Microwave and Ultrasound-Assisted Synthesis of Thiosemicarbazones and Their Corresponding (4,5-Substituted-thiazol-2-yl)hydrazines

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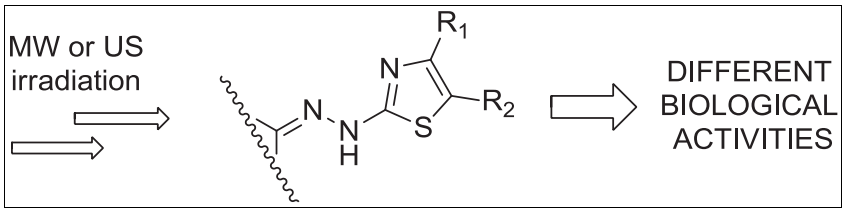
Received June 25, 2012
DOI 10.1002/jhet.1856
Published online 00 Month 2014 in Wiley Online Library (wileyonlinelibrary.com).



Hantzsch cyclization of thiosemicarbazone intermediates is a very popular approach to the synthesis of substituted thiazoles. We developed a convenient microwave and ultrasound-assisted method both for the synthesis of 1-(alkyliden/cycloalkyliden/aryliden)thiosemicarbazone intermediates and their cyclization into (4,5-substituted-thiazol-2-yl)hydrazines. The search for optimal reaction conditions included the use of different catalysts (Lewis acids and resins) and solvents at discrete temperatures, pressures, and irradiation powers. Comparing yields, reaction times, and efforts proved that microwave and ultrasound-assisted techniques outmatch conventional heating and have a remarkable influence on the synthesis.

J. Heterocyclic Chem., **00,** 00 (2014).

INTRODUCTION

Thiazole and thiosemicarbazone derivatives have raised a considerable interest in recent years, as they occupy a prominent position in the drug discovery process and have been extensively employed in the preparation of several important drugs [1]. Previous researches within our group demonstrated that the (thiazol-2-yl)hydrazine moiety could be used as a common scaffold for the synthesis of small molecules that showed a widespread activity as human monoamine oxidase (hMAO) inhibitors [2], epigenetic modulators [3], anti-*Candida* [4], anti-*Toxoplasma* [5], and anti-*Helicobacter pylori* agents [6]. Although many conventional synthetic strategies have been developed for the synthesis of thiazoles, no ultrasound (US) and a few microwave (MW)-assisted methods (often reporting the use of domestic household oven) are available at the moment [7–9]. Nowadays, the application of US and MW irradiation as nonconventional energy sources in organic synthesis is receiving an increasing acceptance and is becoming an essential tool for organic chemists. Both techniques allow achieving significant laboratory time saving and often simplify the reaction work-up. Moreover, they are valuable tools that help organic chemists to limit pollution, enhance reaction rates, improve yields, and do green chemistry [10,11]. Herein, we report on the results obtained by investigating both steps needed for the synthesis of a large number of (4,5-substituted-thiazol-2-yl)hydrazine derivatives using different conditions (solvent, pressure, temperature, and power) and catalysts, under US and MW irradiation.

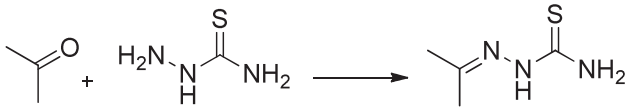
RESULTS AND DISCUSSION

Optimization of the synthesis of thiosemicarbazone derivatives The synthesis of the simplest thiosemicarbazone intermediate (1-(propan-2-yliden)thiosemicarbazide) was used as a model for the following optimization studies. The reaction was conducted under conventional heating and US or MW irradiation (Table 1); diverse Brønsted acids, Lewis acids, and acidic resins were screened (Table 2) as well as different power, temperature, and pressure conditions. According to the results reported in our previous works, good yields were achieved in heating the reaction mixture up to 50°C for 24 h in the presence of catalytic amounts of acetic acid (79%) [2]. To evaluate the effect of MW and US irradiation on this reaction, we preserved the original conditions of catalysis and solvent used in conventional synthesis.

