Transalkylation reaction: green, catalyst-free synthesis of thiosemicarbazones and solving the NMR conflict between their acyclic structure and intramolecular cycloaddition products

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ABSTRACT
A series of arylidene thiosemicarbazides have been prepared by a new method, which was titled as transalkylation. This method is an effective, fast, green and clean method. The mechanism of this reaction has been discussed. Moreover, we clarified the divergences of the structural assignments reported in the literature for the reaction of thiosemicarbazide and aldehydes or ketones in the presence of different catalysts. Where 1,2,4-triazolidine-3-thiones were incorrectly reported as sole product of such reaction, based on occurrence of intramolecular cycloaddition of thiosemicarbazones formed in situ. Our findings proved that the reaction stops at earlier stage of thiosemicarbazone and neither cyclization to 1,2,4-triazolidine-3-thiones nor 2-amino-1,3,4-thiadiazoline take place. We have removed the confusion of the NMR interpretation of thiosemicarbazone and their cycloaddition product by carrying out 1H-NMR, 13C-NMR, 15N-NMR and 1H-15N HSQC experiments with temperature gradient. Furthermore, DFT-NMR calculations have been done to make structural distinguish between the three possible structural isomers for this reaction, namely, 1,2,4-triazolidene-3-thione, 2-amino-1,3,4-thiadiazoline and thiosemicarbazone.

ARTICLE HISTORY
Received 25 February 2019
Accepted 18 July 2019

KEYWORDS
Green chemistry; transalkylation; thiosemicarbazones; 15N-NMR; 1,2,4-triazolidine-3-thione; 2-amino-1,3,4-thiadiazoline

1. Introduction
Thiosemicarbazide and thiosemicarbazone derivatives are especially important due to their diverse biological activity (1–9), including antiviral (10) antibacterial (11), antimalarial (12), antifungal (13), anticancer (14), antitumor (15,16), anti-inflammatory and antiamoebic (17–19) owing to their ease of synthesis and abundance in plants, these compounds have generated great interest for possible therapeutic uses. Furthermore, Metal complexes of thiosemicarbazone (20,21) have gained special attention due to their activity against cancer, small poxvirus, influenza, protozoa, and fungi.

Thiosemicarbazones play a significant role in the regulation of plant growth because of their capability for diffusion through the semipermeable membrane of cell lines (22–24). As well as other industrially important activities, including antifouling and anticorrosion effects (25,26) have also been reported for these compounds. Moreover, The imine bond (C = N) in these compounds are useful in the organic synthesis, in particular for the synthesis of many of pharmaceutical and bioactive heterocycles such as, thiazoles (27–31), 1,3,4-thiadiazoles (32), thiazolidinones (33,34), quinolines (35),...
naphthyridines (36), oxadiazoles (37,38), pyrimidines (39). Water plays an important role in our life. Although, the fact that water as a solvent is the cheapest and most non-toxic solvent, there are many limitations of water use as a solvent in organic synthesis. Additionally, its use as a solvent in organic synthesis avoided sophisticated drying of solvents and substrates before use in many reactions. Therefore, one of the recent challenges, due to the environmental and health concerns, is to use green synthesis in aqueous medium (40–44).

Cyclocondensation of thiosemicarbazide with aldehydes could afford either 1,2,4-triazolidine-3-thiones or 2-amino-1,3,4-thiadiazoline using different reaction conditions (45–56). We observed that there is a structural elucidation confusion between the open structure of thiosemicarbazone and their cycloaddition product with aldehyde. That was obvious in several published articles which reported identical spectral data for both thiosemicarbazones and their cycloaddition product (1,2,4-triazolidine-3-thiones). Thus, many authors incorrectly interpreted the NMR spectral data of alkylidene thiosemicarbazones and reported them as triazolidine-3-thiones (45–48,54,55,57), this confusion arises from the presence of three exchangeable N-H signals in both structures. Herein, we would like to report a green and simple method for synthesis of alkylidene thiosemicarbazide and clarify the structural elucidation confusion between alkylidene thiosemicarbazide, and their cyclized forms.

