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Cyclisation of Carbinyl Radicals onto Imines and Hydrazones

W. Russell Bowman,[a]* Peter T. Stephenson,[b] Nicholas, K.Terrett,[b] and Adrian R. Young[a]

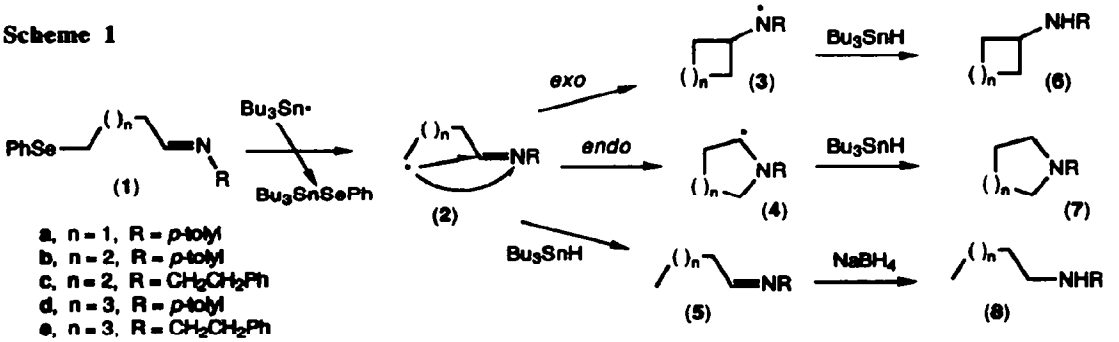
[a] Department of Chemistry, University of Technology, Loughborough, Leics. LE11 3TU, Great Britain
[b] Department of Discovery Chemistry, Pfizer Central Research, Sandwich, Kent CT13 9NJ, Great Britain

Abstract: *The regioselectivity of intramolecular addition of sp^3 carbon-centred radicals onto C=N double bonds of imines and hydrazones is influenced by the position and polarisation of the C=N bond.*

Radical cyclisation onto C-C multiple bonds[1] has been thoroughly studied in recent years, but in contrast, there has been relatively little study of cyclisation onto multiple bonds containing nitrogen atoms. Examples of radical additions to *N*-containing unsaturated bonds include azides,[2] diazenes[3] and diazirines (N=N bonds),[4] nitriles,[5] and oxime-ethers (R_2C=NOR).[6] Addition of radicals to nitrones to yield nitroxyl radicals is well known in spin-trapping techniques. However, only a few individual examples had been reported for cyclisation onto imines.[7] At the time we started our studies, a more detailed investigation of the cyclisation of aryl radicals onto imines was reported.[8] We report our initial studies on the cyclisation of sp^3 carbinyl radicals onto imines which provides a new methodology which can be applied to the synthesis of nitrogen-heterocycles.

We sought to elucidate the factors influencing the *exo/endo* cyclisation for 4 to 7-membered rings as shown in Schemes 1 and 2 and the Table. The required iminyl-alkyl radicals were generated by reaction between the respective ω-benzeneselenyl-alkylimines and Bu_3SnH.[9] The benzeneselenyl group which is readily abstracted by tributyltin radicals (S_H2 reaction) was chosen in place of halides for the studies because of the lack of reactivity with the nucleophilic amine or imine groups present in the synthetic intermediates or precursors.

Scheme 1



Scheme 2

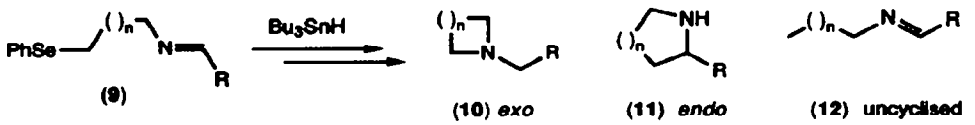


Table. Products and yields from the cyclisation of ω-benzeneselenylalkylimines using Bu_3SnH

