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Anomalous reactivity of benzopinacolone towards 4-phenylthiosemicarbazide, a nucleophile endowed with alpha-effect

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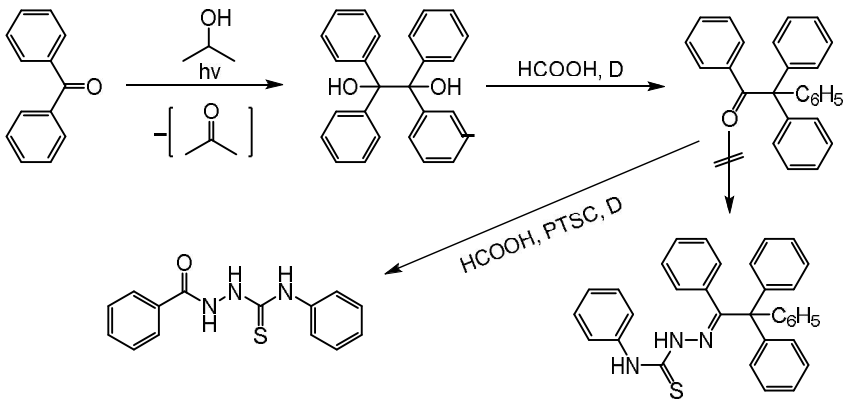
ABSTRACT

In a medicinal chemistry-driven drug discovery program aimed at synthesizing new topically-acting trypanocidal chemotherapeutic agents to treat the African trypanosomiasis, our research group became interested in new chemical entities bearing in their center a thiohydrazide (C=S) NHNH or thiosemicarbazide NH(C=S) NHNH central template flanked on both sides by lipophilic aryl moieties. In this context, benzopinacolone was found to react as a rather unusual acylating agent *via* a mechanism (addition/elimination) involving addition of the nucleophile (a thiosemicarbazide derivative), formation of a resulting tetrahedral adduct, and expulsion of a trityl anion moiety as leaving group, presumably through an anchimeric assistance effect by intram-olecular participation of the thioureido side-chain *via* hydrogen bond formation. The present incidental discovery should be considered at this level as a first inception and further work is now being directed at closely examining the detailed mechanism of this exceptional chemical pathway; in a reaction involving the unusual breaking of a carbon-carbon bond (carbon acid as leaving group) in the rate-determining step and involving the decomposition of the intermediate tetrahedral adduct to get the final unexpected *N*-thiobenzoyl-thiosemicarbazide.

GRAPHICAL ABSTRACT



1. Introduction

In the course of a medicinal chemistry-driven drug discovery program aimed at finding new trypanocidal chemotherapeutic agents to treat the African trypanosomiasis and other life-threatening tropical diseases, our research consortium became interested some ten years ago in pharmaco-molecules containing a thiohydrazide (C=S) NHNH or thiosemicarbazi-de NH(C=S) NHNH central motif flanked on both edges by lipophilic aryl moieties.[1] Accordingly, we considered the general structure **1** (**Fig. 1**) as a potential candidate for our drug discovery program. In particular for the latter, there were already fragmentary previous indications in the literature that such scaffolds are indeed endowed with antibacterial and antiprotozoal properties.[2] As the possibility was offered in our Institute

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(LDRI, UCL, Brussels, Belgium) to perform a broad screening program for discovering agents against tropical parasites and other pathogenic agents, a concise library consisting of some 300 analogs of **1** were assayed. To give just an example (among several hits) one of these showed very attractive inhibitory properties of the D-Alanine—D-Alanine ligase of *Enterococcus faecalis*. D-alanine—D-alanine ligase (EC 6.3.2.4) is a key enzyme in the catalytic dimerization reaction of D-alanine.

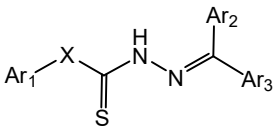


Fig 1. General structure 1 where X is *nihil*, CH_2 (thiohydrazides) or NH (thiosemicarbazones) and $Ar_{1,2,3}$ are aryl groups.