2. Results and discussion

Conventional and unconventional methods for the synthesis of alkylidene thiosemicarbazide had been extensively reported (58–63). Most of these methods involve condensation reaction of carbonyl compounds and thiosemicarbazide in alcohol with catalytic amounts of acetic acid or mineral acids for about 3–72 h at room temperature or under reflux (59–64). Moreover, recently a more facile synthesis under ultrasound or microwave (MW)-assisted methods were reported (58). Herein, we would like to report a catalyst-free, simpler and cleaner (water as solvent) synthesis of alkylidene thiosemicarbazide in only few minutes reflux.

A reaction of acetone with thiosemicarbazide in water as a solvent proceeded effectively to afford isopropylidene thiosemicarbazide (1) in 95% yield. Subsequent reaction of (1) with different aldehydes 2a-i in aqueous medium gave aryldiene thiosemicarbazide (4) instead of the expected aryldiene isopropylidene thiosemicarbazide 3. We explained this reaction in the term of transalkylidation in which the aryldiene group replaces the isopropylidene in good to excellent yields (72–95%) (Scheme 1). To the best of our knowledge, there are no reports published dealing with transalkylidation reaction either for semicarbazones or thiosemicarbazones. Aromatic aldehydes were added to a hot aqueous solution of acetone thiosemicarbazone 1 to afford the corresponding aryldiene which filtered while hot as a pure precipitate. The insolubility of the aryldiene thiosemicarbazide in hot water makes its isolation as pure product is so easy and gives this method an advantage over the previously reported direct condensation methods of the aromatic aldehydes with thiosemicarbazide that need an extra step for purification of the products.

To evaluate the solvent effect, the reaction between benzaldehyde and acetone thiosemicarbazone 1 was selected as a model reaction and was conducted using various type of solvents (non-polar, polar protic and polar aprotic solvents) such as toluene, H2O, EtOH, DMF and CH3CN.

When the reaction was carried out in aprotic solvent either polar or non-polar solvents, DMF, CH3CN and toluene, no product was detected (Table 1, entries 3–5). Whereas in ethanol, the reaction occurred with good yield (80%) but it requires longer reaction time (4 h) to go to completion (Table 1, entry 2). Interestingly, best results obtained in case of employing water as a solvent (Table 1, entry 1). Based on the criteria such as reaction time (5 min), green nature, cost-effective and excellent yield (95%), water as solvent proved to be

Scheme 1. Transalkylidation reaction.
supreme solvent for the present procedure. Given this excellent result, we decided not to try additional optimization for the experimental conditions and used these to investigate the substrate scope of the reaction (Table 2).

2.1. Substrate scope

To examine the scope of the transalkylidation reaction in an aqueous medium for the preparation of thiosemicarbazones, a series of aromatic aldehydes or ketones with structurally divergent functional groups were examined (Table 2).

It was found that transalkylidation method is tolerant for both electron-rich (Me, OH, Me₂N) and electron-deficient (NO₂, Cl) aromatic aldehydes. But less tolerant for aromatic ketone such as acetophenone. This could be attributed to lower reactivity of ketones compared to aldehydes towards nucleophilic attack. Moreover, the reaction proceeded effectively with unsaturated aldehyde (cinnamaldehyde) to afford the corresponding thiosemicarbazone (allylidenethiosemicarbazide). Interestingly, different positions (o, m, p) on the phenyl group did not show any significant effect on the reaction time, purity and yield percent. Unfortunately, when aliphatic aldehydes were employed the reaction gives the corresponding thiosemicarbazones in poor yield. (Table 2, entries 12,13)

2.2. Reaction mechanism

The findlings that the transalkylidation reaction only takes place in polar protic solvent and doesn’t proceed in aprotic polar or non-polar solvents, suggests an important role for the solvent. So, we proposed a mechanism of the transalkylidation reaction as shown in Scheme 2. Nucleophilic attack of water molecule on the carbon atom of imine group (C = N) of acetone thiosemicarbazone induces the nucleophilic attack of the n-electrons of the imine double bond on the carbonyl group (C = O) of the aromatic aldehyde to afford the intermediate I. Then Proton transfer occur in the second step to give the intermediate II, subsequent loss of water and acetone molecules afford the final product. The nucleophilicity of the solvent (water or ethanol) plays a vital part in this mechanism as it initiates the reaction. Furthermore, its polar character stabilizes the ionic intermediates I and II which was formed during the reaction pathway. That was confirmed when, no product detected either in polar aprotic (DMF, CH₃CN) or nonpolar aprotic solvent (toluene) as they are considered to be non-nucleophilic solvents.

