Tetrahedron Vol. 47, No. 48, pp. 10119-10128, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

Oxidation during Reductive Cyclisations using Bu_3SnH

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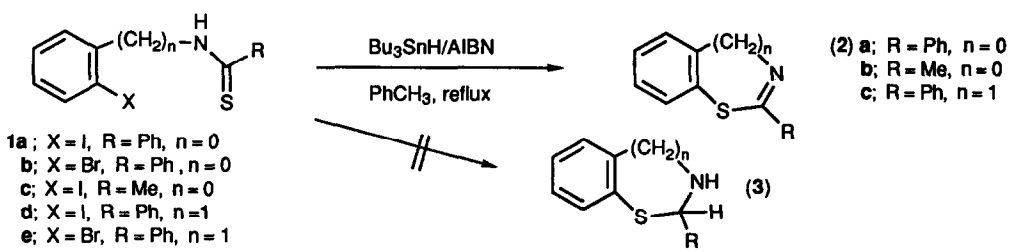
(*Received in UK* 24 *October* 1991)

Key Words: radical cyclisation; tributyltin hydride; $S_{RN}1$ mechanism; radical anions; radicals

Abstract: *Reductive cyclisations using Bu_3SnH include an "oxidation" step if the removal of an acidic proton from the intermediate cyclised radical, by Bu_3SnH acting as a base, is favourable. A "pseudo $S_{RN}1$ mechanism is proposed.*

The use of tri-n-butyltin hydride (Bu_3SnH) for the reductive cyclisations of a wide range of substrates has been widely reported[1] and is a major synthetic method. These reactions involve radical abstraction of groups such as iodine and bromine by $Bu_3Sn\cdot$ radicals to yield an intermediate radical, cyclisation of the radical thus generated onto an unsaturated bond, and reduction of the new intermediate radical by hydrogen abstraction from Bu_3SnH. However, an increasing number of recent publications[2-10] report 'oxidation' during reductive cyclisations with Bu_3SnH. The authors all identified the problem but did not provide an explanation for the unusual oxidation step. Cyclisation of aryl radicals onto arenes by various methods is well known,[2-9] especially with photochemical catalysis.[7] Re-aromatisation in most examples by loss of H_2 from the expected cyclisation product would be a strong driving force but this dihydro product has not been detected in any of the examples. Many of these methods have oxidising agents present to explain the observed oxidation, but many reductive routes, *e.g.* electrochemical reduction,[9] do not. This area of synthesis has been well reviewed.[8] Although many of these reactions/syntheses concern the cyclisation of aryl radicals[2-5,7-9] or alkyl radicals[6] onto arenes, a number do not,[10] and therefore, an appreciation of the apparent common mechanistic features is important. The significant facet that needs to be answered is why most of Bu_3SnH reductions undergo reductive cyclisation (normal and expected) and why a smaller number also exhibit an 'oxidation step'. In considering some of our own results and those in the literature we felt that an explanation would be useful due to the obvious synthetic utility of these reactions. In this paper we report useful synthetic reactions and our observations of 'oxidation' during reductive cyclisation using Bu_3SnH.

Cyclisation of aryl radicals onto thioamides



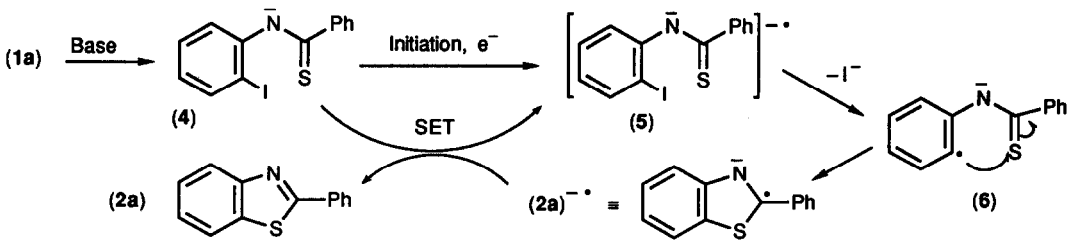
1a; X = I, R = Ph, n = 0
b; X = Br, R = Ph, n = 0
c; X = I, R = Me, n = 0
d; X = I, R = Ph, n = 1
e; X = Br, R = Ph, n = 1

(2) **a**; R = Ph, n = 0
b; R = Me, n = 0
c; R = Ph, n = 1

Scheme 1. Cyclisation of thioamides

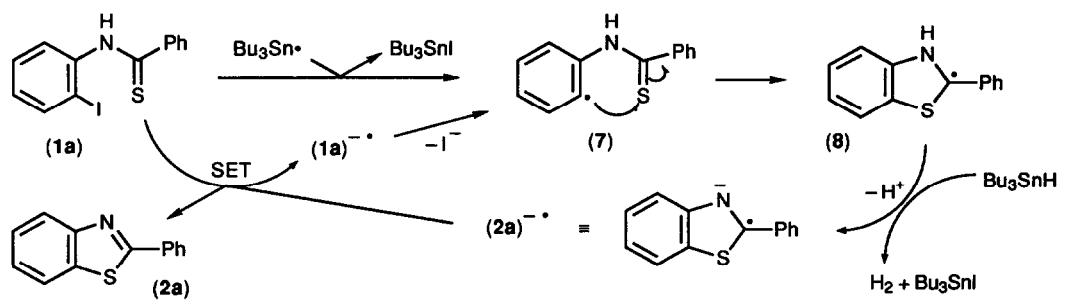
In recent work we sought to exploit the known addition of radicals onto thiocarbonyl moieties[1,11] and were surprised to discover that cyclisation of aryl radicals onto thioamides gave "oxidised" products (Scheme 1) even when oxygen was rigourously excluded. The expected dihydro products (**3**) were not observed in any of the reactions and the formation of the products cannot be explained by normal Bu_3SnH reduction. Reductive cyclisation of the thioamide (**1a**) using Bu_3SnH under standard conditions gave almost quantitative yields of the benzothiazole (**2a**). In order to investigate the mechanism, a number of parameters were altered (see Table 1). Most of the results are obvious; *e.g.* the bromo analogue (**1b**) reacted more slowly and the reaction was faster at higher temperatures. Light is important but not essential; auto-catalysis by C-I bond homolysis is possible but unlikely (very low yield of product in the absence of AIBN). The role of the AIBN is confusing. Similar observations with respect to AIBN have been reported for the cyclisations of ω-iodoalkyl pyridinium salts.[10]

The use of catalytic Bu_3SnH, and DABCO to replace Bu_3SnH as a base, was successful but not significantly different when DABCO alone was used. The use of DABCO or NaH alone gave reasonable yields which strongly suggests initial formation of the thioamide anion and a $S_{RN}1$ mechanism (Scheme 2).[12,13] $S_{RN}1$ reactions have not been previously noted in non-polar solvents and the $S_{RN}1$ reactions of the thioamides (**1a**) and (**1b**) in dipolar aprotic solvents were sluggish.[11] A reaction with Bu_3SnH alone gave a very low yield indicating that it does not act as a base to deprotonate the thioamide (**1a**) in an $S_{RN}1$ reaction.