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

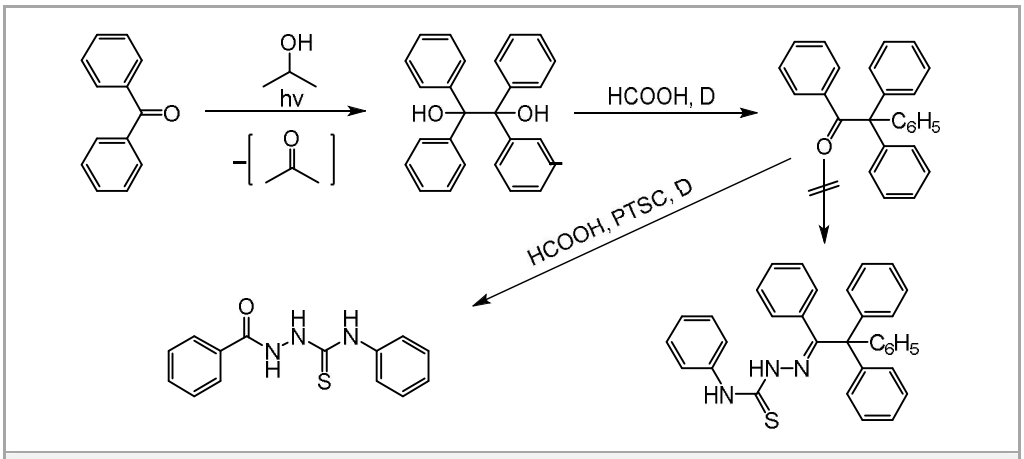
An astounding level of progress has been directed toward the goal of greater sustainability in drug research through the application of Green Chemistry principles.[12-13] These principles have served not only to inspire a great deal of chemical and engineering innovations that have delivered unprecedented science, reduced environmental impact, provided for greater safety, but also concomitantly improved the macroeconomics of drug manufacture.[14-17] As nowadays in the pharmaceutical industry, the key word is lean manufacturing and therefore the demand for “right first time” and “reduced cost and time to market” has become even more critical. In this context, Green Chemistry practices have provided a true differentiator with regard to competitive success in the ever-evolving pharmaceutical industry and academia.[18] Prof. Hendrickson’s prophetic view of synthetic efficiency in Organic Chemistry can be summarized by this simple statement: the ideal synthesis should create a complex skeleton in a sequence only of successive construction reac-tions integrating no intermediary refunctionalizations, and leading directly to the structure of the target, not only its skeleton but also its correctly placed functionality. This “Hendricksonian” perspective on synthetic efficiency tacitly recognizes in a sense the importance of atom and redox economy, regio-, chemo- and stereo-selectivity, as far as possible protecting-group-free chemical synthesis, and the minimization of activation *via* catalytic processes. All these requisites go along with the spirit of Green Chemistry and considerably speed up drug discovery and development processes.[19]

While many methods have been published to get access to benzopinacol, in the present work, we decided to employ the method based on the pioneering work in photochemistry of Cohen of the photochemical reduction originally discovered by Ciamician and Silber because of the ease and simplicity of preparation and isolation of the final product, high yield, and green character.[20-22] Indeed, the major products formed in the photo-hydrodimerization of benzophenone in 2-propanol are benzopinacol and acetone. Formation of 2, 3-dimethyl-2,3-butanediol or diphenylmethanol have been detected rarely. As these impurities are formed only in minor amounts and are readily soluble in 2-propanol, they do not affect the purity of the final product, which crystallizes out virtually quantit-atively at room temperature from the photolysis medium.[23-24] In the litterature, β-benzopinacolone has been prepared by acid-catalyzed rearrangement of benzopinacol using a variety of Bronsted acids or a precursor thereof.[25-27] The present procedure is based on the method originally described by Gomberg and Bachmann substituting however acetic acid (pKa 4.75) by formic acid (pKa 3.75), a stronger acid and omitting traces of now superfluous diiodine, a weal Lewis acid.[28]

While the synthesis of aldonethiosemicarbazones is generally considered not such a big challenge for the synthetic organic chemist, we have encountered a case in which, in spite of our numerous efforts, we could react cyclo-propylphenylketone with 4-phenylthiosemicarbazide.[29] To explain this fact, on the basis of comparison of the reactivity of benzophenone with respect to aldehydes or common ketones, we had to resort that the proper reactivity of a carbonyl is a complex blend of electronic and steric effects. When considering structure of benzopinacolone, we found out that the single bond between the carbonyl and the central

carbon of the trityl moiety was estimated 1.54 Å, a rather high figure for such a single bond, attesting of a weak bond character. Accordingly, we found attractive to test the behavior of such an exceptional acetophenone derivative.

