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Research Article

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Synthesis of antitrypanosomal thiosemicarbazones using anthranilic acid as an innovative *Green* nucleophilic catalyst

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ABSTRACT

Trypanosomiasis constitutes a severe health problem for sub-saharian African and latin American population and there is an urgent need for better drugs to cure this life-threatening disease. In this context, aromatic thiosemicarbazones appears attractive drug candidates. The condensation reaction of thiosemicarbazides with aldehydes and ketone to form thiosemicarbazones is very efficiently catalyzed by nucleophilic catalysis in the general context of generalized acid-base catalysis. In this paper, we developed anthranilic acid as a general purpose green catalyst. Methanol appears to be a performants solvent for this reaction. In general, good to excellent yields in the range of 70-99% were obtained. In the condensation of various ketones with 4-phenylthiosemicarbazide the choice of anthranilic acid as catalyst was rationalized on the basis of mechanistic considerations.

Key words: *Green Chemistry,* Nucleophilic Catalysis, trypanosomal infections, thiosemicarbazones, anchimeric assistance.

INTRODUCTION

Trypanosomiasis is the generic name of several diseases in vertebrates caused by parasitic protozoan trypanosomes of the genus Trypanosoma. It is estimated that approximately 30,000 people in 36 countries of sub-Saharan Africa suffer from human African trypanosomiasis (also called sleeping sickness), which is caused by either *Trypanosomabruceigambiense* or *Trypanosomabruceirhodesiense*[1, 2, 3]. The other human form of trypanosomiasis, called Chagas disease, causes 21,000 deaths per year, mainly in South America. Diagnosis is often not correctly pinpointed in the early phase of the disease due to the non-specific nature of the symptoms. Pentamidine and Suramin are used for treatment in the first phase. Melarsoprol, nifurtimox, and eflornithine are drugs used in second phase of the disease. However, none of these remedies are optimal in terms of adverse side-effects and ease of administration. There is therefore an urgent need for research in this field, especially for discovering new drugs with improved safety and efficacy. [4]

Thiosemicarbazones exhibit a wide variety of important useful therapeutic properties among which we can cite:anti-tumoral [5,6], antimalarial [7] anticonvulsant [8], antibacterial [9,10], antiviral [11, 12], antifungus[13], antitrypanosomal [14,15,16] anti-inflammatory ones [16], analgesic [16], and potential inhibitory properties of many key enzymes [17] .

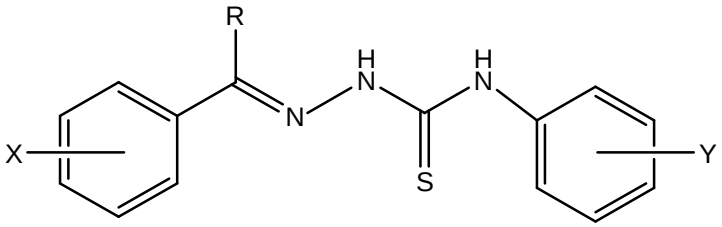

Figure 1: General structure of antitrypanosomal thiosemicarbazones

Over the last 10 years, we became interested in these multi-faceted compounds owing to their significant potential in the treatment of infections caused in particular by trypanosomes. From previous publications in the field from our group, we became able to derive a general structure-activity relationship profile [18, 19]. Best compounds respond to the general structure shown in the Figure 1, where R is an alkyl, aralkyl, or aromatic substituent while X and Y are classical aromatic substituents (typically hydroxy, methoxy, chlorine, etc…). The synthesis of thiosemicarbazones derived from aldehydes and aliphatic ketones is well documented in the literature and this process is not considered as a big challenge for the synthetic organic chemist since, for example for aldehydes, this condensation proceeds in general rapidly even at room temperature. Aromatic ketones, however, are much less reactive and require rather high reaction temperatures and more extended reaction time compared to the former ones. Search for an efficient catalysis and an adequate solvent was thus planned in the context of *green chemistry* [20, 21, 22],to circumvent this crucial problem. *Green chemistry*, also sometimes referred to as sustainable chemistry, is a spirit in chemical research and engineering that encourages the design of products and processes that minimize the use and generation of hazardous substances or pollutants. It should be noted also that the condensation of thiosemicarbazides with ketones is a process of high atom economy (typically superior to 90%). For a example, entry #1 (Table 2) is endowed with an atomic economy of 94.6%. Atom economy is indeed an important concept of green chemistry philosophy and one of the most widely accepted ways to measure the "greenness" of a process or synthesis [23].

