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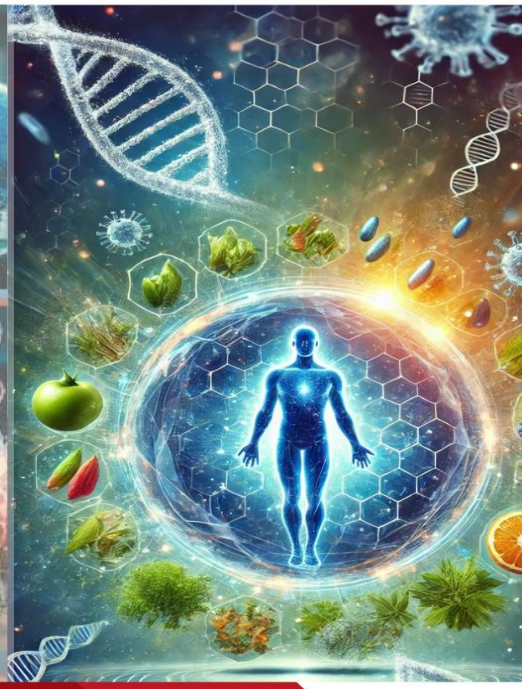

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The unusual impact of benzopinacolone on 4-phenylthiosemicarbazide, a nucleophile with alpha-effect

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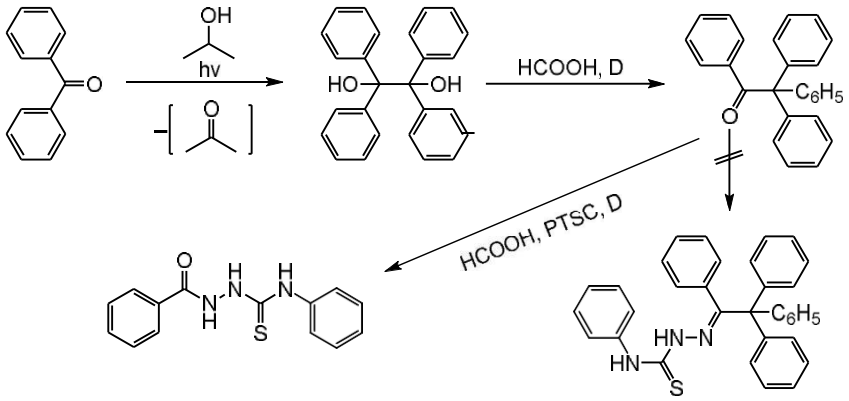
ABSTRACT

We are interested in developing new chemical entities with a thiohydrazide (C=S) NHNH or thiosemicarbazide NH(C=S) NHNH central template flanked on both sides by lipophilic aryl moieties. This is part of a medicinal chemistry-driven drug discovery program that aims to synthesize new topically-acting trypanocidal chemotherapeutic agents to treat African trypanosomiasis. Within this framework, benzopinacolone was discovered to function as an unusual acylating agent through an addition/elimination mechanism. This involved adding a thiosemicarbazide derivative as the nucleophile, forming a tetrahedral adduct, and then removing a trityl anion group as the leaving group. This process was likely aided by an anchimeric effect involving intramolecular hydrogen bond formation involving the thioureido side-chain. Here, the current serendipitous finding should be viewed as the initial spark, and research is currently focused on unraveling the intricate workings of this remarkable chemical pathway; in this reaction, the rate-determining step involves the unusual breaking of a carbon-carbon bond (with carbon acid as the leaving group), and the decomposition of the intermediate tetrahedral adduct is what ultimately leads to the unexpected N-thiobenzoyl-thiosemicarbazide.

GRAPHICAL ABSTRACT



Keywords: Benzopinacolone Green chemistry
N-thiobenzoyl-thiosemicarbazide Photochemistry
Trypanocidal chemotherapeutic

1. Introduction

A drug discovery program driven by medicinal chemistry is currently seeking new trypanocidal chemotherapeutic agents to treat tropical diseases such as African trypanosomiasis. About ten years ago, our research consortium became interested in pharmaco-molecules containing a thiohydrazide (C=S). center motif with lipophilic aryl groups on each side, or thiosemicarbazi-de NH(C=S) NHNH. 1 Hence, we thought the generic structure 1 (Fig. 1) may be a good fit for our drug development program. The second is very important since there is some evidence from the past that these scaffolds have antibacterial and antiprotozoal capabilities. 2 Given that the opportunity was presented at our Institute

A small library of around 300 analogs of 1 were tested as part of a comprehensive screening effort to find agents that may combat tropical parasites and other harmful agents (LDRI, UCL, Brussels, Belgium). One of them indicated very desirable inhibitory characteristics of the Enterococcus faecalis D-Alanine—D- Alanine ligase, to provide just one example among several matches. To catalyze the dimerization process of D-alanine, an enzyme known as D-alanine ligase (EC 6.3.2.4) is essential.