The reaction was accomplished in a rather classical manner (using however formic acid as acid catalyst) and proceeded as expected slowly (24 h refluxing at 110°C in *n*-propanol). To our surprise, the ^{13}C-NMR spectrum (in DMSO-d6) did not correspond to the classical ketone thiosemicarbazone derivatives one would normally expect but to that of 1-benzoyl-4-phenylthiosemicarbazide (1-benzamido-3-phenylurea, IUPAC nomenclature), a feature confirmed by comparison with an authentic sample and thoroughly investigated by spectroscopy and chromatography. Indeed, the resulting material of this operation was found identical in all respects to that obtained by the standard procedure involving treatment at room temperature of equimolecular amounts of benzhydrazide with phenylisothiocyanate in dry methanol. Consequently, benzopinacolone behaves therefore in this reaction as an unusual acylating agent *via* a mechanism (addition-elimination) involving addition of the nucleophile, formation of a tetrahedral adduct, and expulsion of a trityl anion moiety as leaving group, presumably through the anchimeric assistance by participation of the thioureido side-chain *via* hydrogen bond formation. The present incidental discovery should be considered at the present level as a first inception and further work is now being directed at closely examining the detailed mechanism of this exceptional chemical pathway, in a reaction involving the unusual brea-king of a carbon-carbon bond in the rate-determining step involving the decomposition of the tetrahedral adduct to the final *N*-thiobenzoylthiosemicarb-azide.



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

3. Conclusion

In this short note, we explored the reactivity of 4-phenylthiosemicarbazide towards benzopinacolone using a classical method which should normally lead to the formation of benzopinacolone 4-phenylthiosemicarbazone (condensation using an acid catalysis). However, benzopinacolone behaved as a true acylating agent via a mechanism involving addition of the nucleophile, formation of a tetrahedral adduct, and expulsion of a trityl anion moiety as leaving group, in order to give 1-benzoyl-4-phenylthiosemicarbazide, presumably through the anchimeric assisted-participation of the thioureido side-chain.

4. Experimental

4.1. General procedure

Melting points (uncorrected) determined in open capillary tubes using a Büchi SMP20 melting point apparatus. IR spectra were recorded using a fine dispersion of the product in anhydrous potassium bromide disks by means of a Perkin-Elmer Model 297 spectrometer. The ^{1}H- and ^{13}C-NMR spectra (Bruker spectrometer) reported in the delta scale were recorded under ambient conditions using tetramethylsilane (TMS) as internal standard reference. All compounds reported had IR, ^{1}H- 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 traces of ammonia (1:9, v/*v*). All reagents were purchased from Sigma/Aldrich.

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 preserved 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 obtained 11.5 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 Benzopinacolone (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 solution is obtained intermittently while crystallization of benzopinacolone 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).

4.4. Attempted synthesis of benzopinacolone 4-phenylthiosemicarbazone (Access to N-benzoyl-4-phenylthiosemicarbazide, benzamido-3-phenylurea, IUPAC nomenclature)

Into a 100mL round-bottomed flask fitted with a magnetic stirring bar and surmounted with a reflux condenser, a suspension of benzopinacolone (5 mmol) and 4-phenylthiosemicarbazide (10 mmol) in 50 mL of an analytical grade of *n*-propanol doped with 500 µL of formic acid is introduced; the flask is magnetically stirred and slowly heated up in an oil bath until a gentle steady reflux is obtained. Refluxing is then pursued for an additional 24h period during which time the solid starting benzopinacolone gradually gets into solution and a clear solution is obtained; after cooling down to room temperature, crystallization a fine whit crystalline starts to deposit. After one more day, a first crop is collected and washed with cold methanol and after three more days the filtrate leaves a second crop amounting at the total 0.74 g (yield = 58 %).

