academicJournals

Vol. 7(9), pp. 325-329, Sept. 2013
DOI: 10.5897/AJPAC2013.0514
ISSN 1996 - 0840 © 2013 Academic Journals
http://www.academicjournals.org/AJPAC

African Journal of Pure and Applied Chemistry

Full Length Research Paper

Electronic and steric effects in the control of the Anilinium chloride catalyzed condensation reaction between Aldones and 4-Phenylthiosemicarbazide

Urbain C. Kasséhin[1, 2], Fernand A. Gbaguidi[3]*, Coco N. Kapanda[1], Christopher McCurdy[4], André K. Bigot[2] and Jacques H. Poupaert[1]

[1]Medicinal Chemistry, Louvain Drug Research Institute, Université catholique de Louvain. 73, Bte B1.73.10, Av. E. Mounier B-1200 Bruxelles, Belgium.
[2]Unité de Formation et de Recherches en Pharmacie, Faculté des Sciences de la Santé, Université d'Abomey- Calavi, BP-188, Cotonou, Bénin.
[3]Laboratoire de Pharmacognosie/UAC/CBRST ; Porto-Novo, BP 06 Oganla, Benin.
[4]Medicinal Chemistry, School of Pharmacy, 419 Faser hall, P. O. BOX 1848, University, M S 386771848, USA.

Accepted 26 August, 2013

A concise series of aldehydes and ketones were reacted in a condensation reaction with 4-phenylthiosemicarbazide in order to assess the relative influence of the steric and electronic effects in the control of this reaction. While steric effects had a modest impact, electronic effects and in particular the mesomeric donating effect delivered by a phenyl ring produced a strong passivating influence on the reactivity of these aldones. Additionally, the cyclopropyl substituent totally passivated the reaction via the interfering factor of its inherent sigma-aromaticity. When reacted with cyclopropyl-phenylketone, under our standard conditions, 4-phenylthiosemicarbazide gave in 82%, an original 1, 4-dihydrotetrazine via a double consecutive self-condensation.

Key words: Thiosemicarbazone, electronic effect, steric effect, ion catalysis aniline, sigma, aromaticity.

INTRODUCTION

Aldone is a generic term introduced in organic chemistry by the US chemist Hendrikson to qualify aldehydes and ketones by a common name (Pine et al., 1982). Indeed, aldehydes and ketones are characterized in essence by a community of properties they exhibit and reactions they undergo, and their presence in essential oils (Amoussatou et al., 2012) very often has a leading influence on their therapeutic indications. Among this line, it has been long established that aldones react with characteristic reagents to yield crystalline derivatives of definite melting point, among which are oximes, hydrazones, semicarbazones, and thiosemicarbazones. These derivatives are often used for identification of aldones.

Thiosemicarbazones are endowed with a variety of important chemical and pharmacological activities among which for the latter we can cite the anti-tumoral (Cocco et al., 2006; Hu et al., 2006; Wang et al., 2007; Xia et al., 2008; Richardson et al.,2009; Wiecek et al., 2010; Da Sylva et al., 2010), antimalarial (Mallari et al., 2009;

*Corresponding author. E-mail: dnokannou@yahoo.fr. Tel: +32 2 764 73 99.

De Oliviera et al., 2008), anticonvulsant (Aggarwal et al., 2008), antibacterial (Umamatheswari and Kabilan, 2011; Halve et al., 2008), antifungus (Loncle et al., 2004; Pandeya et al., 1999), antiviral (Pandeya et al., 1999; Teitz et al., 1994), antitrypanosomal (Du et al., 2002; Fujii et al., 2005; Glinma et al., 2012, 2011; Greenbaum et al., 2004; Mallari et al., 2008), anti-inflammatory ones (Cocco et al., 2006), analgesic (Cocco et al., 2006; Xia et al., 2008) and potential inhibitors of many enzymes (Singh and Kumar, 2006; Xu et al., 2008; Hassanien et al., 2008). While the thiosemicarbazone general template has been established as a useful pharmacophore for over 50 years and a plethora of papers published on pharmacological probes using this peculiar structural moiety, very few fundamental studies have been reported regarding the synthesis of these target molecules. Indeed, it is generally considered that access to thiosemicarbazones is not considered as an overwhelming task for the trained synthetic organic chemist. A recent study, however, drew attention to some drawbacks encountered upon synthesis of thiosemicarbazone derivatives of diketones and benzile in particular. Along this line, in this paper, we examined the behaviour of a concise series of simple monocarbonylated compounds in their condensation reaction with 4-phenylthiosemicarbazide to examine the relative impact of both steric and electronic effects upon the reactivity of these ketones (Scheme 1).

