



## Original Research Article

# Solar light photo-catalyzed condensation of aldones with 4-phenylthiosemicarbazide, a green chemistry approach

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### ARTICLE INFORMATION

Received: 22 May 2019

Received in revised: 15 July 2019

Accepted: 01 April 2020

Available online: 12 April 2020

DOI: [10.26655/jmchemsci.2020.3.4](https://doi.org/10.26655/jmchemsci.2020.3.4)

### KEYWORDS

Solar light

Aldones

4-phenylthiosemicarbazide

Catalyst

Green chemistry

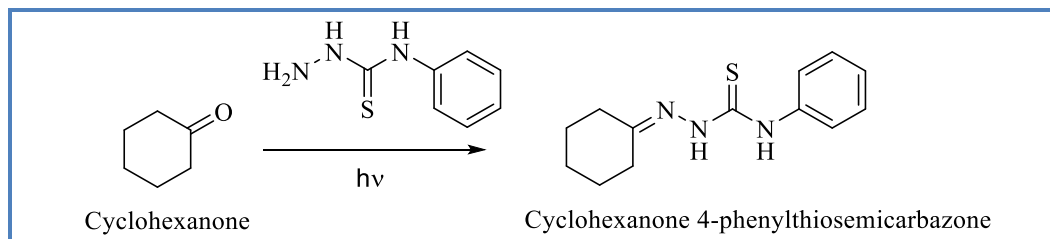
### ABSTRACT

A significant photo-activating effect was evidenced upon investigating the condensation of aldehydes and ketones with 4-phenylthiosemicarbazide in the absence of any type of catalyst (either acido-basic or nucleophilic catalysis). Actual yields were not found superior to those obtained using nucleophilic catalysts; however, the reaction can be run at room temperature with the absence of an additional solvent. A positive hydrophobic effect was also noted. Furthermore, it was found that, the described photo-chemical method did not require an expensive and energy-consuming photo-chemical equipment since the whole process was carried out using natural solar light in regular laboratory glass ware.

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Journal of Medicinal and Chemical Sciences: <http://www.jmchemsci.com/>

### Graphical Abstract

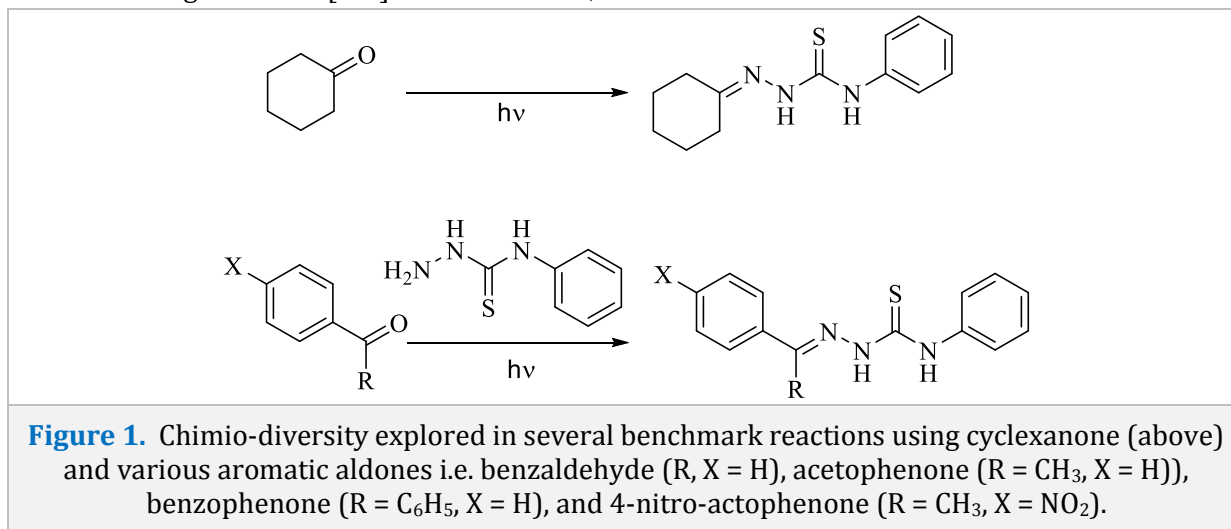




## Introduction

Trypanosomiasis, which has been largely ignored by the pharmaceutical industry sector over the last twenty years or so, can be considered as a neglected disease and constitutes even nowadays a severe health problem for sub-saharian African and Latino-american populations and there remains nowadays an urgent need for less toxic and more importantly affordable drugs to cure this life-threatening infection [1-4]. In this context,

