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Acyl radical cyclisation onto pyrroles

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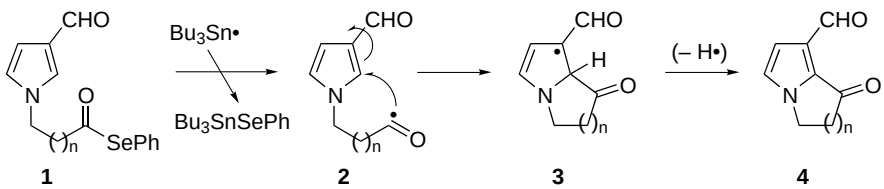
Abstract—Synthetically useful [1,2-*a*]-fused pyrroles, e.g. 2,3-dihydro-1*H*-pyrrolizidines substituted in the 1- and 7-positions, have been generated by acyl radical cyclisation onto pyrroles using *N*-(ω-acyl)-radicals generated from acyl-selenide precursors. The protocol does not require high pressures of CO. Mechanistic studies indicate the key role of azo radical initiators as oxidants of the intermediate π-radicals.

The synthesis of nitrogen heterocycles using radical intermediates has become a common protocol in modern organic chemistry.[1] One of the protocols that has proved useful is the Bu_3SnH and AIBN [**a**zobisiso**b**utyro**n**itrile, or by IUPAC nomenclature, 2-(1-cyano-1-methyl-ethyl-azo)-2-methyl-propio-nitrile] mediated oxidative cyclisation of alkyl or aryl radicals onto heteroarenes. Our earlier studies have reported the cyclisation of *N*-(ω-alkyl)-radicals onto pyrroles and imidazoles with electron withdrawing groups.[2] Similar cyclisation protocols onto indoles[3–5] pyrroles,[3,6] pyridinium salts,[7,8] pyridines[9] and 1,2,3-triazoles[10] have also been reported. Normally in Bu_3SnH mediated reactions reductive cyclisation takes place, whereas in these reactions there is also an oxidative step resulting in rearomatisation. The mechanism of this oxidative step is not clear but the most recent evidence indicates hydrogen abstraction from a π-radical intermediate.[11]

These alkylation reactions can be considered to be the *umpolung* of Friedel–Crafts alkylation, i.e. alkylation of electron-deficient heteroarenes using nucleophilic radicals as opposed to Friedel–Crafts alkylation of electron rich heteroarenes using cationic electrophiles. The logical extension of this work was to study radical cyclisation onto heteroarenes using acyl radicals, i.e. the *umpolung* of Friedel–Crafts acylation. Acyl radicals are also nucleophilic[12] and similar results were predicted. Acyl radicals have been extensively studied, both mechanistically and in synthesis.[12] During our study, related research was published; the cyclisation of acyl radicals, generated by carbon monoxide addition under high pressure onto intermediate *N*-(ω-alkyl)-radicals, onto pyrroles and indoles.[13] The experimental drawback of this methodology is the requirement for CO at 80 atm in the reactions. In this paper we report our initial results showing that cyclisation of acyl radicals can be carried out in high yields from acyl selenide precursors without using high pressures of CO. In this paper we report our initial studies to develop a facile protocol for the synthesis of [1,2-*a*]-fused pyrroles, substituted in both rings, using tributyltin hydride (Bu_3SnH) (Scheme 1).



Scheme 1. Cyclisation of *N*-(ω-acyl) radicals. **a**, $n=1$; **b**, $n=2$; **c**, $n=3$.

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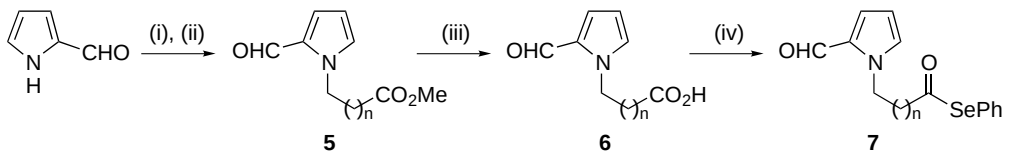
Acyl selenides have proved to be useful precursors of acyl radicals[12,14] and appeared suitable for our putative protocol. 1*H*-Pyrrole-2-carbaldehyde was used to develop the procedure for the synthesis of radical precursors **7** (**a**, $n=1$; **b**, $n=2$; **c**, $n=3$). Standard alkylation with ω-bromo esters gave high yields and purity using DMF as a solvent and lower yields when THF was used. The esters **5** were hydrolysed without purification to yield the required carboxylic acids **6**. Both diphenyl diselenide and *N*-(phenylselenyl)phthalimide (NPSP)[15] were used for the selenation, but the latter gave cleaner reactions.