EXPERIMENTAL PROCEDURE

Melting points were determined using an electrothermal 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}. ^1H- and ^{13}C-NMR spectrum was recorded at ambient temperature on a Brucker Avance 400MHz 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 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: HPTLC plates RP-18 F-254 S (Merk), methanol: water (75/25, v/v). All compounds reported were found homogenous under such TLC and HPLC conditions. All reagents were purchased from Aldrich. All solvents were of the ACS. Reagent grade (Aldrich).

Synthesis of 1-(4-nitrophenyl) ethylidene)-4-phenylthiosemicarbazide

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 and refluxed for 3 h, rapidly cooled in an ice bath, and filtered on a Büchner funnel to give 3.10 g (99% yield) of TLC-pure vacuum-dried yellow crystals. Mp: 196 to198°C (unaffected by recrystallization from methanol), ^1H-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, CH3) , ^{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, 124.61, 14.44

Synthesis of 1.4-dihydro-N^3, N^6-diphenyl-1, 2, 4, 5-tetrazine-3-6-diamine

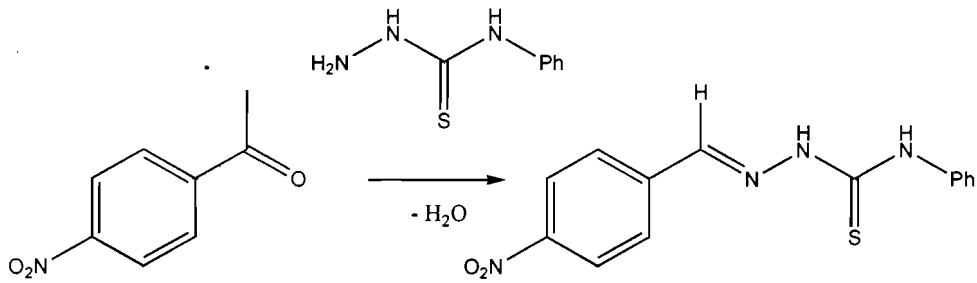
A solution of 4-phenylthiosemicarbazide in 25 mL of glacial acetic acid containing 300 ml of concentrated hydrochloric acid was stirred and refluxed for 240 h, diluted with 100 ml of ice water to give a precipitate of the title compound in 82% yield after recrystallization from ethanol. ^{13}C-NMR (DMSO-d_6) δ (ppm): 155, 63(C-3, C-6), 141.17 (aromatic ipso carbon), 128.95 (aromatic meta carbon), 122.93 (aromatic para carbon), 117.35 (aromatic ortho carbon).

RESULTS AND DISCUSSION

Recent work in our group has evidenced the usefulness of nucleophilic catalysis in this reaction. Indeed, the use of anilinium chloride as catalyst allows for obtaining high yield of thiosemicarbazone in mild conditions of temperature and short reaction time. For example, reaction of 4'-nitroacetophenone with 4-phenylthiosemicarbazide can be performed with 99% yield in 3 h at the reflux temperature of methanol (65°C). Using these standard reaction conditions, we have reacted different ketones with increasing steric and electronic effects as shown in the Table 1. It should be pointed out that applying this standard conditions on simple substrates such as benzaldehyde, cyclohexanone, 4-methoxybenzaldehyde, 2-tetralone quantitative yields of 4-phenylthiosemicarbazone were obtained.