2.3. NMR argument for thiosemicarbazones and their cycloaddition products

All prepared products were fully identified and characterized by analytical, spectroscopic techniques (see supplementary information).

For all of the prepared thiosemicarbazones, the NH₂ group appears as two peaks in proton NMR with one proton for each. This is due to the partial double bond character induced by the thioamide moiety Figure 1, which restricts the free rotation, making the two protons of the NH₂ group diastereotopic or electronically nonequivalent. One is trans to the NH and the other is cis. This is a very common characteristic of many amide or thioamide-containing molecules.

To confirm this assumption, the temperature effect on proton NMR have been investigated for compound 4c. At low temperature, the energy barrier for rotation is high to prevent averaging (fast rotation), the two NH₂ protons are non-equivalent and showed two peaks. Rising up the temperature, signal averaging takes place, and the two protons begin to exchange on the NMR timescale. As this rate of exchange becomes faster, the signal coalescing and finally complete signal averaging to the point where the two protons are equivalent Figure 2.

Additionally, ¹⁵N-NMR and ¹H-¹⁵N Heteronuclear Single Quantum Coherence (HSQC) experiments were carried out for compounds 4c and 4d. As shown in Figures 3 and 4. Three and four ¹⁵N-NMR peaks were observed for 4c and 4d respectively. The four nitrogen peaks of compound 4d were assigned to the three nitrogens of the thiosemicarbazone and the fourth nitrogen corresponds to the nitro group. The cross-peaks due to correlating the ¹⁵N chemical shifts with H chemical shifts which are spin-coupled showed that the nitrogen appeared at highest field correlates to two protons in ¹H-NMR, which clearly proves its chemical nature as NH₂ group. Moreover, cross-peak has been observed between the next nitrogen and the most deshielded
Table 2. Substrate scope for the transalkyldation reaction$^a$.

| Entry | Aldehyde               | Thiosemicarbazone          | Yield |
|-------|------------------------|-----------------------------|-------|
| 1     | \( \text{ArCHO} \)   | \( \text{ArN} = \text{S} = \text{NH}_2 \) | 82    |
| 2     | \( \text{Ph-CH=CHO} \) | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 72    |
| 3     | \( \text{OH-CHO} \)   | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 73    |
| 4     | \( \text{O}_2\text{N-CHO} \) | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 94    |
| 5     | \( \text{Cl-CHO} \)   | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 92    |
| 6     | \( \text{N-CHO} \)    | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 88    |
| 7     | \( \text{NO}_2\text{-CHO} \) | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 95    |
| 8     | \( \text{CHO} \)      | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 78    |
| 9     | \( \text{Cl-CHO} \)   | \( \text{Ph-CH=CH-N} = \text{S} = \text{NH}_2 \) | 77    |

(Continued)
proton indicating NH group. While no cross peak relates the third nitrogen to any proton which corresponds to imine nitrogen (C = N). For compound 4d the most downfield nitrogen appeared is due to the nitro group of the arylidene moiety.

As mentioned before, the reaction of aldehydes or ketones with thiosemicarbazide could afford either condensated product (thiosemicarbazone) or continued further to afford 1,2,4-triazolidene-3-thione or 2-amnio-1,3,4-thiadiazoline as cycloaddition product of thiosemicarbazone intermediate. Herein, we present examples in which incorrect interpretation of NMR was reported. In all of these examples, the products were incorrectly assigned as 1,2,4-triazolidene-3-thione (B) instead of thiosemicarbazones (A) Figure 5. This confusion is due to the appearance of three exchangeable peaks in $^1$H NMR, which wrongly interpreted to three NH peaks correspond to 1,2,4-triazolidene-3-thione instead of NH and NH$_2$ peaks corresponding to thiosemicarbazones. Furthermore, in order to make structural distinguish between the three structural isomers namely: triazolidenethione, thiadiazole and thiosemicarbazone. DFT-NMR calculations were done for the previously optimized possible structures using gauge-including atomic orbital GIAO/B3LYP density functional method with 6-31G basis set by Gaussian 09 software. The atom labelling for the three isomers are shown in Figure 6, and the calculated chemical shifts are listed in Table 3.

