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Solvent effect and catalysis in the synthesis of thiosemicarbazone derivatives from ketones and 4'-phenylthiosemicarbazide

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In this paper, we performed a series of experiments aiming at establishing the solvent effects in the condensation of 4-phenylthiosemicarbazide with 4-nitroacetophenone to form the expected thiosemicarbazone derivative, reaction which was chosen as pilot reaction, having in mind to set up optimal reaction conditions for the future elaboration of a compound library of thiosemicarbazone derivatives. Methanol was found to be a suitable solvent for this purpose. As a general rule, acid catalysis was found to perform better than base catalysis. General acid-base catalysis performed also in a quite satisfactory manner and in this connection, among the catalytic systems, anilinium chloride performed optimally allowing the reaction to go to completion at room temperature in excellent yield within 24 h at room temperature. A series of six bench mark molecules of increasing steric effect were synthesized in fair to good yields using this method.

Key words: Thiosemicarbazone, thiosemicarbazide, solvent effect, acid-base catalysis, alpha-effect, nucleophilic catalysis, anilinium catalysis.

INTRODUCTION

There is nowadays considerable contemporary interest in the medicinal chemistry of Schiff-base compounds. In this regard, thiosemicarbazones have long been known, for they have shown interesting pharmacological activities both as free ligands and their metal complexes (Lovejoy and Richardson 2002; Belicchi-Ferrari et al., 2005).

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Although apparently straight forward, the synthesis of thiosemicarbazone derivatives from aldehydes and ketones with aryl substituents can be hampered by the formation of by-products (Cowley et al., 2005).

Hydrazine derivatives are particularly reactive toward electrophilic centers due to the so-called « alpha effect ». The alpha effect refers to the increased nucleophilicity of a function due to the presence of an adjacent (that is, alpha) atom carrying a lone pair of electrons, as for example in hydrazines and related structures, hydroxylamines, the hypochlorite ion, and the hydroperoxide anion. This effect was first evidenced by Jencks and Carriuolo in a series of kinetics experiments in 1960, which demonstrates the extra-nucleophilicity of these functions without concomitant increase of the basicity (Jencks et al., 1960a, b). Because of the development of charges in the transition state, the alpha effect is also dependent on the solvent but not in a predictable way (Buncel and Um 2004). Thiosemicarbazide, a hydrazine derivative, readily reacts with a variety of aldehydes and ketones (aldones) to yield interesting compounds thiosemicarbazones owing to their promising biological activities. Indeed, thiosemicarbazones and related compounds that is, Semicarbazones, hydrazones, hydrazides, and dithiocarcarbazates have drawn attention in medicinal chemistry due to their potential as antibacterial, antiviral, antineoplastic, and antimalarial activities (Pavan et al., 2010).

Although the literature holds a plethora of methods for synthesizing thiosemicarbazones from aldones and thiosemicarbazides (Sayer and Jencks 1969; Thygesen et al., 2010), very few studies have pointed out the intervention of the *alpha* effect and, to our best knowledge no study so far has been devoted to a, thorough investigation of the effect of the solvent and the catalysis on this chemical process. In this work, we endeavored to create simple and reliable reaction conditions that truly serve the synthetic organic chemists community in the elaboration of a concise thiosemicarbazone compound library.

EXPERIMENTAL

General procedures

Melting points were determined using an electro-thermal melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 457 spectrometer using KBr pellets. Wave numbers are expressed in cm^{-1}, ^{1}H, and ^{13}C-NMR spectra were recorded at ambient temperature on a Brucker Avance 400 MHz spectrometer. Compounds were dissolved in $CDCl_3$ and chemical shifts are expressed in the δ scale with TMS as internal standard. Thin layer chromatography analyses were performed on Merck thin-layer chromatography (TLC) plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All reported compounds were routinely checked in two standard solvents that is, acetone/toluene/cyclohexane (solvent A, 5:2:3, v/v/v) and chloroform/methanol (solvent B, 90/10, v/v). Reverse-phase thin layer chromatography conditions were: high performance thin-layer chromatography (HPTLC) plates RP-18 F-254 S (Merck), methanol: water (75/25, v/v). All compounds reported were found homogenous under such TLC and high-performance liquid chromatography (HPLC) conditions. All reagents were purchased from Aldrich. All solvents were of the ACS. Reagent grade (Aldrich).

