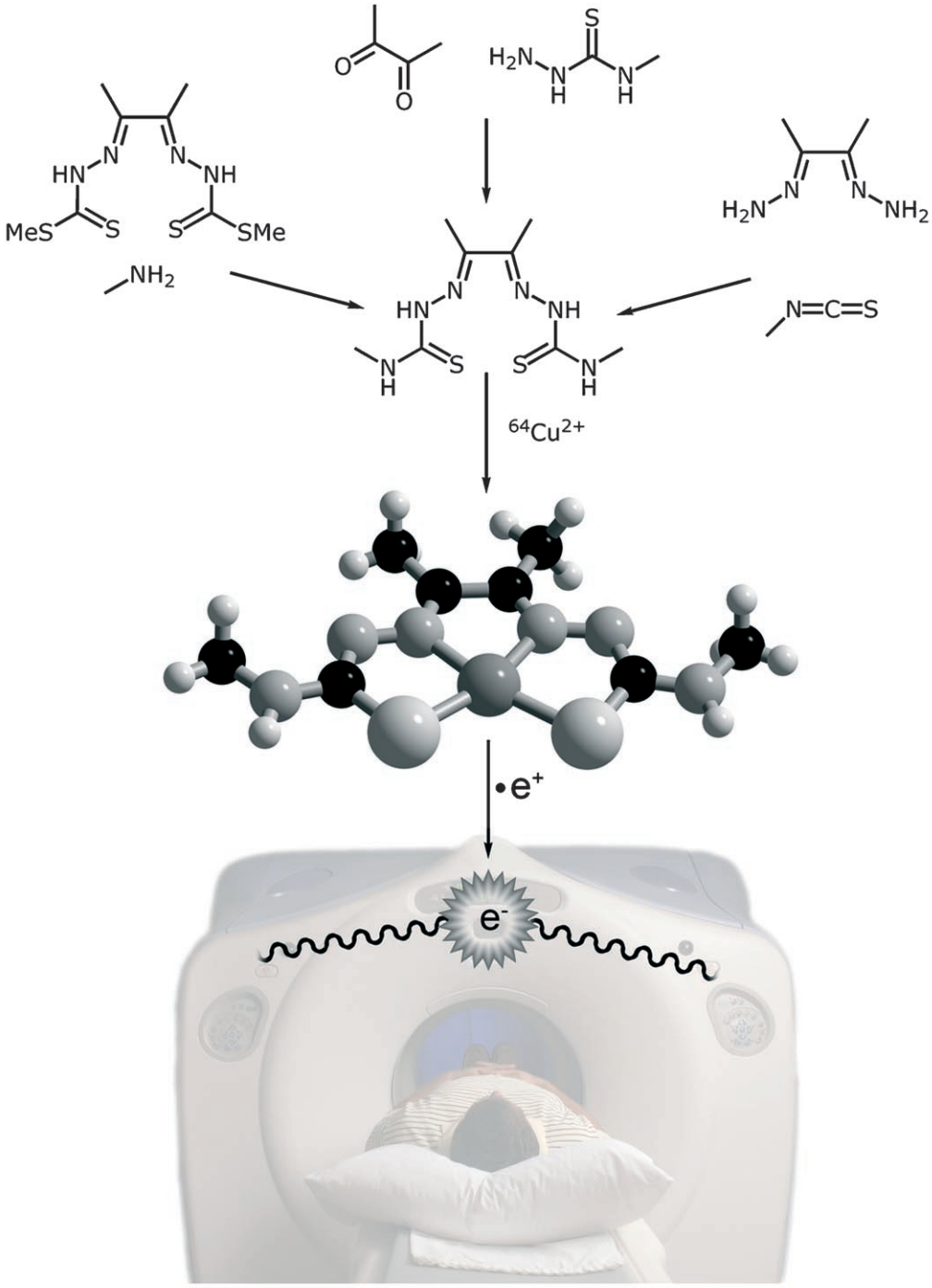
Ligands for Molecular Imaging

How to synthesise bis(thiosemicarbazone) ligands for copper and zinc.



The synthesis of bis(thiosemicarbazones) is challenging, but their importance in molecular imaging makes understanding their chemistry essential.

DOI: 10.1002/chem.200501069

Ligands for Molecular Imaging: The Synthesis of Bis(thiosemicarbazone) Ligands

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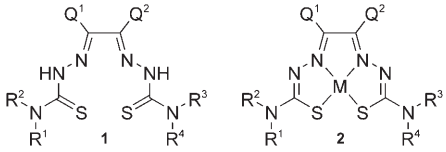
Abstract: Bis(thiosemicarbazones) have been of interest to chemists for over fifty years; they display antitumour, antibiotic and antiviral properties. Recently it has become apparent that they may also provide a convenient way of labelling biologically active molecules by using metallic radionuclides and/or fluorescence. Although apparently simple, the synthesis of bis(thiosemicarbazone) ligands can be problematic. This article provides a summary of the published literature, based on the synthetic strategies used and indicates some of the difficulties that may arise.

Keywords: bis(thiosemicarbazones) · imaging agents · ligand design · mono(thiosemicarbazones) · radiopharmaceuticals

Introduction

Bis(thiosemicarbazones) have been known for over 50 years. There is considerable current interest in their biological activity both as free ligands **1** and as metal complexes **2**.



They have been the subject of at least twelve patents from four different organisations, mainly concerned with their antibacterial properties. In many cases their activity in biological systems is enhanced by coordination and in 1964 Petering wrote that "it is probable that much of the toxicity of these compounds is related in some way to their ability to bind trace metals especially copper and zinc."[1]

The copper complex of diacetylbis(*N*-methylthiosemicarbazone) (atsm; $R^1=R^4=Me$, $R^2=R^3=H$, $Q=Me$) has been used in humans and animals as a highly effective imaging agent for PET studies to locate hypoxic tissue.[2,3] The neutral Cu^{II} species is easily transported into and out of cells, while the reduced Cu^{I} species is trapped inside cells with low oxygen concentration. The complex [Cu(atsm)], which was identified as being hypoxic selective sometime ago, is still the lead complex of Cu for hypoxia imaging; however, its mechanism of selectivity remains unclear although detailed DFT studies have shed some light on some of the chemical process that may relate to its hypoxic selectivity.[4,5]

Recently our group discovered that the zinc complexes are fluorescent. We have been able to show that this fluorescence may be used to image the cellular distribution of [Zn(atsm)] in three human tumour cell lines.[6] A DFT study was able to show how the absorption of light relates to the electronic structure and suggested how to influence the optical properties in these compounds.[7]

To extend and refine the medicinal applications, functional substituents, such as carboxylate groups, have been built into the backbone (at Q^1 or Q^2) to enable biological targeting vectors to be attached.[8–11] The last section of this article details some of the radiolabelling work involving such conjugated species. Ongoing work in our and other groups continues to seek new ways of conjugating metal-containing bis(thiosemicarbazones) to interesting biological targeting vectors.