As shown in Table 1, reaction yields increased both using MW and US in the presence of the acid catalyst (96% and 94%, respectively). Reaction times were reduced instead from 24 h to 5 min and 30 min, respectively. Further studies were performed to define which parameters were affecting the efficiency of the reaction. Because ethanol was a well-investigated solvent in MW-assisted reactions [12], we conducted the thiosemicarbazone synthesis at two discrete temperatures (88°C and 103°C) that had already been reported to correspond to 18 and 33 psi of vial internal pressure, respectively (Figure 1). The higher pressurization of the sealed vessel led to higher yields at each applied power (200–350 W) with a maximum at 300 W (87%).

Table 1

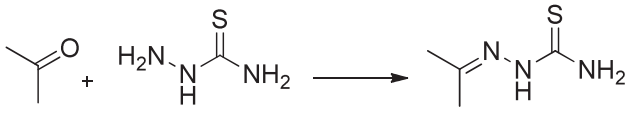
Comparison of microwave (MW)-assisted, ultrasound (US)-assisted, and conventional synthesis of 1-(propan-2-yliden)thiosemicarbazide.



Solvent	Conditions	Yield %
EtOH	50°C, 24 h	72
EtOH, CH_3COOH (cat.)	50°C, 24 h	79
EtOH	50°C, 5 min, variable MW power	89
EtOH, CH_3COOH (cat.)	50°C, 5 min, variable MW power	96
EtOH	50°C, 30 min, 40 kHz (40% of maximum power output)	82
EtOH, CH_3COOH (cat.)	50°C, 30 min, 40 kHz (40% of maximum power output)	94

Table 2

The effect of the substitution of acetic acid with different Lewis acids and acidic ion exchange resins under MW irradiation on yield.



Catalyst	Conditions	Yield %
Catalyst-free	EtOH, 103°C, 5 min, 300 W	61
CH_3COOH	EtOH, 103°C, 5 min, 300 W	87
Amberlyst 15[a] (0.72 g)	EtOH, 103°C, 5 min, 300 W	42
Montmorillonite K10[a] (1 g)	EtOH, 103°C, 5 min, 300 W	84
LiCl	EtOH, 103°C, 5 min, 300 W	78
$ZnCl_2$	EtOH, 103°C, 5 min, 300 W	22
$Zn(OTf)_2$	EtOH, 103°C, 5 min, 300 W	5
$BF_3 \cdot 2\ H_2O$	EtOH, 103°C, 5 min, 300 W	67
$BF_3\ 2\ H_2O$	Free solvent, 103°C, 5 min, 300 W	10
$InCl_3$	EtOH, 103°C, 5 min, 300 W	34
$MgBr_2$	EtOH, 103°C, 5 min, 300 W	78
$FeCl_3$	EtOH, 103°C, 5 min, 300 W	8

[a]The recovered catalyst could be also recycled.

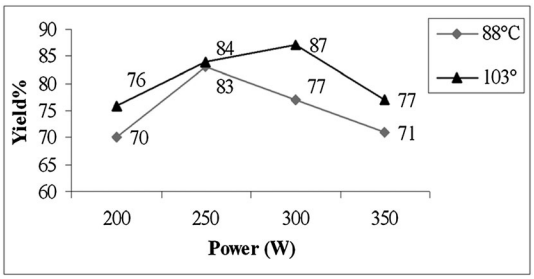


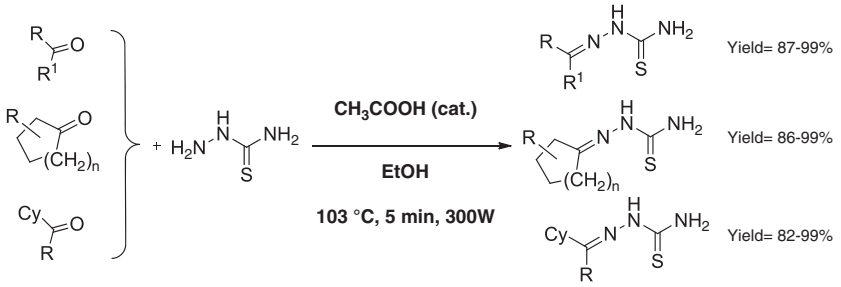
Figure 1. Microwave-assisted synthesis of 1-(propan-2-yliden)thiosemicarbazide in different conditions of applied temperature (°C) and power (W).