As a general rule, the syntheses presented in the Table 1 proceeded as we anticipated. The yields reported concern final compounds purified and recrystallised from ethanol. All compounds behaved as expected and gave satisfactory yields, with exception for the cyclopropyl phenyl ketone substrate (Table 1). In this isolated case, the starting ketone and thiosemicarbazide were indeed recovered unchanged. Various attempts varying solvent, temperature and catalysis were carried out without success. After 10 days reaction, however, a nice white crystalline compound of low Rf in this layer chromatography was isolated by simple filtration and recrystallized from ethanol to give a pure (TLC, NMR) material with a 82% yield. In the assignment of the structure of this compound, the use of ^{13}C-NMR was particularly decisive. In particular, the absence of C=S resonance was initially puzzling. However, this led to the conclusion that the obtained material resulted from a desulfurization process (Scheme 2).

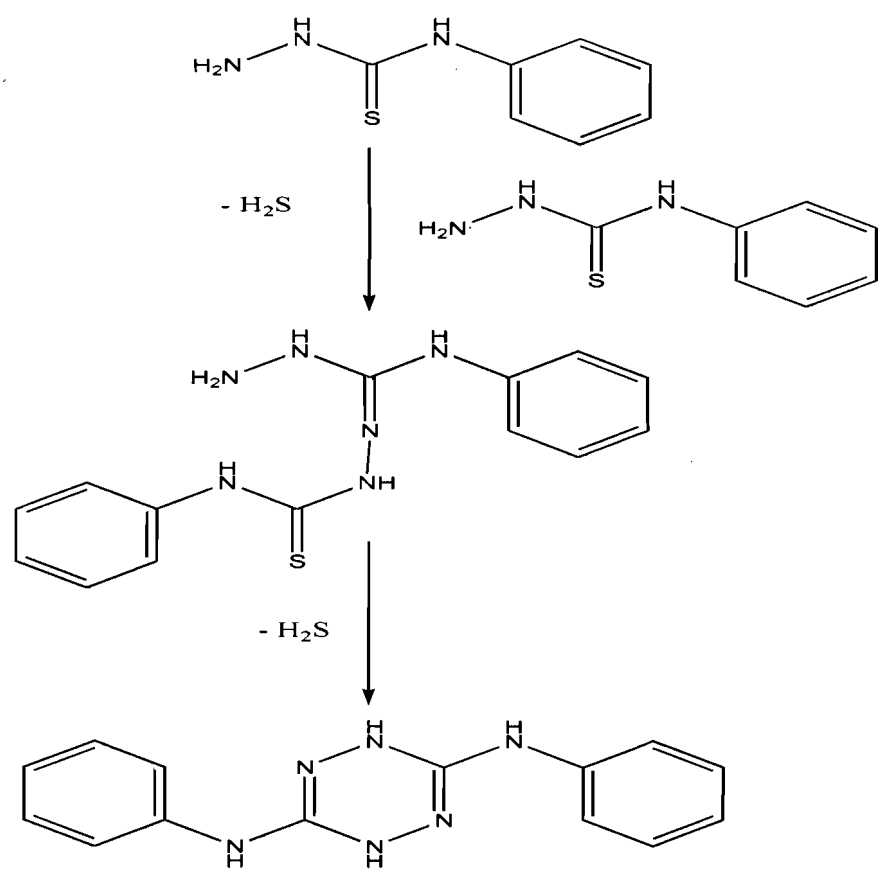
Another interesting feature was the absence of characteristic cyclopropanic carbon signals. Moreover the simplicity of the imprint of aromatic carbons was also very diagnostic to us as it indicated that the resulting compound was necessarily endowed with a high degree of central symmetry. The final establishment of the



Scheme 1. Formation of the pilot molecule.

Table 1. Synthesis of some 4-phenylthiosemicarbazones.

Compound	R^1	R^2	Time (h)	Temperature (°C)	Yield (%)
2	CH_3	t-C_4H_9	3	65	85
3	CH_3	C_6H_5	3	65	78
4	Cyclo-C_3H_5	C_6H_5	240	65	0
5	Cyclo-C_6H_{11}	C_6H_5	3	65	76
6	C_6H_5	C_6H_5	3	65	72
7	t-C_4H_9	C_6H_5	3	65	71



