SYNTHESIS OF HETEROCYCLES VIA FREE RADICAL CYCLIZATION

To My Mother

and the Memory of My Father.

SYNTHESIS OF HETEROCYCLES VIA FREE RADICAL CYCLIZATION

By

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ABSTRACT

Aryl radical ring closures onto the azo functional group were investigated. A series of *ortho*- substituted aryl radicals (**83a-f**) have been generated by bromine abstraction from the corresponding 1-(*ortho*-bromophenyl)-1-methoxy-azoethanes (**82a-f**) by tributyltin radicals. The radicals generated underwent cyclization in the 5-*endo* sense, to ultimately afford the substituted indazoles (**86a-f**). There was also some evidence for cyclization to the other azo nitrogen (closure in the 4-*exo* sense) to form a 4-membered ring. The aryl radical also underwent hydrogen atom abstraction from tributyltin hydride in competition with cyclization. Since the rate constant for hydrogen atom abstraction from tributyltin hydride by aryl radicals is known, this makes it possible to estimate the rate constants for cyclization throughout the series.

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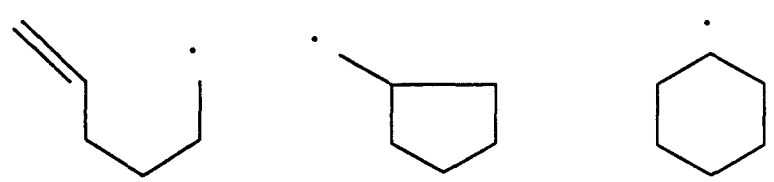
INTRODUCTION

Within the last two decades, synthetic organic chemists have begun to realize the great potential of free radical cyclizations in the synthesis of ring systems. It was believed at one time that the regio- and stereo-selectivity of free radical reactions could not be controlled. Thus free radical reactions were deemed by many chemists to be unpredictable and fruitless. The move towards a change in attitudes has been brought about by physical organic research in the area of rate constants for homolytic addition of free radicals and by investigations into free radical reaction mechanisms.

The ground work for the investigation into free radical reactions was laid down by Lamb[1], who studied the hex-5-enyl radical **1**. This alkyl radical was first generated by the thermolysis of di-6-heptenoyl peroxide. Lamb discovered that the hex-5-enyl radical underwent intramolecular ring closure predominantly in the 5-*exo* sense to afford the cyclopentylmethyl radical **2**, rather than in the 6-*endo* sense to generate the cyclohexyl radical **3**. Thermochemical criteria would lead to



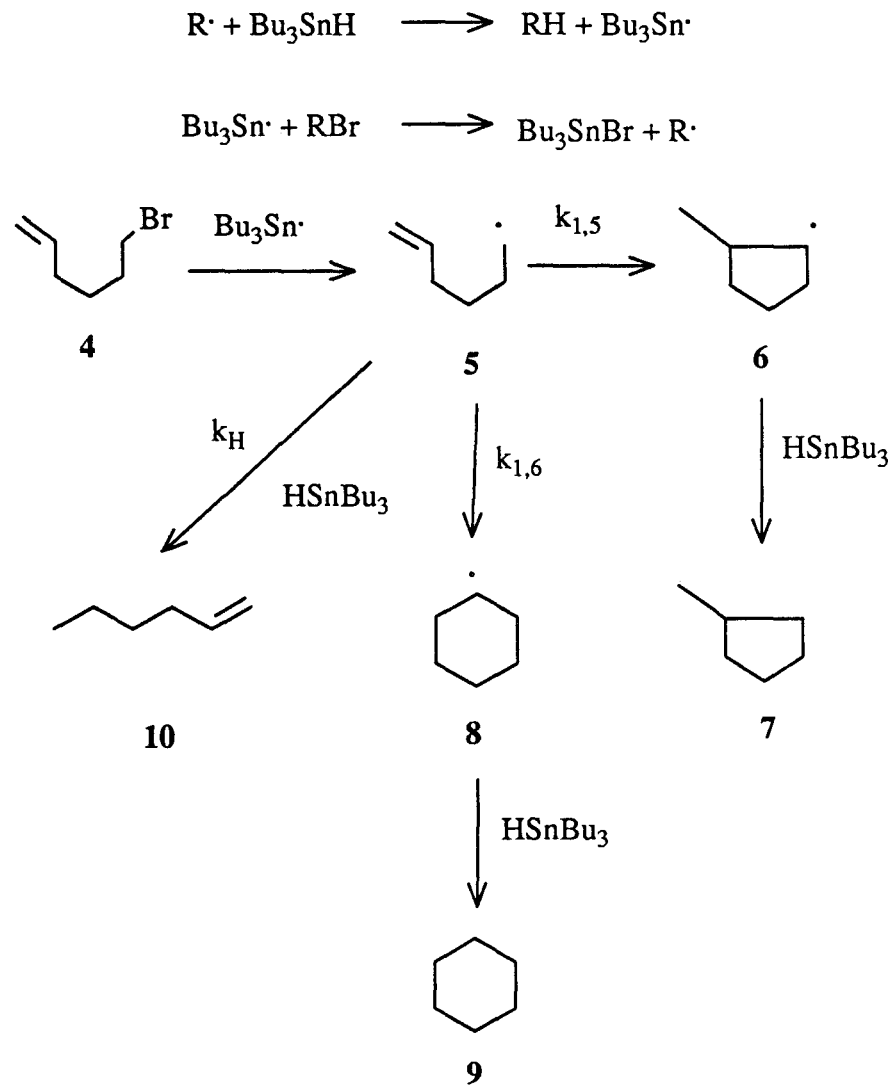
1 **2** **3**

the prediction that ring closure should proceed *via* the most exothermic pathway to

generate the more stable cyclohexyl radical **3**. Furthermore, intermolecular addition to unsymmetrical olefins affords the more substituted radical. Why does the hex-5-enyl radical ring-close to generate the least stable radical?

Further investigation by Walling[2], who studied 6-bromo-1-hexene in the presence of tributyltin hydride as the precursor to the hex-5-enyl radical, again confirmed that the intramolecular addition proceeds in a highly regioselective fashion to generate cyclopentylmethyl radical **6**. These investigations by Lamb

SCHEME 1

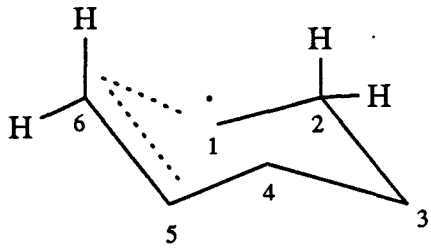


and others led Lamb to devise a simple kinetic scheme which is used as a basis for radical reactions involving the use of tributyltin hydride. The mechanism devised by Lamb is outlined in Scheme 1. The mechanism involves the unimolecular ring closure of the hex-5-enyl radical, which competes with bimolecular hydrogen-atom transfer from tributyltin hydride. Further experimentation supporting this mechanism indicates that both 1,5 and 1,6-ring closure is irreversible[3] and that radicals **5**, **6**, and **8** are discrete species[4,5].

The behavior of the simple hex-5-enyl radical is typical of related substituted species; ring-closure proceeds in a regioselective manner to afford the less stable of two possible cyclic radical products. Three theories have been proposed to account for this unexpected behavior. These theories are based on entropic, steric and stereoelectronic factors.

Capon and Rees[6] accounted for this behavior on the basis of a more favourable entropy of activation associated with the formation of the smaller ring. Ring closure results in a loss of rotational freedom which in turn, causes a decrease in entropy. There is also an increase in the loss of rotational freedom as the length of the chain that is closed increases. As a result, as the ring size increases there is an increasing loss of entropy to the system. Thus it is reasonable to envision 1,6-ring closure (of the hex-5-enyl radical, for example) to have a less favourable ΔS and $\Delta S^{\neq}$ than 1,5-ring closure. Capon and Rees concluded that the difference of $\Delta S^{\neq}$ for the two possible pathways must be sufficiently large to favour formation of the smaller ring. However, determination of activation parameters[7] and theoretical calculations[8] indicate the observed regioselectivity is mainly a result of the difference between the enthalpies of activation of the 1,5 and 1,6-ring closures. Thus, the entropy difference is too small to account for such a high degree of regioselectivity.

An alternate hypothesis has been developed by Julia[9] and co-workers. It suggests that the 1,6-transition structure **11** represents an unfavourable non-bonded interaction between the pseudo-axial proton at C-2 and the *syn* proton at C-6, resulting in a destabilized transition state, in comparison to the transition



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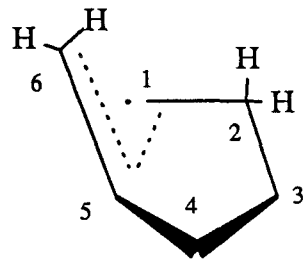
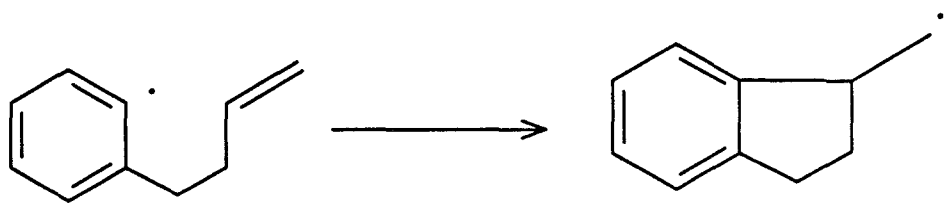


12

state for 1,5-ring closure **12**. In agreement[10] with this hypothesis, it has been shown that regioselectivity is increased when the *syn* proton is substituted by methyl, whereas substitution of the *anti* proton at C-6 by methyl has little or no effect on regioselectivity. However, theoretical calculations performed by Beckwith[11] provide evidence against this hypothesis. Inspection of the results of strain energy calculations shows that the steric interaction between the pseudo axial proton at C-2 and the *syn* proton at C-6 amounts to less than 0.1 Kcal mol^{-1}, hardly sufficient to account for the preferred regiochemistry. Further evidence[12] against Julia's hypothesis came from the results obtained when the *o*-alkenyl-aryl



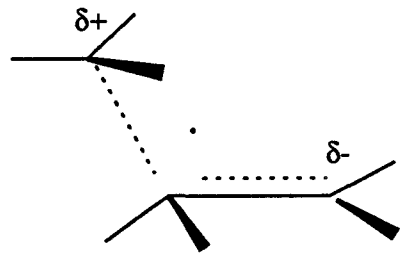
13 **14**

>99%

radical **13** was cyclized. Radical **13** undergoes closure to the 5-membered ring to generate radical **14**, even though this radical does not contain a pseudo-axial

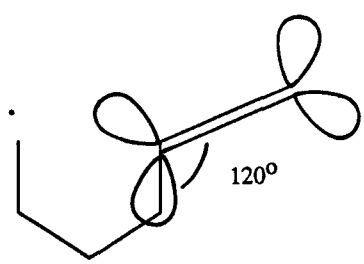
proton at C-2 in the transition state.

An accepted hypothesis for the behavior of the hex-5-enyl and related radicals is based on stereo-electronic factors. Theoretical treatments[13] indicate that the dominant interaction during attack of an alkyl radical on an olefinic bond



15

involves overlap of the semioccupied 2p-orbital with one lobe of the vacant π^*-orbital. The transition state for addition combines the three participating atoms at the vertices of an obtuse triangle orthogonal to the nodal plane of the π-system. The transition structure **15** is considered to be dipolar if the approaching radical is regarded as nucleophilic. On the basis of models and statistical calculations, it is revealed that the alignment of orbitals is much more readily accommodated in the



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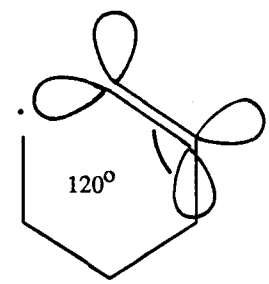


17

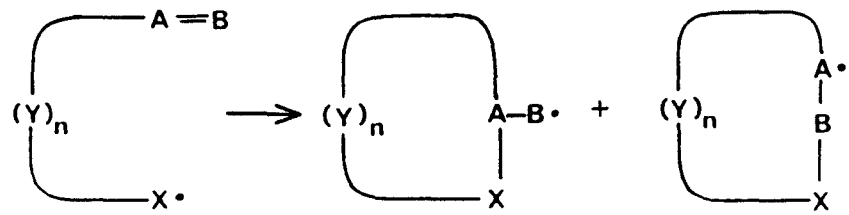
transition complex **16** for 1,5-ring closure of the hex-5-enyl radical than in that for 1,6-ring closure, **17**. The stereoelectronic theory agrees well with experimental data and is supported by theoretical[14] studies performed on the hex-5-enyl radical system.

This hypothesis can be generalized to the outcomes of intramolecular addition reactions of alkenyl radicals and similar species. Beckwith[15] has devised four guidelines which can be used in conjunction with thermochemical criteria in order that the outcomes of free radical reactions can be predicted.

(1) Intramolecular addition under kinetic control in lower alkenyl and alkynyl radicals and related species occurs preferentially in the *exo*-mode.