Scheme 2. $S_{RN}1$ mechanism of cyclisation

We sought a mechanism to explain the reactions. It is possible, however, that several mechanisms are operating. The first steps are the normal S_H2 abstraction of halogen by Bu_3Sn• to yield aryl radical (**7**) and subsequent cyclisation of (**7**) to yield a stable radical (**8**). The cyclisation is thermodynamically favourable because a reactive σ-aryl radical yields a very stable delocalised radical and the addition of radicals to the sulphur in C=S groups is well known.[11] The problem is to explain how the hydrogen is lost. Careful reactions under nitrogen gave similar yields of products which tends to rule out loss of H_2 from the expected dihydro product by air (or other oxidants) oxidation. A mechanism as shown in Scheme 3 for the thioamide (**1a**), based on cyclisations proceeding by the $S_{RN}1$ mechanism,[12,13] appeared to provide the best solution. The lowest energy route is proton abstraction by Bu_3SnH from the radical (**8**) to yield the stable radical anion ($2a^{-\bullet}$).



Scheme 3. Pseudo $S_{RN}1$ mechanism of cyclisation

Table 1. Reactions between *N*-(2-Iodophenyl)thiobenzamide (**1a**) and Bu_3SnH

Reaction conditions[a]	% Recovery of (**1a**)[b]	% Yield of (**2a**)[b]
Standard conditions[a]; Br in place of iodine	0, (<4); 0, (40)	69, (95); 64,(60)
PhH in place of PhMe; PhCl in place of PhMe; PhMe at 80°C	(0); (6); (23)	(75); (94); (77)
Absence of light	72	28
Bu_3SnH (0.1 equiv.); no AIBN	80,0; (91),0	0,46; (8),7
No AIBN & no Bu_3SnH; AIBN (1.1 equiv.) & no Bu_3SnH	polymeric material; 0	polymeric material; 65
Bu_3SnH (0.1 equiv.) and DABCO (1.1 equiv.)	0, (9)	50, (91)
no Bu_3SnH and DABCO (1.1 equiv.)	0	73
no Bu_3SnH, no AIBN, NaH (1.1 equiv.), light catalysis	0	34

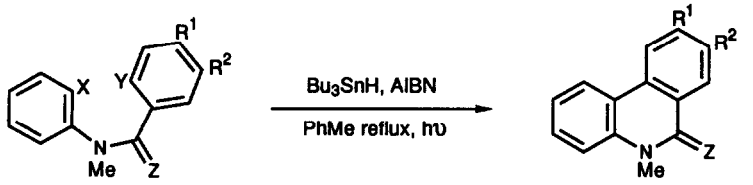
a. Unless otherwise stated the reaction conditions were: Bu_3SnH (1.1 equiv.), AIBN (0.2 equiv.), refluxing toluene, 24 h, light catalysis, nitrogen atmosphere. *b*. The yields are of pure isolated 2-phenyl-1,3-benzothiazole and the yields in parenthesis were measured by HPLC using an internal standard.

In the $S_{RN}1$ mechanism (Scheme 2), cyclisation involves a nucleophile adding to an aryl radical to directly yield the radical anion (**2a**$^{-\bullet}$). Single electron transfer (SET) from the intermediate radical anion (**2a**$^{-\bullet}$) to starting material (**1a**) yields the product (**2a**) and a new radical anion (**1a**$^{-\bullet}$). In $S_{RN}1$ reactions, (**2a**$^{-\bullet}$) is also an intermediate and readily undergoes a less favourable SET with the anion (**4**) to yield product and the radical dianion (**5**). Loss of halide anions (X^-) from $[ArX]^{-\bullet}$ to yield aryl radicals ($Ar\bullet$) is well known and rapid.[12,13] The role of the Bu_3SnH is only catalytic to the radical chain and only the Bu_3SnH can act as both the base and as the radical initiator by halogen abstraction. This loss of a proton is only possible if it is acidic and when abstracted, yields a stable radical anion. In "normal" Bu_3SnH reductive cyclisations an acidic hydrogen is not present. The evolution of hydrogen gas was not observed but would be difficult to see in a reaction under reflux and a stream of nitrogen. Other mechanisms are possible but were considered less probable, *e.g.* disproportionation of a dihydro product (**3**) is ruled out by the high yields. Abstraction of hydrogen ($H\bullet$) by $X\bullet$, $Bu_3Sn\bullet$, or $Me_2C(CN)\bullet$ from the intermediate cyclised radical (**8**) is possible but would terminate the chain reaction. Abstraction of halogen from the starting material (**1a**) by (**8**) would give a chain reaction and loss of HX from the product would be rapid. However, (**8**) is a very stable radical and unlikely to abstract halogen to give the reactive aryl σ-radical (**7**).

The absence of cyclisation onto the phenyl ring of the thioamides (**1a**) and (**1b**) is explained by the preferred *trans*-conformation of the thioamide in which the C=S group is lined up for reaction with the aryl radical and the energy barrier to rotation to the *cis*-conformer is too high. The thioacetamide (**1c**) cyclised to yield the benzothiazole (**2b**) (43%) but the *N*-methyl analogue, which cannot lose an acidic proton from an intermediate radical to yield an intermediate radical anion, gave an intractable tar. The thioamides (**1d**) and (**1e**) also gave cyclisation to the benzothiazine (**2c**) (31 and 41% respectively) but when Bu_3SnH was substituted by DABCO no reaction took place. The thioamide (**1d**) does not undergo a $S_{RN}1$ reaction[12] and therefore the latter result is expected. The carboxamide analogues of (**1c**) and (**1d**) gave 'normal' reduction with loss of iodine to the amides, PhNHCOMe and $PhCH_2NHCOPh$ respectively indicating that the aryl radical does not add to the oxygen of carbonyl groups. All these results are consistent with the pseudo $S_{RN}1$ mechanism.