In two previous publications concerned with the expeditious synthesis of antitrypanosomalthiosemicarbazones derived from aromatic aldehydes and ketones, we clearly demonstrated the benefit of the use of nucleophilic catalysis in the overall context of the so-called generalized acid-base catalysis, according to the definition already proposed in the 1960's in the pioneeringwork of Jenks *et al*. [24, 25]. More precisely, our approach made use of the couple aniline: hydrochloric acid (anilinium chloride) as catalyst. Due to the general instability of anilines towards oxygen, in the practice aniline has to be redistilled prior use. We therefore searched for a more practical and *greener* alternative to this efficient catalyst. Anthranilic acid (*i.e.*2-aminobenzoic acid, **1**) was selected as a valuable candidate for this purpose owing to its good solubility in most usual organic solvents (log P = 1.21), excellent pKa values (pKa_1 2.14, (carboxylic acid), pKa_2 4.95, aniliniumcation) inherent stability toward oxygen and non-toxicity: let us keep in mind that **1** is indeed vitamine L_1. Anthranilic acid (**1**) was also chosen because of its unique molecular structural arrangement with both the nucleophilic moiety ($-NH_2$) and acid catalyst (-COOH) in close vicinity. We anticipated therefore that the carboxylic moiety would provide assistance both in the generation of the activated imine intermediate and in its decomposition by subsequent nucleophilic attack of the hydrazine-nitrogen the 4- phenylthiosemicarbazide. We would like to point out that the whole strategy of nucleophilic catalysis in its principle is based on the fact of substituting a single reaction (direct condensation) by a two consecutive reactions of significantly lower activation energy.

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. ^1H and ^{13}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, ^1H and ^{13}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 analyses were performed on Merck TLC plates (silica gel, 60F 254, E. Merck, Darmstadt, ref. 5735). All compounds reported here were found chromatographically homogenous 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.

2-2 (1-(4-nitrophenyl)ethylidene)-4-phenylthiosemicarbazide(entry # 3)
This synthesis is representative of all the preparations listed in the Table 2.

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 anthranilic acid. The solution turning gradually to a slurry was magnetically stirred at 65° 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 in 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

As can be seen at Figures 3 and 4, which attempt to rationalize the catalysis offered by anthranilic acid, both the imine and thiosemicarbazone moieties are effectively catalyzed by the vicinality of the amine and carboxylic acid moieties. We tested **1** as a potential condensation catalyst in comparison with other known condensation catalyst classical (acetic acid, hydrochloric acid, para-toluenesulfonic acid, etc.) in our benchmark reaction, *i.e.* the condensation of 4-nitroacetophenone with 4-phenylthiosemicarbazide shown in the Figure 2.

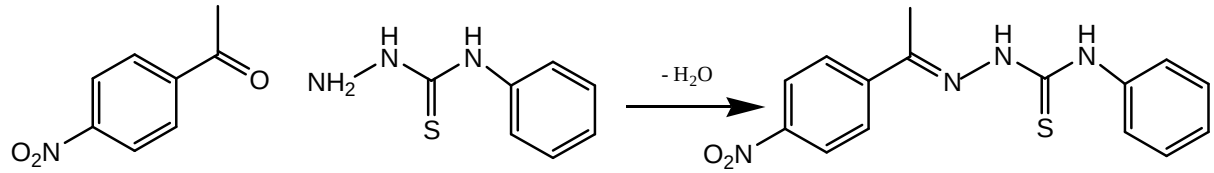

Figure 2: Condensation of 4-nitroacetophenone with 4-phenylthiosemicarbazide

In this context, we found out that **1** performed better than classical catalysts (*i.e.*) and was found in many instances nearly equivalent or slightly superior to anilinium chloride (*Cfr* Table 1). Practically speaking, in preliminary experiments methanol and absolute ethanol were found fairly good solvents and consequently methanol was used throughout Table 1.

To evaluate the generality of applicability of **1** as catalyst we extended our benchmark reaction to a series of ~20 additional substrates aiming at increasing the chimiodiversity, in particular some benzophenone derivatives (*i.a.* tetralones, indanones, fluorenones …) which are relatively more inert than sterically crowded aliphatic or aryl-aliphatic ketones (*Cfr* Table 2). Overall, we can state that **1** performed rather quite satisfactorily giving rise to yields in the range 70-99% with exception for entry #13. This can be ascribed to the fact that this β-dicarbonyl system is strongly enolized, rendering ketonic carbonyl less prone to nucleophilic attack by the thiosemicarbazide reagent.