This guideline implies that *exo*-ring closure is kinetically favoured over the *endo*-ring closure, (Scheme 2) for radicals of the general type **18**, where Y is a chain of atoms ($n \leq 5$) and A=B is an unsaturated bond. Many examples exist which adhere to this guideline; these include alkene[7,17-20], alkyne[21-23], aryl[16],

SCHEME 2



exo *endo*

18 **19** **20**

allene[24], carbonyl[25], imine[26], cyano[27,28], and azo[26] groups. In this scheme, X· can represent a carbon, oxygen[29-31], or nitrogen[26,32] radical centre. This guideline can be utilized in organic synthesis and several review articles by Beckwith/Ingold[16], Surzur[26], Giese[33], and Ramaiah[34] outline such usage.

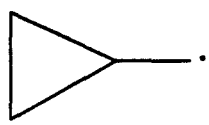
(2) Substituents on an olefinic bond disfavour homolytic addition at the substituted position.

In the hex-5-enyl radical system, substitution at C-5 has a great effect on its cyclization. When substitution of this type is present, the hex-5-enyl radical undergoes mainly six-membered ring formation as a result of retardation of the

1,5-cyclization by the substituent at C-5[17,35]. Similar effects have been observed for intermolecular additions[36]. This change in the cyclization pattern can be attributed to steric effects, and can account for rates and regioselectivity of homolytic inter- and intra-molecular addition to substituted olefins.

(3) Homolytic cleavage is favoured when the bond concerned lies close to the plane of an adjacent semi-occupied orbital or of an adjacent, filled, non-bonding or π-orbital.

For example, the *exo*-radical (**21**) acquires the required orbital overlap whereas the *endo*-type radical (**22**) does not[37], resulting in the former undergoing β-fission much more readily than the latter. Accordingly, cyclopropylmethyl and cyclobutylmethyl radicals undergo ring-opening, but cyclopropyl and cyclobutyl radicals do not undergo β-fission[38,39].



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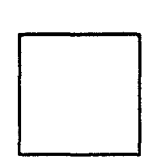

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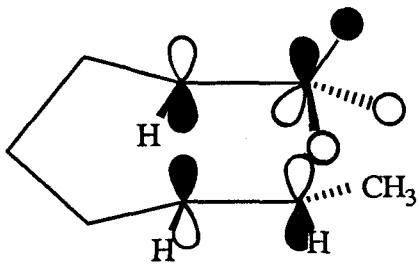
(4) 1,5-Ring closures of substituted hex-5-enyl and related radicals are stereoselective: 1- or 3-substituted systems afford mainly *cis*-disubstituted products, whereas 2- or 4-substituted systems give mainly *trans*-products.

The 1-substituted hexenyl radical affords preferentially the *cis*-product; this has been attributed to the effects of orbital symmetry[40]. In the transition state for the *cis*-product, there exists a secondary interaction between the alkyl substituent and the olefinic bond not found in the transition state for the *trans* isomer(Scheme 3). However, if the substituent at C-1 is bulky, the closure is then governed by steric effects and the *trans*-product dominates. The stereoselectivity

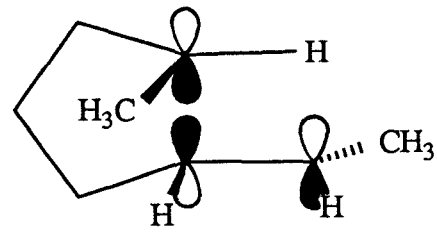
of ring closure in the 2-, 3-, or 4-substituted hexenyl radical system can be ascribed to the conformational preference in a chair-like transition structure[41]. Thus, the

SCHEME 3



cis

23



trans

24

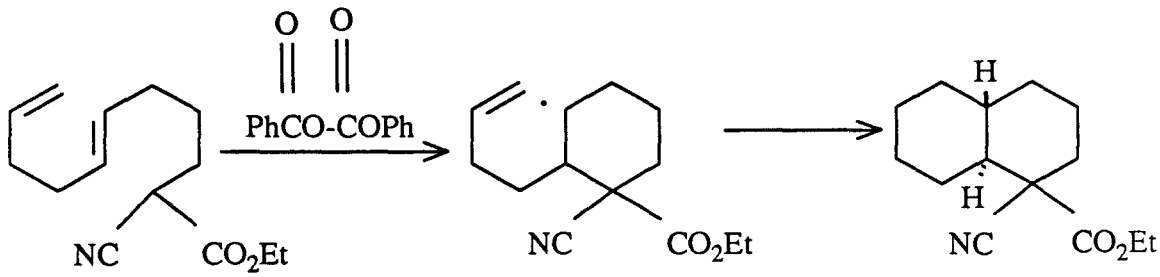
more bulky the substituent, the greater the selectivity.

Baldwin[42] used stereochemical factors to determine another set of rules which also predict the outcomes of different ring closures. These rules can be applied to anionic and cationic, as well as radical closures. Reviews by Beckwith[43] and Beckwith/Ingold[16] discuss other factors which affect rates as well as stereo- and regio- selectivities of radical ring closures.

Studies of the mechanisms of reactions often lead to useful discoveries of a synthetic nature. The case of radical cyclizations is no exception. As has been discussed already, a great deal of study by Julia[9,10], Beckwith[7,11,43], Ingold[16], and many others, into the physical organic aspects of free radical reactions has been carried out. Interestingly enough, some very useful synthetic research has resulted from these studies.

Radical reactions are very useful in synthesis for a number of reasons. The reactions are highly regio- and stereo-selective, and often high yields of products are obtained under the correct conditions. Radical reactions occur under mild conditions and for this reason, many functional groups can tolerate the reaction conditions, eliminating the need for protecting groups. The greatest

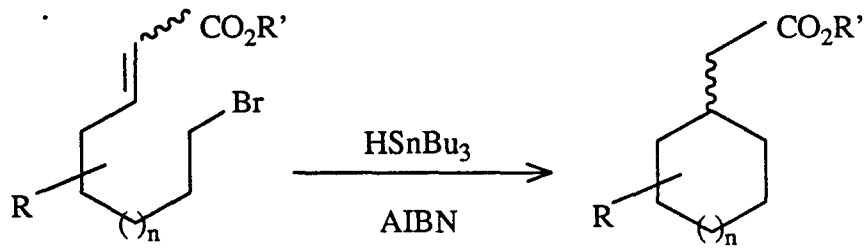
synthetic potential for free radical cyclizations is that, in many cases the bonds formed during the cyclization cannot be generated by any efficient polar coupling reaction. The earliest contribution to the study of alkyl radical cyclizations to form a carbocycle came from Julia[44]. This particular aspect of Julia's work involved a polycyclization in which two sequential hex-5-enyl radical cyclizations resulted in the conversion of **25** to **27**. A more recent example of the synthesis of carbocyclic



25 **26** **27**

(41%)

compounds by intramolecular alkyl radical cyclization is given by Hanessian[45] and co-workers. Several examples of the precursor **28** were prepared and cyclized in the *exo*-sense only, to generate the series of products **29**, with yields ranging from



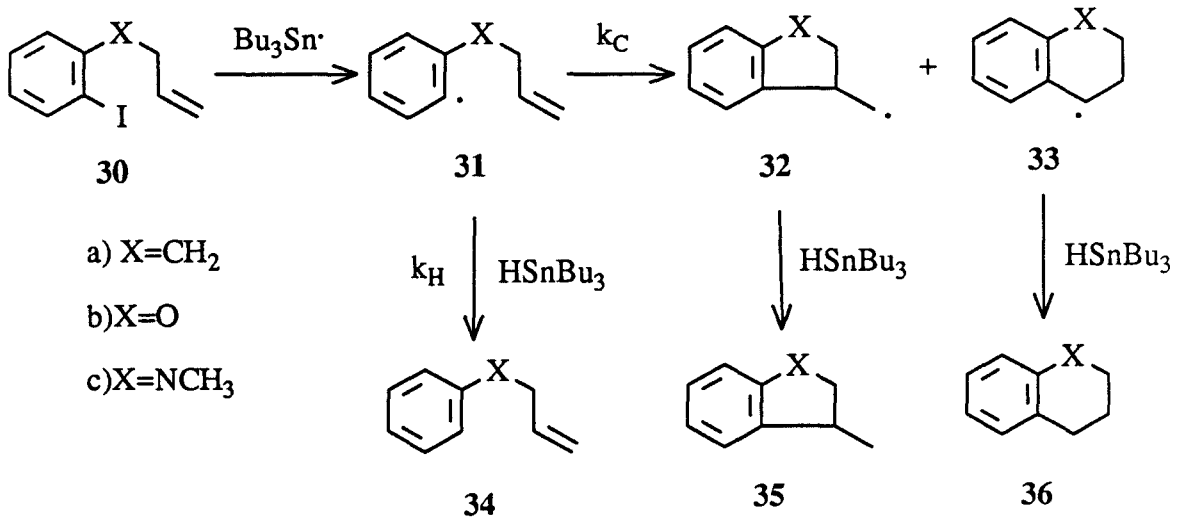
28 **29**

60 to 92%. This example outlines many of the advantages of radical synthesis, such as the high regio- and stereo-selectivity to generate the desired products, as well as the stability of the functional groups (ester in the case of **28**) toward the

reaction conditions.

Carbocycles can also be formed using vinyl radicals[46] as well as aryl radicals. Early work in the area of aryl radical closure was performed by Beckwith[47,48] and co-workers. Aryl radicals of the type **31** were generated by the interaction of the aryl iodides (**30**) with tributyltin hydride. The general pathway is

SCHEME 4



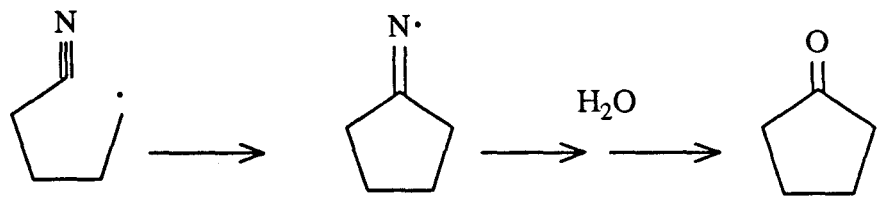
outlined in Scheme 4. Beckwith performed esr studies to confirm that the reaction did indeed follow a radical mechanism, and also to confirm that radical **31a** exclusively underwent 1,5-addition to afford, eventually, carbocycle **35a**.

From these few examples, it is clear that free radical reactions utilizing carbon centred radicals are a valuable tool for the synthesis of carbocycles. A great deal of work which can be found in several review articles by Beckwith[15], Wilt[29], Surzur[26], Giese[33,49], Hart[50], and more recently by Ramaiah[34], has been carried out in this area.

Free radical cyclizations are also important for the synthesis of heterocycles and many examples exist in which radical methodology is used. Work by Beckwith[48] includes examples of the synthesis of heterocycles containing

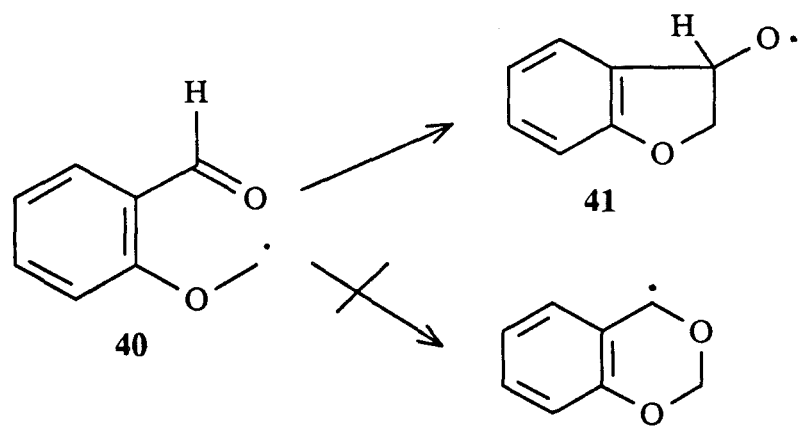
oxygen (**35b**) and nitrogen (**35c**), in which the heteroatom is not involved in the radical closure but is just present in the ring. Much less attention has been placed on radical reactions of heteroatom containing multiple bonds, such as the carbonyl, imine, cyano, or azo groups.

From the limited data available, it appears that radicals of the general type **18**, with heteroatoms present in the A=B positions (Scheme 2) show preference for *exo*-ring closure. Examples include the reaction of the radical **37**[51] to generate the cyclopentylketiminyl radical **38**. Cyclization onto the carbonyl[52]



37 **38** **39**

containing radical **40** generates the *exo*-closure product **41**, rather than the highly

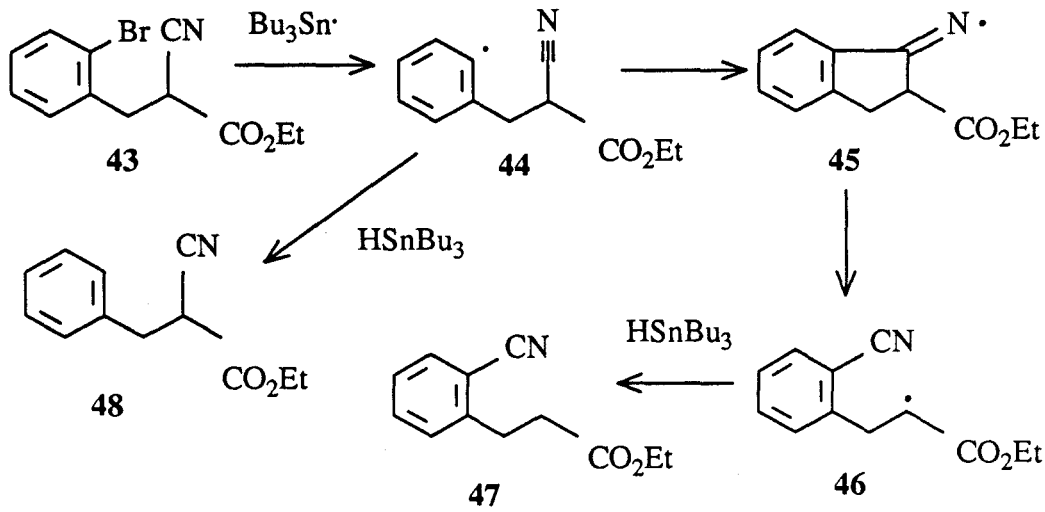


40 **41** **42**

stabilized benzylic radical **42** which would be generated by the *endo*-closure route.