Table 2. Continued.

| Entry | Aldehyde | Thiosemicarbazone | Yield |
|-------|----------|--------------------|-------|
| 10    | ![Image](image1.png) | ![Image](image2.png) | 75    |
| 11    | ![Image](image3.png) | ![Image](image4.png) | 42    |
| 12    | CH$_3$CHO |  | nd$^b$ |
| 13    | ![Image](image5.png) |  | nd$^b$ |

Notes: *reaction conditions: 2 mmol of Aldehyde or ketones, 2 mmol of Acetone Thiosemicarbazone 1, 20 ml water, 5–10 min.*

$^b$nd, not detected.

Scheme 2: Transalkylation reaction mechanism.

Figure 1. Resonance of thioamide group in thiosemicarbazones.
Inspection of Table 3 showed that besides the presence of the thiocarbonyl group (C=S) which appears at $\approx 170$–180 ppm, thiosemicarbazone is characterized by its azomethine proton and carbon at chemical shift $\approx 7$–8 and 140 ppm in 1H NMR and 13C-NMR respectively. While cycloaddition of thiosemicarbazone to afford triazolidene-3-thione or thiadiazoline led to disappearance of the azomethine group and presence of saturated carbon involved in the ring formation. The saturated carbon and its proton should appear at chemical shift $\approx 70$–80 and 4–5 ppm in 13C-NMR and 1H-NMR respectively. Furthermore, the thiocarbonyl moiety still exists in triazolidine but absent in case of thiadiazoline. To confirm the above data, acetylation of 1 with acetic hydride in pyridine to afford thiadiazoline 5 has been done (Scheme 3).

Thiadiazoline 5 showed a peak at 80 ppm in 13C-NMR corresponding to the saturated carbon of the triazolidine ring and disappearance of peak at 179.17 ppm corresponding to thiocarbonyl moiety, which agrees to the theoretical calculation.

Based on these findings, cyclocondensation of thiosemicarbazone and aldehydes or ketones affording 1,2,4-triazolidine-3-thiones has been incorrectly reported several times in the literature, either using uncatalyzed reaction (56,65) or using catalyst such as DMAP (46), malononitrile (66), PEG-400 (48), [C16-MPy]AlCl3Br (47), Nanostructured Samarium Doped Fluorapatites (67,68), iron-doped fluorapatite (65) and Sm2O3/Fluoroapatite (45). In all these reports’ authors based their structural assignment on the presence of three exchangeable protons for three NH groups but both peaks at $\approx 80$ and 4 ppm were missing in 13C-NMR and 1H-NMR respectively. Instead, peaks at 140 and 8 ppm were present, which are characteristic for the imine functionality; Moreover, the three exchangeable protons could also correspond to the NH and NH2 of the acyclic isomers as proven before. This indicates that the reaction stopped at the earlier stage of condensation affording thiosemicarbazone and no cyclization to triazolidine had been taking place. The presence of three exchangeable protons accounts for the confusion between the acyclic and the cyclized form in these reports.

To support our idea, the spectral data (1H and 13C) for previously reported 5-phenyl-1,2,4-triazolidine-3-thione or 5-(4-methoxyphenyl)-1,2,4-triazolidine-3-thione (45–48,56,69) together with the spectral data of their acyclic

**Figure 2.** 1H-NMR spectrum of 4c at different temperatures with the bottom spectrum being at low temperature and the top spectrum being at high temperature.
forms (compounds 4a and 4j respectively) obtained from this work are listed in Tables 4 and 5 respectively. Inspection of Table 4 or 5 showed that the reported spectral data of the cyclic forms are identical to that of the acyclic forms. This shows the misleading in the assignment of the structure in these previous studies.

To the best of our knowledge, successful reported synthesis for triazolidine-3-thione neither done by cycloaddition of thiosemicarbazone nor cyclocondensation of thiosemicarbazide with aldehyde or ketones. Alternatively, 1,2,4-triazolidine-3-thione scaffold is readily accessible through a three-component reaction between hydrazines, aldehydes or ketones and potassium thiocyanate in hydrochloric acid (Scheme 4).

Furthermore, beside this method, there is another reaction titled Criss-Cross Cycloadditions of ketazines led to formation of 3,7-diphenyltetrahydro-[1,2,4]triazolo[1,2-a][1,2,4]triazole-1,5-dithione (71) (Scheme 5).