It is clear that future improvements on the [Cu(atsm)] system will depend on the synthesis of new ligand systems. In this concept article we focus on the known preparations of tetradentate bis(thiosemicarbazone) ligands and present some of the problems that can be encountered and how they can be circumvented. Some of the synthetic difficulties may be addressed by expanding the ligand to include backbones that containing more than two carbon atoms.[12] These

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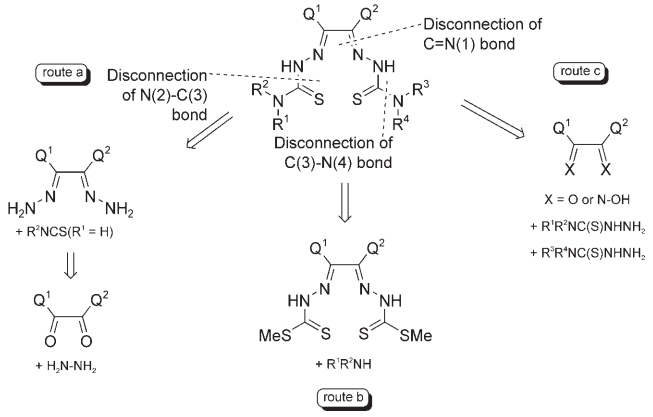
expanded ligands are more flexible than atsm and it's derivatives and may incorporate metal cations that prefer non-square-planar geometries, for example, Cu^{I}. We discuss the synthesis of compounds with expanded backbones; this work is actively being pursued in our laboratories and elsewhere. This article focuses on tetradentate thiosemicarbazone ligands; bi-, tri-, penta- or hexadentate ligands have been specifically excluded.

General Comments

Numbering system for ligands and complexes: The numbering system used for thiosemicarbazones starts with the central backbone carbons as follows $C_{(1)}=N_{(1)}-N_{(2)}H-C_{(3)}(S)-N_{(4)}$; in bis(thiosemicarbazones), the second arm is designated with primed numbers [for example, $N_{(1')}$].

Organisation of this article: This survey is broadly organised according to the synthetic strategy used in making the bis(thiosemicarbazone) (Scheme 1). Three approaches have been used: formation of the $N_{(2)}-C_{(3)}$ bond (route a), formation of the bond $C_{(3)}-N_{(4)}$ (route b) and formation of the $C=N_{(1)}$ bond (route c).

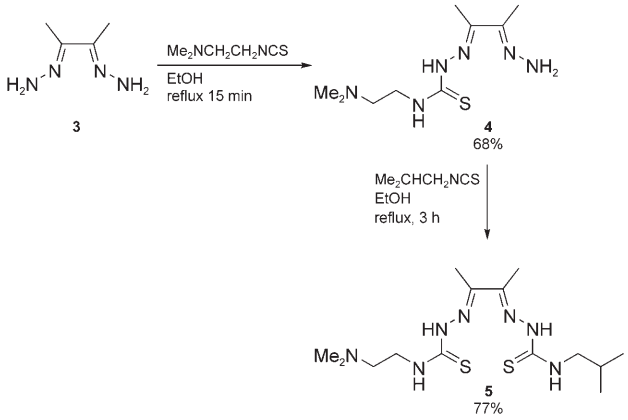


Scheme 1. Retrosynthetic analysis of routes to bis(thiosemicarbazones).

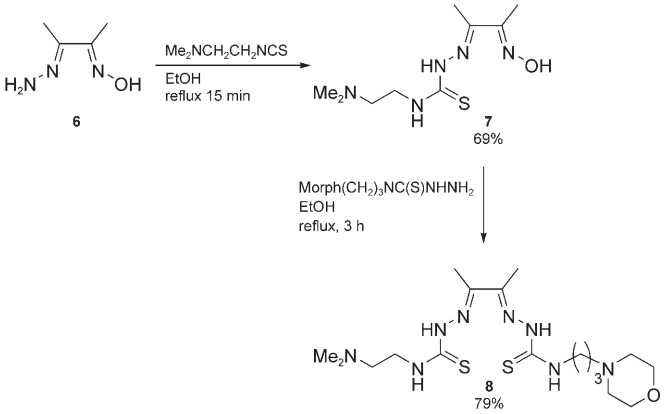
Route a—Formation of the $N_{(2)}-C_{(3)}$ Bond

This is potentially a convenient route to dissymmetric bis(thiosemicarbazones) ($R^2 \neq R^3$, $R^1 \neq R^4$). A representative procedure is as follows: a solution of one equivalent of 2-dimethylaminoethyl isothiocyanate in ethanol was added to a boiling solution of butanedione dihydrazone **3** in ethanol and the resulting mixture was heated to reflux for 15 minutes to give butanedione mono(2-dimethylamino-ethylthiosemicarbazone) monohydrazone **4** in 68% yield. The product was then treated with isobutyl isothiocyanate in ethanol, under reflux, for three hours to give the desired bis(thiosemicarbazone) **5** in 77% yield (Scheme 2).[13,14]

The method has also been used with butanedione hydrazone–oxime **6** to make an intermediate **7** that is elaborated by oxime–hydrazone exchange (see later) to give the desired material **8** (Scheme 3).[15,16]



Scheme 2. Synthesis of dissymmetric bis(thiosemicarbazones) **5** from dihydrazone **3**.



Scheme 3. Synthesis of ligand **8** from hydrazone–oxime **6**.

The second step in this synthesis is an exchange of an oxime group for a hydrazone and this segment of the synthesis is therefore part of route c (see Scheme 1, route c, X = N–OH).

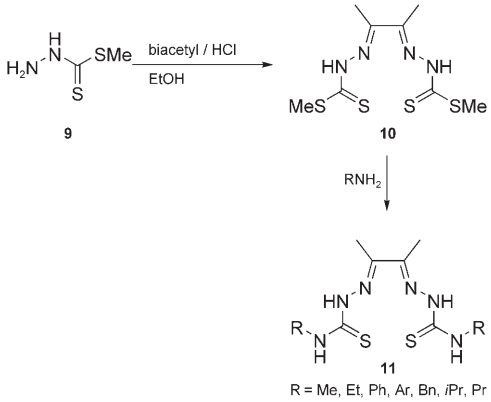
The strategy is limited to 1,2-diketone-derived dihydrazones. The reactions of acyclic 1,3- and 1,4-diketones with hydrazine give diazaheterocycles and cannot be used in this synthetic approach. Access to the isothiocyanates is also required and the presence of reactive functional groups in the isothiocyanate synthesis limits the generality of this route.

We have investigated this synthetic approach and have encountered considerable problems isolating species such as **4** (Scheme 2). A mixture of dihydrazone **3** and phenyl isothiocyanate (2:1 molar ratio) was stirred under reflux in ethanol for 15 minutes. The product obtained was a >7:1 mixture of the desired butanedione bis(4-phenylthiosemicarbazone) and the intermediate butanedione mono(4-phenylthiosemicarbazone) monohydrazone in 86% yield. When the experiment was repeated with a 1:1 molar ratio, an 8:1 mixture of

butanedione mono(4-phenylthiosemicarbazone) monohydrazone and butanedione bis(4-phenylthiosemicarbazone) in 75% yield was obtained. The mixtures could not be separated. In our experience, dissymmetric bis(thiosemicarbazones) are better made by route c (see below).

Route b—Formation of the $C_{(3)}$–$N_{(4)}$ Bond

When *S*-methyldithiocarbazide **9** and concentrated HCl in ethanol were added, dropwise, to a solution of butanedione in ethanol and heated under reflux for an hour, the intermediate **10** was obtained.[17] Reaction of **10** with amines in ethanol for 3 h under reflux was reported to give bis(thiosemicarbazone) **11** (Scheme 4). No yields were given for these reactions.

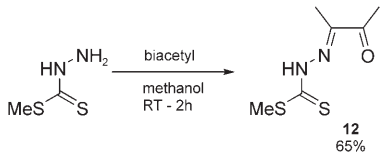


Scheme 4. Synthesis of **11** from hydrazide **9**.

As represented above, the approach is limited to the synthesis of symmetric compounds **11**; the synthesis of products **1** ($R^1 \neq R^4$, $R^2 \neq R^3$) is complicated by the formation of statistical mixtures.