Cyclisation of aryl radicals onto arenes

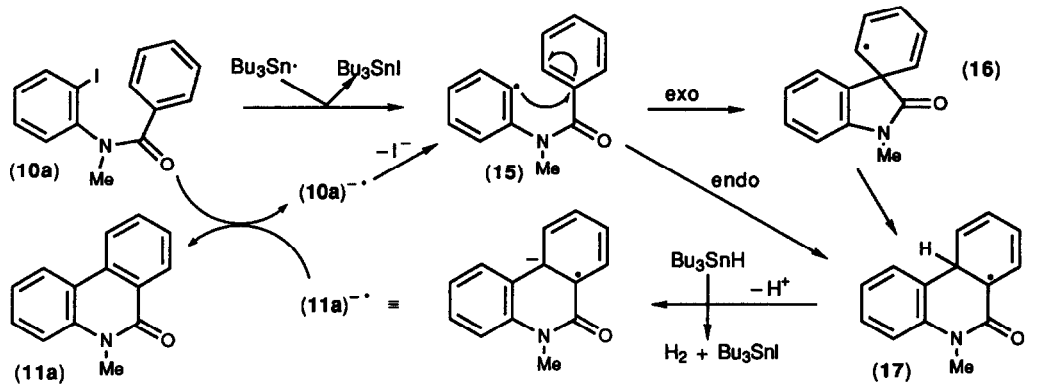
A range of *N*-methylhalogeno-benzanilides (**10a, 10b, 12**) and -thiobenzanilides (**13a, 13b**) were reacted with Bu_3SnH to yield 'oxidised' products, phenanthridinones (**11a, 11b**) and thiophenanthridinone (**14**) respectively, as the sole products. The results are shown in Scheme 4. The lowish yields are due to difficulty in purification caused by tributyltin residues. Yields were not optimised. No spiro or dihydro-products were observed. Other examples of cyclisation of aryl radicals onto arenes were reported[2-6] during our studies.



(**10a**) X = I, Y = R^1 = R^2 = H, Z = O
(**10b**) X = I, Y = H, R^1 = R^2 = OCH_2O, Z = O
(**12**) X = R^1 = R^2 = H, Y = I, Z = O
(**13a**) X = I, Y = R^1 = R^2 = H, Z = S
(**13b**) X = Br, Y = R^1 = R^2 = H, Z = S

(**11a**) R^1 = R^2 = H, Z = O; 45% (24 h)
(**11b**) R^1 = R^2 = OCH_2O, Z = O; 29% (48 h)
(**11a**) 15% (24 h) + 38% (**12**)
(**14**) R^1 = R^2 = H, Z = S; 29% (24 h)
(**14**) 13% (24 h)

Scheme 4. Cyclisation of *N*-Methyl benzanilides and thiobenzanilides

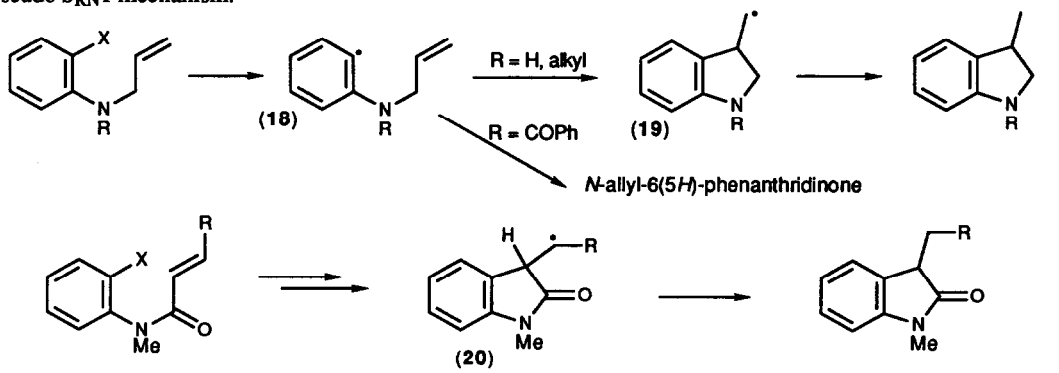


Scheme 5. Pseudo $S_{RN}1$ mechanism for the cyclisation of *N*-(2-iodophenyl)-*N*-methyl-benzamide

The same mechanistic arguments as proposed for the cyclisation onto C=S bonds can be used for these cyclisations as shown in Scheme 5. Abstraction of halogen will yield the aryl radical (**15**) which cyclise onto the other aryl ring faster than reduction by Bu_3SnH. Some *exo* cyclisation to the spiro radical (**16**) would be predicted from evidence in the literature[7-9,14] but under the conditions of the reaction, rapid rearrangement to the more stable *endo* radical (**17**) would be expected.[7-9,14,15] Alternatively, (**15**) cyclises directly to the *endo* radical (**17**). The cyclisation takes place whether the halogen is on the aniline ring (**10a**, **10b**) or on the benzoyl ring (**12**). Aryl radicals are relatively neutral in philicity[1,16] and these reactions do not appear to be affected by substituents. Attempts to replace Bu_3SnH as a base by DABCO in the cyclisation of (**10a**) failed and starting material was recovered, but in the cyclisation of the thioamides (**13a**, **13b**) the benzothiazole (**2a**) was isolated (24% and 99% respectively). The thioamide anion is a better leaving group than the carboxamide anion and is generated by S_N2 attack on the *N*-methyl of (**13a**, **13b**) by DABCO (with or without Bu_3SnH and AIBN) forming the methiodide of DABCO. The anion (**4**) thus generated undergoes an $S_{RN}1$ reaction to yield the benzothiazole (see Scheme 2). The cyclisation of the methylenedioxy-benzanilide (**10b**) to the respective phenanthridinone (**11b**) provides a simple synthesis of an unnamed *Amaryllidaceae* alkaloid.[17] Attempts to reduce and ring-open (**11b**) with $LiAlH_4$ to yield the alkaloid, ismine[18] (6-hydroxymethyl-2'-methylamino-3,4-methylenedioxybiphenyl), failed and the respective *N*-methyl-5,6-dihydrophenanthridine was obtained.