3. Materials and methods

Unless otherwise stated, CH₃CN, DMF and toluene were purified and dried by distillation over 4A molecular sieves. Thiosemicarbazide, aldehydes and ketones were purchased from Sigma-Aldrich and used without further purification. ¹H NMR, ¹³C NMR, and ¹⁵N NMR spectra were recorded at room temperature on a Bruker AC 300 FT, an Avance Bruker DPX 300, or on a Bruker Avance DRX 400 spectrometers.

3.1. Synthesis of 2-(propan-2-yldene)hydrazinecarbothioamide

A hot solution of thiosemicarbazide (0.91 g, 10 mmol) in 20 mL of water was added to Acetone (10 mmol), Then the mixture was heated under reflux for 2 h. After cooling, the reaction mixture was filtered, and the obtained white solid was washed with water. The crude product was purified by crystallization from hot water.

3.2. General procedure for synthesis of alkylidene thiosemicarbazide

Aldehyde or ketones (2 mmol) were added to hot solution of Acetone Thiosemicarbazone 1 (2 mmol) in 20 ml water then the suspension was heated and
stirred for few minutes until starting material 1 is consumed as detected from TLC. The precipitate formed was collected by filtration while hot.

3.3. Synthesis of N-(4-Acetyl-5,5-dimethyl-4,5-dihydro-1,3,4-thiadiazol-2-yl) acetamide (5)

The thiosemicarbazone 1 (1.0 eq.) was added to a stirring solution of acetic anhydride (5.0 eq.) and 3 drops of pyridine. The reaction mixture was heated for 5 h at 100°C. The mixture was poured on ice and the resulting suspension was filtered and washed with water and diethyl ether.

3.4. Computational details

All calculations were performed using the GAUSSIAN 09W. (72) Initially a conformational search for obtaining the most stable conformer was done using the semi-empirical PM3 method, the most stable conformer was subjected to full geometrical optimizations using the DFT and Becke’s three-parameter hybrid exchange functional in combination with the gradient-corrected correlation functional of Lee, Yang and Parr B3LYP/6–31++G(d,p) method (73–75). For all optimizations, the vibrational frequencies were checked for imaginary frequencies to ensure all

Figure 4. (i) $^{15}$N-NMR in DMSO-d$_6$, (ii) $^1$H-$^{15}$N (HSQC) 2D-NMR experiment at ambient temperature (iii) and its expansion for compound 4d.

Figure 5. Structure of thiosemicarbazones A and 1,2,4-triazolidene-3-thiones B.
final geometries corresponded to a true minimum on the electronic potential energy surface. $^1$H-NMR chemical shifts of the previously optimized compound have been calculated using gauge-including atomic orbital GIAO/B3LYP density functional method with 6-31G basis set. To evaluate the relative chemical shifts, the tetramethylsilane (TMS) shielding constants calculated at B3LYP/6-31G method. The inclusion of solvent in the calculations was done via the inclusion of the polarizable continuum model (PCM) (76).

2-(propan-2-ylidene)hydrazinecarbothioamide (1)
$^1$H NMR (300 MHz, DMSO) $\delta$ 9.86 (s, 1H, NH), 7.96, 749 (2s, 2H, NH$_2$), 1.90 (s, 3H, CH$_3$), 1.88 (s, 3H, CH$_3$).$^{13}$C NMR (75 MHz, CDC13) $\delta$ 179.17 (C = S), 152.62(C), 25.87(CH$_3$), 18.41(CH$_3$).

2-benzylidenehydrazinecarbothioamide (4a) (77)$^a$
$^1$H NMR (300 MHz, DMSO-d6) $\delta$ 11.44 (s, 1H, NH), 8.21, 7.99(2s, 2H, NH$_2$), 8.06 (s, 1H, CH = N), 7.78 (dd, $J$ = 6.4, 2.8 Hz, 2H, Phenyl H), 7.42–7.35 (m, 3H, Phenyl H).$^{13}$C NMR (75 MHz, CDC13) $\delta$ 178.83 (C = S), 143.20 (CH = N), 134.98(C), 130.70(CH), 129.51(CH), 128.13(CH).