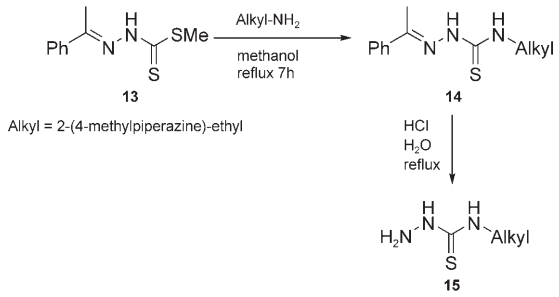
The synthesis of **9** must be carried out with good temperature control. Failure to do so gives evolution of methyl sulfide and mixtures of dimers and higher oligomers. Our attempts to displace the methyl sulfide group in **9** with benzyl amine were not successful, presumably because the hydrazinic nitrogen in **9** is a better nucleophile than benzylamine.

Synthesis of butanedione mono(*S*-methyldithiocarbazone) **12** was straightforward (Scheme 5), but attempts to displace the methyl sulfide with benzylamine or aniline failed, even after prolonged heating at 90°C in DMF.



Scheme 5. Synthesis of mono-*S*-methylthiocarbazone **12**.

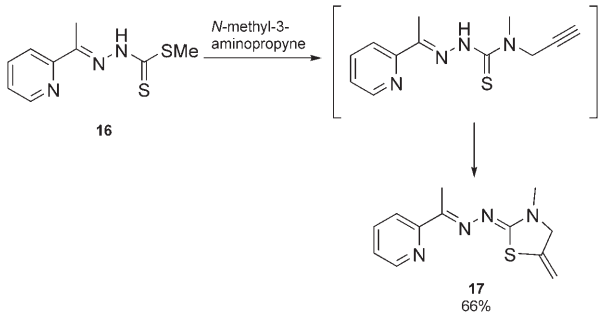
Barrett et al. showed that *S*-methyldithiocarbazide **9** could be condensed with acetophenone to give a simple *S*-methyldithiocarbazone (**13**; Scheme 6).[17] The methylsulfide group



Scheme 6. Displacement of the *S*-methyl group in **13**.

could then be displaced with an alkyl amine **14** and then the acetophenone removed with aqueous acid to release the alkylthiosemicarbazide **15**.

In principle, this could be a solution to the synthesis of *N*-alkylthiosemicarbazides, which are otherwise difficult to prepare. We found this process successful with benzylamine (50%), although we had to heat to 90°C in DMF overnight to get any appreciable displacement.[7] Aniline did not react even after prolonged heating in DMF. Interestingly, reaction of **16** with *N*-methyl 3-aminopropyne is reported to give **17** in 66% yield (Scheme 7).[18] The desired *N*-methyl-*N*-propy-

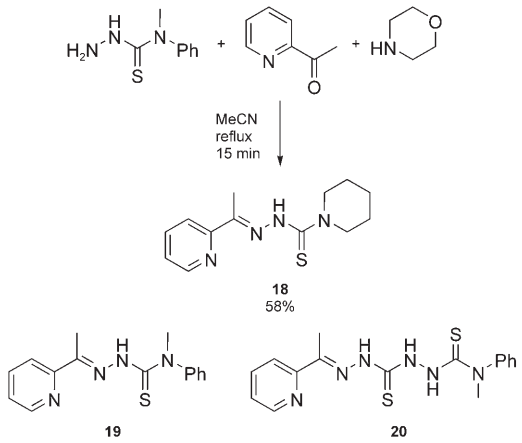


Scheme 7. Displacement of *S*-methyl group with *N*-methyl 3-aminopropyne.

nylthiosemicarbazide was made from propynyl isothiocyanate.

Scovill reported that a mixture of Me,Ph–thiosemicarbazide, morpholine, and 2-acylpyridine, when heated under reflux for 15 minutes in acetonitrile, gave **18** in 58% yield.[19] It has been shown that compounds such as **14** and **18** form complexes with zinc and copper (Scheme 8).[20,21] Surprisingly, when **19** was heated for 45 minutes in acetonitrile the product reported was **20** in 89% yield.[18,22]

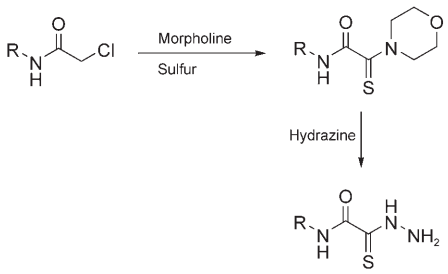
Scovill reported that *N*-methylaniline may be displaced from Me,Ph–thiosemicarbazide by treatment with an alkyl amine under reflux for 15 minutes in acetonitrile.[19] We were able to reproduce this result using morpholine (26%



Scheme 8. Synthesis of **18** and rearrangement reaction of **19**.

yield; compare with the literature value of 53%) and pyrrolidine (41% yield; compare with the literature value of 72%) as the alkyl amines. Again this represents a potentially valid method for the synthesis of thiosemicarbazides by $C_{(3)}$–$N_{(4)}$ bond formation, but the yields are low, and the scope is limited if the amine used is difficult to make or not commercially available.

The range of $N_{(4)}$ substituents may be expanded to include amide groups (Scheme 9).[23] Subsequent reaction of the thiohydrazide with 1,2-diketones gives the corresponding bis(thioacylhydrazone) in the usual way.



Scheme 9. Synthesis of a thiohydrazide.

Route c—Formation of the C=$N_{(1)}$ Bond

This is the most commonly used route to bis(thiosemicarbazone) ligands. However, this route sometimes throws up unexpected complexities; these problems will be discussed in this section and in the section on cases that give unexpected results. A large range of compounds has been prepared; Table 1 gives a representative survey with references and yields. Dissymmetric bis(thiosemicarbazones) may be derived from two sources. Either they are prepared from nonsymmetric dicarbonyl compounds, or from the stepwise condensation of a symmetric dicarbonyl compound with two different thiosemicarbazides. It is worth recording here the comments of Gringas et al. who, despite some success, point out that; "The reaction of dicarbonyl compounds with H_2–thiosemicarbazide is not simple and mixtures of products are usually obtained. The separation of these mixtures is complicated by the low solubility of the various components and the discrepancies encountered in the literature concerning their melting points."[24]

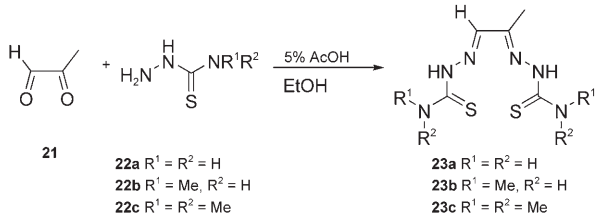
Typically, the bis(thiosemicarbazone) is made by heating a thiosemicarbazide under reflux with an α-diketone in an alcoholic solvent with an acid catalyst. A representative published procedure is as follows: pyruvaldehyde **21** (Q^1 = Me, Q^2 = H) was added dropwise over 30–40 minutes, as a solution in water or 50% ethanol, to a solution of thiosemicar-

Table 1. Representative substituents on published bis(thiosemicarbazones).