As the MW best conditions of temperature, pressure, and solvent were determined, we investigated the effect of exchanging the Brønsted acid catalyst with a large number of Lewis acids or acidic ion exchange resins (Table 2). Not one of the tested acid catalysts showed to be more effective than acetic acid, even though Montmorillonite K10 confirmed to be a good acidic support in MW-assisted synthesis [13].

The best conditions obtained were applied to the synthesis of several thiosemicarbazone derivatives bearing aliphatic, cycloaliphatic, and (hetero)cyclic moieties (Scheme 1). The new MW-assisted method improved the yields and times of reaction we reported for these compounds in our previous communications [2].

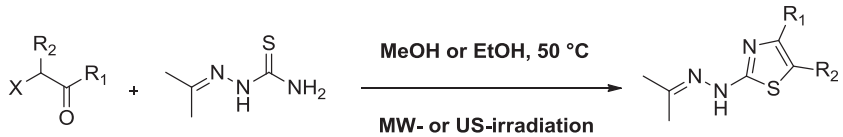
Optimization of the synthesis of (thiazol-2-yl)hydrazine derivatives. According to the good results we obtained using MW irradiation in the synthesis of the thiosemicarbazone derivatives, we applied the same methodology to the Hantzsch cyclization (Scheme 2).

Scheme 1. Application of the optimized conditions to the synthesis of aliphatic, cycloaliphatic, and (hetero)cyclic thiosemicarbazones.



R= R_1= H, alkyl; Cy= heteroaryl, aryl, cyclohexyl, coumarin, benzodioxole, indole, naphtalene; n= 1-4

Scheme 2. Hantzsch cyclization to (4,5-substituted-thiazol-2-yl)hydrazines. Reagents and conditions: EtOH or MeOH, 50°C, 24 h; microwave (MW) or ultrasound (US) irradiation, different solvents, 50°C.



X= Cl, Br
R_1= CH_3, COOEt, Ar, substituted Ar, (hetero)aryl
R_2= H, CH_3

The optimization of reaction conditions also included the screening of apolar (THF), polar protic (water, methanol, and ethanol), and nonprotic (acetone, DMF, and MeCN) solvents. Temperature and time parameters were set according to those previously reported in the literature [14,15]. To test the feasibility of the reaction under greener conditions, we also performed this step in the absence of any solvent, in water, or using only neutral alumina as a support for dehydrohalogenation (Table 3). At 50°C under MW irradiation, the thiazole ring was formed in 10 min against the 24 h required by conventional synthesis [2]. The best yields were obtained in polar solvents: methanol (98%) and acetone (91%). This evidence could be explained by considering that polar solvents tend to absorb the power applied by MW irradiation and transfer it to the reagents better than apolar ones. Moreover, high yields were obtained even without the use of any solvent (79%) or in water (68%): such results provided a scarcely polluting pathway toward the synthesis of (thiazol-2-yl)hydrazine derivatives.

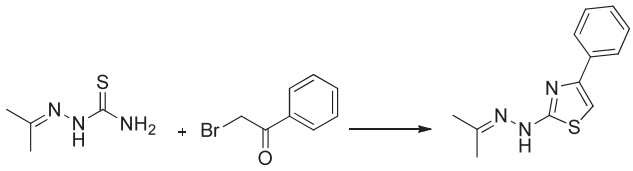
Further investigations were needed to determine the optimum power to apply to reaction mixture to reach the highest yield in methanol. Two new experiments were conducted setting power values from 200 to 350 W at two discrete temperatures (90°C and 115°C) that corresponded to 16 and 48 psi of vessel internal pressure, respectively (Figure 2). The obtained results outlined how increasing both temperature and power had a negative effect on final yields. Moreover, although higher temperature seemed to give better yields at high power values (see yield values at 250, 300, and 350 W), when the applied power decreased, the two curves (90°C and 115°C) tended to coalescence.