(E)-2-((E)-3-phenylallylidene)hydrazinecarbothioamide (4b)
$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 11.40 (s, 1H, NH), 8.18 (s, 1H, aromatic H), 7.90 (d, $J$ = 7.7 Hz, 1H, allylidene H), 7.61, 7.33 (2s, 2H, NH$_2$), 7.56 (m, 2H, aromatic H), 7.03 (d, $J$ = 19.0 Hz, 1H, allylidene H), 6.86 (dd, $J$ = 18.3, 6.6 Hz, 1H, allylidene H).$^{13}$C NMR (101 MHz, DMSO-d6) $\delta$ 178.15(C = S), 145.14, 139.31, 136.35, 129.36, 129.31, 127.39, 125.53.

(E)-2-(4-hydroxybenzylidene)hydrazinecarbothioamide (4c) (77)$^a$
$^1$H NMR (400 MHz, DMSO-d6) $\delta$ 11.26 (s, 1H, NH), 9.88 (s, 1H, OH), 8.09, 7.84 (2s, 2H, NH$_2$), 7.96(s, 1H, CH = N), 7.61 (d, $J$ = 8.5 Hz, 2H, aromatic H), 7.78 (d, $J$ = 8.5 Hz, 2H, aromatic H).

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**Figure 6.** Atom labelling for x-substituted benzylidene thiosemicarbazide and its cycloaddition products.

**Scheme 3.** Acetylation of acetone thiosemicarbazone.

| Table 3. Experimental and calculated NMR chemical shifts for thiosemicarbazones 4a, 4d and 4j and their cyclized forms. |
| Assignment | $^1$H NMR chemical shifts$^b$ | $^{13}$C NMR chemical shifts$^c$ |
| --- | --- | --- |
| $^1$H NMR chemical shifts$^b$ | --- | --- |
| Assignment | Exp.$^a$ | Calc.$^b$ | Calc.$^c$ | Calc.$^d$ |
| $^1$C NMR chemical shifts$^c$ | --- | --- | --- | --- |
| Assignment | Exp.$^a$ | Calc.$^b$ | Calc.$^c$ | Calc.$^d$ |
| $X = H$ | | | | |
| H-$16$ | 11.44 | 7.41 | 5.47 | 4.04 |
| H-$13$ | 8.06 | 7.63 | 5.71 | 6.60 |
| H-$19$ | 7.99 | 6.81 | 4.95 | 3.37 |
| H-$20$ | 6.21 | 5.33 | 5.08 | 3.08 |
| $X = OMe$ | | | | |
| H-$16$ | 11.32 | 6.58 | 4.17 | 4.43 |
| H-$13$ | 8.00 | 6.81 | 4.91 | 5.71 |
| H-$19$ | 8.12 | 4.53 | 4.76 | 6.71 |
| H-$20$ | 7.92 | 6.04 | 4.29 | 3.80 |
| $X = NO_2$ | | | | |
| H-$16$ | 11.70 | 6.59 | 4.33 | 4.49 |
| H-$13$ | 8.09 | 6.81 | 5.10 | 5.75 |
| H-$19$ | 8.39 | 4.54 | 4.82 | 7.41 |
| H-$20$ | 8.25 | 6.04 | 4.46 | 3.90 |

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$^a$Exp. is the experimental chemical shift in dimethyl sulfoxide for thiosemicarbazones prepared by transalkylation.

$^b$Calc. is the calculated chemical shift for thiosemicarbazone as acyclic structure.

$^c$Calc. is the calculated chemical shift for 1,2,4-triazolidine-3-thione derivative.

$^d$Calc. is the calculated chemical shift for 1,3,4-thiadiazoline derivative.
Table 4. Comparison between NMR data for (E)-2-benzylidenehydrazine carbothioamide A prepared in this work and for 5-phenyl-1,2,4-triazolidine-3-thione B previously reported in the literature.

| A | B |
|---|---|
| δ₁ (mult, integ) | δ₂ |
| 11.44, 1H | 178.83 |
| 8.21, 1H | 143.20 |
| 8.06, 1H | 134.98 |
| 7.99, 1H | 129.51 |
| 7.78, 2H | 128.13 |

| δ₁ (mult, integ) | δ₂ |
| 11.49, 1H | 178.45 |
| 8.21, 1H | 142.71 |
| 8.04, 1H | 134.64 |
| 8.00 | 130.28 |
| 7.78, 2H | 127.75 |

| δ₁ (mult, integ) | δ₂ |
| 11.49, 1H | 178.45 |
| 8.21, 1H | 142.71 |
| 8.04, 1H | 134.64 |
| 8.00 | 130.28 |
| 7.78, 2H | 127.75 |