More recently, Beckwith and O'Shea[53] have studied aryl ring closures onto the cyano and carbonyl groups. Ring closure onto the cyano group by aryl radical **44** was found to occur quite readily in the 5-*exo* sense to generate radical

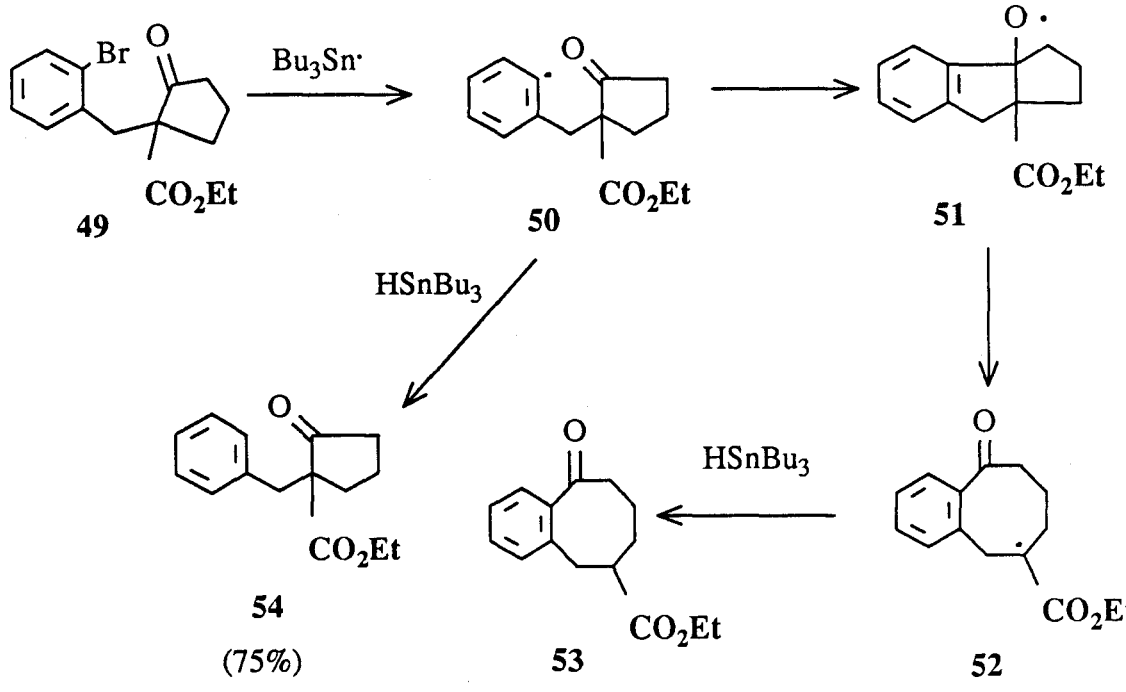
45. Radical **45** then underwent ring opening with net migration of the nitrile group to afford nitrile **47** in 59% yield. The minor product was the open-chain nitrile **48** in 12% yield. Aryl radical **44** cyclized exclusively in the 5-*exo* sense with rate



constant $k_C(80°C) = 2.2 \times 10^8\ s^{-1}$.

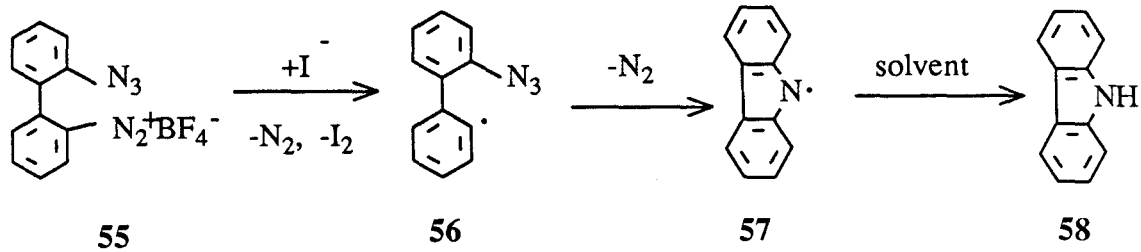
With the results from aryl radical closures onto cyano groups, Beckwith and O'Shea then studied aryl ring closures onto the carbonyl group. They envisaged that aryl radical closure onto a carbonyl group would lead to a migration of the carbonyl group similar migration observed in the cyano case. If this were the case, then the synthesis of macrocyclic systems would be a logical extension. Radical **50**, generated from treatment of **49** with tributyltin hydride, underwent radical ring closure in the 5-*exo* sense to generate radical **51**. Alkoxy radical **51** underwent β-scission to afford radical **52**, which in turn, abstracted a hydrogen atom from tributyltin hydride to generate macrocycle **53** in 14% yield.

Very few examples exist in which radical closure takes place by addition to sp^2-nitrogen. The first example involves cyclization onto the azido group[54] to generate radical **57**. The second example involves cyclization onto the azo group[55]. Radical **59** underwent 5-*exo* cyclization to generate radical **60** which

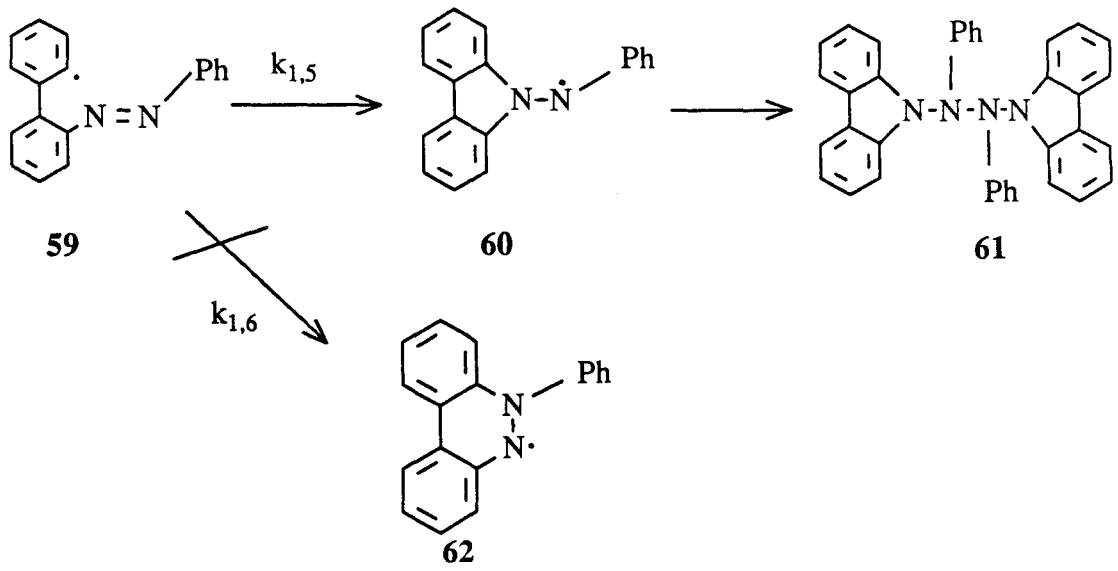


in turn, dimerized to afford **61** in 80% yield. No products from the alternative pathway involving 6-*endo* closure were observed.

More recently, Warkentin[56] and co-workers studied radical ring closures to form N-heterocycles from azo compounds. Radicals of type **64**, and their alkyl analogues, cyclized to give radicals **65** and **66** with a preference for 6-*endo* closure to afford eventually **69**. This preference for 6-*endo* closure is not



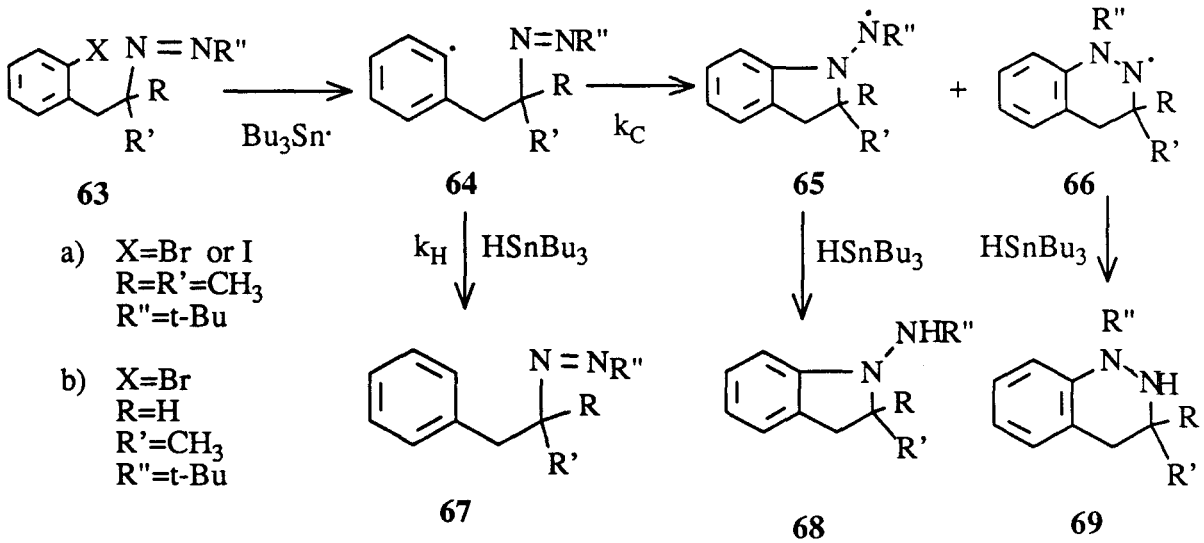
what is observed for the analogous carbon system[12]. Radical **13** undergoes almost exclusive 5-*exo* closure to afford radical **14**. These striking results for the nitrogen system have been attributed to the geometry of the azo compounds compared to



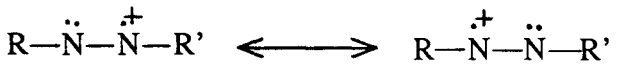
that of alkenes, as well as the resonance stabilization observed in hydrazyls.

The azo system does not seem to follow the expectations of radicals of type **18**, with N=N present in the A=B positions, (Scheme 2) which should show a

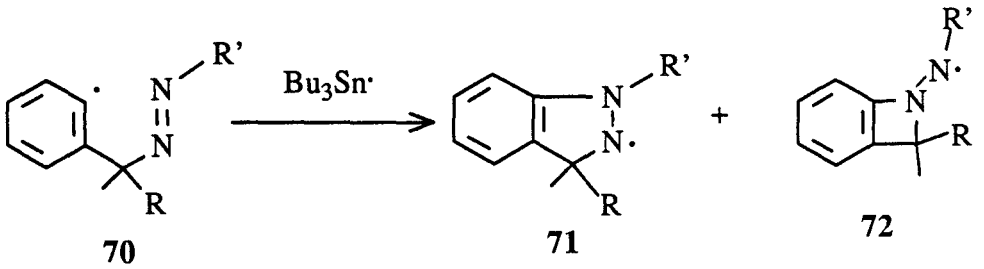
Scheme 5



preference for *exo*-ring closure. Would it be possible to obtain exclusively, the *endo*-closure product? Will the aryl radical **70** cyclize regioselectively to generate



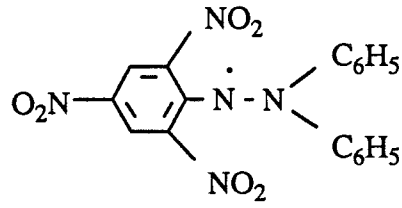
radical **71**? Or will *exo*-closure compete to afford radical **72**? Such questions initiated the investigation into the cyclizations of azo-aryl radicals.