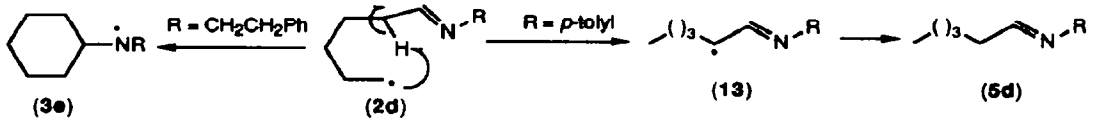
ω-benzeneselenylimine	**1a**	**1b**	**1c**	**1d**	**1e**	**9a**	**9b**	**9c**	**9d**	**9e**
exo product (%)	0	39	47	0	43	0	54	42	7	0
endo product (%)	0	0	5	0	0	0	6	18	0	0
uncyclised imine (%)[a]	0	0	0	35	0	71	0	0	40	39

[a] Determined as the amine after $NaBH_4$ reduction of the imine

The required precursors were each synthesised in three high yielding steps. The ω-benzeneselenylalkylimines were prepared by quantitative condensation[10] of the respective ω-benzeneselenylalkylamines and aldehydes or ω-benzeneselenyl-aldehydes and amines. Careful reduction ($LiAlH_4$) of ω-benzeneselenylnitriles, prepared by reaction between ω-bromonitriles and benzeneselenide,[11] gave the the required ω-benzeneselenylalkylamines. Reaction between ω-bromoesters and benzeneselenide[11] gave ω-benzeneselenylesters which were reduced with DIBAL to yield the relevant ω-benzeneselenylaldehydes.

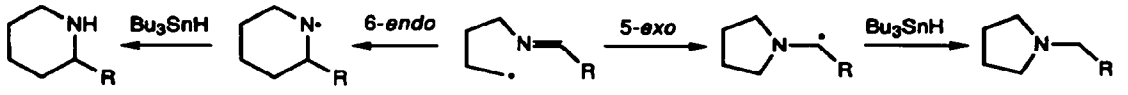
Four factors were observed to influence the cyclisations: stereoelectronic effects (*exo*/*endo*), polarisation of the imine bond, ring size, and stability of the resulting radical. In the *C*-(ω-benzeneselenyl)imines reactions (Scheme 1), 5-*exo* cyclisation onto the *C*-atom of the imine was favoured as predicted from studies of the analogous alkenes,[1] *i.e.* (**1b**) and (**1c**) gave the aminocyclopentanes, (**6b**) and (**6c**), in 39% and 47% yield respectively. Clearly the stereoelectronic effects and imine polarisation are the dominant factors and not the stability of the intermediate radicals. The nucleophilic alkyl radical prefers attack on the electropositive imine *C*-atom. While (**1b**) gave only *exo*-cyclisation, (**1c**) gave a small amount (5%) of *endo* cyclisation to yield piperidine (**7c**). The exclusive *exo*-cyclisation of (**1b**) is possibly influenced by aryl stabilisation of the intermediate anilyl radical (**3b**). In anilyl radicals, the unpaired electron rather than the lone pair overlaps most strongly with the π-electron cloud.[12] α-Aminoalkyl radicals (**4**), the intermediates for *endo* cyclisation, which are stabilised by overlap of the unpaired electron with the nitrogen lone pair of electrons,[13] do not appear to influence the course of the reaction, *i.e.* the cyclisations are not under thermodynamic control.

The competition between 6-*exo* cyclisation and 1,5-hydrogen abstraction [(**1d**) and (**1e**)] is determined by the nature of the *N*-substituent. 1,5-Hydrogen abstraction is favoured when the intermediate radical (**13**) is stabilised by conjugation to the aryl substituent [(**1d**) gave 35% uncyclised product] but not when an aliphatic substituent is present [(**1e**) gave 43% of the cyclohexylamine (**6e**) *via* (**3e**)]. The influence of the imine polarisation is not sufficient to allow 7-*endo* cyclisation. The reaction of (**1a**), as expected, gave no *endo*-cyclisation (5-*endo*) and only polymeric products were obtained. Fast ring-opening[14] of the intermediate cyclobutylaminyl radical (**3a**) prevents 4-*exo* cyclisation products for (**1a**).