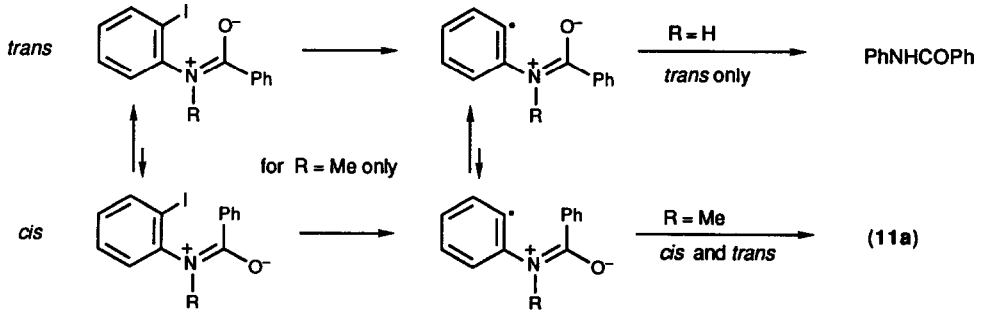
Interestingly, the *N*-allyl analogue of (**10a**) undergoes cyclisation to *N*-allyl-6(5*H*)phenanthridinone,[3] whereas the aryl radical (**18**) derived from *N*-allyl-2-halogenoanilines[3] rapidly cyclises onto the alkene to yield the 3-methyl-indoline by 'normal' Bu_3SnH reductive cyclisation (Scheme 6). This suggests that the intermediate

radical (**18**) cyclises faster onto the arene than onto the alkene. Cyclisations of 2-(*N*-allyl, *O*-allyl, and *S*-allyl)-halogenoanilines with Bu_3SnH yield 3-methylindoline, 3-methyl-2,3-dihydrobenzofuran, and 3-methyl-2,3-benzothiophene respectively.[19] Loss of H_2 to yield the respective aromatic compounds would take place if this was the mechanism for the reductive cyclisation to benzothiazoles. However, the intermediate radical (**19**) does not have an acidic hydrogen. In contrast, the intermediate radical (**20**) in the 'normal' cyclisation of the α,β-unsaturated amide analogues (Scheme 6) to oxindoles[20] has an acidic hydrogen (3-H) but loss of a proton does not yield a particularly stable radical anion. These observations provide further circumstantial evidence for the pseudo $S_{RN}1$ mechanism.



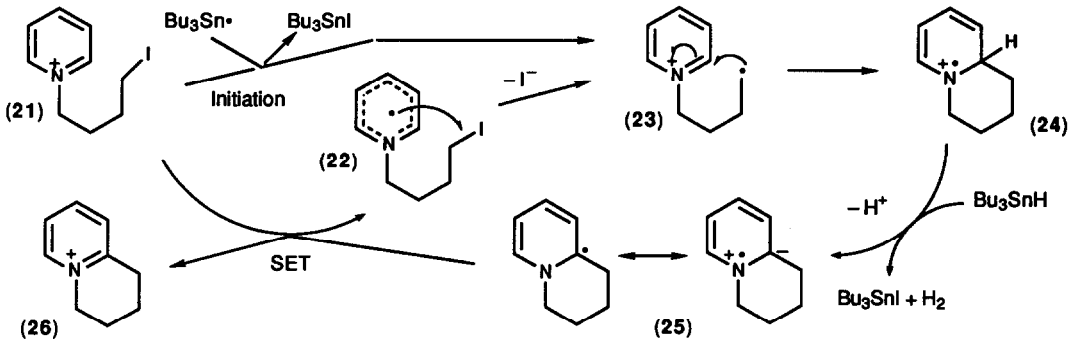
Scheme 6. 'Normal' Bu_3SnH reductive cyclisation to indolines and oxindoles

A comparison between the reactions of the NH and NMe carboxamides and thioamides is of interest. The NH amides only exist in the *trans* conformation (Scheme 7, R = H) and have a large energy barrier to rotation. Reduction of *N*-(2-iodophenyl)benzamide with Bu_3SnH gave benzanilide (46%) but the reactions of the NMe benzanilides (**10a, 10b, 12**) gave cyclisation to the respective phenanthridinones (Schemes 4 and 5). The barrier to rotation is less for the *N*-methyl amide[14,21] and some of the *cis* conformer exists (Scheme 7, R = Me), allowing cyclisation onto the aryl ring. This suggests that cyclisation of the aryl radical intermediate onto the other aryl ring is faster than reduction by Bu_3SnH, again showing that this cyclisation is a rapid reaction. The energy barrier to rotation is likely to be lower in the energetic intermediate aryl radicals than in the starting materials. This is supported by the photolysis of the NH amides [2-(*N*-halogenophenyl)-benzamides and 2-halogeno-*N*-phenylbenzamides] which yields cyclisation; *i.e.* isomerisation takes place because of the higher energy of the intermediate excited state. The NMR spectra of most of the NMe benzanilides and thiobenzanilides showed peaks which were assigned to a small amount of the *cis* conformer as reported[22] for similar amides.



Scheme 7. Influence of *cis-trans* isomerisation

In the thiobenzanilides the NH amide (**1a**) is also only in the *trans* conformation and cyclises by attack of the aryl radical on the *cis* C=S bond (Schemes 1 and 3) whereas the NMe amide exists in both conformers and cyclisation onto the other aryl ring is favoured (Schemes 4 and 5). The cyclisation onto the aryl ring must be unusually favoured, *i.e.* faster than cyclisation onto C=S and alkenes or reduction by Bu_3SnH. Reaction with alkenes should be faster than with arenes, *e.g.* bimolecular addition of aryl radicals onto 1-hexene is *ca.* 500 times faster than onto benzene.[23] A likely explanation is that the *cis* conformation has the σ-aryl radical in the correct orientation and proximity for rapid reaction with the π-system of the other aryl ring.



Scheme 8. Pseudo $S_{RN}1$ mechanism for the cyclisation of *N*-(4-iodoalkyl)pyridinium salts.

Conclusion

The test of a putative mechanism is whether it can be applied to a range of examples. The work of Murphy and co-workers[10] provides an interesting example which can also be explained by the same mechanism (Scheme 8) except that alkyl radicals are involved and each species is at one-electron less oxidation state. Loss of H^+ from the intermediate radical cation (**24**) yields a stable π-radical (**25**) which should be readily oxidised by the pyridinium salt (**21**), thereby continuing the chain reaction [*i.e.* SET between the starting material (**21**) and radical (**25**) to yield the product (**26**) and the new intermediate radical (**22**)]. Pyridinium salts, *e.g.* NAD^+, are well known as one-electron oxidants. The delocalised π-radical (**22**) is likely to be the initial result of SET. Intramolecular SET from the pyridine ring to the C-I bond would give dissociation to yield iodide and the radical (**23**) because the radical anions of alkyl iodides are not stable species.[24] Evidence has been reported for most of these steps in the extensive studies on the bimolecular addition of radicals to pyridinium salts by Minisci and co-workers.[25] The same mechanism[25] is proposed except that the radical anion is oxidised by a metal oxidant in a non-chain mechanism instead of SET to the starting material in a chain reaction. Giese[26] proposes that the bimolecular addition of radicals to pyridinium salts yields an intermediate radical analogous to (**24**) which undergoes proton loss followed by electron loss, *i.e.* as proposed for the pseudo $S_{RN}1$ mechanism.