70 **71** **72**

RESULTS AND DISCUSSION

It has been established that in carbon systems, 5-*exo* closure is favoured greatly over 6-*endo* closure, and much work has been carried out on rates and synthetic applications. Beckwith and O'Shea[53] have begun with preliminary rate measurements to investigate radical closures onto the cyano and carbonyl groups. If radical ring closures onto the azo group were to be performed, the radical generated would be a hydrazyl, a relatively stable free radical. Some hydrazyls, such as diphenylpicrylhydrazyl (DPPH) (**73**) are, in fact, quite stable. For this reason, one would expect radical cyclizations to the azo group to occur



73

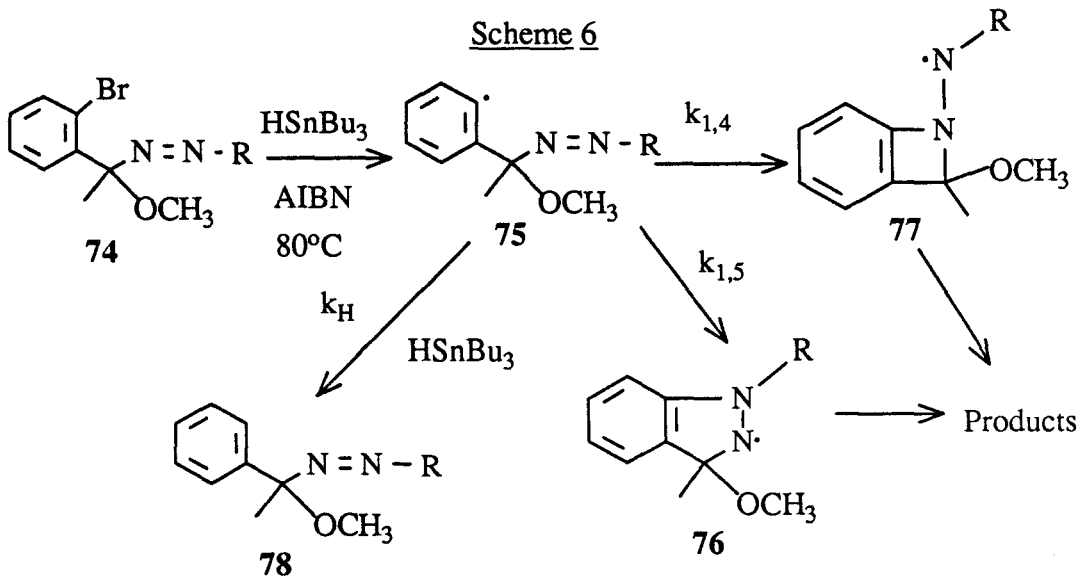
quite readily, and it is surprising that an investigation of this sort has not been undertaken earlier.

It has been shown earlier[54,55] that the aryl radical will cyclize onto the azo group, but no rate work has been carried out on this type of system. Radical cyclizations onto the azo group might be expected to show similar regiochemical preferences to those of analogous carbon systems. Moreover, 5-*endo* closure should be slow, again by analogy to carbon-carbon double bond reactivity.

In order to investigate radical cyclizations onto the azo group, an *ortho*-substituted aryl azo radical (**75**) was prepared, which could undergo either

5-*endo* closure or 4-*exo* closure. If 5-*endo* cyclization were slow, as predicted, then closure in the 4-*exo* sense might be expected to compete, or neither cyclization might be competitive with hydrogen atom abstraction from tributyltin

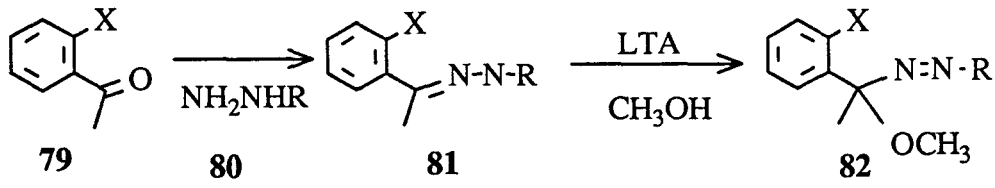
Scheme 6



hydride. Scheme 6 shows the initial radical reactions that could occur.

The construction of a suitable radical precursor incorporating the azo functional group is outlined in Scheme 7. It involves initial preparation of the *o*-substituted hydrazone (**81**) followed by oxidation of the hydrazone to the azo ether (**82**), using lead tetraacetate (LTA). The reaction of *o*-bromoacetophenone with the corresponding hydrazine (**80**) afforded a series of hydrazones (**81a-f**). The hydrazones were then treated with LTA to generate a series of azo ethers (**82a-f**). To generate authentic samples of compound **78**, a similar procedure was followed using acetophenone as the starting ketone, to generate a series of non-halogenated hydrazones (**81g-l**). These hydrazones were also subjected to LTA oxidation to afford a series of non-halogenated azo ethers (**82g-l**). Yields and ^{1}H nmr data for all the hydrazones are given in Tables 1 and 2 and yields and spectral data for all the azo ethers are given in Tables 3, 4, 5, and 6.

Scheme 7



79 **80** **81** **82**

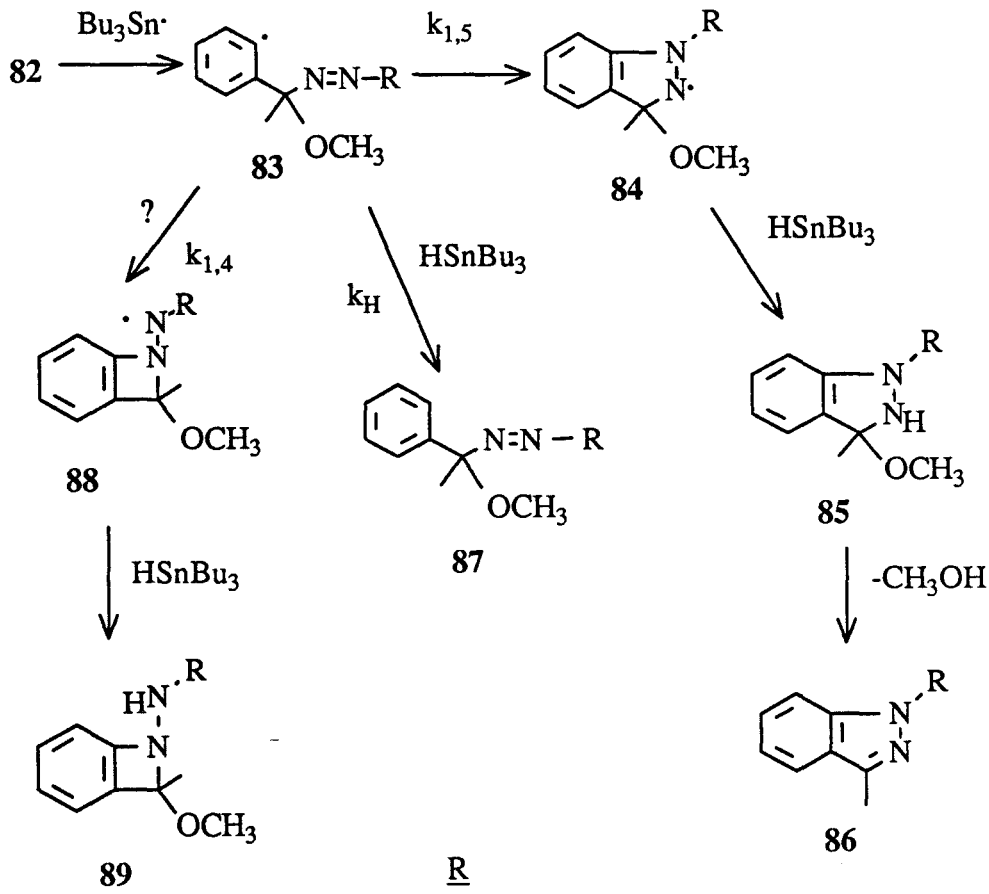
	X	R
a)	Br	c-C_6H_{11}
b)	Br	$C(CH_3)_3$
c)	Br	$CH_2C_6H_5$
d)	Br	$CH(CH_3)_2$
e)	Br	CH_3
f)	Br	C_6H_5

	X	R
g)	H	c-C_6H_{11}
h)	H	$C(CH_3)_3$
i)	H	$CH_2C_6H_5$
j)	H	$CH(CH_3)_2$
k)	H	CH_3
l)	H	C_6H_5

When the bromo-compounds(**82**) were heated in benzene solution with tributyltin hydride and azobisisobutyronitrile (AIBN) as initiator, in sealed, evacuated reaction tubes at 80°C, a clean reaction ensued with the corresponding indazoles (**86**) being formed in quantitative yields. Scheme 8 outlines the reactions that resulted. At first, it was concluded that 5-*endo* closure was favoured over 4-*exo* closure since none of product **89** was observed. The structures of the reaction products were assigned using ^1H nmr spectroscopy.

In addition to the tests performed on the bromo-compounds, control tests were performed on the products (**86, 87**) obtained, to gauge their stabilities towards the reaction conditions. It was observed that the indazoles formed as a result of 5-*endo* closure, were completely stable towards the reaction conditions.

Scheme 8



R

a) c-C_6H_{11}

b) $C(CH_3)_3$

c) $CH_2C_6H_5$

d) $CH(CH_3)_2$

e) CH_3

f) C_6H_5

The products (**87**) which would result from H-atom abstraction from tributyltin hydride however, were found not to survive the reaction conditions. In all cases, the compounds (**87**) decomposed upon heating in tributyltin hydride, to products which could not be identified. Thus, competition between unimolecular ring closure and bimolecular H-atom transfer would be difficult to observe directly.

For this reason, modifications to the rate equation were necessary to determine a value for $k_{5\text{-}endo}$.

Since unimolecular ring closure is known to compete with bimolecular H-atom abstraction from tributyltin hydride in analogous carbon systems, it was assumed a similar competition was occuring in this system. Since the rate constant (k_H) for abstraction from tributyltin hydride ($HSnBu_3$) by aryl radicals has been determined by Beckwith[57] to be $k_H(80°C)= 9 \times 10^8\ M^{-1}\ s^{-1}$, it is possible to estimate the rate constant of the cyclization reaction using scheme 8 and the following rate expressions derived from it: Division of these equations,

$$\frac{d(\mathbf{86})}{dt} = k_{5\text{-}endo}[\mathbf{83}]$$

$$\frac{d(\mathbf{87})}{dt} = k_H[\mathbf{83}]\,[HSnBu_3]$$

equating relative rates of formation of **86** and **87** to final product ratios, and rearrangement yields: Since products **87** are known not to

$$k_{5\text{-}endo} = k_H \frac{[HSnBu_3]\ (\text{yield } \mathbf{86})}{(\text{yield } \mathbf{87})}$$

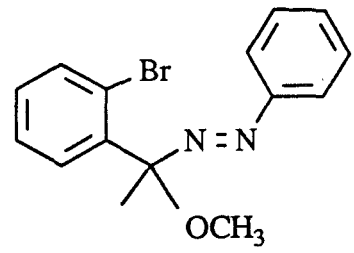
survive the reaction conditions and their respective decompositon products are not known, it is only possible to obtain a minimum rate constant using the following equation: In this modified equation, it is assumed that the fraction of

$$k_{5\text{-}endo} = k_H \frac{[HSnBu_3]\ (\text{yield } \mathbf{86})}{100 - (\text{yield } \mathbf{86})}$$

radical **83** generated, which does not go on to form indazole (**86**) forms, instead, the H-atom abstraction product (**87**) which, in turn, decomposes under these

conditions. Thus, the denominator is determined by difference and is assumed to be representative of the % yield of H-atom abstraction product obtained prior to decomposition. Therefore, it is important to keep in mind that any rate constants thus estimated are minimum rate constants. Yields of indazole formed, along with the minimum rate constants (at 80°C) for each cyclization are given in Table 7. The spectral data for the indazoles formed are given in Tables 8, 9 and 10.

It is necessary to discuss the poor yield of indazole for the case where R=C_6H_5 (**82f**). That compound is styrene-like and can allow for addition of



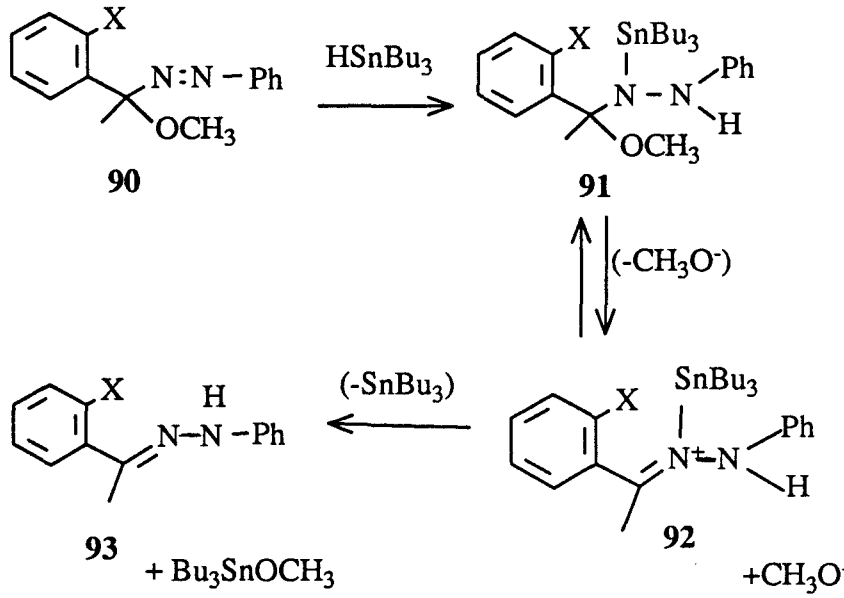
82f

tributyltin hydride across the azo system. Experiments indicate that the bromo-starting material (**82f**) undergoes decomposition to hydrazone faster than it can undergo cyclization to the indazole. A possible mechanism is outlined in Scheme 9. The *ortho-* substituent can be either a bromine or a hydrogen depending on whether the tributyltin radicals abstract a bromine atom prior to addition of tributyltin radicals to the azo group.