2H, aromatic H. ^1^C NMR (101 MHz, DMSO-d₆) δ 177.86 (C = S), 159.70(CH), 129.52(CH), 125.60(C), 116.00(CH). ^1^N NMR (41 MHz, DMSO) δ 306.31(N=), 165.64(NH), 103.35(NH₂).

(E)-2-(4-nitrobenzylidene)hydrazinecarbothioamide (4d) (77)

^1^H NMR (400 MHz, DMSO-d₆) δ 11.70 (s, 1H, NH), 8.39, 8.25 (2s, 2H, NH₂), 8.23 (d, J = 8.0 Hz, 2H, aromatic H), 8.12 (d, J = 8.0 Hz, 2H, aromatic H), 8.09 (s, 1H, CH = N).

Table 5. Comparison between NMR data for (E)-2-(4-methoxybenzylidene)hydrazine carbothioamide A prepared in this work and for S-(4-methoxyphenyl)-1,2,4-triazolidine-3-thione B previously reported.

| A | B |
|---|---|
| δ₁ (mult, integ) | δ₂ |
| 11.32, 1H | 178.05 |
| 8.12, 1H | 161.14 |
| 8.00, 1H | 142.67 |
| 7.92, 1H | 129.37 |
| 7.74, 2H | 127.20 |
| 6.96, 2H | 114.60 |
| 3.79, 3H | 55.73 |

| δ₁ (mult, integ) | δ₂ |
| 11.35, 1H | 177.89 |
| 8.12, 1H | 161.55 |
| 7.99, 1H | 142.46 |
| 7.92, 1H | 129.41 |
| 7.75, 2H | 127.20 |
| 6.97, 2H | 114.18 |
| 3.78, 3H | 55.66 |

| δ₁ (mult, integ) | δ₂ |
| 11.26 | 177.48 |
| 8.03 | 160.67 |
| 7.99, 1H | 142.44 |
| 7.86, 1H | 128.88 |
| 7.01, 1H | 126.58 |
| 6.94 | 114.13 |
| 3.76, 3H | 55.22 |

2H, aromatic H. ^1^C NMR (101 MHz, DMSO-d₆) δ 178.99(C = S), 148.06(C), 141.22(CH), 128.64(CH), 124.24(CH). ^1^N NMR (40.5 MHz, DMSO) δ 366.31(NO₂), 325.15(N=), 169.45(NH), 106.50(NH₂).

2-(4-chlorobenzylidene)hydrazinecarbothioamide (4e) (77)

^1^H NMR (400 MHz, DMSO-d₆) δ 11.48 (s, 1H, NH), 8.24, 8.08 (2s, 2H, NH₂), 8.02 (s, 1H, CH = N), 7.84 (d, J = 8.2 Hz, 1H, aromatic H), 7.46 (d, J = 8.1 Hz, 1H, aromatic H).
aromatic H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 178.54 (C = S), 141.28 (CH = N), 134.68 (C), 133.67 (C), 129.42 (CH), 129.16 (CH).

2-(4-dimethylamino)benzylidene)hydrazinecarbothioamide (4f) (77)

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.17 (s, 1H, NH), 7.99, 7.76 (2s, 2H, NH$_2$), 7.93 (s, 1H, CH = N), 7.58 (d, J = 8.4 Hz, 2H, aromatic H), 6.70 (d, J = 8.5 Hz, 2H, aromatic H), 2.96 (s, 6H, 2CH$_3$). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 177.47 (C = S), 151.85, 143.78, 129.08, 122.00, 112.15, 40.25 (CH$_3$).

2-(3-nitrobenzylidene)hydrazinecarbothioamide (4g) (77)

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.62 (s, 1H, NH), 8.66 (s, 1H, NH), 7.96–7.90 (2s, 1H, NH$_2$), 7.93 (s, 1H, CH = N), 7.58 (d, J = 8.4 Hz, 2H, aromatic H), 6.70 (d, J = 8.5 Hz, 2H, aromatic H), 2.96 (s, 6H, 2CH$_3$). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 178.80 (C = S), 148.87, 140.36, 136.66, 134.01, 130.59, 124.40, 121.85.