Scheme 2. 1,4-dihydro-N^3, N^6–diphenyl-1,2,4,5-tetrazine-3,6-dismine. $C_{14}H_{14}N_6$: Exact mass, 266.13; Mol wt, 266.3; m/e, 266.13(100.0%), 267.13(17.5%), 268.13(1.4%). C, 63.14; H, 5.30; N, 31.56.

structure was accomplished based on a mechanistic hypothesis. We anticipated that the complete desulfurization was due to a reciprocal consecutive double self-condensation between the hydrazinic nucleophilic nitrogen and the 3-thiocarbonyl moiety. The paucity of aromatic carbon resonances, which reflects the high degree of symmetry of the inner template, could be rationalized by an auto-condensation process resulting in a central 1, 4-dihydrotetrazine heterocycle with a C_2 symmetry axis. Simulation of the ^{13}C–NMR spectrum gave to our pleasure a spectrum in complete accord with the experimental spectrum in DMSO-d_6.

At this level of the discussion, we remain now with two major key questions: firstly, what is the reason of the inerty of the cyclopropanic substrate? Secondly, what is the driving force behind the cyclothiodehydration process undergone by 4-phenylthiosemicarbazide to yield ultimately a 1, 4-dihydrotetrazine heterocycle?

In Table 1, we have implemented in the R1 column the substituents according to their steric effect as ranked in accord with Taft's equation. We can see conclusively that the steric effect has a modest impact on the yield as when going from methyl to tertio-butyl, this change is accompanied with a loss of yield of only 7%. However, substituting *t*-butyl by phenyl (see R2 column) produces an equal loss of yield 7%. This means that the mesomeric donating effect of the phenyl group has clearly a passivating effect. Introduction of a 4'-nitro substituent in acetophenone leads a boost of the yield of 21%. As expected, the 4'-nitro substituent will indeed obviously decrease the overall mesomeric donating effect produced by the 4-nitrophenyl moiety. Consequently, while we can rationalize Table 1 in terms of steric (R_1) and electronic pi-aromaticity (R_2) effects, the behaviour of the cyclopropanic term remains apparently controlled by an elusive additional extra effect.

A thorough literature search revealed an attractive hypothesis. In the 1980's, von Schleyer et al. introduced the new concept of sigma-aromaticity (Li et al., 2005). In this regard, cyclopropane and adamantane are sigma-aromatic and cyclobutane and cubane are sigma anti-aromatic. Consequently, sigma-aromaticity of cyclopropane may tentatively add an additional increment of passivating effect for the ketones, which possibly explains the complete inertness of the cyclopropanic term. As all alkyl and alicyclic substituents are endowed with hyperconjuguation properties, we can exclude this electronic feature as a dominating factor in the behavior of the cyclopropanic term.

This heterocyclic structure with such high nitrogen content, resulting from the spontaneous acid-catalyzed self-condensation of 4'-phenylthiosemicarbazide is quite uncommon in organic chemistry. This assembly of two guanidinium moieties interlaced with a C_2-symmetry axis is a 1,4-dihydrotetrazine heterocycle which possesses an exceptional stability toward atmospheric oxygen oxidation. This is due most likely to the fact that the reaction is carried out in acidic conditions as reflected by the $M.2H_{++}$ ion observed in mass spectrometry for the resulting material. As the cyclization is accompanied by release of two molecules of hydrogen sulfide, this means that this bimolecular condensation is entropy-driven and leads to the kinetic product.

Conclusion

We have established that the reaction of condensation of aldones with a thiosemiocarbazone derivative is catalysed optimally using anilinium chloride. While steric effects had a modest impact, electronic effects and in particular the mesomeric donating effect delivered by a phenyl ring produced a strong passivating influence on the reactivity of these aldones. Additionally, the cyclopropyl substituent totally passivated the reaction via the interfering factor of its inherent sigma-aromaticity. When reacted with cyclopropyl-phenylketone, under our standard conditions, 4-phenylthiosemicarbazide gave in 82% an original 1,4-dihydrotetrazine via a double consecutive self-condensation. Further work is now under progress to corroborate this aspect. Conclusively, we can state that our pilot reaction is controlled by steric effects and more importantly by electronic effects.

ACKNOWLEDGEMENT

One of us (U. C. K.) is deeply indebted for a Ph. D fellowship awarded by the CTB (Cooperation Technique Belge, Brussels, Belgium).