Q^1	Q^2	R^1 and R^4	R^2 and R^3	Yield[e]	Ref.
Me	H	Me	H	NG	[1]
Me	H	Me	H	NG	[1]
Me	Bu, Ph	H	H	NG	[24]
Me	H	H	H	NG	[40]
Me, Pr, $MeOCH_2CH_2OC(Me)H$	H	H, Me,	H, Me	NG	[42]
Me, Et, MeCH(OEt), Pr, *i*Pr, Bu, Ph	H	H, Me, Et	H, Me	NG	[41]
MeCH(OR)[a or b]	H	H, Me	H, Me, Et, Pr, *i*Pr, RC(O)[d]	NG	[42–44]
MeCH(OR)[c]	H	H, Me, Ph, Bn, $pBrC_6H_4$	H	NG	[45]
2-pyr[f]	2-pyr	Et	Et	NG	[31,32]
2-pyr	2-pyr	C_5H_{10}		NG	[31,32]
2-pyr	2-pyr	C_6H_{12}		NG	[31,32]
2-pyr	2-pyr	Pr	Pr	NG	[31]
C_3H_6		H	H	81	[57]
C_4H_8		H	H	45	[57]
C_5H_{10}		H, H	H, Me	80, 85	[57]
C_6H_{12}		H	H	19	[57]
$CH_2CH_2C(H)MeCH_2CH_2$		H	H	36	[57]
$CH_2CH_2CH_2C(H)Me$		H	H	22	[57]
C_5H_{10}		H	H	60	[58]
C_3H_6, C_4H_8		Me, Et	Bu, Me	NG	[58]

[a] R = Me, Et, Ac. [b] R = H, Me, Et, Pr, *i*Pr, MeC(O), EtC(O) or PrC(O). [c] R = Me, Et, Pr, Bu. [d] R = Me, Et, Pr, *i*Pr. [e] NG = not given in the referenced literature. [f] 2-pyr = 2-pyridyl.

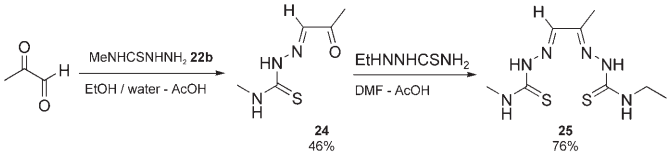
bazide **22a** ($R^1=R^2=H$), Me–thiosemicarbazide **22b** ($R^1=H$, $R^2=Me$) or Me_2–thiosemicarbazide **22c** ($R^1=R^2=Me$) in water, with 5% AcOH, at 50–60°C. The mixture was left to stand at ambient temperature for several hours and was then refrigerated for two days. The products **23a–c** were collected by filtration (crude yield 75–80%) and recrystallised from boiling methanol (85% recovery) after addition of an equal volume of water (Scheme 10).[1]



Scheme 10. Synthesis of **23** from pyruvaldehyde and a thiosemicarbazide.

West et al. have discussed the crystal structures of a number of bis(thiosemicarbazones), derived from butanedione, and their metal complexes.[25] The thiosemicarbazides, which were not commercially available, were made according to the Scovill procedure.[19] We have also prepared a number of bis(thiosemicarbazones) and their copper(II) complexes by this method.[26]

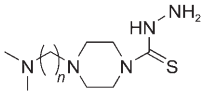
Stepwise condensation of a dicarbonyl with two different thiosemicarbazides: Taft and Shepherd have reported the synthesis of mono(thiosemicarbazones) and bis(thiosemicarbazones) from butanedione.[27] Conducting the reaction in ethanol under reflux gives the bis(thiosemicarbazones) in 56% yield with a 12% yield of the mono(thiosemicarbazones). The mono(thiosemicarbazone) was formed selectively (53%) by stirring the neat reagents at room temperature. Barry et al. have also made compounds from pyruvaldehyde ($R^1=Me$, Et; $R^2=H$). In a representative procedure (Scheme 11): Me–thiosemicarbazide **22b** was suspended in water and $NaHCO_3$ added. The mixture was warmed until a clear solution was obtained. The resulting solution was added to butanedione (1 equiv) in ethanol. The mixture was heated under reflux for 15 minutes. The product **24** (46%) could be isolated by filtration after removal of some of the solvent. The mono(thiosemicarbazone) **24** was then treated with 4-ethyl-thiosemicarbazide in DMF with acetic acid catalysis. The bis(thiosemicarbazone) **25** was isolated (in 76% yield) by filtration.[12] We have had considerable success



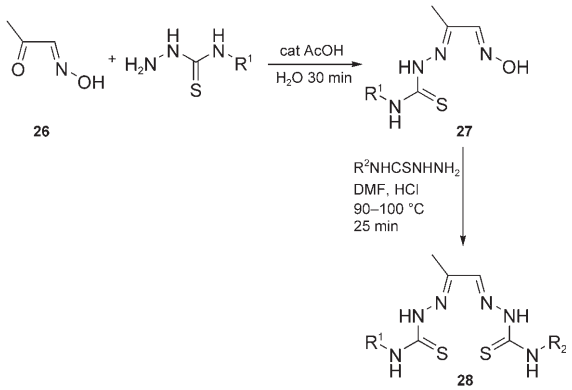
Scheme 11. Stepwise addition of two thiosemicarbazides to 2-oxopropanal.

with this approach following the method of Gummerus.[28] Whichever procedure is followed for the synthesis of asymmetric thiosemicarbazides, great care has to be employed to ensure that mixtures are not generated, and even if the pure dissymmetric bis(thiosemicarbazide) is generated it can disproportionate to give mixtures if heated in solution. Claims to the synthesis of dissymmetric bis(thiosemicarbazones) should therefore be treated with caution.

Several coccidiostats have been based on [4-(ω-dimethylaminoalkyl)-1-piperazinyl]thiosemicarbazides (shown here: $n=1$, 2 or 3), several species of gut parasite being controlled by oral dosing.[17,29,30] There has also been interest in using pyridil as the starting diketone, as the two pyridine rings are a site for coordination of a second metal atom.[31,32]



Stepwise synthesis of bis(thiosemicarbazones) from precursors other than diketones: The displacement of hydroxylamine from isonitrosoacetone **26** by thiosemicarbazide is known. The ketone group reacts first to give **27**. A second thiosemicarbazide may then be added to displace the oxime and give the final product **28**. A substantial range of compounds were made with various alkyl groups on the nitrogen atoms (Scheme 12; $R^1=H$, Me,

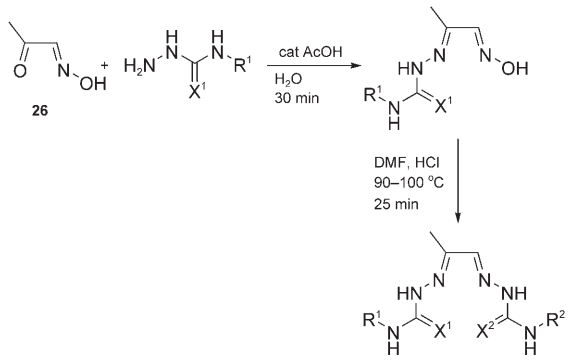


Scheme 12. Use of isonitrosoacetone **27** as a starting material.

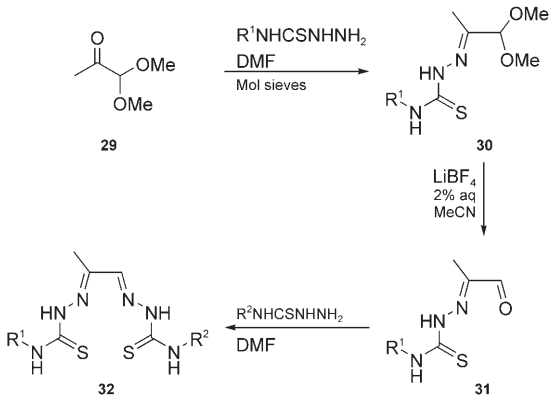
Et, Pr, *i*Bu, Bn, *c*Hex, allyl and amyl; $R^2=H$, Me, Et, Pr, *i*Bu, *c*Hex, allyl and amyl).[12] Few yields were given (one example $R^1=Me$ 97% first step: $R^2=H$, 75% second step).