Murphy and co-workers[27] have shown that under certain conditions there is a delicate balance between hydride delivery and radical reactions with Bu_3SnH. Bu_3SnH exhibits weak hydride activity and reacts with HX acids to liberate H_2, and undergoes various ionic reactions. We suggest that the possible ionic reactions of Bu_3SnH should be considered when planning syntheses using radicals or elucidating mechanisms. Our results and those in the literature do not prove the pseudo $S_{RN}1$ mechanism but we consider that the putative mechanism will provide an understanding of the process. There are likely to be other examples in the literature, unknown to us, in which 'oxidation' during reductive cyclisation can be explained by the pseudo $S_{RN}1$ mechanism. The unique ability of trialkyltin hydrides to act both as a generator of radicals and as a base provides a new synthetic method for cyclisation for suitable substrates involving loss of HX rather than replacement of X with H as observed for "normal" Bu_3SnH reductive cyclisations. There are less restrictive synthetic methods for carrying out cyclisation with loss of HX, *e.g.* palladium catalysed Heck reactions[28] and Co(I) catalysis.[29]

Acknowledgements

We gratefully thank the Boots Company PLC, Nottingham for generous financial support and the S.E.R.C. for a CASE Post-graduate Research Studentship (BMJ). We thank Dr John Murphy, Nottingham University, for helpful discussions.

EXPERIMENTAL

General Procedures

^{1}H-NMR spectra were recorded with a Varian EM360A spectrometer at 60 MHz using $CDCl_3$ as solvent with TMS as an internal standard unless otherwise stated. p-Dimethoxybenzene was used as an internal standard to measure yields of products in mixtures by ^{1}H NMR spectroscopy. IR spectra were recorded with a Pye PU 9516 spectrometer and mass spectra on a Kratos MS80 spectrometer. HPLC analyses (reverse phase) were carried out on a Waterman analytical apparatus linked to a Pye-Unicam 4020 UV detector set at 230 nm using an ODS column with mixtures of H_2O, THF, and MeOH. Acetamide was used as an internal standard and calibration curves were drawn using standard concentrations of authentic materials. Microanalyses were performed by The Boots Company PLC. TLC was performed on aluminium plates coated with Merck silica gel 60F254 and compounds visualised by UV light or exposure to iodine vapours. Solvents were purified by standard procedures. Tungsten white light fluorescent lamps (2 x 150 W) were used for irradiation.

Synthesis of carboxamides

Carboxamides were prepared by reaction between the respective aniline and acid chloride. The acid chlorides of piperonylic acid and 2-bromo- and 2-iodo-benzoic acid were prepared using oxalyl chloride.

N-(2-*Iodophenyl)-benzamide*: *General procedure for carboxamide synthesis*. 2-Iodoaniline (5 g, 22.8 mmol) was suspended in aqueous NaOH solution (10%, 70 ml) and benzoyl chloride (3.69 g, 26.3 mmol) was added dropwise over 2 h and stirred for a further 2 h. The crystals were filtered, washed with water, and recrystallised (aq. EtOH) to yield *N*-(2-iodophenyl)benzamide (4.98 g, 68%), m.p. 140-141.5°C (lit.[30] 139°C); υ_{max} 3210 and 1645 cm^{-1}; δ_H ($CDCl_3$/d^6-DMSO) 6.60-8.65.

(a) N-(2-*Bromophenyl)benzamide*. Benzoylation of 2-bromoaniline gave colourless needles (69%), m.p. 116-118°C (absolute EtOH) [lit.,[30] 116°C]; υ_{max} (Nujol) 3220 and 1650 cm^{-1}; δ_H ($CDCl_3$/d^6-DMSO) 6.5-8.8.

(b) N-(2-*Iodophenyl)acetamide*: Acetylation (CH_3COCl) of 2-iodoaniline gave N-(2-*iodophenyl)acetamide* (1.65 g, 28%), m.p. 111-113°C; (Found: C, 36.8; H, 3.1; N, 5.4; I, 48.5. C_8H_8INO requires: C, 36.8; H, 3.05; N, 5.35; I, 48.6%); υ_{max} (KBr) 3272, 1658, and 752 cm^{-1}; δ_H (90 MHz) 2.21 (3 H, s, CH_3) and 6.68-8.32 (5 H, m, aromatic and amide H); *m/z* 261 (M^+, 24%) and 134 (M^+-I, 100).

(c) N-(2-*Iodobenzyl)benzamide*. 2-Iodobenzylbromide was prepared by the literature procedure[31] (66%), m.p. 48-53°C [lit.[31] 55.5°C]; υ_{max} (neat) 1565, 1440, and 760 cm^{-1}; δ_H 4.46 (2 H, s, CH_2Br) and 6.6-7.86 (4 H, m, aromatic H). 2-Iodobenzylbromide (3.4 g, 11.45 mmol) was added dropwise to a solution of hexamine (1.7 g, 12.6 mmol) in CCl_4 (45 ml) and heated under reflux for 5 h. The crystalline hexamine adduct was filtered (4.06 g, 81%), m.p. 158-163°C. The adduct was refluxed for 5 h in ethanol (20 ml), water (4 ml) and concentrated HCl (10 ml). Evaporation to dryness gave a semi-crystalline residue which was basified to pH 9 with 10% aq. NaOH and extracted with diethyl ether. The organic extracts were washed with water and extracted with dil. hydrochloric acid. The aqueous extracts were basified to pH 14 with 10% aq. NaOH and extracted with diethyl ether and the organic extracts washed with water, dried and the solvent evaporated to dryness to yield the amine as a yellow oil (1.57 g, 59%). Kugelruhr distillation yielded 2-iodobenzylamine as a pale yellow oil (0.66 g, 25%), b.p. 92°C (1.5 mmHg); υ_{max} (neat): 3385, 3290, and 750 cm^{-1}; δ_H 1.45 (2 H, brs, NH_2); 3.76 (2 H, d, J = 4 Hz, CH_2NH_2) and 6.64-7.87 (4 H, m, aromatic H). 2-Iodobenzylamine (520 mg, 2.2 mmol) was benzoylated to yield colourless crystals (EtOAc) of *N*-(2-iodobenzyl)benzamide (300 mg, 40%), m.p. 157-159°C (lit.[31] m.p. 154°C); υ_{max} (Nujol) 3260, 1635, and 1435 cm^{-1}; δ_H 4.6 (2 H, d, J = 6 Hz, CH_2NH), and 6.35-7.92 (10 H, m, aromatic and amide H).

(d) N-(2-*Bromobenzyl)benzamide*. 2-Bromobenzylamine hydrochloride gave N-(2-*bromobenzyl)benzamide* (67%), m.p. 141-142°C (EtOH) (Found: C, 58.4; H, 4.3; N, 5.0; Br, 27.8. $C_{14}H_{12}BrNO$ requires: C,

58.2; H, 4.2; N, 4.8; Br, 27.5%); υ_{max} (Nujol) 3290, 1630, 750, 720, 690, and 655 cm^{-1}; δ_H 4.6-4.7 (2 H, d, J = 6 Hz, CH_2) and 6.8-7.9 (10 H, m, aromatic and amide H); *m/z* 210 (M^+-Br, 92%).