REFERENCES

Aboul-Fadl T, Bin-Jubair FAS (2010). Anti-tubercular activity of isatin derivatives. Int. J. Res. Pharm. Sci. 1:113-126.

Aggarwal N, Aggarwal R, Mishra P, Jain JS, Bansal SK, Jha KK (2008). Design and evaluation of semicarbazones and thiosemicarbazones as novel anticonvulsants. Cent. Nerv. Syst. Agents. Med. Chem. 1:26-28.

Amoussatou S, Kpoviessi SDS, Gbaguidi F, Cosme Kossouoh, Joanne Bero, Quetin-Leclercq J, Moudachirou M, Poupaert J, Accrombessi GC (2012). Selective trypanocide activity of some substituted thiosemicarbazones of citral from Benin cymbopogon citrates essential oil and their toxicity against Artemia salina leach. IJRRAS. 12(3):454-462.

Cocco MT, Congiu C, Lilliu V Onnis V (2006). Synthesis and *in vitro* antitumoral activity of new hydrazinopyrimidine-5-carbonitrile derivatives. Bioorg. Med. Chem. 14(2):366-372.

Da Silva AP, Martini MV, de Oliveira CMA, Cunha S, de Carvalho IE, Ruiz ALTG, Da Silva CC (2010). Antitumor activity of (-)-α-bisabolol-based thiosemicarbazones against human tumor cell lines. Eur. J. Med. Chem. 45:2987-2993.

De Oliviera RB, De Souza-Fagundes EM, Soares RPP, Andrade A, Krettli EU, Zani CL. (2008). Synthesis and antimalarial activity of semicarbazone and thiosemicarbazone derivatives. Eur. J. Med. Chem. 43:1983-1988.

Du XGC, Hansell E, Doyle SP, Caffrey CR, Holler TP, McKerrow JH, Cohen FE (2002). Synthesis and structure-activity relationship study of potent trypanocidal thiosemicarbazone inhibitors of the