Table1: Comparison of catalytic systems in the condensation of 4-nitroacetophenone with 4-phenylthiosemicarbazide

Entry	Time(h)	Temperature(°C)	Solvent	Catalyst[a]	Yield (%)
1	3	65	Methanol	Aniline/aceticacid	70
2	3	65	Methanol	Aniline/formicacid	82
3	3	65	Methanol	Aniline/hydrochloricacid	88
4	3	65	Methanol	L-Proline	75
5	3	65	Methanol	Guanidine hydrochloride	59
6	3	65	Methanol	Aceticacid	86
7	3	65	Methanol	Montmorillonite K-10	32

[a]1 % vol. catalyst was used through-out the whole series of experiments presented in Table1

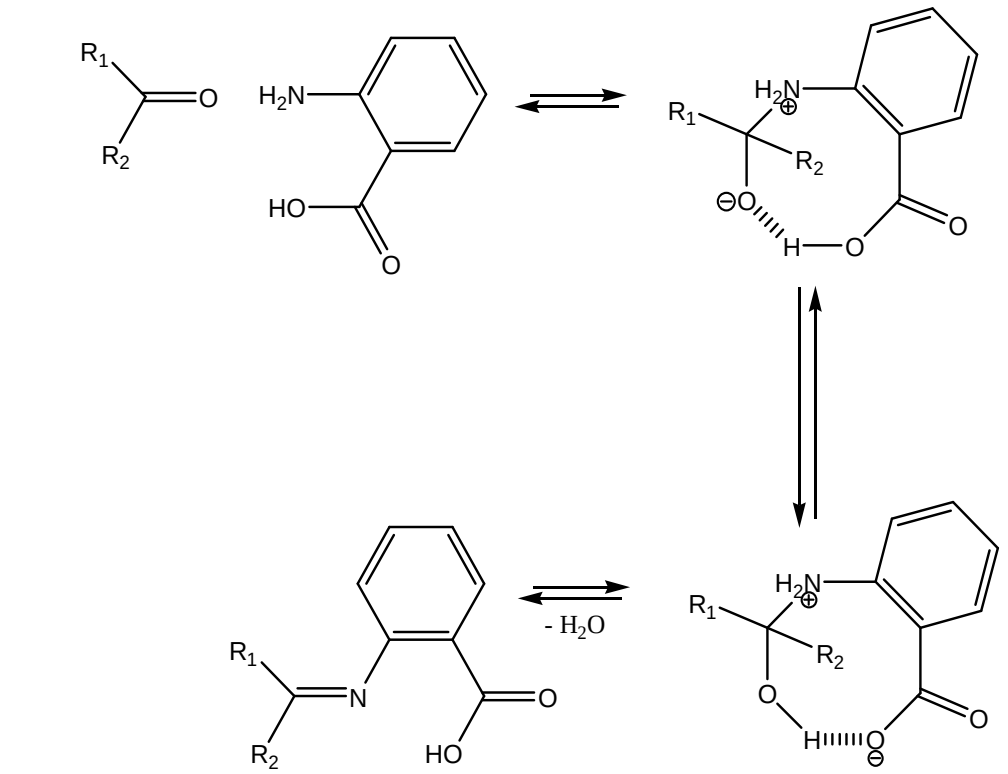

Figure 3: Formation of intermediate imine with participation of the vicinal carboxylic acid moiety (anchimeric assistance)