A second reason for the poor yield observed when R=Ph, could be due to the size of the Ph-substituent. The Ph-substituent is small enough that addition of tributyltin radicals can take place at the azo nitrogen site bearing the Ph-substituent (Scheme 10). This type of addition can also result in decomposition of the starting material.

The loss of tributyltin radical in the final step, to generate the hydrazone can occur by two possible pathways. In pathway (a), a tributyltin

Scheme 9



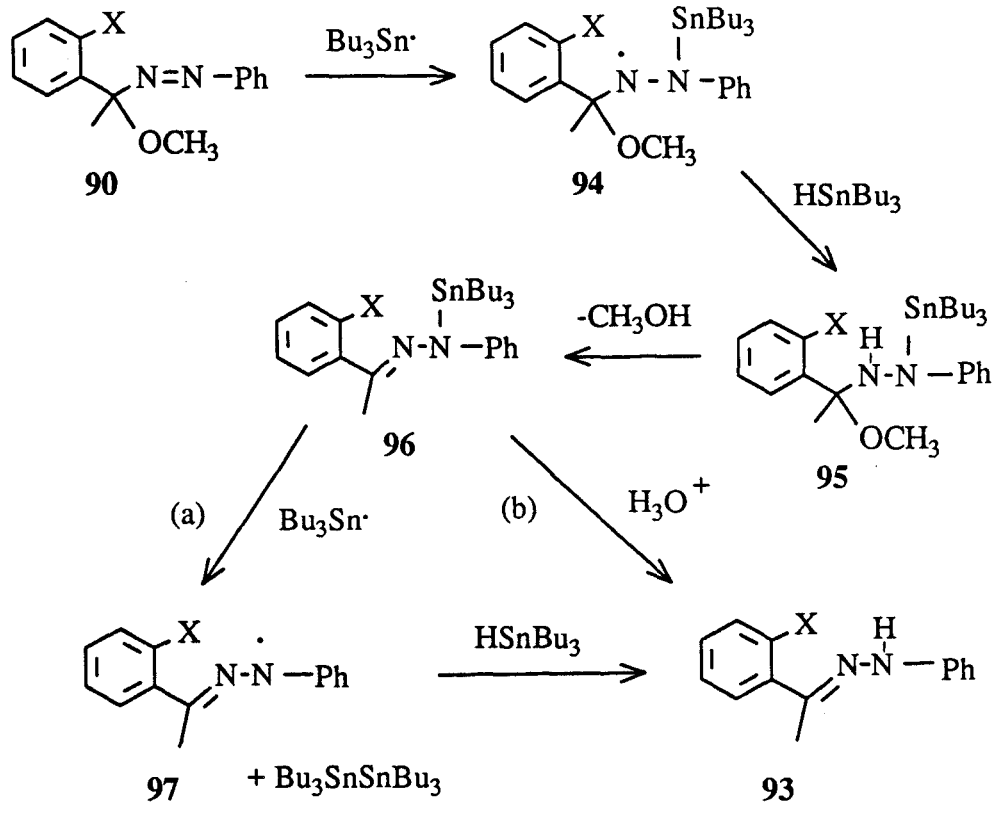
90 **91** **93** **92**

X= Br, H

radical abstracts the tributyltin substituent from compound **96** to generate hexabutylditin. Radical **97** then abstracts a hydrogen atom from tributyltin hydride to generate hydrazone **93**. In pathway (b), hydrazone **93** is formed by hydrolysis , as a result of workup of the reaction mixture on a silica plate. Precedent for this type of hydrolysis is shown in the following example by Stork[46] (Scheme 11).

When radical **83c** was subjected to the cyclization conditions, indazole **86c** was formed, as well as another compound believed to be the isoindazole **105**. Closure in the 4-*exo* sense is the only route by which the isoindazole can be generated. Scheme 12 outlines the mechanisms by which the isoindazole could be formed. Whatever the final step may be, 4-*exo* closure, a β-scission, and a recyclization would seem to be required. It has been shown[58] that isoindazoles rearrange to the more stable indazoles by a 1,5 sigmatropic shift. This rearrangement does occur for isoindazole **105**, as observed by ^{1}H nmr. As a result

Scheme 10

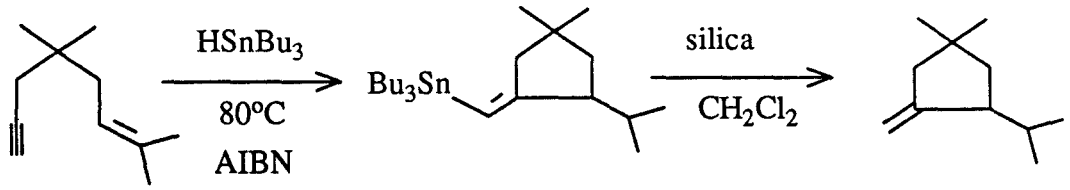


X = Br, H

of this observation, the pathway by which the radical closes, to generate the indazole must be reexamined. The question now arises as to which route of closure the radical is using. Is the indazole generated by exclusive 4-*exo* closure, followed by rearrangement to the isoindazole, which in turn, rearranges to the indazole? Or does there exist a competition between 4-*exo* closure and 5-*endo* closure, which both eventually lead to the same product?

In an attempt to investigate this problem, it was necessary to synthesize another radical precursor which would cyclize to give two distinct products (**109**, and **111**) from each possible closure route. When radical **83c**

Scheme 11



98 **99** **100**

90 %

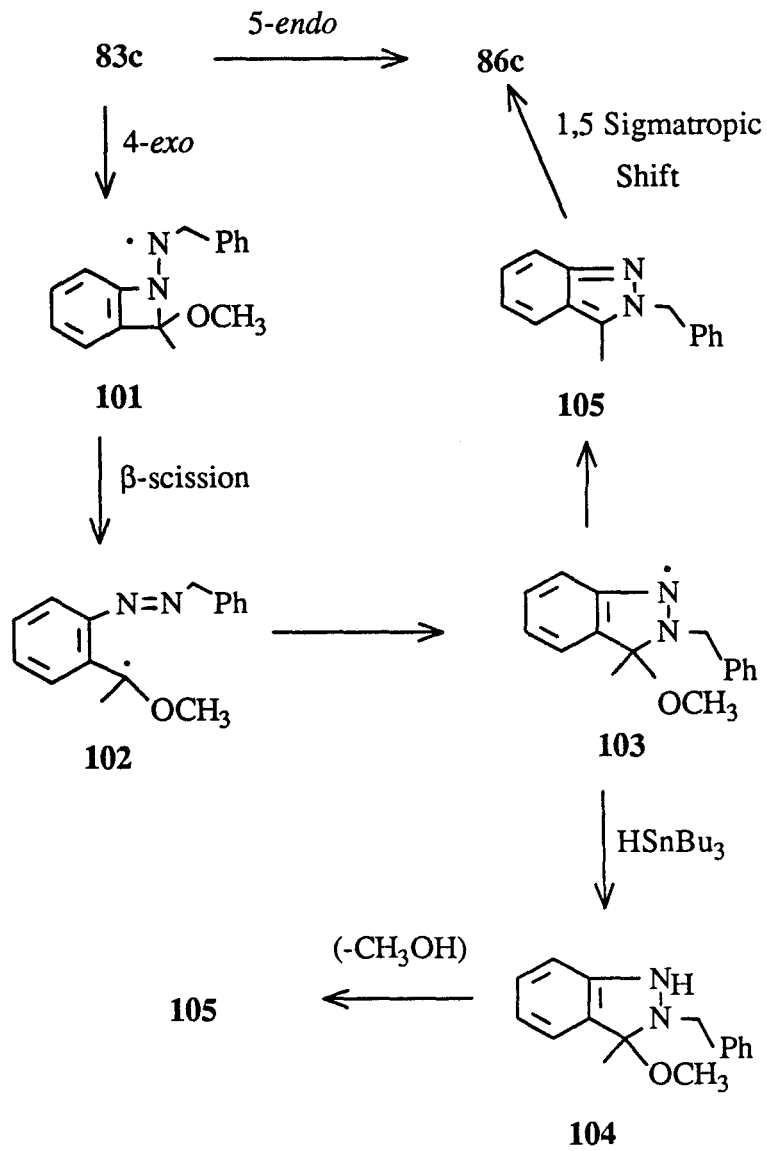
E=CO_2CH_3

underwent 4-*exo* closure, subsequent rearrangements and loss of methanol resulted in the formation of isoindazole **105**, which then underwent a 1,5 sigmatropic shift to generate indazole **86c**. The bromo-compound **106** was synthesized, with the methoxy substituent being replaced by a methyl group. This eliminated the possibility of rearrangement of the two possible radicals to the same final product. Scheme 13 outlines the two possible pathways by which radical **107** can cyclize when subjected to the same cyclization conditions as compound **83c**.

Unfortunately, the products formed could not be analyzed by ^1H nmr during the reaction, since tributyltin hydride gives signals in the high field region, which mask the region of interest for any products formed. Following the low field region showed only that a reaction did take place, but no structure analysis could be performed on the products formed. When the tributyltin hydride was removed from the reaction mixture, it was found that the reaction products formed were highly oxidizable and the decomposition products could not be assigned any specific structures. As a result, the exact pathway by which these radicals cyclize is not completely known at this time. It is still important to realize however, that closures onto the azo group in either direction (4-*exo* or 5-*endo*) are much faster than similar closures in the analogous carbon system.

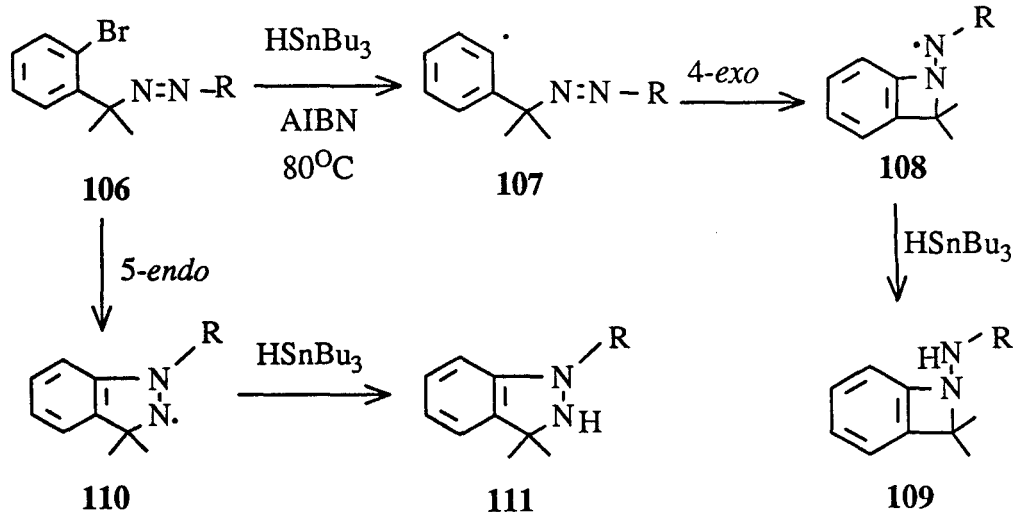
Since aryl radical ring closures of a similar type are well known in

Scheme 12



carbon systems, and their rate constants have been determined, it is interesting to compare them to the azo system. The analogous 5-*endo* closure is shown in Scheme 14. The rate constant for 5-*endo* closure in this system, though not actually determined, is estimated to be 1 x 10^7 s^{-1}, at 80°C. The 4-*exo* closure product is not observed in this case. The rate constants [k_C(80°C)] for cyclization in the azo systems range from 1.04 x 10^8 s^{-1} to 1.82 x 10^{10} s^{-1}, a 10 to 100-fold

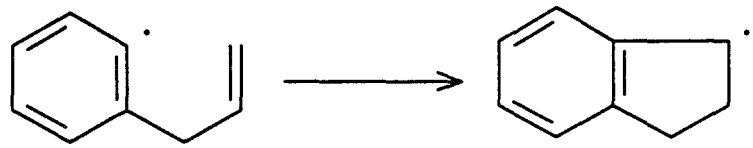
Scheme 13



R=t-Bu

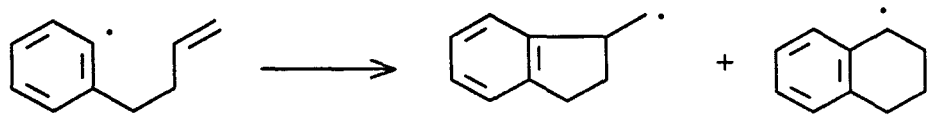
increase in rate, in going from the carbon system to the nitrogen system. Rate constants have been determined by Warkentin[56] and co-workers for the aryl azo

Scheme 14



112 **113**

system (**64a**) in which 5-*exo* closure competes with 6-*endo* closure (Scheme 5). Closure in the 6-*endo* sense to afford radical **66a** occurs with a rate constant $k_{6\text{-}endo}$= 2.3 x 10^9 s^{-1} and closure in the 5-*exo* sense to generate radical **65a** occurs with a rate constant $k_{5\text{-}exo}$= 1.5 x 10^9 s^{-1}, at 80°C. For radical **64b**, closure in the 6-*endo* sense gives radical **66b** with rate constant $k_{6\text{-}endo}$= 9.7 x 10^8 s^{-1} and in the 5-*exo* sense, radical **65b** with rate constant $k_{5\text{-}exo}$= 4.5 x 10^8 s^{-1}, at 80°C. Radical cyclization of **114** to give **115** and **116** in the analogous carbon system has the following rate contants at 80°C; $k_{6\text{-}endo}$= 1.8 x 10^7 s^{-1} and $k_{5\text{-}exo}$= 9.4 x 10^8 s^{-1}.