Setting the temperature at 90°C and applying to the reaction, the highest power value reached in the variable power test in methanol (150 W); it followed a surprising increase in yield (95%). We concluded that the Hantzsch cyclization was not compatible with high temperature, pressure, or power values. The mild conditions required by Hantzsch cyclization led us back to explore the US-assisted methodology. The reaction was conducted at 50°C under US irradiation. Comparing the yields obtained for compound **2** using the three different methodologies (conventional heating, MW, and US), the best suitable approach resulted to be the MW one (Table 4). To expand the scope of this procedure, a variety of (4,5-substituted-thiazol-2-yl)hydrazine derivatives were synthesized by reacting 1-(propan-2-yliden)thiosemicarbazide with differently functionalized halo-ketones (Table 4).

It is worth noting that the change of electronics in α-chloro and α-bromo-ketones did not affect the overall yields. Even if the yields obtained for Hantzsch reaction using MW, US, and conventional methods were comparable (**2a–2c**), MW irradiation allowed us to synthesize the desired compounds in shorter times and very high yields (see compounds **1**, **2a**, **7**, **9**, **11–14**). In conclusion, we developed an alternative MW and US-assisted procedure both for the thiosemicarbazone synthesis and the following thiazole ring closure (Hantzsch cyclization). The mild reaction conditions,

Table 3

Hantzsch reaction: influence of apolar, polar protic, and aprotic solvents on final yields.



Solvent	Conditions	Yield (%)
THF	50°C, 10 min, variable MW power	57
H_2O	50°C, 10 min, variable MW power	68
EtOH	50°C, 10 min, variable MW power	90
MeOH	50°C, 10 min, variable MW power	98
CH_3COCH_3	50°C, 10 min, variable MW power	91
DMF	50°C, 10 min, variable MW power	76
MeCN	50°C, 10 min, variable MW power	69
Neutral Al_2O_3 (1.5 g)	50°C, 10 min, variable MW power	88
Solvent-free	50°C, 10 min, variable MW power	79

MW, microwave.

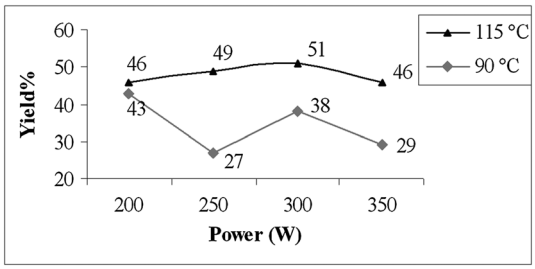


Figure 2. Microwave-assisted Hantzsch cyclization at different applied temperatures (°C) and powers (W).

short reaction times, ease of work-up, and the environmentally friendly nature of the synthetic pathway make the present method an improvement to the known heterocyclic chemistry.

EXPERIMENTAL

Microwave-assisted reactions were performed in a Biotage Initiator 2.0 (Sweden) US-assisted synthesis was performed in a FALC ultrasonic processor (Italy). Chemicals, common solvents, and spectral grade solvents were purchased from Aldrich (Italy) and used without further purification. Melting points (uncorrected) were determined automatically on an FP62 apparatus (Mettler-Toledo). ^{1}H-NMR and ^{13}C-NMR spectra were recorded at 25°C on a 400 MHz Bruker spectrometer using DMSO-d_6 or $CDCl_3$ as solvent. Chemical shifts are expressed as δ units (parts per million) relative to the solvent peak. Coupling constants *J* are valued in Hertz. Elemental analyses for C, H, and N were recorded on a Perkin-Elmer 240 B microanalyzer, and the analytical results were within ±0.4% of the theoretical values for all compounds. Laboratory glassware was oven dried and cooled in a desiccator ($CaCl_2$ desiccant) prior to its use. All reactions were monitored by TLC on 0.2-mm thick silica gel plates (60 F_{254} Merck). Plates were visualized by exposing them to ultraviolet (254 nm) radiation. Merck silica gel 60 70–230 mesh and 0.063–0.200 mm were used for preparative chromatography. Some compounds have been previously reported by others (Table 4), and their chemical–physical data were in full agreement with those reported in the literature.

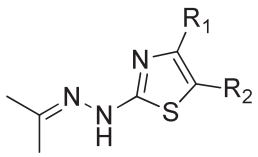
Procedure for the conventional heating synthesis of 1-(alkyliden/cycloalkyliden/aryliden)thiosemicarbazide. The ketone/aldehyde (3.4 mmol), with or without catalytic amounts of acetic acid, was added to a stirring suspension of thiosemicarbazide (0.30 g, 3.4 mmol) in 10 mL of ethanol at 50°C. After 24 h, the suspension was filtered, and the obtained solid was washed with petroleum ether, *n*-hexane, and diethyl ether. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane).