aromatic-substituted thiosemicarbazones (cfr General Template in Figure 1) have been extensively explored as potential drug candidates. The condensation reaction of thiosemicarbazides with aldehydes and ketones (sometimes referred to as aldones, a generic term) implemented to form thiosemicarbazones is acceptably well catalyzed by acid or base catalysis in the general framework of generalized acid-base catalysis [5, 6].



Indeed, in several of our previous publications, we have clearly demonstrated the benefit of the use of nucleophilic catalysis according to the definition already proposed in the 1960's in the pioneering work of *Jenks et al* [7, 8]. Initially, our approach made use of the already described couple aniline: hydrochloric acid (anilinium chloride) as catalyst. It should be pointed out that the whole strategy of nucleophilic catalysis in its fundamental principle is based on the fact of substituting a single reaction (direct condensation) by a two or more consecutive reactions of significantly lower activation energy [9].

This anilinium chloride catalyst is toxic and difficult to be recycled and disposed [10]. In this connection, we therefore developed several

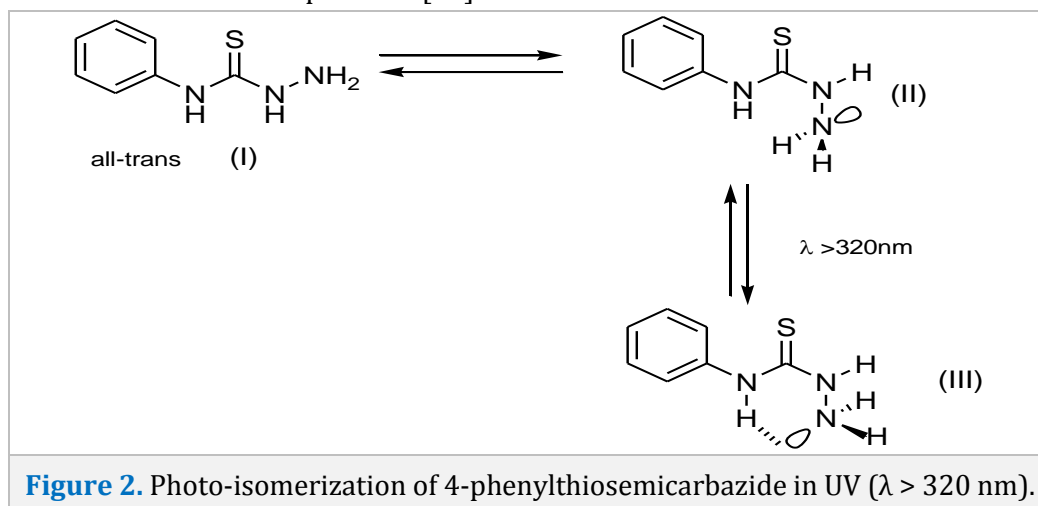
green catalysts (anthranilic acid, and natural aminoacids) in the more general context of green chemistry [9]. These nucleophilic green catalysts represent indeed a substantial progress over older classical acidic catalysts as they allow in general to run these reactions in smooth conditions (lower temperatures, green solvents such as ethanol or even water) [11]. However, these catalysts present the disadvantage that they are generally to be used at least in nearly stoichiometric amounts and in general they are not easily recyclable. It has been known for a long time that solar light may promote many chemical processes and more recently our attention was drawn on the conformational change induced long UV radiations on thiosemicarbazide, which was

likely to boost its reactivity. In order to shed some light into this hypothesis, we ran some benchmark condensation reactions between 4-phenylthiosemicarbazide and various aldehydes and ketone. The purpose of this paper is therefore to report our endeavor along this line.