(**3e**) (**2d**) (**13**) (**5d**)

6-*endo* Cyclisation is more favoured in the *N*-(ω-benzeneselenyl)imine reactions [*e.g.* (**9c**) in Scheme 2] than in the *C*-(ω-benzeneselenyl)imines reactions [*e.g.* (**1c**) in Scheme 1] indicating the influence of the imine polarisation; *e.g.* the 5-*exo*/6-*endo* ratio for (**1c**) of 0.11 rises to 0.43 for (**9c**). Again the stabilisation of the intermediate radicals is not a major factor; even though in this case the *exo*-radical (**15**) is more stable than the *endo*-radical (**14**), more *endo*-cyclisation is observed in the reactions of (**9b**) and (**9c**) than for (**1b**) and (**1c**),

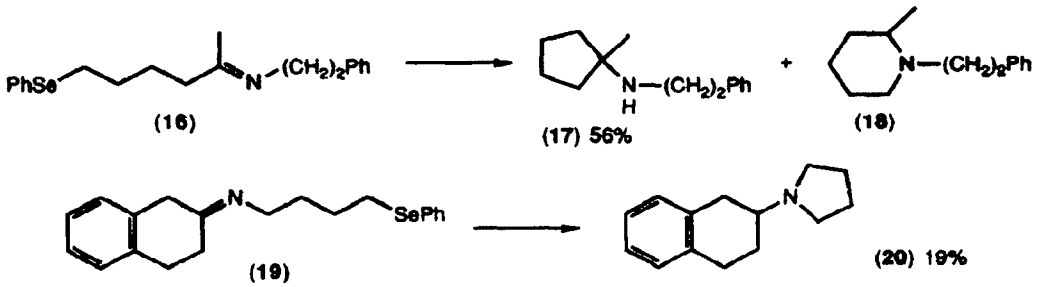


(**11b/c**) (**14**) (**15**) (**10b/c**)

i.e. the effect of the imine polarisation is dominant over the intermediate radical stability. However, the stabilisation of (**15**) may explain the lower 5-*exo*/6-*endo* ratio (0.11) for (**9b**), with aryl- as well as nitrogen-stabilisation, as compared to the *exo*-intermediate for (**9c**) (0.43). In contrast, the reactions with aryl radicals,[8] analogous to (**9b**) and (**9c**), give almost complete 6-*endo* cyclisation to yield 1,2,3,4-tetrahydroisoquinolines.

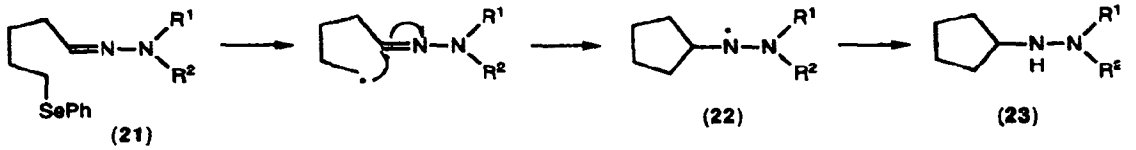
The reaction of (**9a**) gave the imine (**12a**) [isolated after reduction with $NaBH_4$ to the respective amine (71%)] which can be explained by 1,5-hydrogen abstraction of the imine α-hydrogen to yield a stable arene- and *N*-stabilised intermediate [ArC(•)=NR].[8,15] In the reactions of (**9d**) and (**9e**), 1,5-hydrogen abstraction again predominates over 6-*exo* cyclisation and the nature of the imine *C*-substituent does not appear to be important.

