1H, H_{10e}), 3.69–3.74 (dd, 1H, H_{9a}, $J_{9a,10e} = 2.16$, $J_{9a,10a} = 16.40$), 7.20 (s, 1H, H_1), 7.43–7.83 (m, 8H, H_{arom}), 8.39 (s, 1H, H_4); ^{13}C NMR (δppm): 21.4, CH_3 at C-6, 22.6 CH_3 at C-6, 32.6, C-10, 42.4, C-6, 60.8, C-9, 69.8, C-7, 80.1, C-5, 128.0–129.8 $-C_{arom}$, 137.7, 141.4, 158.0, 158.4 *ipso*-C, 180.0 C-3.

Conclusion

To conclude, we have developed a rapid and convenient microwave-assisted solvent-free protocol for the formation of 1,2,4-triazolidin-3-thiones using non-toxic and an inexpensive $NaHSO_4.SiO_2$ catalyst. The advantages of this environmentally benign and safe protocol include a simple reaction set-up, high

product yields, short reaction times and the elimination of solvents.

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