(e) N-(2-*Iodophenyl*)-2,3-*methylenedioxybenzamide*. 2-Iodoaniline and piperonyl chloride gave N-(2-*iodophenyl*)-2,3-*methylenedioxybenzamide* (38%), m.p. 123-124°C (EtOH) (Found: C, 45.5; H, 2.9; N, 3.85; I, 34.6. $C_{14}H_{10}INO_3$ requires: C, 45.8; H, 2.7; N, 3.8; I, 34.95%); υ_{max} (Nujol) 3200, 1645, 755, 725, and 680 cm^{-1}; δ_H 6.00-6.10 (2 H, s, CH_2) and 6.6-8.5 (8 H, m, aromatic and amide H); *m/z* 367 (M^+, 10%), 240 (M^+-I, 37%), 149 (100), 121 (18), 91 (12) and 65 (19).

(f) N-*Methyl*-N-*phenyl* -2-*iodobenzamide* (**12**). 2-Iodobenzoyl chloride and *N*-methylaniline gave an oil which was recrystallised from light petroleum (b.p. 60-80°C) to give (**12**), m.p. 69-70.5°C [lit.[14] 69-71°C]; υ_{max} (Nujol) 3058-2932, 1662, 740 and 638 cm^{-1}; δ_H 3.00 (3 H, s, NMe and 6.50-7.97 (9 H, m, aromatic H).

(g) N-*Methyl*-N-*phenyl*-2-*bromobenzamide*. Colourless crystals, m.p. 51-52°C (Found: C, 57.5; H, 4.1; N, 4.5; Br, 27.3. $C_{14}H_{12}BrNO$ requires: C, 57.9; H, 4.1; N, 4.8; Br, 27.6%); υ_{max} 3056-2980, 1652, 770, 748, 732, 698, 672 and 640 cm^{-1}; δ_H 3.50 (3 H, brs, NMe), 6.90-7.73 (9 H, m, aromatic H); *m/z* 290 (M^+, 5%), 210 (M^+-Br, 22%) and 183 (100).

N-Methylation of Carboxamides

(a) N-(2-I*odophenyl)*-N-*methylacetamide*. *General procedure for methylation of carboxamides*. *N*-(2-Iodo-phenyl)acetamide (3.38 g, 12 mmol) in DMSO (10 ml) was added to a stirred suspension of sodium hydride (342 mg, 14 mmol) in DMSO (50 ml) over 20 min under nitrogen and stirred for 1 h. Methyl iodide (3.42 g, 24 mmol) was added, the reaction mixture stirred for 20 min, poured into water, and extracted with EtOAc. The organic extracts were washed with dil. hydrochloric acid and water, dried, evaporated to dryness, and the residue recrystallised from aqueous MeOH to give N-2-*(iodophenyl)*-N-*methylacetamide* (1.49 g, 45%), m.p. 60-64°C (Found: C, 39.3; H, 3.7; N, 5.0; I, 45.1. $C_9H_{10}INO$ requires: C, 39.3; H, 3.6; N, 5.1; I, 45.2%); υ_{max} (KBr): 2924, 1646, and 776 cm^{-1}; δ_H 1.80 (3 H, s, CH_3), 3.20 (3 H, s, NMe), 6.80-7.50 (3 H, m, aromatic H) and 7.70-7.90 (1 H, d, J = 8 Hz, ortho-H to iodine); *m/z* 148 (M^+-I, 100%).

(b) N-(2-*Iodophenyl)*-N-*methylbenzamide* (**10a**). (66%), m.p. 138-139°C (EtOH) (Found: C, 49.9; H, 3.6; N, 4.2; I, 38.0. $C_{14}H_{12}INO$ requires: C, 49.85; H, 3.55; N, 4.15; I, 37.7%); υ_{max} (KBr): 2950, 1628, 772, 724, and 710 cm^{-1}; δ_H 3.4 0 (3 H, s, CH_3) and 6.50-8.00 (9 H, m, aromatic H); *m/z* 210 (M^+-I, 96%), 105 (100) and 77 (48).

(c) N-(2-*Iodophenyl)*-N-*methyl*-2,3-*methylenedioxybenzamide* (**10b**). (54%), m.p. 97-97.5°C (Found: C, 47.5; H, 3.3; N, 3.7; I, 33.7. $C_{15}H_{12}INO_3$ requires: C, 47.25; H, 3.15; N, 3.65; I, 33.35%; υ_{max} (Nujol mull): 1640, 750, and 715 cm^{-1}; δ_H 3.40 (3 H, s, NMe), 5.90 (2H, s, CH_2) and 6.30-7.90 (7 H, m, aromatic H); *m/z* 252 (M^+-I, 100%).

(d) N-*Methyl*-6(5H)-*Phenanthridinone* (**11a**). (56%), m.p. 108.5°C (Found: C, 80.0; H, 5.5; N, 6.6. $C_{14}H_{11}NO$ requires: C, 80.3; H, 5.26; N, 6.6%; υ_{max} (CH_2Cl_2) 2980-2860, 1650, 770, 720, and 650 cm^{-1}; δ_H 3.75 (3 H, s, NMe), 7.05-7.75 (5 H, m, aromatic H), 8.05-8.25 (2 H, d, J = 8 Hz, aromatic H), and 8.35-8.55 (1 H, d, J = 8 Hz, aromatic H); *m/z* 209 (M^+, 100%), 178 (22), 152 (15), and 113 (10).

Synthesis of Thioamides

(a) N-(2-*Iodophenyl)thiobenzamide* (**1a**). *General procedure for the conversion of carboxamides to thioamides*: *N*-(2-Iodophenyl)benzamide (2 g, 6.2 mmol) and Lawesson's reagent (0.89 g, 4 mmol) were dissolved in de-oxygenated toluene under nitrogen and heated under reflux for 4 h. The yellow solution was cooled and evaporated to dryness. Chromatography on neutral alumina with CH_2Cl_2 as the eluent gave *N*-(2-iodophenyl)thiobenzamide (**1a**) as yellow crystals (1.18 g, 56%), m.p. 92-96°C (EtOH) (lit.[32] 96-99°C].