In order to test the scope of the synthetic application, we extended our studies to ketimines. Cyclisation of hex-5-en-1-yl radicals is hindered by substitution on the 5-position[1] and therefore cyclisation onto ketimines was not predicted to be favourable. Ketimine (**16**), the keto analogue of (**1c**), gave 56% of the 5-*exo* product (**17**) and traces of the *endo*-amine (**18**) indicating that α-substitution on the imine is not limiting. However, cyclisation of ketimine (**19**) was less successful and gave only 19% of the 5-*exo* amine (**20**), no *endo* product, and 20% of the uncyclised product.



Cyclisation of carbon-centred radicals onto hydrazones

With the success of cyclisation onto imines and the reported cyclisations with oxime-ethers,[6] the studies were extended to hydrazones. Although one study of radical cyclisation onto hydrazones (5-*exo* cyclisation onto *N*-aziridinylimines) has been reported,[16] there has been no systematic study of the use of hydrazones. A range of hydrazones (**21**) were synthesised by condensation of 5-benzeneselenylpentanal with different hydrazines and reacted with Bu_3SnH[9] under the standard conditions (Scheme 3).



a, R^1 = H, R^2 = Ph; **b**, R^1 = R^2 = Ph; **c**, R^1 = H, R^2 = COPh; **d**, R^1 = H, R^2 = $CONH_2$
Yields: (**23a**) = 18%; (**23b**) = 32%; (**23c**) = 50%; (**23d**) = 60%

Scheme 3. Cyclisation of carbon-centred radicals onto hydrazones

Only products resulting from 5-*exo* cyclisation were isolated, and no *endo*-cyclised or uncyclised products were detected. The 5-*exo* cyclisation is favoured both by the stereoelectronic effects and by stabilised hydrazyl radical intermediates (**22**). Attempts to optimise the yield of (**23a**) (18%) from (**21a**) failed; the intermediate radical (**22a**) is stable and electron-rich and therefore slow reaction with the nucleophilic Bu_3SnH is predicted. Side reactions such as disproportionation reactions to hydrazines and diazenes become likely. The formation of diazenes are supported by the observation of bright red colours during the reaction. The yield of (**23b**) was higher (32%), possibly explained by the absence of a hydrogen on the other *N*-atom of the hydrazyl

intermediate (22b). The best yields were obtained for (21c) and (21d) in which the α-position of the hydrazone is more electropositive encouraging faster intramolecular addition by the nucleophilic alkyl radicals. The intermediate hydrazyl radicals (23c) and (23d) are relatively electrophilic because of the electron withdrawing carbonyl and therefore reaction with Bu_3SnH should be fast thereby preventing side-reactions.

In summary, 5- and 6-*exo* cyclisation onto the α-C of imines proceeds well and provides a new method for generating aminyl radicals[14,17] in tandem cyclisations with suitably placed alkenes for the synthesis of nitrogen heterocycles. Synthesis of pyrrolidines by 5-*exo*-cyclisation onto the *N*-atom of imines is promising but 1,5-hydrogen abstraction prevents the synthesis of piperidines by 6-*exo* cyclisation. The results for alkyl radical cyclisation onto imines and hydrazones are generally in accord with cyclisations onto alkenes.

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9. A solution of Bu_3SnH (1.33 equiv.) and AIBN (0.33 equiv.) in toluene was added using a syringe pump to a toluene solution of the imine under an atmosphere of nitrogen over 5 h. Certain reactions were treated with $NaBH_4$ prior to workup to reduce imine products. Products were separated from tin residues by extraction with dil. hydrochloric acid. Products compositions were determined by isolation and/or by ^1H NMR spectroscopic or GLC analysis by comparison with independently prepared products.
10. The condensations to form imines were carried out using sodium sulfate for imines synthesised from aromatic aldehydes and all others by use of a Dean-Stark water separator or molecular sieves with toluene as solvent. Although most imines were used directly without purification, characterisation was carried out in each case by TLC and NMR and IR spectroscopy.
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