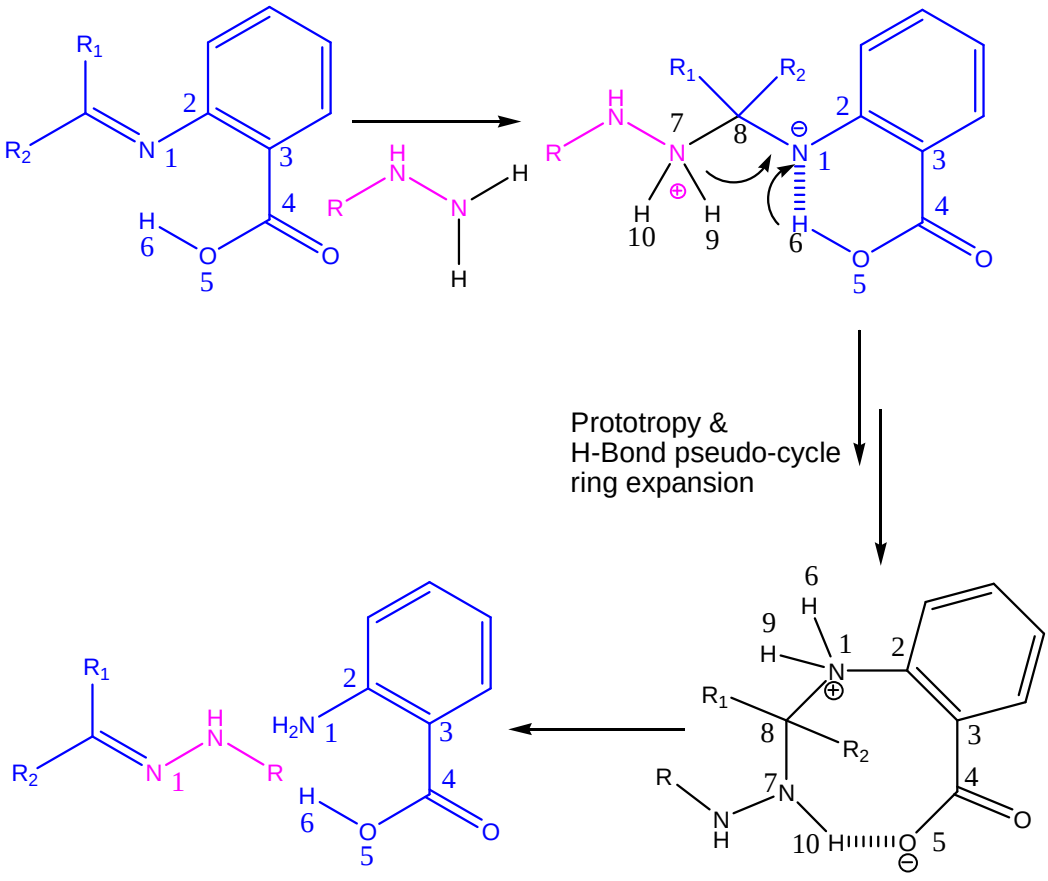

Figure 4: Thiosemicarbazone formation *via* decomposition of the tetrahedral adduct generated by nucleophilic attack of thiosemicarbazide on imine intermediate

The mechanism of catalysis by anthranilic acid, which involves anchimeric assistance, takes place in two steps: first, activation reaction there is the formation of an imine species between the ketone and anthranilic acid (see Figure 3) which proceeds *via* the formation of a tetrahedral adduct in which the negative charge on oxygen is stabilized by an intramolecular hydrogen bond offered by the carboxylic acid ideally located in the vicinity owing to its ortho position. Subsquent water elimination leads to the expected imine species. In the second step (see Figure 4), attach of the nucleophilic thiosemicarbazide nitrogen on the previously formed imine species leads a tetrahedral adduct which again is stabilized by an internal hydrogen bond in which hydrogen 6 is locked in a so-called ‘’proton cage ‘’. Prototropy and proton cage rearrangement leads to the expected thiosemicarbazone species with regeneration of the anthranilic acid catalyst. This final act creates a catalytic loop.

Table 2: Reaction of ketones with 4-phenylthiosemicarbazide catalyzed by anthranilic acid

Entry	Ketone	Solvent	Yield (%)
1	4-Nitroacetophenone	1,2-propanediol	85
2	4-Nitroacetophénone	1,3-propanediol	85
3	4-Nitroacetophenone	Methanol	99
4	Benzophenone	Trifluoroethanol	75
5	Bromoacetophenone	Methanol	96
6	4-Bromo-Phenylglyoxal	Methanol	71
7	Camphre	Methanol	60
8	Butyrophenone	Methanol	98
9	1-Indanone	Methanol	91
10	9-Fluorenone	Methanol	90
11	7-Methoxy-1-tetralone	Methanol	95
12	1-Tetralone	Methanol	78
13	Acetylacetanilide	Methanol	38
14	4-Acetylbiphenyl	Methanol	99
15	Acetophenone	Methanol	85
16	Propriophenone	Methanol	96

CONCLUSION

Further work is now being devoted to expanding this model of catalysis based on a BrØnsted-Lowry acid approach to a more generalized Lewis paradigm. Conclusively, in this paper, we disclose the discovery of anthranilic acid as an utmost valuable nucleophilic *green* catalyst in the general framework of the synthesis of antitrypanosomalthiosemicarbazones.

Methanol was found to be a good solvent in the condensation of different ketone substrates with 4-phenylthiosemicarbazide. The catalyst role of anthranilic acid is supported by mechanistic approach involving anchimeric assistance.

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