Procedure for the ultrasound-assisted synthesis of 1-(alkyliden/cycloalkyliden/aryliden)thiosemicarbazide. The ketone/aldehyde (3.4 mmol) was added to a stirring suspension of thiosemicarbazide (0.30 g, 3.4 mmol) in 2 mL of absolute ethanol in the presence or not of catalytic amounts acetic acid. The reaction mixture was sonicated for 30 min at 50°C in a US-processor (285 W FALC ultrasonic processor operating at 40 kHz at 40% of the maximum power output). The final suspension was filtered and the obtained solid washed with petroleum ether, *n*-hexane, and diethyl ether. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane).

Procedure for the microwave-assisted synthesis of 1-(alkyliden/cycloalkyliden/aryliden)thiosemicarbazide. The ketone/aldehyde (3.4 mmol) and the corresponding catalyst (reported in Table 2) were added to a suspension of thiosemicarbazide (0.30 g, 3.4 mmol) in 2 mL of absolute ethanol in a 5-mL vessel suitable for MW reactor (2.45 GHz high-frequency microwaves, power range 0–300 W). The vessel

Table 4

Microwave (MW)-assisted synthesis of variously substituted (thiazol-2-yl)hydrazine derivatives in comparison with the ultrasound (US)-assisted and the conventional ones.



Compound	R_1	R_2	Conditions	Yield %
1 [ref. 16]	CH_3	H	MeOH, 90°C, 10 min, MW	99
2 [ref. 16]	Phenyl	H	(a) MeOH, 90°C, 10 min, MW	95
			(b) MeOH, 50°C, 24 h, conventional heating	80
			(c) MeOH, 50°C, 40 kHz, 30 min, US	84
3	Phenyl	CH_3	MeOH, 90°C, 10 min, MW	83
4 [ref. 17]	COOEt	H	MeOH, 90°C, 10 min, MW	89
5 [ref. 3b]	3-Methoxy-phenyl	H	MeOH, 90°C, 10 min, MW	82
6	3-Nitro-phenyl	H	MeOH, 90°C, 10 min, MW	87
7	4-Methoxy-phenyl	H	MeOH, 90°C, 10 min, MW	92
8	4-Fluoro-phenyl	H	MeOH, 90°C, 10 min, MW	79
9 [ref. 18]	4-Chloro-phenyl	H	MeOH, 90°C, 10 min, MW	99
10	4-Bromo-phenyl	H	MeOH, 90°C, 10 min, MW	76
11 [ref. 19]	4-Phenyl-phenyl	H	MeOH, 90°C, 10 min, MW	98
12	2,4-Dichloro-phenyl	H	MeOH, 90°C, 10 min, MW	99
13	2,4-Dimethoxy-phenyl	H	MeOH, 90°C, 10 min, MW	95
14	Naphtalen-2-yl	H	MeOH, 90°C, 10 min, MW	99
15 [ref. 7]	Coumarin-3-yl	H	MeOH, 90°C, 10 min, MW	79

was sealed; the mixture prestirred for 30 s and then heated by MW irradiation for 5 min at fixed temperatures (50°C, 88°C, and 103°C). If not set, the irradiation power reaches its maximum at the beginning of reaction and then decreases to lower and constant values. The vial internal temperature was controlled by an equipped IR sensor. After cooling in a stream of pressurized air, the reaction mixture was filtered and the obtained solid washed with petroleum ether, *n*-hexane, and diethyl ether. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane).

Procedure for the conventional synthesis of 1-(2-phenylthiazol-4-yl)-2-(propan-2-ylidene)hydrazine (2b). 1-(2-Propyliden)thiosemicarbazide (0.2 g, 1.5 mmol) was added to a stirring solution of α-bromo-acetophenone (1.5 mmol) in methanol (2 mL) at 50°C. After 24 h, the suspension was filtered and the obtained solid washed with *n*-hexane and diethyl ether. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 1:1).