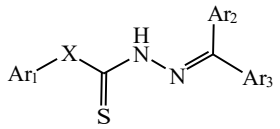


Fig 1. General structure 1 where X is *nihil*, CH_2 (thiohydrazides) or NH (thiosemicarbazones) and $Ar_{1,2,3}$ are aryl groups.

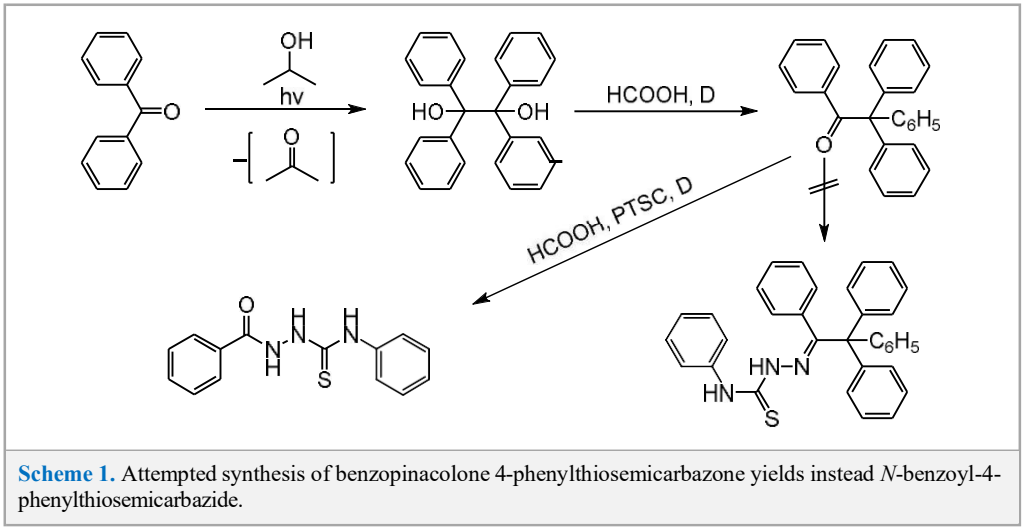
Hydrazine derivatives are particularly reactive toward electrophilic centers due to participation of the so-called
«alpha-effect». The alpha-effect refers to the increased nucleophilicity of a function due to the presence of an adjacent (that is in alpha-position) atom carrying a lone pair of electrons, 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 an elaborated series of elegant kinetics experiments in 1960, which demonstrated the extra- nucleophilicity of these functions without concomitant increase of the basicity.[3] Because of the development of charges in the transition state, the alpha-effect is also somewhat dependent on the solvent but unfortunately not in a straightforward predictable manner.[4-5]Thiosemicarbazides, which are actually hydrazine derivatives, readily react with a wide variety of aldehydes and ketones (aldones) to yield biologically interesting thiosemica-rbazone compounds owing to their promising pharmacologi-cal properties. Indeed, thiosemicarbazones and many of their related isosters, *i.e.*semicarbazones, hydrazones, hydrazides, and dithiocarc- arbazates have drawn close attention in the medicinal chemistry sphere due to their potentials as anti-bacterial,[6] antiviral,[7] antineoplastic,[8] and interestingly enough antimalarial activities[9] both as such or *via* their derivatives.[10] Although even the recent literature holds a multitude of methods for synthesizing thiosemica-rbazones by condensing aldones with thiosemicarbazides,[11] only few studies have pointed out the intervention of the alpha-effect and to the best of our knowledge, no thorough studies so far have been devoted to an in-depth investigation of the miscellaneous surrounding effects impacting this apparently simple chemical process. In this work, we endeavored to create in the greenest way possible reliable reaction conditions that may truly serve the synthetic organic chemists community in the elaboration of a concise thios-emicarbazone compound library choosing the reaction of benzopinacolone (1,2,2,2-tetraphenylethanone) with 4-pheny-lthiosemicarbazi-de as our benchmark for a case study.