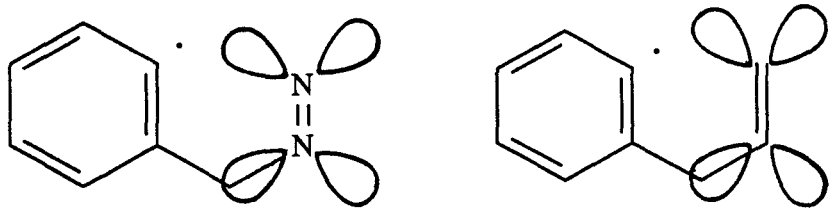


114 **115** **116**

Thus the azo system shows a preference for 6-*endo* closure product which is opposite to what is observed for the carbon system. Further investigation by Wang and Warkentin[59] into the alkyl analogs of radicals **64** yields similar results.

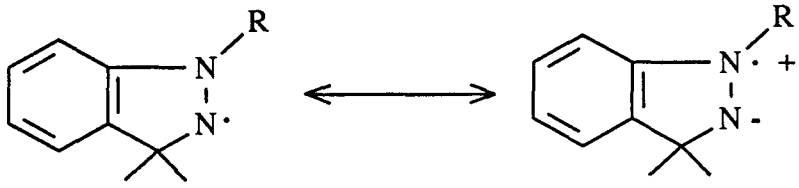
In order to account for the large rate increase in going from the carbon to the nitrogen system it is necessary to compare the geometry of the azo and alkene compounds and to ask how any differences might affect the stereo-electronic factors. The N=N bond length[60] is 1.22 Å and the N=N-C angle is 114-115°. For the alkene system, the C=C bond length is 1.34 Å, and the C=C-C angle is ca 120°. The decrease in bond length for the N=N bond and angle tightening of the azo system results in improved interorbital alignment between the semioccupied 2p-orbital and the π^*-orbital in the transition structures for both 5-*endo* and 4-*exo* closure. Orbital alignment in the carbon system on the other hand, is poor for 5-*endo* closure (Scheme 15).

Scheme 15

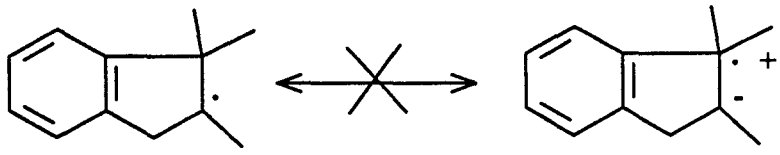


117 **118**

Finally, the azo system forms a hydrazyl radical upon cyclization in either direction. Hydrazyl radicals have an odd electron delocalized to the adjacent nitrogen which results in a resonance stabilization not available to the carbon system. As a result of hydrazyl stabilization, the reaction rates for either closure



119 **120**



121 **122**

route for the nitrogen system may be enhanced.

CONCLUSIONS

Radical cyclizations onto the azo group differ from those of analogous carbon systems. Treatment of a series of 1-(*ortho*-bromophenyl)-1-methoxy-azoethanes (**82a-f**) with tributyltin hydride, resulted in cyclization of the radicals **83a-f** to afford eventually a series of indazoles (**86a-f**). These cyclizations occurred with large rate constants; $k_C(80°C)=1.40 \times 10^8$ to 1.82×10^{10} s^{-1}. Though it is believed that the majority of radicals **83a-f** cyclize in the 5-*endo* sense, there also exists evidence that 4-*exo* closure is competing, with a significant rate constant. There is a large rate enhancement in going from an analogous carbon system to the nitrogen system. This large rate enhancement shows great promise for future work in the area of free radical cyclization reactions for the formation of heterocycles.

Table 1: Yields and ^{1}H nmr Data of Hydrazones(**81a-f**)

HYDRAZONE	YIELD (%)	^{1}H nmr (ppm)[a] ISOMER (a)	ISOMER (b)
81a	82	0.64-2.35 (m, 13 H);[b] 3.24 (m, 1 H); 7.02-7.78 (m, 4 H).	
81b	92	1.12 (s, 9 H); 2.09 (s, 3 H); 7.02-7.82 (m, 4 H).	1.25 (s, 9 H); 2.18 (s, 3 H);
81c	85	2.10 (s, 3 H); 4.32 (s, 2 H); 6.88-7.82 (m, 9 H).	2.18 (s, 3 H); 4.50 (s, 2 H);
81d	82	1.09 (d, 6 H); 2.09 (s, 3 H); 3.15 (sept., 1 H); 7.00-7.80 (m, 4 H).	1.22 (d, 6 H); 2.44 (d, 6 H);
81e	90	2.08 (s, 3 H); 2.88 (s, 3 H); 7.00-7.80 (m, 4 H).	2.18 (s, 3 H); 3.06 (s, 3 H);
81f	--[c]	2.18 (s, 3 H); 6.80-8.00 (m, 9H).	2.25 (s, 3 H);

[a]All of the brominated hydrazones existed as a mixture of isomers which could not be separated. Only singlets could be distinguished for each isomer and their δ-values are denoted under the headings isomer (a) and isomer (b). Multiplets which could not be resolved with respect to each isomer, are denoted by their respective δ-values and are located between each isomer heading.

[b]Superimposed upon the multiplet corresponding to the cyclohexyl ring, are two singlets, representing three hydrogens each. These two singlets correspond to the methyl group of each isomer and are included in the total hydrogen count for the multiplet denoted by δ 0.64-2.35 ppm.

[c]The azo ether was donated, thus no yield for the hydrazone was obtained.

Table2: Yields and ^{1}H nmr Data for Hyrazones (**81g-l**)

HYDRAZONE	YIELD (%)	^{1}H nmr (ppm)
81g	81	0.72-2.40 (m, 13 H);[a] 3.24 (m, 1 H); 7.18-8.10 (m, 5 H).
81h	75	1.28 (s, 9 H); 2.08 (s, 3 H); 7.12-7.92 (m, 5 H).
81i	84	2.08 (s, 3 H); 4.54 (s, 2H); 7.06-8.08 (m, 5 H).
81j	86	1.22 (d, 6 H); 2.06 (s, 3 H); 3.59 (sept., 1 H); 7.06-8.10 (m, 5 H).
81k	57	2.05 (s, 3 H); 3.08 (s, 3 H); 7.12-7.82 (m, 5 H).
81l	55	2.20 (s, 3 H); 6.72-8.04 (m, 10 H).

[a]Superimposed upon the multiplet corresponding to the cyclohexyl ring is one singlet representing three hydrogens. This singlet corresponds to a methyl group and is included in the total hydrogen count for the multiplet denoted by δ 0.72-2.40 ppm.

Table 3: Yields and ^{1}H nmr Data of Azo Ethers (**82a-f**)

AZO ETHER	YIELD(%)	^{1}H nmr (ppm)
82a	73	1.06-2.19 (m, 13 H);[a] 3.24 (s, 3 H); 3.68 (s, 3 H); 7.05-7.84 (m, 4 H).
82b	43	1.29 (s, 9 H); 1.74 (s, 3 H); 3.24 (s, 3 H); 7.06-7.84 (m, 4 H).
82c	45	1.69 (s, 3 H); 3.24 (s, 3 H); 5.12 (s, 2 H); 7.02-7.75 (m, 9 H).
82d	70	1.32 (d, 6 H); 1.69 (s, 3 H); 3.25 (s, 3 H); 3.92 (sept., 1 H); 7.02-7.80 (m, 4 H).
82e	64	1.69 (s, 3 H); 3.25 (s, 3 H); 3.94 (s, 3 H); 7.00-7.82 (m, 4 H).
82f	--[b]	1.86 (s, 3 H); 3.38 (s, 3 H); 7.08-8.04 (m, 9 H).

[a]Superimposed upon the multiplet corresponding to the cyclohexyl ring is one singlet representing three hydrogens. This singlet corresponds to a methyl group and is included in the total hydrogen count for the multiplet denoted by δ 1.06-2.19 ppm.

[b]The azo ether was donated, thus no yield was obtained.

Table 4: Yields and ^{1}H nmr Data of Azo Ethers (**82g-l**)

AZO ETHER	YIELD (%)	^{1}H nmr (ppm)[a]
82g	59	0.76-2.08 (m, 13 H); 3.30 (s, 3 H); 3.60 (m, 1 H); 7.10-7.70 (m, 5 H).
82h	56	1.28 (s, 9 H); 1.66 (s, 3 H); 3.30 (s, 3 H); 7.20-7.74 (m, 5 H).
82i	36	1.60 (s, 3 H); 3.30 (s, 3 H); 5.05 (s, 2 H); 6.91-8.15 (m, 10 H).
82j	54	1.24 (d, 3 H); 1.32 (d, 3 H); 1.59 (s, 3 H); 3.30 (s, 3 H); 3.85 (sept., 1 H); 7.10-7.64 (m, 5 H).
82k	58	1.65 (s, 3 H); 3.36 (s, 3 H); 3.94 (s, 3 H); 7.21-7.78 (m, 5 H).
82l	52	1.68 (s, 3 H); 3.34 (s, 3 H); 7.02-7.90 (m, 10 H).

[a]Superimposed upon the multiplet corresponding to the cyclohexyl ring is one singlet representing three hydrogens. This singlet corresponds to a methyl group and is included in the total hydrogen count for the multiplet denoted by δ 0.76-2.08 ppm.

Table 5: Spectral Data of Azo Ethers (**82a-f**)

AZO ETHER	UV DATA [λ_{MAX} (log ϵ)]	IR DATA (cm^{-1})
82a	220 (3.61) 259 (2.67)	3065, 2985, 2930, 2850, 2830, 2230, 1742, 1564, 1588, 1462, 1448, 1430, 1422, 1362, 1342, 1272, 1235, 1185, 1158, 1135, 1098, 1080, 1045, 1015.
82b	202 (2.82) 218 (3.69)	3070, 2975, 2920, 2875, 2835, 1745, 1590, 1565, 1465, 1430, 1365, 1385, 1275, 1238, 1205, 1190, 1145, 1050, 1020.
82c	222 (3.91) 258 (3.08)	3095, 3070, 3040, 2995, 2965, 2940, 2835, 2250, 1745, 1630, 1610, 1595, 1570, 1500, 1468, 1458, 1438, 1430, 1372, 1298, 1276, 1245, 1195, 1145, 1105, 1085, 1055, 1025.
82d	218 (2.88) 256 (2.05) 262 (2.03) 360 (1.69)	3075, 2980, 2940, 2835, 1745, 1592, 1568, 1468, 1434, 1365, 1311, 1275, 1238, 1191, 1138, 1100, 1050, 1020.
82e	216 (3.83) 258 (3.17) 358 (2.88)	3075, 2945, 2840, 1592, 1568, 1465, 1425, 1368, 1278, 1240, 1192, 1165, 1138, 1102, 1055, 1020.
82f	216 (4.21) 264 (4.13)	3075, 3000, 2945, 2835, 1968, 1815, 1745, 1592, 1568, 1525, 1468, 1455, 1432, 1368, 1310.

Table 6: Spectral Data of Azo Ethers (**82g-l**)

AZO ETHER	UV DATA [λ_{MAX} (log ϵ)]	IR DATA (cm^{-1})
82g	220 (3.30) 250 (2.37)	3085, 3060, 3025, 2980, 2930, 2850, 2825, 2655, 2235, 1955, 1890, 1815, 1752, 1602, 1490, 1446, 1362, 1342, 1320, 1255, 1235, 1195, 1175, 1140, 1105, 1078, 1040, 1020.
82h	216 (4.06)	3090, 3060, 3030, 2970, 2930, 2870, 2825, 1602, 1488, 1465, 1445, 1384, 1362, 1345, 1310, 1198, 1175, 1145, 1100, 1080, 1065, 1048, 1022.
82i	212 (3.83) 216 (3.85)	3085, 3060, 3030, 2985, 2935, 2825, 2230, 1968, 1890, 1810, 1744, 1705, 1686, 1602, 1584, 1492, 1445, 1362, 1310, 1244, 1195, 1176, 1145, 1098, 1078, 1045, 1022.
82j	216 (3.76) 260 (3.05)	3090, 3060, 3030, 2970, 2930, 2865, 2830, 1600, 1490, 1462, 1444, 1378, 1362, 1308, 1250, 1196, 1178, 1150, 1128, 1105, 1068, 1045, 1022.
82k	216 (3.61) 255 (2.92)	3080, 3060, 3025, 2990, 2935, 2910, 2830, 1960, 1900, 1815, 1725, 1688, 1600, 1582, 1492, 1448, 1430, 1365, 1312, 1264, 1195, 1175, 1125, 1070, 1046, 1022.
82l	216 (3.87) 262 (3.89)	3085, 3060, 3035, 2985, 2955, 2930, 2870, 2830, 2235, 1955, 1895, 1810, 1738, 1600, 1588, 1525, 1489, 1475, 1452, 1445, 1365, 1305, 1296, 1240, 1198, 1022, 1015.