## Results and Discussion

There is a say in Green Chemistry which states that the best solvent is no solvent. To this, we would like to add that the best catalyst is no *added* catalyst. This may seem paradoxical as catalysis is among the major pillars. As a matter of fact, when working under heterogeneous catalysis conditions, the catalyst can filtered out at the end of the reaction and thus easily recycled, this way of proceeding can be included in the good green laboratory practices [12]. In order to go even further along this path, another perspective is to use light as catalyst. Ancient examples of this approach can be found in the photo-bromination of toluene and the photo-reductive dimerization of benzophenone [13].

Recently, our attention was drawn on a peculiar photo-chemical effect, *i.e.* the dramatic photo-chemically induced configurational isomerization of thiosemicarbazide. A photo-transformation converting the less stable form of the compound into the most stable conformer was induced by irradiation in the UV ( $\lambda > 320$  nm). This photo-chemical effect allowed separation of the IR spectra of the observed thione forms. Structures of both observed isomers were identified by comparison of the separated experimental IR spectra with the calculated spectra for two most stable forms of the compound. The population ratio of the two conformers, prior to irradiation, was estimated to be equal  $\approx 2:1$ . Irradiation of thiosemicarbazide at shorter wavelength UV ( $\lambda > 270$  nm) light induced a photo-tautomeric equilibration generating thiol forms of the compound. A structural representation of this event in Figure 2 depicts that different equilibria were involved. Generally (thio)semicarbazides are found in the crystal in their planar zig-zag (or all-trans) configuration.



**Figure 2.** Photo-isomerization of 4-phenylthiosemicarbazide in UV ( $\lambda > 320$  nm).

This molecular assembly phenylthiosemicarbazones is *per se* relatively rigid due to extensive conjugation of the (thio)carbonyl with the neighboring (thio)ureido nitrogens. The chain-terminal

hydrazino nitrogen is also electronically coupled to its nitrogen neighbor due to a so-called specific *alpha-effect* [6, 14-15]. Upon irradiation at accessible wavelength in the solar spectrum ( $\lambda > 320$  nm), the system undergoes

two motional mutations leading to a flip-flap inversion of the hydrazino nitrogen. In one configurational isomer, the nitrogen lone-pair is *exo* and in the other one, the hydrazino lone-pair is *endo*, leading to an internally hydrogen-bonded. The latter stereoisomer (III) is likely to be less reactive than the form (II) where the lone-pair is externally exposed and therefore by far more nucleophilic than the hydrogen bond stabilized species. Due to the photo-induced interplay of species (I), (II), and (III), it was clearly anticipated that a carefully selected ketone could scavenge species (II) on its passage from (I) to (III), and this more readily than the other ones (I and III).

For the first proof of concept of our project, the choice of the ketone candidate is obviously of paramount importance. The road map was therefore established as such: (a) moderate but sufficient reactivity (aldehydes react too easily and are not challenging candidates); (b) adequate VIS/UV transparency. In this regard, let us keep in mind that we want to demonstrate the catalytic promoting effect of solar light on the condensation of 4-phenylthiocarbazide with a ketone, therefore we do not want to photo-activate the ketone partner, because this would lead to side-reactions and side-products; (c) green character of the ketone candidate (low hazardousness, low toxicity). After thorough examination of different potential candidates, the choice fell finally on cyclohexanone owing to different intrinsic properties: (a) fair reactivity (it was used successfully as benchmark in a previous work; (b) suitable low UV transmittance in the solar spectrum ( $\lambda_{\text{max}} = 280 \text{ nm}$ ); (c) good solvating power (dipolar moment = 3.25; dielectric constant = 18.2, hydrogen bond acceptor) necessary to dissolve the 4-phenylthiosemicarbazide component; (d) possibility to run the reaction in aqueous solution (1 M solution at 25°C); (e) ease of recovery of the ketone substrate (after adding

water, azeotrope cyclohexanone:water boils at 96°C and contains 43% of cyclohexanone).