2. Result and discussion

By using Green Chemistry principles, a remarkable amount of progress has been made towards the objective of more sustainable medication discovery. 12–13 These ideas have not only improved the macroeconomics of medicine production, but they have also inspired several chemical and technical advancements that have brought about unparalleled research, decreased environmental effect, and allowed for higher safety. 14-17 "Right first time" and "reduced cost and time to market" are more important than ever before since lean manufacturing is all the rage in the pharmaceutical sector these days. Here, Green Chemistry methods have been a game-changer for staying competitive in the dynamic pharmaceutical business and universities. 18 A succinct statement summarizing Professor Hendrickson's foretelling view of synthetic efficiency in Organic Chemistry is as follows: an ideal synthesis would involve building the target structure—including its skeleton and correctly placed functionality—through a series of sequential reactions without any intermediate refunctionalizations. Atom and redox economy, regio-, chemo-, and stereo-selectivity, protecting-group-free chemical synthesis to the best of our ability, and activation minimization via catalytic processes are all aspects that this "Hendricksonian" view of synthetic efficiency implicitly acknowledges. All of these requirements are in line with Green Chemistry and will greatly shorten the time it takes to find new drugs. 19 Although there are numerous published methods for obtaining benzopinacol, we opted to use the method developed by Cohen based on the photochemical reduction first found by Ciamician and Silber. This method offers several advantages, including a high yield, a relatively easy process for preparation and isolation of the final product, and a relatively green character. 20-22 Benzopinacol and acetone are the primary byproducts of benzophenone photo-hydrodimerization in 2-propanol. In rare cases, diphenylmethanol or 2, 3-dimethyl-2,3-butanediol have been shown to form. The final product crystallizes out almost quantitatively from the photolysis medium at room temperature, unaffected by these impurities since they are generated in small quantities and easily soluble in 2-propanol. 23-24 A number of Bronsted acids or their precursors have been used to acid-catalyze the rearrangement of benzopinacol, resulting in β-benzopinacolone in the literature. 25-27 Based on the original technique reported by Gomberg and Bachmann, this approach uses formic acid (pKa 3.75), a stronger acid, instead of acetic acid (pKa 4.75), and it eliminates any trace of diiodine, a weal Lewis acid that is now unnecessary. 28
Even though synthetic organic chemists usually don't have a hard time synthesizing aldonethiosemicarbazones, we ran into a situation where we could still react cyclo-propylphenylketone with 4-phenylthiosemicarbazide. 29 In order to shed light on this matter, we compared benzophenone's reactivity to that of aldehydes and common ketones. Our conclusion was that a carbonyl's correct reactivity is a complicated combination of electronic and steric influences. While analyzing the molecular make-up of benzopinacolone, we discovered that the central

A fairly high value for such a single bond, 1.54 Å, was predicted for the carbon of the trityl moiety, indicating that the bond is weak. So, it seemed appealing to us to investigate the actions of this remarkable acetophenone derivative.
Reacting slowly (24 hours of refluxing at 110°C in n-

propanol), the reaction was carried out in a fairly conventional fashion (with formic acid serving as the acid catalyst, however). As a result of extensive spectroscopy and chromatographic investigation, as well as confirmation by comparison with an authentic sample, we were surprised to find that the 13C-NMR spectrum in DMSO-d6 did not match the expected classical ketone thiosemicarbazone derivatives but rather that of 1-benzoyl-4-phenylthiosemicarbazide (1-benzamido-3-phenylurea, IUPAC nomenclature). In fact, the material that came out of this process was determined to be completely indistinguishable from what was created using the conventional method, which involves treatment at ambient temperature. temperature of dry methanol containing benzhydrazide and phenylisothiocyanate in equimolecular proportions. Therefore, benzopinacolone acts as an unusual acylating agent in this reaction by using an addition-elimination mechanism that involves adding the nucleophile, forming a tetrahedral adduct, and then removing a trityl anion group as the leaving group. This process is likely aided by the anchimeric assistance provided by the thioureido side-chain via hydrogen bond formation. At this early stage, this coincidental finding should be seen as a first step, and researchers are focusing their efforts on delving further into the specifics of this remarkable chemical pathway, which involves the unusual breaking of a carbon-carbon bond in the rate-determining step of breaking down the tetrahedral adduct to produce the N-thiobenzoylthiosemicarb-azide.



Scheme 1. Attempted synthesis of benzopinacolone 4-phenylthiosemicarbazone yields instead *N*-benzoyl-4-phenylthiosemicarbazide.