Procedure for the ultrasound-assisted synthesis of 1-(2-phenylthiazol-4-yl)-2-(propan-2-ylidene)hydrazine (2c). 1-(2-Propyliden)thiosemicarbazide (0.2 g, 1.5 mmol) was added to a solution of α-bromo-acetophenone (1.5 mmol) in methanol (2 mL). The reaction mixture was sonicated for 30 min at 50°C. The final suspension was filtered and the obtained solid washed with *n*-hexane and diethyl ether. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 1:1).

General procedure for the microwave-assisted synthesis of 1-(2,4-substituted-thiazol-2-yl)hydrazines (1–15). 1-(2-Propyliden)thiosemicarbazide (0.2 g, 1.5 mmol) was added to a solution of the correspondent α-halo-ketone in 2 mL of the chosen solvent (THF, water, ethanol, methanol, acetone, DMF, or acetonitrile), directly mixed with the α-halo-ketone (solvent-free conditions), or in presence of neutral alumina (1.5 g). The mixture was prestirred in a sealed vessel for 3 min and then heated up by MW irradiation for 10 min at fixed temperatures (50°C, 90°C, and 115°C). The reaction mixture was cooled down with pressurized air and filtered, and the obtained solid was washed with *n*-hexane and diethyl ether. The crude mixture was purified by column chromatography (SiO_2, ethyl acetate/*n*-hexane 1:1).

Characterization data for new compounds

1-(5-Methyl-4-phenylthiazol-2-yl)-2-(propan-2-ylidene)hydrazine (3). Gray solid, mp 235–237°C. IR (KBr): ν 3474, 3073, 2951, 1597 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 1.97 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 2.33 (s, 3H, CH_3), 7.38–7.41 (m, 1H, Ar), 7.54–7.58 (m, 2H, Ar), 7.59–7.62 (m, 2H, Ar), 12.46 (br s, 1H, NH, D_2O exch). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 8.52, 18.56, 23.85, 100.87, 126.84, 128.47, 130.73, 134.15, 142.64, 157.55, 169.37. *Anal*. Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13. Found: C, 63.40; H, 5.93; N, 17.01.

1-(4-(3-Nitrophenyl)thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (6). Light yellow solid, mp 215–216°C. IR (KBr): ν 3461, 3083, 2943, 1590 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 2.08 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 6.97 (s, 1H, C_5H-thiaz.), 7.62–7.66 (m, 1H, Ar), 8.12–8.14 (m, 1H, Ar), 8.19–8.22 (m, 1H, Ar), 8.56–8.57 (m, 1H, Ar), 12.42 (bs, 1H, NH, D_2O exch). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 19.89, 25.12, 101.98, 117.73, 127.60, 129.15, 147.12, 159.10, 161.24, 169.08. *Anal*. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.16; H, 4.38; N, 20.28. Found: C, 52.30; H, 4.22; N, 20.16.

1-(4-(4-Methoxyphenyl)thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (7). Yellow solid, mp 230–231°C. IR (KBr): ν 3474, 3073, 2951, 1597 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 2.12 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 6.53 (s, 1H, C_5H-thiaz.), 6.98–7.00 (d, J_o = 8.7 Hz, 2H, Ar), 7.64–7.66 (d, J_o = 8.7 Hz, 2H, Ar), 12.29 (bs, 1H, NH, D_2O exch). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 19.44, 24.89, 55.83, 100.41, 116.23, 125.62, 128.45, 146.48, 159.61, 160.74, 169.12. *Anal*. Calcd for $C_{13}H_{15}N_3OS$: C, 59.74; H, 5.79; N, 16.08. Found: C, 59.87; H, 5.66; N, 15.85.

1-(4-(4-Fluorophenyl)thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (8). Light yellow solid, mp 185–187°C. IR (KBr): ν 3471, 3065, 2947, 1593, 1128 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 2.06 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 6.65 (s, 1H, C_5H-thiaz.), 7.21–7.23 (d, J = 7 Hz, 2H, Ar), 7.72–7.74 (d, J = 7 Hz, 2H, Ar), 12.64 (br s, 1H, NH, D_2O exch.). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 18.79, 24.58, 100.38, 116.27, 128.62, 130.09, 148.53, 159.60, 162.84, 170.11. *Anal*. Calcd for $C_{12}H_{12}FN_3S$: C, 57.81; H, 4.85; N, 16.85. Found: C, 57.65; H, 4.79; N, 16.64.