(b) N-(2-*Iodophenyl)thioacetamide* (**1c**). (41%), m.p. 101-102°C (Found: C, 42.1; H, 3.8; N, 6.3; I, 55.2; S, 14.1. C_8H_8INS requires: C, 42.3; H, 3.4; N, 6.1; I, 55.9; S, 14.1%); υ_{max} (Nujol) 3128, 1553, 770, and 725 cm^{-1}; δ_H 2.30, 2.80 (3 H, 2s, CH_3) and 6.90-8.30 (5 H, m, aromatic, amide H); *m/z* 150 (M^+-I, 100%).

(c) N-(2-*Iodobenzyl)thiobenzamide* (**1d**). (91%), m.p. 97-100°C (lit.[32] 97-110°C).

(d) N-(2-*Bromobenzyl)thiobenzamide* (**1e**). (82%), m.p. 87-88°C (Found: C, 55.1; H, 4.0; N, 4.5; S, 10.2. $C_{14}H_{12}BrNS$ requires: C, 54.9; H, 3.9; N, 4.55; S, 10.45%); υ_{max} (KBr): 3250, 1520, 1375, 750, and 720 cm^{-1}; δ_H 5.00 (2 H, d, J = 6 Hz, CH_2) and 7.00-8.20 (10 H, m, aromatic H); *m/z* 226 (M^+-Br, 100%).

(e) N-(2-*Iodophenyl)*-N-*methylthioacetamide*. (66%), m.p. 120-122°C (Found: C, 37.0; H, 3.5; N, 4.6; S, 11.2; I, 43.0. $C_9H_{10}INS$ requires: C, 37.1; H, 3.45; N, 4.8; S, 11.0; I, 43.65%); υ_{max} (KBr): 1486, 1462, 1438, and 766 cm^{-1}; δ_H (90 MHz) 2.30 (3 H, s, CH_3), 3.66 (3 H, s, NMe), 7.00-7.60 (3 H, m, aromatic H), and 7.90-8.16 (1 H, d, J = 8 Hz, ortho-H to iodine); *m/z* 291 (M^+, 3%) and 164 (82).

(f) N-(2-*Iodophenyl)*-N-*methylthiobenzamide* (**13a**). (50%), m.p. 140-141°C (Found: C, 47.8; H, 3.6; N, 4.1; I, 35.6; S, 8.8. $C_{14}H_{12}INS$ requires: C, 47.59; H, 3.4; N, 3.95; I, 36.0; S, 9.06%); υ_{max} (KBr): 2920, 1570, 1470, 1375, 765, and 720 cm^{-1}; δ_H (90 MHz) 3.40 and 3.80 (3 H, 2 x s, CH_3) and 6.65-8.20 (9 H, m, aromatic H); *m/z* 226 (M^+-I, 100%).

(g) N-(2-*Bromophenyl)*-N-*methylthiobenzamide* (**13b**). (43%), m.p.110-111°C (Found: C, 48.0; H, 3.4; N, 3.95; S, 9.4. $C_{14}H_{12}BrNS$ requires: C, 47.6; H, 3.4; N, 3.95; S, 9.0%); ν_{max} (Nujol) 1460, 1375, 760, and 700 cm^{-1}; δ_H 3.80 (3 H, s, CH_3) and 6.90-7.85 (9 H, m, aromatic H); *m/z* 226 (M^+-Br, 100%).

(h) N-*Methyl*-6(5H)-*thiophenanthridinone* (**14**). (25%), m.p. 194-195°C (Found: C, 74.5; H, 5.1; N, 6.2; S, 15.4. $C_{14}H_{11}NS$ requires: C, 74.6; H, 4.8; N, 6.2; S, 14.2%); ν_{max} (Nujol) 1455, 1375, 1335, 740, and 710 cm^{-1}; δ_H (60 MHz, $CDCl_3$): 4.35 (3 H, s, N-CH_3), 7.30-7.90 (5 H, m, aromatic H), 8.10-8.20 (2 H, t, J = 8 Hz, aromatic H), and 9.00-9.30 (1 H, d, J = 8 Hz, aromatic H); *m/z* 225 (M^+, 100%).

Reduction of Halogeno-Amides and -Thioamides with Bu_3SnH

General conditions for cyclisations and attempted cyclisations of halogeno-amides and -thioamides. The amide or thioamide to be reacted was dissolved in the toluene (75 ml) and de-oxygenated under a stream of dry nitrogen for 45 min. The reaction was heated to reflux and Bu_3SnH (1.1 equiv.) and AIBN (0.3 equiv.) added. (NaH or DABCO were added at this point where specified). The reaction was heated under reflux under nitrogen for 24 h. The solvent was evaporated to dryness and normally, crude products were dissolved in dry acetonitrile and washed with dry hexane to remove tributyltin residues. The products were purified by chromatography and recrystallisation. Results and alternative reaction conditions are presented in the discussion. The residue after removal of the toluene was used for HPLC analysis.

(a) *Cyclisation of* N-(2-*iodophenyl)thiobenzamide* (**1a**) *to* 2-*phenyl*-1,3-*benzothiazole* (**2a**). The above conditions were used and alternative conditions are reported in Table 1. 2-Phenyl-1,3-benzothiazole (**2a**) was purified by recrystallisation (EtOH), m.p. 115-116°C. The bromo-analogue (**1b**) was reacted as above

(b)*Cyclisation of* N-(2-*iodophenyl)thioacetamide* (**1c**) *to* 2-*methyl*-1,3-*benzothiazole* (**2b**). 2-Methyl-1,3-benzothiazole (43%) was purified by distillation, b.p. 120°C (0.7 mmHg).

(c) *Cyclisation of* N-(2-*iodobenzyl)thiobenzamide* (**1d**)*to* 2-*phenyl*-4H-1,3-*benzothiazine* (**2c**). 2-Phenyl-4*H*-1,3-benzothiazine was distilled to yield a light yellow oil (31%), b.p. 40.8-42.6°C (26 mmHg); υ_{max} (neat) 2980-2820, 1574, 1430 cm^{-1}; δ_H 4.70 (2 H, s, CH_2N), 6.90-7.40 (7 H, m, aromatic H), and 7.80-8.00 (2 H, m, aromatic H).

(d) *Cyclisation of* N-(2-*bromobenzyl)thiobenzamide* (**1e**) *to* 2-*phenyl*-4H-1,3-*benzothiazine* (**2c**). The reaction was heated for 48 h to yield 2-phenyl-4*H*-1,3-benzothiazine (**2c**) (41%).

(e) *Reduction of* N-(2-*iodophenyl)benzamide*. *N*-(2-Iodophenyl)-benzamide was reacted for 48 h and the product recrystallised (EtOH) to yield benzanilide (223 mg, 46%), m.p. 163-165°C. The IR and NMR spectra and TLC were identical with those of authentic material.The reaction was repeated several times (46-76%).