The experimental set up (deliberately chosen as green as possible, see Experimental Section) was established in this way: 48 h experimentation time to allow for 2 X 6 h daylight solar irradiation over two days, room temperature (no heating, no cooling), no solvent compared to solvent adding, yields reported are actual yields, *i.e.* pure material obtained by single recrystallization and chromatographic check-up. It should be stressed out that this work was carried out in the Brussels, Belgium, EU area (50°51'1.62"N, 4°20'55.61"E) which is not a typically sunny region, and this reinforces the idea that we do not need to be in special areas of the planet to carry out such reactions. Other works somewhat similar to this one, which will be reported under a separate cover, were equally carried out successfully in Cotonou, Benin, West Africa (6°21'55" N, 2°25'05" E).

The results of the various salient experiments are tabulated in Table 1. First, we had to establish the zero line, *i.e.* reaction in the dark in absence of catalyst. The most salient experimental set-ups are to be found in the [Table 1](#). While many photochemical experiments are done in absence of oxygen and in the presence of trace amounts of a Bronsted acid (*i.a.* such as acetic acid), we did not take this precaution initially. As one can see, these precautionary measures were unimportant since they did not affect significantly the final yield. As a general rule, although of a good grade reagents, solvents were used as such, straight from the bottle! Reaction carried out in absence of solvent was found very effective. However, it required significant handling (and energy expenditure) after the reaction to isolate the final compound in a pure state (see Experimental Section). Altogether, best practical reaction conditions were met in the

presence of water, for example by using the azeotropic mixture obtained by distillation after recovering the final compound by addition of water and distilling excess of cyclohexanone (see Experimental Section). It is noteworthy that all experiments did not require any stirring over the whole process.

The puzzling fact is as to why better yields were obtained when the reactions were performed in the presence of small increments

of water. It is likely that water create a hydrophobic effect and therefore generates lipophilic clusters where both partner are imprisoned and submitted to high pressure due to the water hydrogen bond continuum (positive participation of a hydrophobic effect). Moreover, water is more translucent than cyclohexanone in this part of the solar light spectrum.

**Table 1.** Reaction set-up conditions for the condensation of 4-phenylthiosemicarbazide with cyclohexanone.

Exp	light exposure (h)	solvent	T (°C)	Yield (%)
1	Dark (24)	none	22	trace
2	Dark (24)	1% AcOH	22	Trace
3	Dark (2)	1% AcOH	80	72
4	Sun (12)	none	18-27	67
5	Sun (12)	none	18-27	98
6	Sun (12)	2-PrOH	18-27	82

## Experimental Section

### General procedures

Melting points (uncorrected) were determined in open capillary tubes using a Büchi SMP 20 melting point apparatus. IR spectra were recorded using a dispersion of the product in KBr disks by means of a Perkin-Elmer Model 297 spectrometer. <sup>1</sup>H and <sup>13</sup>C-NMR spectra were recorded using a 400 MHz Bruker spectrometer. The NMR spectra were recorded at ambient temperature using tetramethylsilane (TMS) as internal reference. All compounds reported had IR, <sup>1</sup>H and <sup>13</sup>C-NMR, MS, and elemental analysis data consistent with their structure. The experimental elemental analysis figures were found within 0.4% of the calculated values. Thin layer chromatography (TLC) analyses were performed on Merck TLC plates (silica gel, 60F 254, E. Merck, Darmstadt, Germany, ref. 5735). All compounds reported here were found chromatographically homogeneous in two standard solvents, i.e.

acetone/toluene/cyclohexane (5:2:3, v/v/v) and methanol/chloroform equilibrated with ammonia (1:9, v/v). All reagents were purchased from Sigma/Aldrich. The synthesis of cyclohexanone 4-phenylthiosemicarbazide is representative of all other benchmark reactions done using solar light as reaction-activating component and a set of selected aldones (benzaldehyde, 4-nitroacetophenone, and benzophenone) to cover up a field of chimio-diversity.