1-(4-(4-Bromophenyl)thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (10). Light brown solid, mp 240–243°C. IR (KBr): ν 3477, 3060, 2943, 1586, 1027 cm^{-1}. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.94 (s, 3H, CH_3), 1.96 (s, 3H, CH_3), 7.32 (s, 1H, C_5H-thiaz.), 7.60–7.63 (d, J = 10 Hz, 2H, Ar), 7.79–7.81 (d, J = 10 Hz, 2H, Ar), 10.78 (br s, 1H, NH, D_2O exch.). ^{13}C-NMR (100.57 MHz, DMSO-d_6): δ 18.38, 25.26, 104.89, 121.27, 128.13, 132.02, 133.40, 147.50, 170.35. *Anal*. Calcd for $C_{12}H_{12}BrN_3S$: C 46.46; H, 3.90; N, 13.55. Found: C 46.59; H, 4.06; N, 13.32.

1-(4-(2,4-Dichlorophenyl)thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (12). Light brown solid, mp 183–185°C. IR (KBr): ν 3481, 3075, 2944, 1598, 1098 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 2.15 (s, 3H, CH_3), 2.21 (s, 3H, CH_3), 7.01 (s, 1H, C_5H-thiaz.), 7.44–7.46 (dd, J = 8 Hz, J = 4 Hz, Ar), 7.57–7.58 (d, J = 4 Hz, 1H, Ar), 7.65–7.67 (d, J = 8 Hz, 1H, Ar), 12.84 (br s, 1H, NH, D_2O exch.). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 19.36, 24.78, 100.25, 127.44, 128.21, 130.27, 130.89, 133.64, 135.71, 148.73, 151.31, 169.88. *Anal*. Calcd for $C_{12}H_{11}Cl_2N_3S$: C, 48.01; H, 3.69; N, 14.00. Found: C, 47.90; H, 3.52; N, 13.86.

1-(4-(2,4-Dimethoxyphenyl)thiazol-2-yl)-2-(propan-2-ylidene) hydrazine (13). Light yellow solid, mp 110–112°C. IR (KBr): ν 3474, 3073, 2951, 1597 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 0.93 (s, 3H, CH_3C═), 0.96 (s, 3H, CH_3C═), 3.73 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 6.02 (s, 1H, C_5H-thiaz.), 7.35–7.41 (m, 1H, Ar), 7.53 (s, 1H, Ar), 7.62–7.68 (m, 1H, Ar), 11.06 (bs, 1H, NH, D_2O exch). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 19.31, 24.86, 55.79, 56.18, 100.13, 100.95, 107.38, 113.27, 130.67, 148.73, 148.91, 158.29, 163.16, 170.22. *Anal*. Calcd for $C_{14}H_{17}N_3O_2S$: C, 57.71; H, 5.88; N, 14.42. Found: C, 57.54; H, 5.69; N, 14.33.

1-(4-(Naphthalen-2-yl)thiazol-2-yl)-2-(propan-2-ylidene)hydrazine (14). Gray solid, mp 222–223°C. IR (KBr): ν 3475, 3076, 2953, 1602 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$, Me_4Si): δ 2.14 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 6.81 (s, 1H, C_5H-thiaz.), 7.56–7.59 (m, 2H, Ar), 7.69–7.73 (m, 1H, Ar), 7.86–7.91 (m, 3H, Ar), 8.46 (s, 1H, Ar), 12.46 (br s, 1H, NH, D_2O exch). ^{13}C-NMR (100.57 MHz, $CDCl_3$): δ 19.53, 24.88, 100.89, 122.19, 124.75, 125.57, 127.25, 127.66, 128.98, 129.52, 133.77, 134.15, 135.69, 140.589, 1459.69, 169.68. *Anal*. Calcd for $C_{16}H_{15}N_3S$: C, 68.30; H, 5.37; N, 14.93. Found: C, 68.52; H, 5.46; N, 14.74.

Acknowledgments. This work was supported by MIUR (Italy).

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