Barry et al. reported that the reactions between pyruvaldehyde and H_2-thiosemicarbazide were unpredictable.[33] They regarded the synthesis from isonitrosoacetone as superior.

Barry et al. also made a series of compounds by stepwise condensation of isonitrosoacetone with H_2–thiosemicarbazide (X=S), semicarbazides (X=O) and azasemicarbazides (X=NH) (Scheme 13 and Table 2).[12] Few yields were given (e.g., $R^1=Me$, $X^1=S$, 97% first step: $R^2=H$, $X^2=NH$, 21% second step). Similar systems were made by simply condens-



Scheme 13. Synthesis of bis(thiosemicarbazones), bis(semicarbazones), bis(azasemicarbazones) and mixed dissymmetric derivatives.



Scheme 14. Alternative two-step synthesis of dissymmetric bis(thiosemicarbazones).

Table 2. Variants on the bis(thiosemicarbazone) theme (Scheme 13).

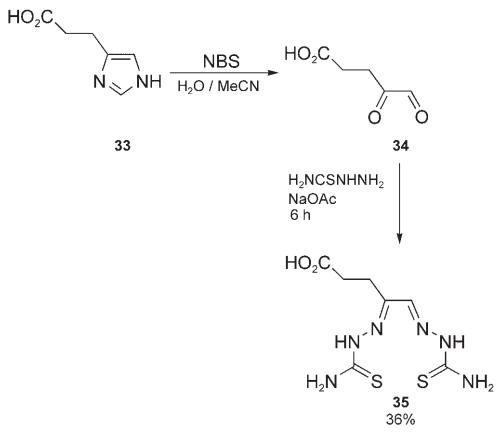
R^1	X^1	X^2	R^2	Ref.
Me	S	NH	H	[25]
H	NH	S	Me	[25]
H	S	NH	H	[25]
H	NH	O	H	[25]
H	O	NH	H	[25]
H	O	S	Me	[25]
H	O	O	H	[38]
H	S	S	H	[38]
H	NH	NH	H	[38]

ing two equivalents of the appropriate thiosemicarbazide, semicarbazide or azasemicarbazide with pyruvaldehyde.

Green et al. reported having difficulty repeating the methods, outlined above, based on the use of isonitrosoacetone.[34] Although they were able to isolate compounds such as **27**, treatment with a second thiosemicarbazide gave mixtures of symmetric and dissymmetric bis(thiosemicarbazones). As an alternative they used an α-ketoacetal **29** as the starting material.[34] The ketone reacts first to give iminoacetal **30** (R^1 = H, Me: 60–80% yield), which is then converted to the aldehyde **31** by a Lewis acid and water (90% yield) before addition of the second thiosemicarbazide to give **32** in 50–60% yields (Scheme 14). The scope of this route has been expanded to include a range of alkyl and alicyclic groups at $N_{(4)}$.[35]

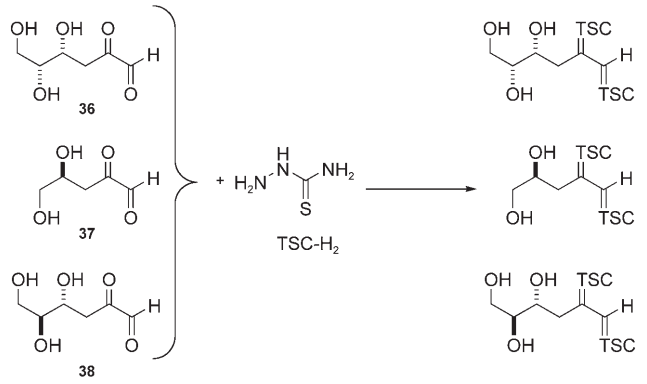
Use of non-symmetrical dicarbonyls: West et al. used the standard conditions, with H_2SO_4 added, to prepare $N_{(4)}$-methyl- and $N_{(4)}$-ethyl-substituted bis(thiosemicarbazones) from 1-phenyl-1,2-propanedione[36] and phenylglyoxal.[17,37–39] Pyruvaldehyde[40] and various alkyl-substituted glyoxals[41,42] have been prepared, along with a series of compounds derived from branched chain diketones.[43–45] 3-Phenanthrylglyoxal has been used as the dicarbonyl precursor[46] and a series of compounds made from cyclohexylglyoxal, 1-phenyl-2,3-dioxobutane and 3-ethoxy-2-oxobutanal have also been reported.[17] Petering used a range of ketoaldehydes with oxygenated side chains, including ethoxypyruvaldehyde[1] and 3-methoxy-2-oxobutanal.[47] Despite the range of 1,2-dicarbonyl compounds that have been used, apparently successfully, to make the bis(thiosemicarbazones), unique difficulties were encountered with benzil (discussed below).

The synthesis of bis(thiosemicarbazones) has been used to trap the dicarbonyl products of the oxidation of imidazole. *N*-Bromosuccinimide (NBS) oxidation of a substituted imidazole **33** gives a substituted glyoxal **34**, which reacts with H_2–thiosemicarbazide to give **35**; the result may be used to quantify the formation of dicarbonyl compound (Scheme 15).[48] The carboxylate group in compound **35** has the potential to be used a conjugation site for biological molecules.



Scheme 15. Quantification of the oxidation of imidazole **34**.

Cao and West et al. were able to prepare bis(thiosemicarbazones) and their metal (Cu^{II} and Ni^{II}) complexes from diketones derived from ribose **36**, galactose **37** and glucose **38** (Scheme 16).[49] There has been much interest in these sugar-derived structures;[50–55] for example, Horton et al.[51] noted that the use of 2-methoxyethanol as solvent gives better results than the use of ethanol or methanol. It was suggested that 2-methoxyethanol allows a higher concentration and temperature. Preliminary studies with copper, plati-



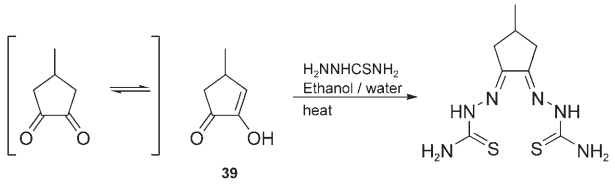
Scheme 16. Preparation of bis(thiosemicarbazones) from sugar-derived dicarbonyls.

num and palladium complexes have shown activity against the poliovirus type 1.[52] Testing against the murine L-1210 tumour line was also reported.[51]

Bis(thiosemicarbazones) derived from *para*-substituted phenyl glyoxals: A series of bis(thiosemicarbazones) was prepared from *para*-substituted phenylglyoxals and H_2–thiosemicarbazide under acidic conditions.[56] The authors report that the elemental analysis of the bis(thiosemicarbazone) shows that the H_2–thiosemicarbazide is still present; they removed it with DOWEX resin. The *para*-substituents examined were SO_3^-, CN, SMe, CO_2H, OCH_2CO_2H, SO_2Me, $C(O)NH_2$ and N(H)COMe; only the derivative with a sulfate group failed to produce the required bis(thiosemicarbazone). The copper(II) complexes were made in hot methanol from the metal acetate. When the phenyl ring bore a carboxylate substituent, a ligand exchange reaction between the acetate groups and the carboxylate groups occurred, as indicated by IR spectroscopy. The products were not fully characterised.

Cyclic diketones: Cyclic 1,2-diketones have also been used;[57,58] bis(thiosemicarbazones) were made from cyclopentanedione, cyclohexanedione, cycloheptanedione and cyclooctanedione.