3. Conclusion

This brief paper describes an investigation into the benzopinacolone 4-phenylthiosemicarbazide reactivity by a conventional approach that, in theory, should produce benzopinacolone 4-phenylthiosemicarbazone (via condensation with acid catalysis). Benzopinacolone, on the other hand, acted as a genuine acylating agent by delivering 1-benzoyl-4-phenylthiosemicarbazide—likely via the anchimeric assisted-participation of the thioureido side-chain—through a process that included adding the nucleophile, forming a tetrahedral adduct, and releasing a trityl anion motif as a leaving group.

4. Experimental

4.1. General procedure

Using a Büchi SMP20 melting point instrument, the uncorrected melting points were obtained in open capillary tubes. Using a Perkin-Elmer Model 297 spectrometer, infrared spectra were acquired by dispersing the product finely in anhydrous potassium bromide disks. Bruker spectrometer 1H and 13C NMR spectra shown on the delta scale were acquired at room temperature using tetramethylsilane. (TMS) was used as the internal reference standard. Chemical structure-conforming data was obtained via elemental analysis, infrared and 1H and 13C NMR, mass spectrometry, and all compounds that were reported. Results from the elemental analysis experiments were within a margin of error of 0.4% from the predicted values. The investigations were carried out on Merck TLC plates (silica gel, 60F 254, E. Merck, Darmstadt, ref. 5735) using thin layer chromatography. The compounds listed below were all determined to be chromatographically homogeneous in two standard solvents: methanol/chloroform equilibrated with traces of ammonia (1:9, v/v) and acetone/toluene/cyclohexane (5:2:3, v/v/v). Sigma/Aldrich was the source for all of the reagents.

4.2. General procedure for the preparation of Benzopinacol (1,1,2,2-tetraphenylethane-1,2-diol)

A mixture of 15.0 g. (82 mmol) of benzophenone, 30µL of glacial acetic acid (syringe), and 100 mL of analytical grade of 2-propanol is prepared in a round glass stopper dry flask at room temperature. The flask is filled up to the stopper and tightly closed. After 12 hours of irradiation to bright sun light, crystals of benzopinacol begin to separate and sediment at the bottom of the flask; after 24 hours of light exposure, the flask is filled with crystals of benzopinacol. The solution is chilled in a refrigerator overnight and the crystalline product is filtered with suction over a Buchner funnel, washed with a small amount of ice-cold 2-propanol, and allowed to dry in an

ventilated oven thermostated at 90 °C. The filtrate is preserv- ed eventually for subsequent reductions. The yield of an analytical pure grade of benzopinacol, mp 188–190 °C, is 140 g (93% yield). On the basis of its TLC behavior and ^{1}H- and ^{13}C-NMR spectra, this product is judged sufficiently pure for the next step. It may be crystallized with some loss in absolute ethanol. After cooling in ice and filtering there is obtained11.5 g of a nice crystalline product. The melting point is not significantly affected by this additional recrystallization. To the isopropyl alcohol filtrate is added another 15.0 g portion of benzophenone, and the solution is exposed to sunlight as in the first batch reduction. The benzopinacol which separates out is filtered out and dried as described above. The yield in the second and subsequent runs is circa 14.0 g. (94% yield). If need be, this procedure can be indeed repeated with the same filtrate several times without significant detrimental effect on the yield or purity of the resulting product.

4.3. General procedure for the preparation of Benzopinac- olone (1,2,2,2-tetraphenylethanone)

Into a 100mL round-bottomed flask fitted with a magnetic stirring bar and surmounted with a reflux condenser, a suspension of 10.0 g of benzopinacol (27 mmol) in 50 mL of an analytical grade of formic acid is introduced; the flask is magnetically stirred and gently heated in an oil bath until a gentle reflux is obtained. Refluxing is then pursued for 15 additional min during which time the solid benzopinacol gradually gets dissolved and a clear slightly yellowish soluti- on is obtained intermittently while crystallization of ben- zopinacolone starts. The solution is then quickly transferred into a beaker, and, upon slow cooling at room temperature, the benzopinacolone slowly separates in fine threads. The product is then filtered with suction over a Buchner funnel, washed with two 50 mL portions of cold 95% ethanol to discharge any smell of formic acid, and dried in an oven. The yield of practically pure benzopinacolone melting at 178–179°C is 9.0 g (95% yield). To get a purer product, the material can be recrystallized classically from a large volume of 95% ethanol with some loss (mp: 181-182 °C).

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