(f) *Cyclisation of* N-(2-*iodophenyl)*-N-*methylbenzamide* (**10a**) to N-*methyl*-6(5H)-*phenanthridinone* (**11a**). The product (**11a**) was purified by column chromatography on silica gel using light petroleum (b.p. 60-80°C)/EtOAc as eluent (45%). The spectroscopic data, TLC, and m.p. agreed with those of authentic material.

(g) *Cyclisation of* N-(2-*iodophenyl)*-N-*methyl*-2,3-*methylenedioxybenzamide* (**10b**) *to* N-*methyl*-2,3-*methylenedioxy*-6(5H)-*phenanthridinone* (**11b**): The crude product was recrystallised from EtOH (29%), m.p. 245-247°C (lit.[16] 244-245°C); υ_{max} (KBr) 2785, 1647, 778, 757, and 736 cm^{-1}; δ_H 3.80 (3 H, s, NMe), 6.20 (2 H, s, CH_2) and 7.20-8.20 (6 H, m, aromatic H); *m/z* 253 (M^+, 100%).

(h) *Cyclisation of* N-*methyl*-N-*phenyl*-2-*iodobenzamide* (**12**) to N-*methyl*-6(5H)-*phenanthridinone* (**11a**) The reaction mixture analysed by ^{1}H NMR using an internal standard [(**11a**) (15%) and (**12**) (38%)].

(i) *Cyclisation of* N-(2-*iodophenyl*)- and N-(2-bromophenyl)- N-*methylthiobenzamide* (**13a** and **13b**) to N-*methyl*-6(5H)-*thiophenanthridinone* (**14**). The crude products were recrystallised from light petroleum (b.p. 60-80°C)/diethyl ether/toluene to give (**14**) (29% and 13% respectively). The m.p, TLC, and IR and NMR spectra were identical to those of authentic material.

References

1. Curran, D. P. *Synthesis*, **1988**, 417-439; 489-513; Ramaiah, M. *Tetrahedron*, **1987**, *43*, 3541-3676; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: N.Y. 1986.
2. Narasimhan, N.S.; Aidhen, I.S. *Tetrahedron Lett.*, **1988**, *29*, 2987-2988.
3. Togo, H.; Kikuchi, O., *Tetrahedron Lett.*, **1988**, *29*, 4133-4134.
4. Rosa, A.M.; Prabhakar, S.; Lobo, A.M. *Tetrahedron Lett.*, **1990**, *31*, 1881-1884.
5. Bachi, M.D.; Denenmark, D. *J. Am. Chem. Soc.*, **1989**, *111*, 1886-1888.
6. Estevez, J.C.; Villaverde, M.C.; Estevez, R.J.; Castedo, L. *Tetrahedron Lett.*, **1991**, *32*, 539-530.
7. Grimshaw, J.; de Silva, A.P. *Chem. Soc. Rev.*, **1981**, *10*, 181-203.
8. Sainsbury, M., *Tetrahedron*, **1980**, *36*, 3327-3359; and references therein.
9. Grimshaw, J.; Hamilton, R.; Trocha-Grimshaw, J. *J. Chem. Soc., Perkin Trans. 1*, **1982**, 229-234.
10. Murphy, J.A.; Sherburn, M.S. *Tetrahedron Lett.*, **1990**, *31*, 1625-1628; 3495-3496.
11. Crich, D.; Quintero, L. *Chem. Rev.*, **1989**, *89*, 1413-1432.
12. Bowman, W.R.; Heaney, H.; Smith, P.H.G. *Tetrahedron Lett.*, **1982**, *23*, 5093-5096.
13. Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, ACS: Washington, 1983.
14. Hey, D.H.; Jones, G.H; Perkins, M.J. *J. Chem. Soc. C.*, **1971**,116-122.
15. Abeywickrema, A.N.; Beckwith, A.L.J.; Gerba, S. *J. Org. Chem.*, **1987**, *52*, 4072-4078.
16. Laird, E.R.; Jorgensen, W.L. *J. Org. Chem.*, **1990**, *55*, 9-27.
17. Fuganti, C. in *The Alkaloids, Volume 15*, Manske, R.H.F. Ed. Academic Press: New York, 1975, pp 83-164.
18. Highet, R.J. *J. Org. Chem.*, **1961**, *26*, 4767-4768; Prakhabar, S.; Lobo, A.M.; Marques, M.M.; Tavares, R.J. *J. Chem. Res. (S)*, **1985**, 394-395.
19. Beckwith, A.L.J.; Gara, W.B. *J. Chem. Soc., Perkin Trans. 2* , **1975**, 795-802.
20. Wright, C.; Shulkind, M.; Jones, K.; Thompson, M. *Tetrahedron Lett.*, **1987**, *28*, 6389-6390; Wright, C.; Jones, K.; Thompson, M. *J. Chem. Soc., Chem. Commun.*, **1986**, 115-116.
21. Thyagarajan, B.S.; Kharasch, N.; Lewis, H.B.; Wolf, W. *J. Chem. Soc., Chem. Commun.*, **1967**, 614-615.
22. Ori, M. *Application of Dynamic NMR Spectroscopy to Organic Chemistry*, VCH Publishers: New York, 1985, Chapter 2.
23. Burkey, T.J.; Griller, D.; Lunazzi, L.; Nazran, A.S. *J. Org. Chem.*, **1983**, *48*, 3704-3707.
24. Symons, M.C.R. *Pure and Appl. Chem.*, **1981**, *53*, 223-238; *Chemical and Biochemical Aspects of Electron Spin Resonance Spectroscopy*, Van Nostrand Reinhold: New York, 1978; pp. 101-103.
25. Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. *J. Am. Chem. Soc.*, **1984**, *106*, 7146-7150; Minisci, F.; Vismara, E.; Fontana, F. *J. Org. Chem.*, **1989**, *54*, 5224-5227.
26. Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon Press: New York. 1986; pp. 222-224.
27. Murphy, J.A.; Sherburn, M.S.; Dickinson, J.M.; Goodman, C. *J. Chem. Soc., Chem. Commun.*, **1990**, 1069-1070.
28. Grigg, R.; Sridharan, V.; Stevenson, P.; Sukurthalingam, S.; Worakun, T. *Tetrahedron*, **1990**, *46*, 4003-4018; and references therein.
29. Patel, V.F.; Pattenden, G. *J. Chem. Soc., Chem. Commun.*, **1987**, 871-872; and references therein.
30. Bunnett, J.F.; Hrutfiord, B.F. *J. Am. Chem. Soc.*, **1961**, *83*, 1694-1697.
31. Bacon, R.G.R.; Lindsay, W.S. *J. Chem. Soc.*, **1958**, 1375-1382.
32. Smith, P.H.G. *Ph.D. thesis*, Loughborough University, **1985**.