Table 7: Yields and Rate Constants for Formation of Indazoles (**86**)

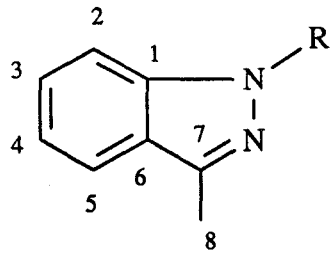
INDAZOLE	YIELD(%)	MIN. RATE CONSTANT $[k_C(80°C)]$ (s^{-1})
86a	92	1.82×10^{10}
86b[a]	80	6.01×10^{8}
86c	70	$4.05 \times x10^{8}$
86d	49	8.07×10^{8}
86e	39	1.04×10^{8}
86f	<5	4.78×10^{6}

[a]This indazole was a solid with mp=56-57°C.

Table 8: ^{1}H nmr Data of Indazoles (**86**)

INDAZOLE	^{1}H nmr (ppm)
86a	1.05-2.24 (m, 10 H); 2.56 (s, 3 H); 4.32 (m, 1 H); 6.94-7.78 (m, 4 H).
86b	1.75 (s, 9 H); 2.58 (s, 3 H); 6.95-7.84 (m, 4 H).
86c	2.60 (s, 3 H); 5.54 (s, 2 H); 6.95-7.84 (m, 9 H).
86d	1.55 (d, 6 H); 2.60 (s, 3 H); 4.78 (sept., 1 H); 6.90-7.84 (m, 4 H).
86e	2.56 (s, 3 H); 3.98 (s, 3 H); 6.98-7.82 (m, 4 H).
86f	2.66 (s, 3 H); 7.05-8.94 (m. 9 H).

Table 9: ^{13}C nmr Data of Indazoles



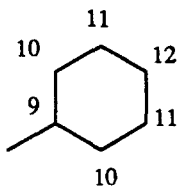
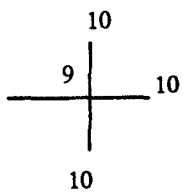
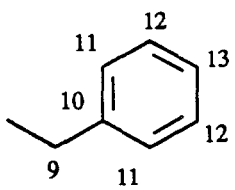
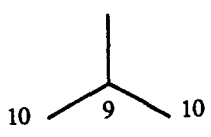
R	CARBON #	^{13}C nmr	CARBON #	^{13}C nmr
 **86a**	1	129.77	7	135.18
	2	108.87	8	11.83
	3	119.30	9	57.72
	4	120.26	10	32.62
	5	125.76	11	25.82
	6	123.20	12	25.76
 **86b**	1	138.90	6	124.79
	2	111.91	7	139.43
	3	118.97	8	13.49
	4	120.39	9	58.92
	5	125.16	10	11.73
 **86c**	1	140.44	8	11.81
	2	126.20	9	52.44
	3	126.93	10	123.62
	4	128.52	11	120.29
	5	137.14	12	119.65
	6	137.14	13	109.02
	7	141.65		
 **86d**	1	139.39	6	123.35
	2	108.86	7	140.84
	3	119.36	8	13.50
	4	120.32	9	49.87
	5	125.66	10	22.03

Table10: Spectral Data of Indazoles (**86**)

INDAZOLE	UV DATA [λ_{MAX} (log ϵ)]	IR DATA (cm^{-1})
86a	220 (4.19) 260 (3.41) 296 (3.80)	3060, 2940, 2860, 2800, 1744, 1616, 1576, 1508, 1490, 1452, 1430, 1405, 1390, 1350, 1324, 1285, 1265, 1248, 1198, 1188, 1162, 1135, 1082, 1038, 1032, 1018, 1008.
86b	218 (4.94) 262 (4.08) 296 (4.49) 308 (4.40)	3070, 3045, 2990, 2940, 2880, 1618, 1578, 1508, 1490, 1455, 1432, 1405, 1390, 1368, 1350, 1288, 1214, 1158, 1135, 1094, 1070, 1008.
86c	216 (4.35) 256 (3.61) 296 (3.83)	3120, 3060, 3035, 2955, 2920, 2850, 1702, 1685, 1625, 1585, 1575, 1508, 1495, 1450, 1422, 1402, 1382, 1345, 1325, 1305, 1292, 1250, 1195, 1174, 1150, 1130, 1085, 1064, 1022, 1004.
86d	220 (4.48) 262 (3.64) 296 (4.07) 308 (3.98)	3060, 2985, 2935, 2875, 1618, 1578, 1505, 1488, 1454, 1432, 1405, 1390, 1368, 1352, 1288, 1215, 1156, 1135, 1090, 1070, 1008.
86e	218 (4.70) 258 (3.27) 296 (3.61) 306 (3.52)	3082, 2930, 1621, 1580, 1512, 1455, 1422, 1402, 1351, 1295, 1232, 1170, 1135, 1060, 1008.
86f	214 (3.90) 250 (4.15) 306 (3.74)	3045, 2920, 1615, 1595, 1508, 1492, 1472, 1452, 1425, 1398, 1375, 1345, 1310, 1292, 1212, 1198, 1135, 1098, 1075, 1062, 1025, 1005.

EXPERIMENTAL

GENERAL

Infrared (ir) spectra were obtained on a Perkin-Elmer model 283 spectrophotometer using neat film unless otherwise indicated. Only major and diagnostic bands are reported, in wavenumbers, and these bands were calibrated against the 1601.4 cm^{-1} band of polystyrene. Melting points (mp) were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Proton magnetic resonance (^1H nmr) spectra were recorded on a Varian EM-390 spectrometer, using deuterochloroform ($CDCl_3$) as the solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts are reported in δ values (ppm), followed, in parentheses, by the multiplicity symbol (s= singlet, d= doublet, t= triplet, pent.=pentet, sept.= septet and m= multiplet) and the relative signal intensity. Carbon-13 nuclear magnetic resonance (^{13}Cnmr) and ^1H nmr spectra were obtained on the Bruker AM-500 (125.76 MHz for ^{13}C and 500.13 for ^1H) spectrometer. Deuterochloroform ($CDCl_3$) was the solvent used for both ^{13}C nmr and ^1H nmr, with the peaks being calibrated against the 77.20 ppm (^{13}C) and 7.24 ppm (^1H) peak of $CDCl_3$. Deutrobenzene (C_6D_6) was used for some of the ^1H and ^{13}C nmr spectra with the peaks being calibrated against the 7.15 ppm (^1H) and 128.00 ppm (^{13}C) peak of C_6D_5H.

Ultraviolet (uv) spectra were obtained from a Hewlett Packard 8451A Diode Array spectrophotometer, using hexanes as solvent.

Gas chromatograms were obtained from a Hewlett Packard 5890A gas chromatograph. The column employed was an HP-1 (methyl silicone gum) Instrument Test, 5 m x 0.53 mm with 2.65 μm film thickness. The conditions employed were the following. The injector temperature was 200°C, the detector temperature was 250°C, and the initial column temperature was set at 60°C with a rate of increase in temperature of 5°C per minute to a maximum of 200°C. The flow rate of helium carrier gas was 18 ml per minute.

Mass spectra (ms) were recorded on a VG 70-70F double focussing or a VG ZAB-E triple focussing mass spectrometer. The samples were introduced into the spectrometer system via a direct insertion probe. The energy of the ionizing electrons was 70 eV.

Centrifugal chromatography was performed on the Model 7924T Chromatotron, fitted with a silica (Merck, Kieselgel 60 PF_{254}) coated glass plate. The adsorbant thickness 2 mm. The solvent mixture used for all separations was 2% ethyl acetate in low boiling petroleum ether. These solvents were distilled prior to usage.

The chemicals and solvents used were purchased from Aldrich, Matheson Coleman and Bell, Caledon, Mallinckrodt, J.T. Baker, BDH, or Fisher Scientific. The chemicals were used without any further purification. The 1-(*o*-bromophenyl)-1-methoxy-1- phenylazoethane was graciously supplied by Dr. John Warkentin.

Cyclohexylhydrazine. Cyclohexyl bromide (25.08 g, 0.15 mol) in 25 mL of ethanol was added dropwise to hydrazine hydrate (50 g, 1.0 mol) in 50 mL of ethanol. The reaction mixture was heated for 27.5 hours at a temperature of 74°C. The ethanol was removed and the residue was extracted continuously for 2

days with 300 mL of ether. The ether solution was dried over magnesium sulphate and the ether was removed to give the title hydrazine (3.12 g, 18%). The compound was used in the next step without purification. ^{1}H nmr ($CDCl_3$, 90 MHz): 0.48-2.80 (m, 10 H); 3.14-4.18 (m, 4H). Note that the pentet due to the methyne hydrogen is superimposed upon the multiplet due to the three hydrazine hydrogens.

o-Bromoacetophenone cyclohexylhydrazone(**81a**). In a 250 mL round-bottomed flask equipped with a magnetic stirring bar and a condenser were placed 2.13 g (0.011 mol) of *o*-bromoacetophenone, 1.45 g (0.013 mol) of cyclohexylhydrazine and 25 mL of ether. The resulting mixture was brought to reflux and left to stir at the refluxing temperature under a blanket of nitrogen for 41 hours. The ether was removed to give the title hydrazone (3.16 g, 82%) as a 60:40 mixture of isomers. The compound was used in the next step without purification. ^{1}H nmr data are given in table 1.

1-(*o*-Bromophenyl)-1-methoxy-1-cyclohexyl- azoethane (**82a**). To a 250 mL round-bottomed, two-necked flask equipped with a magnetic stirring bar were added 5.83 g (0.013 mol) of lead tetraacetate and 30 mL of methanol. A solution of *o*-bromoacetophenone cyclohexylhydrazone (3.16 g, 0.011 mol) in 25 mL of methanol was added through a dropping funnel. The reaction mixture was cooled in ice and left to stir at the ice bath temperature for 8 hours. Most of the methanol was removed using a rotory evaporator and 50 mL of ice water was added. Dichloromethane was added and both the organic and aqueous phases were filtered through Celite under suction. The aqueous phase was extracted twice more with fresh dichloromethane and the combined organic extracts were washed

sequentially with two volumes of ice water, once with cold, dilute sodium bicarbonate solution, twice more with ice water and once with cold brine solution. The dichloromethane layer was dried over magnesium sulphate. The dichloromethane layer was removed leaving the azo-ether as a mixture of products. The yield of pure azo-ether after purification using centrifugal chromatography was 2.43 g (73%). Spectral data are given in tables 3 and 5.

Acetophenone cyclohexylhydrazone(**81g**). The procedure described above for the synthesis of *o*-bromoacetophenone cyclohexylhydrazone gave, from acetophenone (1.02 g, 0.008 mol) and cyclohexylhydrazine (1.17 g, 0.010 mol) the title hydrazone (1.49 g, 81%). ^{1}H nmr data are given in table 2.

1-Phenyl-1-methoxy-1-cyclohexylazoethane(**82g**). The procedure described above for the synthesis of 1-(*o*-bromophenyl)-1-methoxy-1-cyclohexylazoethane gave, from acetophenone cyclohexylhydrazone (1.49 g, 0.007 mol) and lead tetraacetate (4.51 g, 0.010 mol), the title azo ether as a mixture of products. The yield of pure azo ether after purification using centrifugal chromatography was 1.02 g (59%). Spectral data are given in tables 4 and 6.

o-Bromoacetophenone-*tert*-butylhydrazone(**81b**). In a 250 mL round-bottomed flask equipped with a magnetic stirring bar and a condenser, were placed 1.05 g (0.005 mol) of *o*-bromoacetophenone, 0.85 g (0.007 mol) *tert*-butylhydrazine hydrochloride, 0.57 g (0.007 mol) of sodium acetate, 10 mL of water and 25 mL of methanol. The homogeneous solution was brought to reflux and left to stir at the reflux temperature under a blanket of nitrogen for 64 hours.

To the resulting mixture were added, 20 g of ice and 20 mL of ether. The aqueous phase was extracted two times with ether. The combined ether extracts were washed once with 5% sodium bicarbonate solution and dried over magnesium sulphate. The ether was removed to give the title hydrazone as a 60:40 mixture of isomers (1.24 g, 92%). ^{1}H nmr data are given in table 1. The compound was used in the next step without purification.

1-(*o*-Bromophenyl)-1-methoxy-1-*tert*-butylazo- ethane(**82b**). *o*-Bromoacetophenone-*tert*-butylhydrazone (1.24 g, 0.005 mol) was oxidized using lead tetraacetate (2.52 g, 0.006 mol) by the procedures described previously, to give 0.56 g (43%) of the title azo-ether. Spectral data are given in tables 3 and 5.

Acetophenone-*tert*-butylhydrazone(**81h**). *tert*-Butylhydrazine hydrochloride (5.03 g, 0.04 mol) was condensed with acetophenone (4.86 g, 0.04 mol) and sodium acetate (6.62 g, 0.081 mol), by the procedure described previously for *o*-bromoacetophenone-*tert*-butyl- hydrazone, to give 5.75 g, (75%) of the title hydrazone. ^{1}H nmr data are given in table 2.

1-Phenyl-1-methoxy-1-*tert*-butylazoethane(**82h**). Acetophenone-*tert*-butylhydrazone (2.16 g, 0.011 mol) was oxidized using lead tetraacetate (5.37 g, 0.012 mol), by the procedures described previously to give 1.15 g (56%) of the title azo ether. Spectral data are given in tables 4 and 6.