trypanosomal cysteine protease cruzain. J. Med. Chem. 45:2695-2707.
Fujii N, Mallari JP, Hansell EJ, Mackey Z, Doyle P, Zhou YM, Gut J, Rosenthal PJ, McKerrow JH, Guy RK (2005). Discovery of potent thiosemicabazones inhibitors of rhodesain and cruzain, Bioorg. Med. Chem. 15 (1):121-123.
Greenbaum DC, Mackey Z, Hansell E, Doyle P, Gut J, Caffrey CR, Lehrman J, Rosenthal PJ, McKerrow JH, Chibale K (2004). Synthesis and structure-activity relationships of parasiticidal thiosemicarbazone cysteine protease inhibitors against *P. falciparum*, *T. brucei* and *T. cruzi*. J. Med. Chem. 47(12):3212-321.
Glinma B, Gbaguidi AF, Kpoviessi SDS, Fatondji HR, Poupaert J, Accrombessi CG (2011). Characterization and antiparasitic activity of benzophenone thiosemicarbazones on *Trypanosoma* brucei brucei. St. Cerc. St. CICBIA. 12:033-040.
Glinma B, Kpoviessi SDS, Gbaguidi FA, Kapanda CN, Bero J, Quetin-Leclercq J, Moudachirou M, Poupaert J, Accrombessi GC (2012). Synthesis, characterization, trypanosomal activities on *Trypanosoma brucei brucei* and toxicity against *Artemia salina* Leach of N (4)-aryl semicarbazones and thiosemicarbazones. J. Chem. Pharm. Res. 4:1016-1021.
Halve AK, Bhashkar B, Sharma V, Bhadauria R, Kankoriya A, Soni A, Tiwari K (2008). Synthesis and *in vitro* antimicrobial studies of some new 3-[phenyldiazenyl] benzaldehyde N-phenyl thiosemicarbazones., J. Enzy. Inhib. Med. Chem. 23(1):77-81.
Hassanien MM, Gabr IM, Abdel-Rhman MH, El-Asmy AA (2008). Synthesis and structural investigation of mono-and polynuclear copper complexes of 4-ethyl-1-(pyridin-2-yl) thiosemicarbazide. Spectrochimica Acta A. 71:73-79.
Hu W, Zhou W, Xia C, Wen X (2006). Synthesis and anticancer activity of thiosemicarbazones., Bioorg. Med. Chem. Lett. 16(8):2213-2218.
Küçükgüzel SG, Mazi A, Sahin F, Öztürk S, Stables JP (2003). Synthesis and Biological activities of diflunisal hydrazide-hydrazones., Eur. J. Med. Chem. 38(11-12):1005-1013.
Li ZH, Moran D, Fan KN, Schleyer PV (2005). Sigma-aromaticity and sigma-antiaromaticity in saturated inorganic rings, J. Phys. Chem A. 109(16):3711-3716.
Loncle C, Brunel JM, Vidal N, Dherbomez M, Letourneux Y (2004). Synthesis and antifungal activity of cholesterol-hydrazone derivatives. Eur. J. Med. Chem. 39(12):1067-1071.
Mallari JP, Shelat A, Kosinski A, Caffrey CR, Michele C, Zhu F, McKerrow JH, Guy RK (2008). Discovery of trypanocidal thiosemicarbazone inhibitors of *rhodesain* and TbcatB. Bioorg., Med. Chem. Lett. 18(9):2883-2885.
Mallari JP, Guiguemde WA, Guy RK (2009). Antimalarial activity of thiosemicarbazones and purine derived nitriles. Bioorg. Med. Chem. Lett. 19(13):3546-3549.
Melnyk P, Leroux V, Sergheraert C, Grellier P (2006). Design, synthesis and *in vitro* antimalarial activity of an acylhydrazone library., Bioorg. Med. Chem. Lett. 16(1):31-35.
Pine SH, Hendrickson JB, Cram DJ, Hammond GS (1982). Organic chemistry, 4th Edition, J. Chem. Educ. 59(2):PA66.
Pandeya SN, Yogeeswari P, Sriram D, de Clercq E, Pannecouque C, Witvrouw M. (1999). Synthesis and screening for anti-HIV activity of some N-Mannich bases of isatin derivatives. Chemotherapy 4:19.
Richardson DR, Kalinowski DS, Richardson V, Sharpe PC, Lovejoy DB, Islam M., Bernhardt PV (2009). 2-Acetylpyridine thiosemicarbazones are potent iron chelators and antiproliferative agents: redox activity, iron complexation and characterization of their antitumor activity. J. Med. Chem. 52(5):1459-1470.
Singh PK, Kumar DN (2006). Spectral studies on cobalt (II), nickel (II) and copper (II) complexes of naphthaldehyde substituted aroylhydrazones., Spectrochimica Acta Part A. 64(4):853-858.
Teitz Y, Ronen D, Vansover A, Stematsky T, Rigg JL (1994). Inhibition of human immunodeficiency virus by N-methylisatin-β-4':4' diethylthiosemicarbazone and N-allyl isatin-β-4':4' diallylthiosemicarbazone., Antiviral Res. 24:305-14.
Umamatheswari S, Kabilan S (2011). Synthesis and antimicrobial studies of novel 2,4-diaryl-3-azabicyclo[3.3.1]nonan-9-one 4'-phenylthiosemicarbazones., J. Enzyme. Inhib. Med. Chem. 26(3):430-439.
Wang Y, Serradell N, Bolos J, Rosa E (2007). MK-0518, HIV integrase inhibitor. Drugs Fut. 32:118-122.
Wiecek J, Kovala Demertzi D, Ciunik Z, Zervou M, Demertzis MA (2010). Diorganotin complexes of a thiosemicarbazone, synthesis: properties, X-ray crystal structure, and antiproliferative activity of diorganotin complexes., Bioinorg. Chem. Appl. Article ID 867195, P. 9.
Xia YL, Chuan-Dong F, Zhao BX, Zhao J, Shin DS, Miaom JY (2008). Synthesis and structure-activity relationships of novel 1-arylmethyl-3-aryl-1Hpyrazole-5carbohydrazide hydrazone derivatives as potential agents against A549 lung cancer cells, Eur.J. Med. Chem. 43:2347–2353.