This material is homogenous in chromatography. ^{1}H-RMN (DMSO-d_6) 7.76-7.02 (broad complex multiplet); ^{13}C-NMR (DMSO-d_6) 181.32 (C=S), 164.37 (hydrazide C=O), 132.12 (4-benzoyl), 130.45 (4-anilino CH), 130.36 (3-anilino CH), 127.95 (3-benzoyl CH), 127.85 (2-benzoyl CH), 126.66 (2-anilino CH). This material is identical to that obtained by treatment at room temperature of equimolecular amounts of benzhydrazide with phenylisothiocyanate in dry methanol.

References

1. U.C. Kasséhin, F.A. Gbaguidi, C.N. Kapanda, C. McCurdy, J.H. Poupaert, Afr. J. Pure Appl. Chem. 2014, 8, 110.
2. U.C. Kasséhin, F.A. Gbaguidi, C.N. Kapanda, C. McCurdy, J.H. Poupaert, J. Chem. Pharm. Res. 2015, 7, 48.
3. D. Herschlag, W.P. Jencks, J. Am. Chem. Soc.1990, 112, 1951.
4. E. Bunce, I.H. Um, Angew. Chem. 2008, 120, 7633.
5. S. Umamatheswari, S. Kabilan, J. Enzyme. Inhib. Med. Chem. 2011, 26, 9.
6. S.N. Pandeya, P. Yogeeswari, D. Sriram, E. Clercq, C. Pannecouque, M. Witvrouw, Chemotherapy. 1999, 4, 6.
7. H.D. Houngue, B.S. Aguida, U.C. Kasséhin, J.H. Poupaert, F.A. Gbaguidi, MOJ. Biorg. Org. Chem. 2017, 1, 1.
8. J.P. Mallari, W.A. Guiguemde, R.K. Guy, Med. Chem. Lett. 2009, 19, 3546.
9. U.C. Kasséhin, F.A. Gbaguidi, C. McCurdy, J.H. Poupaert, J. Chem. Pharm. Res .2014, 6, 607.
10. J.M. Sayer, W.P. Jencks, J. Am. Chem. Soc.1969, 91, 6353.
11. P.J. Dunn, Chem. Soc. Rev. 2012, 41, 1452.
12. P.T. Anastas, J.C. Warner, Green Chemistry: Theory and Practice. Ed. New-york, Oxford University Press, 1998. 1-135.
13. P.T. Anastas, N. Eghbali, Chem. Soc. Rev. 2010, 39, 301.
14. P.T. Anastas, M.M. Kirchhoff, Acc. Chem. Res. 2002, 35, 686.
15. P.T. Anastas, Aldrichimica. 2015, 48, 3.
16. P.T. Anastas, R.L. Green Chem. 2000, 2, 289.
17. R.A. Sheldon, Chem. Soc. Rev. 2012, 41, 1437.
18. G.G. Wubbels, Acc. Chem. Res. 1983, 16, 285.
19. E. Cohen, Rec. Trav. Chim. 1920, 39, 243.
20. G. Ciamician, P. Silber, Chemische Lichtwirkungen. Ber. 1900, 33, 2911.
21. L.C. Potey, S.B. Kosalge, R.S. Sarode, Int. J. Pharm. Drug. Anal. 2014, 2, 55.
22. G. Dormán, H. Nakamura, A. Pulsipher, G.D. Prestwich, Chem. Rev. 2016, 116, 1528.
23. M. Migita, Bcsj. 1932, 7, 334.
24. G. Zhao, T. Jiang, H. Gao, B. Han, J. Huanga, D. Suna, Green Chem. 2004, 6, 75.
25. M. Gómez-Martínez, A. Baeza, D.A. Alonso, Chem. Cat. Chem. 2017, 9, 1032.
26. N. Drosos, E. Ozkal, B. Cacherat, W. Thiel, B. Morandi, Angew. Chem. 2017, 56, 13377.
27. J.R. Beadle, S.H. Korzeniowski, D.E. Rosenberg, B.J. Garcia-Slanga, G.W. Gokel, J. Org. Chem. 1984, 49, 1594.
28. U.C. Kasséhin, F.A. Gbaguidi, C.N. Kapanda, C. McCurdy, A.K. Bigot, J.H. Poupaert, Afr. J. Pure Appl. Chem. 2013, 7, 325.