A cyclic 2-hydroxyenone **39** was also used as a starting material and condensed with H_2–thiosemicarbazide (Scheme 17).[59]



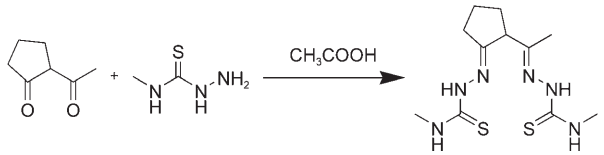
Scheme 17. Synthesis of a bis(thiosemicarbazone) from **39**.

We were able to follow the work of McCleverty[60,61] and others[62] and repeat the synthesis of bis(thiosemicarbazone) from cyclohexanedione. We had hoped to follow this work by using cyclic diones: camphorquinone, 9,10-phenanthrenequinone and 1,10-phenanthroline-5,6-dione; however, in our hands these compounds could only be induced to condense with one thiosemicarbazide, leaving one ketone group untouched. McCleverty claimed the synthesis of a bis(thiosemicarbazone) from camphorquinone,[60,61] but we were only able to obtain the bis(thiosemicarbazone) in the presence of a zinc template; even then significant levels of mono(thiosemicarbazone) were present.

Cases That Give Unexpected Results

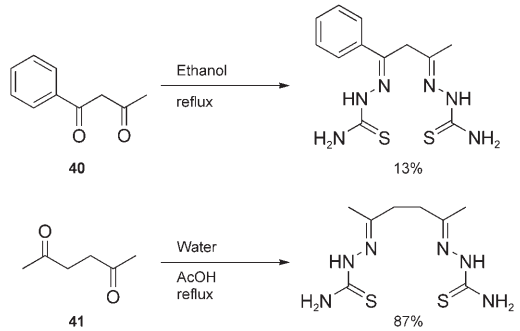
Many of the published syntheses of bis(thiosemicarbazones) and related compounds follow the generalisations given above. In the following paragraphs we discuss the cases where the syntheses are not straightforward.

Syntheses using 1,3-, 1,4- and higher related dicarbonyls: We were able to isolate the bis(thiosemicarbazone) from treatment of 2-acetylcyclopentanone with Me–thiosemicarbazide (Scheme 18).



Scheme 18. Synthesis of bis(thiosemicarbazone) from 2-acetylcyclopentanone.

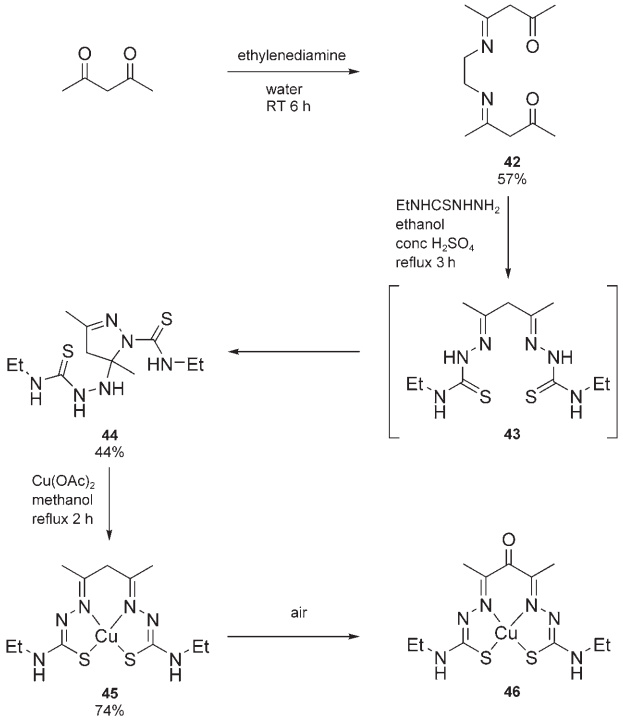
Gringas et al. reported trying to make a range of bis(thiosemicarbazones) with variation in the backbone.[24] In their paper they report the synthesis of bis(thiosemicarbazones) from 1-phenyl-1,3-butanedione **40** (13% yield) and 2,5-hexanedione **41** (87% yield). The reactions were conducted in boiling ethanol and water/acetic acid, respectively (Scheme 19). The authors comment that they failed to isolate either mono- or bis(thiosemicarbazone) from the reaction of H_2–thiosemicarbazide with 2,4-pentanedione. They



Scheme 19. Use of 1,3- and 1,4-diketones as the dicarbonyls.

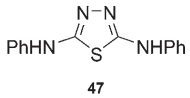
were able to isolate acetyl thiosemicarbazide [Me-C(O)NHNHC(S)NH_2] showing that the 1,3-diketone is degraded under the reaction conditions.

We also found that 2,4-pentanedione could be used directly as a starting material in the synthesis of bis(thiosemicarbazones), but that we achieved better yields with a slightly different approach:[63] the diketone was treated with 1,2-ethylenediamine to give 1,2-bis(1-methyl-3-oxobutylideneamino)ethane (**42**; Scheme 20). Reaction of **42** with Et–thiosemicarbazide gave not the expected product **43**, but rather a cyclised form, pyrazoline **44**. This is consistent with the results reported by Davies et al.[64] and Hunter et al.[65] Fortunately the cyclisation proved to be reversible and treatment of **44** with a metal cation (Cu^{II} or Ni^{II}, but not Zn^{II} or Cu^{I}) gave the desired product **45**. The structures of **44** and the copper complex **45** were confirmed by X-ray crystallography.[63] Exposure of the metal complexes to air results in oxidation of the backbone methylene unit to give **46**.



Scheme 20. Synthesis of copper complex **45** from 2,4-pentanedione.

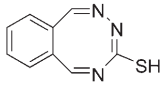
The synthesis above worked well for Me– and Et–thiosemicarbazides. When we tried to use Ph–thiosemicarbazide a new problem appeared. The reaction of **42** with Ph–thiosemicarbazide gave impure material from which crystals of *N,N′*-diphenyl-[1,3,4]thiadiazole-2,5-diamine **47** were isolated. Satisfactory metal complexes similar to **45** could be prepared from the impure material, but a significant side reaction is evidently occurring.



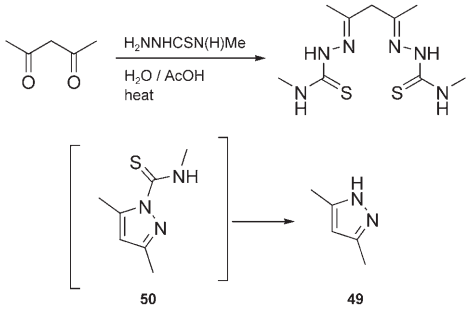
47

The direct synthesis of **47** from Ph–thiosemicarbazide alone has been independently reported.[66]

McCleverty et al. reported the synthesis of bis(thiosemicarbazones) from treatment of 2,5-hexanedione (75–85% yield), (*Z*)-hex-3-ene-2,5-dione (45–62% yield) and *o*-phthalaldehyde (50% yield) with H_2– and Me–thiosemicarbazide.[60,61] During the reaction of Me–thiosemicarbazide with 1,2-diacetylbenzene, a side product was observed which the authors suggest may be **48**. The reaction of thiosemicarbazide with 2,6-diacylpyridine proceeds without complications.[67]

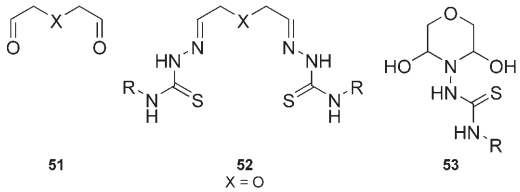

48

During their work with 2,4-pentanedione, Barry et al. reported isolating a pyrazole **49**, which they believe was formed from **50**.[68] Examination of the crude reaction mixture by IR spectroscopy indicated the presence of methyl isothiocyanate, which may have been formed during the decomposition of **50** (Scheme 21).