### Cyclohexanone 4-phenylthiosemicarbazone

4-Phenylthiosemicarbazide (1.67 g, 10 mmol) and cyclohexanone (9.8 g, 100 mmol) were irradiated under solar light on a bright sunny day for 12 h, treated with excess water (100 mL), the resulting mixture was distilled in order to remove the cyclohexanone:water azeotrope (which boils at 95 °C and contains 39% of cyclohexanone), the resulting residue was then rapidly cooled in an ice bath and the formed crystals were washed with a small volume of a diluted solution of hydrochloric acid, (0.01 N) to

dissolve any residual 4-phenylthiosemicarbazide. When reactions were performed directly in neat water, the resulting crystals formed a somewhat gummy material which had to be recrystallized from little ethanol to give shiny glossy crystals. Mp: 186-188°C (unaffected upon further recrystallization from 95% ethanol), <sup>1</sup>H-RMN (CDCl<sub>3</sub>): δ (ppm): 9.3 (s, 1H, -CSNH-Ph); 8.6 (s, 1H, =NNH-); 7.6 (s, 2H, ortho ArH); 7.3 (s, 2H, meta ArH); 7.2 (s, 1H, para ArH); 2.4 (s, 4H, alicyclic H); 1.7 (s, 6H, alicyclic H); <sup>13</sup>C-RMN (CDCl<sub>3</sub>): δ (ppm): 173.4 (C=S); 154.45 (C=N); 136.52 (ipso aromatic C); 127.21 (meta aromatic C); 124.31 (para aromatic C); 122.61 (ortho aromatic C); 33.91; 25.53; 25.37; 24.39; 23.92 (alicyclic C).

*1-(4-nitrophenyl) ethylidene)-4-phenylthiosemicarbazide.*

A room temperature solution of 4-nitroacetophenone (165 mg, 1 mmol) and 4-phenylthiosemicarbazide (167 mg, 1 mmol) in 2.5 mL of methanol were placed in a scintillation-counter stoppered glass tube and exposed to bright sun light for 2 x 6 h. The solution turned gradually to a slurry, after exposure it was cooled in an ice bath for 1 h, and filtered on a Büchner funnel to give 300 mg (98% yield) of TLC-pure vacuum-dried yellow crystals. Mp: 196-198°C (unaffected by further recrystallization from methanol), <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ(ppm): 9.35 (s, 1H, NH), 8.92 (s, 1H, NH), 8.27-7.27 (m, 9H, ArH), 2.41 (s, 3H, CH<sub>3</sub>), <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ(ppm): 177.13 (C=S), 148.99 (C=N), 145.05, 143.82, 138.23 (aromatic C), 129.60, 128.21, 127.81, 127.20, 125.00, 124.61 (aromatic CH), 14.44 (CH<sub>3</sub>).

## Conclusion

Conclusively, we found a significant photo-promoting effect showing the validity of our

initial assumptions. However, this approach has some drawbacks and especially with regard to the scope of the reaction. In other words, the domain of applicability remains somewhat limited by the photo-stability of the ketone partner substrate. For instance, the question can be raised whether benzophenone will undergo photo-reductive dimerization much faster than condensation with the thiosemicarbazide nucleophile. However, the range of applicability could possibly be extended using more potent and more wavelength-selective light sources as well as additional photo-sensitizers or UV-filters. We are now further exploring these pathways along the lines exposed above. Additionally, as it could be anticipated, on a pure pragmatism point of view, actual yields were not far superior to those obtained using nucleophilic catalysts; however, the reaction can be run at room temperature and in absence of adjunct solvent, and furthermore it does not require special expensive and energy-consuming photo-chemical equipment since the overall process can be carried out using natural solar light in regular glass ware. As such, the photo-chemical method presented above is to be regarded as an approach which complies to the requirements of Green Chemistry. Additional works need to be done to clearly define the scope of the solar-light promoted reaction described above. Also, it would be worthwhile to revisit many supposedly "old" reactions on the point of view of their photo-chemical promotion provided one of the protagonist components is light-sensitive and that this characteristic can be used to our green chemist's advantage.

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**How to cite this manuscript:** Steeve M. Adjibodé\*, Urbain C. Kasséhin, Sedami Fagla Medegan, Joëlle Quetin-Leclercq, Fernand A. Gbaguidi, Jacques H. Poupaert, Solar light photo-catalyzed condensation of aldones with 4-phenylthiosemicarbazide, a green chemistry approach. *Journal of Medicinal and Chemical Sciences*, 2020, 3(3), 228-234. DOI: [10.26655/jmchemsci.2020.3.4](https://doi.org/10.26655/jmchemsci.2020.3.4)