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

To a room temperature solution of 4-nitroacetophenone (1.65 g, 10 mmol) and 4-phenylthiosemicarbazide (1.67 g, 10 mmol) in 50 ml of methanol were added in sequence 500 mg of freshly redistilled aniline and 500 µl of concentrated hydrochloric acid. The solution turning gradually to a slurry was magnetically stirred at room temperature for 24 h, rapidly cooled in an ice bath, and filtered on a Büchner funnel to give 310 mg (99% yield) of TLC-pure vacuum-dried yellow crystals.

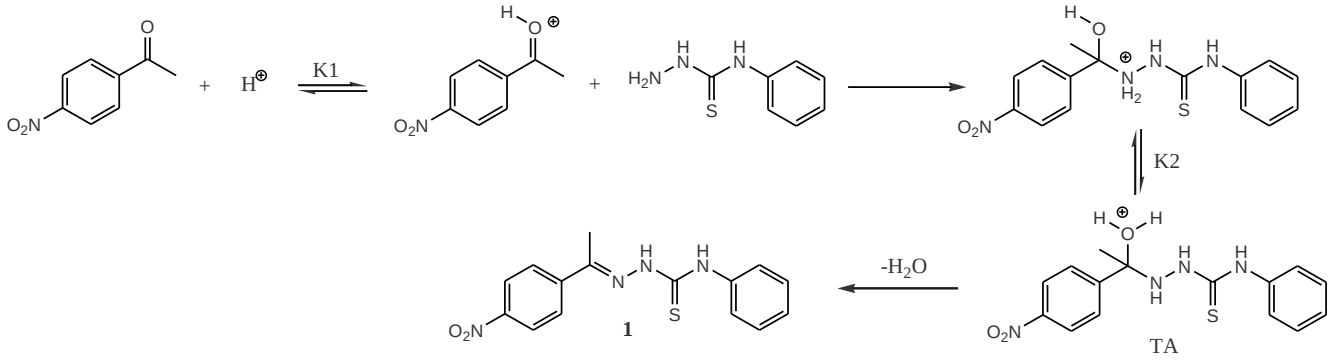
Mp: 196-198°C (unaffected after recrystallization from methanol), ^{1}H-NMR ($CDCl_3$) δ(ppm): 9.35 (s, 1H, NH), 8.92(s,1H, NH), 8.27-7.27(m, 9H, ArH), 2.41(s, 3H, CH_3), ^{13}C-NMR ($CDCl_3$) δ(ppm): 177.13, 148.99, 145.05, 143.82, 138.23, 129.60, 128.21, 127.81, 127.20, 125.00, 14.44

RESULTS AND DISCUSSION

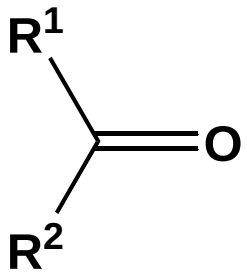
According to Jenks and Carriuolo (1960a, b); Sayer et al. (1969; 1973), Cordes and Jenks (1962a) and Palmer and Jencks (1980) thiosemicarbazides formation exibits a change in rate-determining step at ~ pH 4 with rate-determining nucleophilic attack to form the tetrahedral adduct (TA) below and rate-determining dehydration of this transition state above this pH. On the basis of this and other observations, the authors concluded that thiosemicarbazone formation is submitted to general acid base catalysis. Accordingly, the mechanism of thiosemicarbazone formation can be summarized as shown in the Scheme 1 and 2. Since water is produced in the final step and all steps are reversible, it can be anticipated that addition of water in the reaction medium will inhibit the overall reaction.

The theoretical works carried out by Jenks and Carriuolo (1960a); Sayer and Jencks (1969, 1973); Cordes and Jenks (1962b) and Palmer and Jencks (1980) have paved the road in our set-up of the experimental part. Initially, we decided to use a mole to mole interaction of 4'-nitroacetophenone with 4-phenylthiosemicarbazide as pilot-reaction, due to the insolubility and crystallinity of the end- product, which allow for straightforward recovery of the pure target compound by simple filtration. Moreover, we carried out a limited series of experiments aiming to establish the solvent effect. As most of the reported syntheses use methanol or ethanol as solvent and glacial acetic acid as catalyst, we first examined the reaction in methanol at room temperature without catalyst (entry 1, Table 1). A very modest yield of 16% was obtained after 10 days equilibration.