2-(3-methylbenzylidene)hydrazinecarbothioamide (4h) (77)

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.17 (s, 1H, NH), 8.20 (s, 1H, CH = N), 8.24 (d, J = 6.5 Hz, 1H, aromatic H), 8.20 (d, J = 7.6 Hz, 1H, aromatic H), 7.69 (m, 1H, 1H, aromatic H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 178.38 (C = S), 142.84, 138.39, 134.57, 130.99, 128.99, 128.04, 125.17, 21.31 (CH$_3$).

2-(2-chlorobenzylidene)hydrazinecarbothioamide (4i) (77)

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.62 (s, 1H, NH), 8.47 (s, 1H, aromatic H), 8.31 (s, 1H, CH = N), 8.12, 8.29 (2s, 2H, NH$_2$), 7.48 (d, J = 7.5 Hz, 1H, aromatic H), 7.44–7.32 (m, 2H, aromatic H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 178.69 (C = S), 138.60, 133.57, 131.95, 131.63, 130.20, 127.92, 127.79.

(E)-2-(4-methoxybenzylidene)hydrazinecarbothioamide (4j) (77)

$^1$H NMR (400 MHz, CDCl$_3$) δ 11.32 (s, 1H, NH), 8.12, 7.92 (2s, 1H, NH$_2$), 7.93 (s, 1H, CH = N), 7.58 (d, J = 8.4 Hz, 2H, aromatic H), 6.96 (d, J = 8.5 Hz, 2H, aromatic H), 3.79 (s, 3H, OCH$_3$). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 178.05 (C = S), 161.14 (C), 142.67 (CH), 129.37 (CH), 127.20 (CH), 114.60 (CH), 55.73 (OCH$_3$).

(E)-2-(1-phenylethylidene)hydrazinecarbothioamide (4k) (77)

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 10.22 (s, 1H, NH), 8.28 (s, 1H, NH$_2$), 8.20 (s, 1H, CH = N), 7.96–7.90 (m, 3H, aromatic H), 7.54–7.15 (m, 3H, aromatic H), 2.30 (s, 3H, CH$_3$). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 179.38 (C = S), 148.30 (C = N), 138.05 (C), 129.67 (CH), 128.70 (CH), 14.46 (CH$_3$).

N-(4-acetyl-5,5-dimethyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetamide (5) (60)

$^1$H NMR (400 MHz, DMSO-d$_6$) δ 11.47 (s, 1H, NH), 2.11 (s, 1H, NH), 8.20 (s, 2H, NH$_2$), 8.24 (d, J = 6.5 Hz, 1H, aromatic H), 8.20 (d, J = 6.3 Hz, 1H, aromatic H), 8.14 (s, 1H, aromatic H). $^{13}$C NMR (101 MHz, DMSO-d$_6$) δ 169.66 (C = O), 168.74 (C = O), 143.18 (C = N), 76.37 (C), 28.82 (CH$_3$), 16.48 (CH$_3$).

Conclusions

In conclusion, we introduced a new, green and a more facile reaction titled transalkylidation which can be used for replacing isopropylidene moiety by arylidene group according a green synthesis of a variety of arylidene thiosemicarbazide. Based on the presence of three exchangeable protons for thiosemicarbazones and their cycloaddition products, it was not so easy to distinguish between them. This confusion promotes us to make full identification for each isomer using spectral data and DFT calculations. Furthermore, simple distinguish between the three isomers could be done using $^{13}$C-NMR. Where the appearance of peaks at $\approx$80 ppm in $^{13}$C-NMR indicates the existence of triazolidine-3-thione ring while lacking a peak at $\approx$80 ppm and presence of peak at 180 ppm only proves the presence of the acyclic form. Furthermore, appearance of a peak at 80 ppm and absence of peak at 180 ppm verifies the presence of thiadiazoline ring Table 6.
Acknowledgements

The authors thank Mr Pasquale Illiano (UNIMI) for doing some NMR spectrum.

Disclosure statement

No potential conflict of interest was reported by the authors.

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