Scheme 21. Side products formed during the reaction of Me-thiosemicarbazide with 2,4-pentanedione.

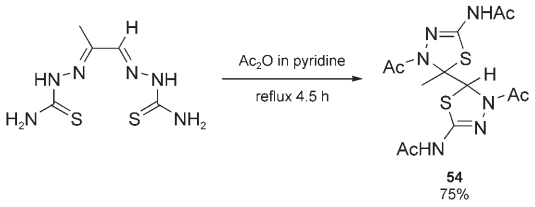
Barry et al. have also reported their results using 1,5-dicarbonyls.[69] They found that when 1,5-dicarbonyl **51** was treated with two equivalents of thiosemicarbazide in water in the presence of acetic acid the corresponding bis(thiosemicarbazone) **52** could be isolated in good yields (R = Me, 55%; R = Pr, 79%; R = 95%). However, when a single equivalent of thiosemicarbazide was used, the morpholine derivative **53** was the only product (R = H, Me, CH_2CH_2OH, Pr, Bn in 79, 44, 38, 45 and 73% yield, respectively). Dialdehyde **51** (X = O) with a benzyloxy substituent on one of the methylene groups gave only morpholine products regardless of how much thiosemicarbazide was used: conversely the dialdehyde **51** (X = S) only gives bis(thio-


51
52
X = O
53

semicarbazones) even when only one equivalent of thiosemicarbazide is used. For dialdehydes **51** (X = NAr), although condensation with hydroxylamine proceeded as above, the formation of bis(thiosemicarbazones) had to be undertaken in the absence of acid (R = H: X = NPh 44% yield, NC_6H_5Cl 70% yield).

Barry et al. have shown that bis(thiosemicarbazones) may be prepared from dicarbonyl compounds with a 1,6- or higher relationship between the carbonyl groups.[68] They successfully prepared bis(thiosemicarbazones) from: 1,6-; 1,9-; 1,10-; 1,13- and 1,14-related diketones. They have reported the synthesis of polymeric thiosemicarbazides from sugar-derived polymeric dialdehydes.[70,71] Bis(thiosemicarbazones) have been made from 1,1′-diacetylferrocene and H_2–thiosemicarbazide.[72] The complexes with Co^{II} and Cd^{II} are dimetallic dimers, showing coordination of the metal to both arms of a bis(thiosemicarbazone) unit and one arm of the second bis(thiosemicarbazone): in contrast, the tetrametallic Cu^{I} species only shows two different metal environments, each metal coordinated to one arm of each bis(thiosemicarbazone).

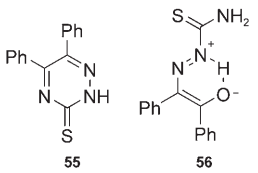
Compounds derived from H_2–thiosemicarbazide: Two papers have published on a cyclisation reaction that occurs with bis(thiosemicarbazones) derived from H_2–thiosemicarbazide itself. In both papers it is reported that treatment of the bis(thiosemicarbazone) with acetic anhydride in pyridine caused a double cyclisation event.[54,55] Exposure to acetic anhydride for one hour at room temperature gave a 29% yield of cyclised product, 4.5 h under reflux gave cyclised product **54** in 75% yield (Scheme 22). These are not commonly reported results, but many attempts at bis(thiosemicarbazone) synthesis report low to moderate yields and this type of cyclisation may be possible under acidic, Lewis acidic or other acylation/alkylation conditions and represent a possible competing side reaction in the synthesis or elaboration of any bis(thiosemicarbazone).



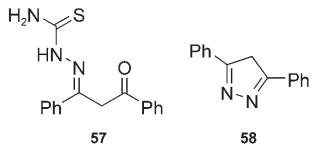
Scheme 22. Double cyclisation of bis(thiosemicarbazone) derived from pyruvaldehyde.

Syntheses using benzil as the diketone starting material: The use of benzil as the dicarbonyl introduces a number of complicating side reactions that either do not occur in the absence of the two phenyl rings or are much reduced.

The presence of an NH_2 group on the thiosemicarbazide allows double condensations to occur. The phenyl rings allow extensive delocalisation, which presumably explains the formation of compounds such as **55**. Gringas et al., examined both benzil and 1,3-diphenyl-1,3-propanedione.[24] In contrast to their observations with glyoxal and phenyl glyoxal, they report that benzil gives a mixture of mono- and bis-(thiosemicarbazone) and a triazine product **55**. An analysis of the spectral data for the mono(thiosemicarbazone) suggests a structure **56**, in which a considerable degree of hydrogen bonding is present. This may explain why the formation of bis(thiosemicarbazone) is difficult.

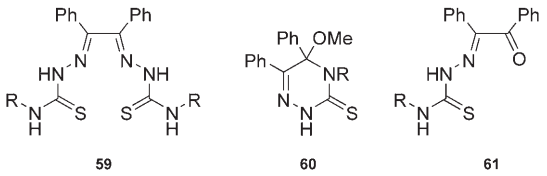


Treatment of 1,3-diphenyl-1,3-propanedione with H_2–thiosemicarbazide gave the mono(thiosemicarbazone) **57** (14% yield) and 3,5-diphenylpyrazole (**58**; 35% yield); this result stands in contrast to that obtained with 1-phenyl-1,3-butanedione (Scheme 19), but is consistent with the results highlighted in Scheme 21.

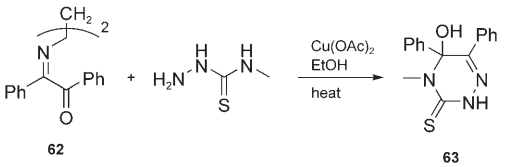


Reaction of benzil with two equivalents of H_2–, Me– or Ph–thiosemicarbazide in methanol gave the crude bis(thiosemicarbazone) **59** (R = H, Me or Ph) and this could be purified by rapid recrystallisation from DMF–methanol.[73]

Slow recrystallisation gave both the bis(thiosemicarbazone) **59** and the cyclised material **60**, which was identified by X-ray crystallography. Cyclic product **60** has been reported by others.[74] Recrystallisation from water gave only the mono(thiosemicarbazone) **61**. Since isolation of the desired bis(thiosemicarbazone) is possible under the right crystallisation conditions, the bis(thiosemicarbazone) is present but not stable with respect to partial solvolysis. Formation of the cyclic intermediate **60** is not limited to H_2–thiosemicarbazide. Jasinski et al. found that when bis(benzil)-1,3-diiminopropane **62** was treated with Me–thiosemicarbazide the isolated product was a triazine thione **63** (Scheme 23).[75]



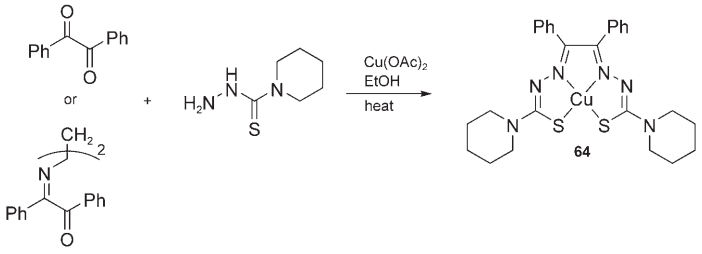
Use of a 4,4-disubstituted-thiosemicarbazide seems to prevent this problem. Jasinski et al. recently reported an attempt to prepare copper complex **64** from a mixture of



62 63

Scheme 23. Unexpected synthesis of triazine **63**.

benzil, copper acetate and piperidylthiosemicarbazide (Scheme 24).[75] In contrast to the trouble free use of pyridil in making thiosemicarbazones, no identifiable products were isolated using this method.