When the reaction was performed using acetic acid 1% (v/v) as catalyst, a more than acceptable yield of 86% was obtained after 24 h (entry 2). Heating the same



Scheme 1. Mechanism of thiosemicarbazone formation according to Jenks and Carriuolo (1960a, b); Sayer et al., (1969, 1973) Cordes and Jenks (1962a) and Palmer and Jencks (1980).



Scheme 2. General structure of Aldones.

Table 1. Evaluation of solvent effect on the reaction yield.

Entry	Time (h)	Solvent	Catalyst	Yield (%)
1	~ 240[a]	Methanol	no catalyst	16
2	24[b]	Methanol	Acetic acid	86
3	3[b]	Methanol	Acetic acid	88
4	3[b]	Ethanol	Acetic acid	58
5	3[b]	2-Propanol	Acetic acid	67
6	3[b]	Dioxane	Acetic acid	33
7	3[b]	Acetonitrile	Acetic acid	91
8	3[b]	Tetrahydrofuran	Acetic acid	45

a = Reaction performed at room temperature (~ 22°C), b = reaction performed at 65°C.

reaction mixture under reflux for 3h resulted in a yield of 88% (entry 3). Following entries (entries 4-8) using the same reaction conditions reflect the influence of the solvent polarity as a diminution of the dielectric constant leads to a concomitant decrease of the yield with an apparent exception for ethanol. The apparent counter-performance (entry 4) is due to the fact that ethanol contains 5% water, and water is known to inhibit this condensation. A second series of experiments was set up to establish the effect of acid catalysis (Table 2, entries 3 and 9-14). Here we observe the impact of the acid strength. As the pKa diminishes, the yield increases.

In the Table 3 (entries 15-20) we examined the base catalysis. As this level, roughly speaking, when the base strength diminishes, the yield equally decreases (compare entry 15 to entry 20). When we compare the behavior of triethylamine (entry 15, pKa 10, 65) to aniline (entry 20, pKa 4, 62), we observe a net decrease of the yield, and the intermediate compounds proceed according to the same correlation.

Table 2. Evaluation of acid catalysis effect on the reaction yield.

Entry	Time (h)	Solvent	Catalyst	pKa	Yield (%)
3	3	Methanol	Acetic acid	4.76	86
9	3	Methanol	Formic acid	3.77	95
10	3	Methanol	2-hydroxyacetic acid	3.83	92
11	3	Methanol	Trifluoroacetic acid	0.23	99
12	3	Methanol	Montmorillonite K-10	-3.0	32
13	3	Methanol	Hydrochloric acid	-8.0	99
14	3	Methanol	Phosphoric acid	-2.12	98

Table 3. Evaluation of base catalysis effect on reaction yield.

Entry	Time (h)	Solvent	Catalyst	pKa	Yield (%)
15	3	Methanol	Triethylamine	10.65	81
16	3	Methanol	Morpholine	8.36	71
17	3	Methanol	Piperidine	11.22	73
18	3	Methanol	Piperazine	5.68	68
19	3	Methanol	*N,N*-dimethylaniline	5.07	51
20	3	Methanol	Aniline	4.62	43

Table 4. Evaluation of general acid-base catalysis effet on the reaction yield.

Entry	Time (h)	Temperature (°C)	Solvent	Catalyst[a]	%
21	3	65	Methanol	Aniline/acetic acid	70
22	3	65	Methanol	Aniline/formic acid	82
23	3	65	Methanol	Aniline/ hydrochloric acid	99
24	3	65	Methanol	Triethylamine/ hydrochloric acid	91
25	3	65	Methanol	L-Proline	75
26	3	65	Methanol	TEAB/NaOH	75
27	3	65	Methanol	Piperidine /hydrochloric acid	68
28	3	65	Methanol	4-aminopiperidine hydrochloride	97
29	3	80	Ethanol	Aniline/hydrochloric acid	92
30	24	20	Methanol	Aniline/hydrochloric acid	99
31	1	20	Methanol	Aniline/hydrochloric acid	92
32	3	65	Methanol	Guanidine hydrochloride	59

[a]1 % vol. catalyst was used through-out the whole series of experiments presented in Table 1.