1-(*o*-Bromophenyl)-1-methyl-1-*tert*-butylazoethane . To a 100 mL three-necked flask fitted with a stirring bar, condenser, septum, dropping funnel, and a nitrogen bubbler was added *o*-bromo-acetophenone-*tert*- butyl- hydrazone

(2.41 g, 0.009 mol) in 4 mL of dry tetrahydrofuran (THF). The reaction vessel was cooled to dry ice/acetone temperature and butyllithium (3.6 mL, 0.009 mol) was added with a syringe over 15 minutes. Methyliodide (2.75 g, 0.019 mol) in 5 mL of THF was added dropwise over 5 minutes. The reaction mixture was allowed to warm to room temperature and to stir overnight. The THF was evaporated off and the mixture was made acidic with 6% hydrochloric acid solution. The aqueous layer was extracted twice with ether. The organic layer was washed once each with potassium carbonate solution (5%), water, and brine solution and dried over magnesium sulphate. The ether was removed leaving the title compound as a mixture of products. The yield of pure compound after centrifugal chromatography was 0.38 g (15%). ^{1}H nmr($CDCl_3$, 90MHz): 1.24 (s, 9 H); 1.59 (s, 6 H); 6.68-7.49 (m, 4 H). Ultra violet (λ_{max} [log ϵ]): 208 (3.72); 212 (3.82). Infrared (cm^{-1}): 3085, 3060, 2965, 2930, 2865, 1588, 1565, 1468, 142, 1430, 1420, 1372, 1356, 1275, 1242, 1225, 1202, 1170, 1104, 1040, 1015.

Benzylhydrazine. Benzyl chloride (2.19 g, 0.17 mol) in 25 mL of ethanol was dropped into a solution of hydrazine hydrate (50 g, 1.0 mol) in 50 mL of ethanol at room temperature. The resulting solution was stirred for 20 hours at 40°C. The ethanol was removed with a rotary evaporator and the residue was extracted continuously for three days with 300 mL of ether. The ether solution was dried over magnesium sulphate and the ether was removed to give 19.6 g (95%) of benzyl hydrazine which was used in the next step without purification. ^{1}H nmr ($CDCl_3$, 90 MHz): 3.28 (s, 3 H); 3.90 (s, 2 H); 7.39 (s, 5 H).

o-Bromoacetophenone benzylhydrazone(**81c**). To a 250 mL round-bottomed flask equipped with a magnetic stirring bar and condenser, were added

5.00 g (0.025 mol) *o*-bromoacetophenone,(3.75 g 0.031 mol) benzyl hydrazine and 25 mL of ether. The resulting mixture was brought to reflux and left to stir at the reflux temperature under a blanket of nitrogen for 43 hours. The ether was removed to give the title hydrazone (6.47 g, 85%) as a 60:40 mixture of isomers. ^{1}H nmr data are given in table 1. The compound was used in the next step without purification.

1-(*o*-bromophenyl)-1-methoxy-1-benzylazoethane (**82 c**). To a 250 mL two-necked flask equipped with a magnetic stirring bar, were added 4.04 g (0.009 mol) of lead tetraacetate and 50 mL of a 2:1 mixture of dichloromethane and methanol. A solution of *o*-bromo- acetophenone benzylhydrazone (3.21 g, 0.011 mol) in 25 mL of the dichloromethane methanol solution was added. When the reaction was complete, an additional 50 mL of dichloromethane was added along with 50 mL of ice water. The resulting mixture was filtered through Celite and the aqueous layer was extracted twice with dichloromethane. The organic layer was washed twice each with ice water, cold sodium bicarbonate solution, cold water and once with cold brine solution. The organic layer was then dried over magnesium sulphate. The dichloromethane was evaporated leaving the azo ether mixed with other products. The yield of the azo ether after purification using centrifugal chromatography was 1.52 g (45%). Spectral data are given in tables 3 and 5.

Acetophenone benzylhydrazone(**81i**). The procedure described above, for the synthesis of *o*-bromo- acetophenone benzylhydrazone gave, from acetophenone (3.0 g, 0.025 mol) and benzyl hydrazine (3.68 g, 0.030 mol), the title hydrazone, 4.71 g (84%). ^{1}H nmr data are given in table 2.

1-Phenyl-1-methoxy-1-benzylazoethane(**82i**). The procedure described above for the synthesis of 1-(*o*-bromophenyl)-1-methoxy-1-benzylazoethane gave, from acetophenone benzylhydrazone (0.020 mol) and lead tetraacetate (10.81 g, 0.024 mol), the title azo ether as a mixture of products. The yield of pure azo ether obtained after centrifugal chromatography was 1.82 g, (36%) and spectral data are given in tables 4 and 6.

2-Bromopropane. Isopropyl alcohol (55g 0.92 mol) was placed in a 500 mL distilling flask fitted with a long Liebig condenser. To the alcohol was added 460 g (5.68 mol) of constant boiling point hydrobromic acid. The mixture was allowed to distill slowly (1-2 drops per second) until about half of the liquid had passed over. The lower alkyl bromide layer was separated from the aqueous layer. The aqueous layer was returned to the distilling flask and a further 40 g (0.67 mol) of isopropyl alcohol was added. This mixture was allowed to distill to obtain a second batch of the crude bromide. The combined alkyl bromide layers were extracted once each with concentrated hydrochloric acid, water and dilute (5%) sodium bicarbonate solution. The alkyl bromide layer was then dried over anhydrous magnesium sulphate. The yield of 2-bromopropane was 103 g (53% yield). ^{1}H nmr ($CDCl_3$, 90 MHz): 1.72 (d, 6 H); 4.29 (sept., 1 H).

Isopropylhydrazine. 2-Bromopropane (25.6 g, 0.21 mol) in 25 mL of ethanol was added dropwise to hydrazine hydrate (50 g, 1.0 mol) in 50 mL of ethanol. The reaction mixture was allowed to stir overnight at room temperature. The ethanol was removed and the residue was extracted continuously for two days with 300 mL of ether. The ether solution was dried over magnesium sulphate and

the ether was removed to give the title hydrazine (11 g, 71%). The compound was used in the next step without purification. ^{1}H nmr ($CDCl_3$, 90 MHz): 1.09 (d, 6 H); 2.81 (sept., 1 H); 3.76 (s, 3 H).

o-Bromoacetophenone isopropylhydrazone(**81d**). In a 250 mL round-bottomed flask equipped with a magnetic stirring bar and a condenser, were placed 2.54 g (0.013 mol) of *o*-bromoacetophenone, 1.58 g (0.021 mol) isopropylhydrazine, and 25 mL of anhydrous ether. The resulting mixture was brought to reflux and left to stir at the reflux temperature under a blanket of nitrogen for 5 days. The solution was extracted three times with 5% sodium bicarbonate solution and dried over magnesium sulphate. The ether was removed to give the title hydrazone (2.66 g, 82%) in a 50:50 mixture of isomers. The compound was used in the next step without purification. Spectral data are given in table 1.

1-(*o*-Bromophenyl)-1-methoxy-1-isopropylazoethane (**82d**). To a 250 mL round-bottomed, two necked flask equipped with a magnetic stirring bar, were added 5.53 g (0.012 mol) of lead tetraacetate and 30 mL of methanol. A solution of *o*-bromoacetophenone isopropylhydrazone (2.66 g, 0.010 mol) in 25 mL of methanol was added through a dropping funnel. The reaction mixture was cooled in ice and left to stir at the ice-bath temperature, for 4 hours. Most of the methanol was removed by distillation, and the mixture was made alkaline with 5% sodium bicarbonate solution. Ether was added and both the organic and the aqueous phases were filtered through Celite under suction. The aqueous layer was extracted twice more with ether and the combined ether layers were extracted once with saturated sodium chloride solution and dried over magnesium sulphate. The

ether layer was evaporated leaving the azo ether mixed with other products. The azo ether was separated from the mixture using centrifugal chromatography. The yield of pure azo-ether was 2.01 g (70%). Spectral data are given in tables 3 and 5.

Acetophenone isopropylhydrazone(**81j**). The procedure described above, for the synthesis of *o*-bromoacetophenone isopropylhydrazone gave, from acetophenone (2.5 g, 0.021 mol) and isopropylhydrazine (2.5 g, 0.034 mol), the title hydrazone (3.18 g, 86%). ^{1}H nmr data are given in table 2.

1-phenyl-1-methoxy-1-isopropylazoethane(**82j**). The procedure described above for the synthesis of 1-(*o*-bromophenyl)-1-methoxy-1-isopropylazoethane gave, from acetophenone isopropylhydrazone (3.18 g, 0.018 mol) and lead tetraacetate (8.86 g, 0.02 mol) the title azo ether as a mixture of products. The pure azo ether was separated from the mixture using centrifugal chromatography. The yield was 2.02 g (54%) data are given in tables 4 and 6.

o-Bromoacetophenone methylhydrazone(**81e**). Methyl hydrazine (0.3 g, 0.007 mol) was condensed with *o*-bromoacetophenone (1.0 g, 0.005 mol), by the procedures described previously, to give 1.02 g (90%) of the title hydrazone as a 60:40 mixture of isomers. ^{1}H nmr data are given in table 1.

1-(*o*-Bromophenyl)-1-methoxy-1-methylazoethane (**82 e**). *o*-Bromoacetophenonemethyl-hydrazone (1.02 g, 0.004 mol) was oxidized using lead tetraacetate (2.49 g, 0.006 mol) by the procedures described previously, to give 0.62 g (64%) of the title azo-ether. Spectral data are given in tables 3 and 5.

Acetophenonemethyl-hydrazone(**81k**). Methyl hydrazine (2.02 g, 0.044 mol) was condensed with acetophenone (3.5 g, 0.029 mol), by the procedures described previously to give 2.45 g (57%) of the title hydrazone. ^{1}H nmr data are given in table 2.

1-Phenyl-1-methoxy-1-methylazoethane(**82k**). Acetophenone methylhydrazone (2.25 g, 0.015 mol) was oxidized using lead tetraacetate (9.92 g, 0.022 mol) by the procedures described previously, to give 1.41 g (58%) of the title azo ether, which was purified using centrifugal chromatography. Spectral data are given in tables 4 and 6.

Acetophenone phenylhydrazone(**81l**). To a 250 mL round bottomed flask fitted with a stirring bar and a condenser were added 5.0 g (0.042mol) acetophenone, 7.78 g (0.072 mol) of phenylhydrazine, 6.53 g (0.060 mol) monobasic potassium phosphate, 0.51 g (0.004 mol) dibasic sodium phosphate and 160 mL of water. The reagents were mixed together and allowed to stir under nitrogen at room temperature for 6 hours. After 6 hours, 8 g (0.137 mol) of sodium chloride was added and the reaction mixture was stirred overnight. The aqueous solution was extracted with dichloromethane and the combined organic layers were washed with saturated sodium chloride solution and dried over magnesium sulphate. The yield was 4.85 g (55%) and spectral data are given in table 2.

1-Phenyl-1-methoxy-1-phenylazoethane(**82l**). Acetophenone phenylhydrazone (2.00 g, 0.009 mol) was oxidized using lead tetraacetate (4.64 g, 0.010 mol) by the procedures described previously to give 1.12 g (52%) of the title

azo ether. Spectral data are given in tables 4 and 6.

Cyclization reactions. All of the cyclization reactions were carried out in a similar manner using various concentrations of tributyltin hydride and substrates. A sample cyclization procedure is outlined below for the cyclization of 1-(*o*-bromophenyl)-1- methoxy-1-cyclohexylazoethane: To a reaction tube were added 512 mg (1.66 mmol) of the azo ether, 576 mg (1.98 mmol) of tributyltin hydride, 13.5 mg (0.08 mmol) of azobisisobutryonitrile (AIBN), and 10 mL of benzene. The reaction mixture was degassed on a vacuum line and immediately sealed. The reaction mixture was placed in a constant temperature oil bath set at 80°C for 30 hours. The tube was cooled before it was opened and the benzene was distilled off. The residue was separated using centrifugal chromatography and the products obtained were weighed and analyzed by ^{1}H and ^{13}C nmr, ir, uv, and mass spectrometry. Yields and spectral data for the indazoles (**86a-f**) formed are given in tables 7, 8, 9, and 10. Mass spectra for the indazoles are given in the appendix.

APPENDIX

Table 11: Mass Spectral Data of Indazoles (**86**)

INDAZOLE	EXACT MASS[a]	m/z (REL. ABUNDANCE)[a]	
86a	214.1463	42(18)	132(100)
		55(10)	133(15)
		58(8)	145(90)
		69(5)	146(10)
		77(12)	158(8)
		104(8)	171(23)
		119(7)	213(15)
		131(32)	214(50)
86b	188.1321	77(10)	133(14)
		131(28)	173(26)
		132(100)	188(28)
86c	222.1166	51(16)	131(19)
		65(28)	145(21)
		77(22)	180(10)
		91(100)	207(21)
		92(18)	221(50)
		105(10)	222(100)
86d	174.1160	77(11)	159(100)
		131(19)	160(14)
		132(14)	174(40)

[a]The exact masses are rounded off to four decimal places.

[b]m/z values are recorded for peaks with relative abundance greater than 5%.

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