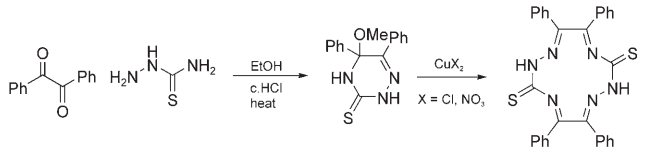


62 64

Scheme 24. Synthesis of **64**.

Instead, bis(benzil)-1,3-diiminopropane **62** was used in place of benzil (Scheme 24). It seems that imine to imine conversion is easier than ketone to imine conversion. This should probably be seen in the same light as the observation that acetal-to-acetal conversion is easier than making acetals from carbonyls. The use of a 4,4-disubstituted thiosemicarbazide prevented formation of **60** or **63**. Lacking a hydrogen atom at $N_{(4)}$ does not allow formation of the cyclic structures; however, the comparison has to be cautious since it is not known whether the copper acted as a template or stabilised the product and prevented degradation to the mono(thiosemicarbazone).

Formation of a cyclised intermediate was also observed by Mendiola et al.[76] In the presence of copper(II) the triazine thione **60** was converted to a macrocycle **65** in 2 h (Scheme 25). The authors picture **65** as in Scheme 25; that is, as a head-to-tail dimer of the mono(thiosemicarbazone) **61** (R = H), but they only report elemental analysis, IR and NMR data. This information given does not allow us to exclude the equivalent head-to-head dimer, or a polymeric structure. Interestingly elemental analysis shows no copper

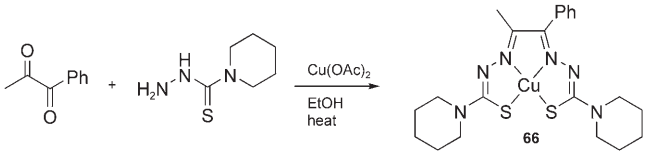


60 65

Scheme 25. Unexpected synthesis of macrocycle **65**.

in the sample and the role of the copper in the macrocyclisation is not clear. Although a model was proposed for a copper template, no copper coordinated species was isolated and the metal cation may simply promote ring-opening of **60**. The formation of macrocycle **65** also occurs in the presence of a mercury cation; this time the product is isolated as a 1:1 complex with mercury(II). The authors suggest loss of two protons and coordination through the two sulfur atoms, although the diagram they use implies some rather unusual bond angles at the carbon and nitrogen atoms; it is possible that HgL aggregates are formed in which each mercury cation is bound to two ligands.

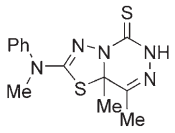
Despite the results just quoted, there were no problems with the synthesis of **66** from 1-phenylpropane-1,2-dione and piperidylthiosemicarbazide.[75] The reaction proceeded smoothly in the presence of copper acetate (Scheme 26).



66

Scheme 26. Successful synthesis of **66**.

Bis(thiosemicarbazones) from butanedione and 4,4-disubstituted-thiosemicarbazides: The nature of the substituents on the 4-position of the thiosemicarbazide has a significant impact of the course of the reaction of thiosemicarbazides with butanedione. Generally, if the thiosemicarbazide is 4-monosubstituted then the reaction to form the bis(thiosemicarbazone) will proceed smoothly. However, when we tried to form the bis(thiosemicarbazone) from Me,Ph–thiosemicarbazide and butanedione by heating the mixture under reflux in ethanol–water (1:1) for 2 h the bicyclic compound **67** was obtained.[77]

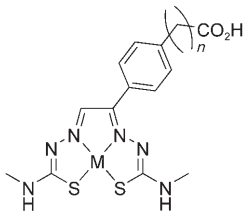


67

Conjugation and Radiolabelling

The majority of interest shown in the medical application of bis(thiosemicarbazones) has been inspired by the intrinsic biological activity of both the compounds and their metal complexes. However, attempts have been made to conjugate the metal complexes of bis(thiosemicarbazones) to antibodies and small proteins.

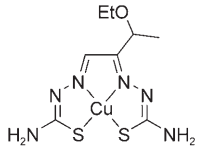
McPherson et al., prepared ^{64}Cu-labelled **68**.[10] They tried several labelling strategies



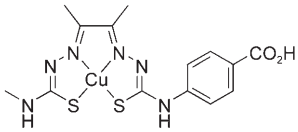
68

before finding that the labelling was most effective when $n=2$ and when the metal was introduced before conjugation to bovine serum albumin via formation of the tetrafluorophenyl ester. The copper labelling was found to be stable for up to one hour (>80% label remains) when challenged with EDTA, but that after 24 h only 50% of the label remained, decreasing to virtually zero at 48 h. Interestingly they found that if the free bis(thiosemicarbazone) was conjugated to the protein, copper labelling still occurred and occurred exclusively at the bis(thiosemicarbazone).

Arano et al. made a series of compounds with a carboxylate group tethered to the backbone through a phenyl ring **68**.[8,11] The phenyl ring is critical; a simple alkyl chain allows cyclisation involving the free acid to dominate the reaction used for the preparation of the bis(thiosemicarbazone). Arano's group combined the assumed ^{99m}Tc(V)–oxo complex with HSA and monoclonal antibody IgG (56C). The conditions must be carefully controlled to ensure that only one complex is introduced per protein. The Arano group has also studied the ^{64}Cu complex **69** in vivo.[9] Good brain uptake was observed when the labelling conditions were controlled to ensure that monometallic species were formed.



69



70

We have also had some success conjugating bis(thiosemicarbazones) to peptides, this time through a phenylcarboxylate mounted on the terminal nitrogens.[78] We prepared a sample of bis(thiosemicarbazone) **70** that was labelled with both Cu and ^{64}Cu; the radiolabelling proceeding smoothly under the same conditions as used to complex the Cu. The Cu complexes were coupled to H_2N-Lys(Boc)-OH and the pendant Phe-NH_2 residue of octreotide. Again the coupling proceeded through an active ester, in this case the *N*-hydroxysuccinimdyl ester.

Conclusion

The biological activity of the bis(thiosemicarbazones) and their metal complexes has, historically, been the driving force for the interest shown in this interesting class of compounds. The metal complexes of bis(thiosemicarbazones) are useful both as biological agents and as tools for fluorescence imaging and radiomedicine.

Although the retrosynthetic analysis of bis(thiosemicarbazones) appears straightforward, there are pitfalls for the unwary. Methods lack generality and when bis(thiosemicarbazone) products are obtained there can be real difficulties in purification. The literature is often inconsistent and the products intractable. In this article we have attempted to bring together most of the literature on the synthesis of bis(thiosemicarbazones), to compare the findings of the contributors to this field and to add our own experiences and those from the laboratory of our collaborator Dr. Jo Peach. We hope that this review will assist others in finding the appropriate precedent for their work and help them evaluate the potential difficulties.

Acknowledgements

Thanks are due to all the people who have contributed their unpublished experiences to this review, especially: Hannah Claughton, Rachel Dobson, Dr. Paul Donnelly, Julia Heslop, Rebecca Ling, Christine McGibbon, Dr. Jo Peach, Dr. Steven Ratcliffe and Harriet Struthers. We thank GlaxoSmithKline for a fellowship (M.C.) and acknowledge the use we have made of the Web of Knowledge (http://wok.mimas.ac.uk). Our thanks to Karl Harrison for his help with graphics.

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Published online: June 23, 2006