Finally, in the Table 4 (entry 21 to entry 28), we investigated the generalized acid-base catalysis. As expected according to the works of Jenks and Carriuolo. (1960a); we found out that aniline hydrochloride was the best performer (entry 23). Indeed, catalysis of semicarbazone formation by aniline proceeds via the rate-determining formation of a Schiff base between substrate and catalyst, followed by a rapid attack of semicarbazide on the Schiff base to give the semicarbazone.

Catalysis by anilinium ions is much more efficient than catalysis by other acids of comparable acid strength (Cordes and Jenks 1962a; Dirksen et al., 2006). It has been shown, (Cordes and Jenks 1962b; Dirksen et al., 2006; Thygesen et al., 2010) also that aniline accelerates hydrazone formation from alpha diketones and hydrazide *via* the transitory formation of an iminium intermediate. The same finding (aniline nucleophilic catalysis) was reported in the case of carbohydrate oxime formation. 4-Aminopyridinium chloride (entry 28) mimicks the behavior of anilinium (entry 23). All other salts (Table 4) perform in a less efficient manner. Interestingly enough, we can claim that anilinium chloride was able to improve the score of ethanol (entry 4) pushing up the yield up to 92% (entry 29). To further validate the value of the couple MeOH: anilinium chloride, we performed

Table 5. Synthesis of benchmark molecules.

Compounds	R^1	R^2	Yield (%)
2	CH_3	H	99
3	CH_3	C_6H_5	78
4	CH_3CH_2	C_6H_5	82
5	Cyclo-C_6H_{11}	C_6H_5	80
6	C_6H_5	C_6H_5	72
7	t-C_4H_9	C_6H_5	71

reaction at room temperature (entries 30-31). Reaction went to completion after 24 h equilibration (entry 30) and a decent 92% yield was reached already after 1 h reaction (entry 31).

The synthesis of thiosemicarbazones and hydrazones is generally considered as a not very challenging task for the synthetic organic chemist. However, already at the very early beginning of this research, it became clearly apparent that reaction conditions had a deep impact on the actual yield of the pilot reaction, and this reinforced our interest in pursuing our endeavor in finding appropriate reaction conditions for the elaboration of a compound library. At this stage, it is worth noting that Anayive et al. (2007) reacted the same 4-nitroacetophenone with 4-methylthiosemicarbazide, a reagent known to be more reactive than 4-phenylthiosemicarbazide (David et al., 2007) (compare entry 1 and 2, and following entries).

These authors indeed had in order to complete this reaction to reflux the reaction medium containing ethanol for 7 h in the presence of sulfuric acid while in our conditions, using anilinium chloride as catalyst, the reaction can be performed in 1 h at room temperature with a 90% yield. In order to further warrant our conclusion, as a proof of concept, we carried out a short series of syntheses of benchmark molecules using simple carbonyl substrates of increasing steric effect using the same conditions as in experiment entry 30 (Table 5). The thiosemicarbazones were obtained in fair to good yields (71 to 99%).

Conclusion

In this paper, we performed a series of experiments aiming at establishing the solvent effect and the catalysis (acid, base and acido-basic conditions) in the formation of (1-(4-nitrophenyl)ethylidene)-4-phenylthiosemicarbazide (**1**) from 4-nitroacetophenone and 4-phenylthiosemicarbazide chosen as pilot reaction, having in mind to set up optimal reaction conditions for the future elaboration of a compound library of thiosemicarbazone derivatives. Methanol was found to be an optimal solvent for this purpose. Among the catalytic systems, anilinium chloride was the best performer allowing the reaction to go to completion at room temperature in excellent yield, and in our continuing efforts to find medecines against *Trypanosoma brucei brucei*. It should be noted that compound **1** was found to exhibit a good antitrypanosomal activity (IC_{50} =12, 06 µM) and a more important selectivity (IS=102, 98). We are therefore now using this method to synthesize a first compound library of approximately 500 thiosemicarbazone congeners (Kasséhin et al., 2013).

Conflict of Interest

The authors have not declared any conflict of interest.

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