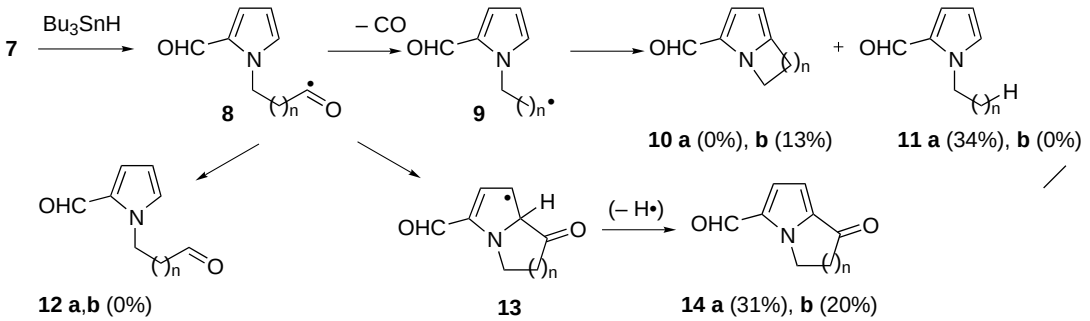
The cyclisations were initially studied using 'normal' conditions for Bu_3SnH mediated oxidative radical reactions [Bu_3SnH (2.2 equiv., addition by syringe pump over 5–6 h), AIBN or AMBN [**a**zobis**m**ethyliso**b**utyro**n**itrile, or by IUPAC nomenclature, 2-(1-cyano-1-methyl-propylazo)-2-methyl-butyronitrile] (2.0 equiv., added portion-wise every 30 min), cyclohexane, reflux under N_2] (Scheme 3). The expected cyclised ketones **14** were obtained in each case in moderate yield along with a mixture of other products. Significant decarbonylation took place from the acyl radical intermediates **8a**,**b** to yield the alkyl radical intermediates **9a**,**b**. The precursor **7b** gave cyclisation to the known pyrrolizidine **10b**[2] and **7a** gave reduction to **11a**.[2] Alternative conditions were determined because these reactions were not satisfactory for synthesis.

Decarbonylation is an exothermic process and the rate of CO loss (ca. 2×10^2 M^{-1} s^{-1} at 80°C to yield primary alkyl radicals) is much slower than CO addition (6.3×10^5 M^{-1} s^{-1} at 80°C for primary alkyl radicals).[12] Therefore, we reasoned that an atmospheric pressure of CO may be sufficient to prevent decarbonylation and nitrogen was replaced with CO using the free-thaw technique to ensure that CO was the only gas present. The atmosphere of CO, together with the use of a two-phase solvent system of acetonitrile and cyclohexane and heating at 80°C, gave the best yields of the required cyclised products **14** with only traces of products from CO-loss and reduction. The precursors **7a**–**c** and AIBN are soluble in acetonitrile and not cyclohexane, whereas the Bu_3SnH is soluble in the cyclohexane thereby keeping a low concentration in the acetonitrile which facilitates cyclisation over reduction. The yields were as follows: **14a** (55%, 2 h syringe pump addition of reagents) and **14c** [31%, reagents added in two portions at the beginning and after 4 h and sealed in a Schlenk tube and heated at 80°C for a total of 8 h). In the latter reaction the acyl radical intermediate **8c** was also reduced to the uncyclised aldehyde **12c** (46%).

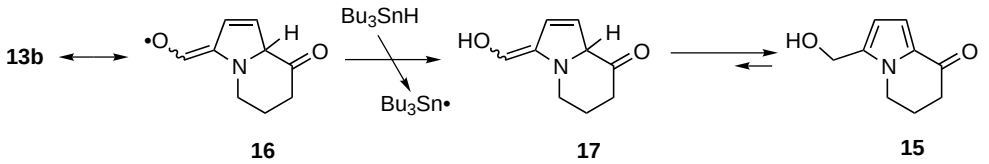
Precursor **7b** gave a reduced product, 3-(hydroxymethyl)-5,6,7,8-tetrahydroindolizin-8-one **15** (65%, all reagents added at the beginning of the reaction and sealed in a Schlenk tube). The formation of a reduced product **15** from **7b** is unusual and suggests a 'normal' reductive Bu_3SnH reaction as shown in Scheme 4. The product **15** was not present in the crude reaction mixture and only formed after extraction of products in dilute hydrochloric acid indicating that a basic product was formed in the reaction, e.g. **17**. Rapid tautomerism would yield the more stable pyrrole **15**. A possible explanation is that the *O*-centred canonical form **16** has an electrophilic centre, which reacts sufficiently fast with the nucleophilic Bu_3SnH to give a reduced product such as **17**. The six-membered ring cyclisation is under much less strain than the five- and seven-membered ring cyclisation and possibly facilitates this different delocalisation of the unpaired electron in the π-radical (**13b**/**16**).



Scheme 2. Synthesis of 1*H*-pyrrole-2-carbaldehyde radical precursors. **a**, $n=1$; **b**, $n=2$; **c**, $n=3$. (i) NaH, dry DMF, 30 min, room temperature; (ii) $BrCH_2(CH_2)_nCO_2Me$, 2 h at 0°C then 24 h at room temperature; (iii) LiOH, $EtOH/H_2O$, 4 h, room temperature: **6a**, $n=1$ (73%); **6b**, $n=2$ (95%); **6c**, $n=3$ (100%); (iv) Bu_3P (2.5 equiv.), CH_2Cl_2, room temperature: $(PhSe)_2$ (1.5 equiv.), 24 h: **7a**, $n=1$ (59%) and **7b**, $n=2$ (57%); NPSP (1.5 equiv.), 6 h: **7c**, $n=3$ (63%).



Scheme 3. Cyclisation of pyrrole-2-carbaldehyde radical precursors **7** using 'normal' Bu_3SnH conditions.



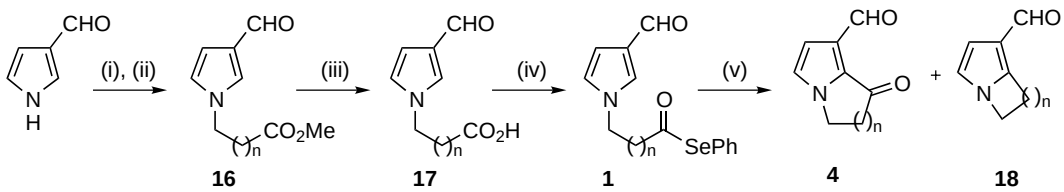
Scheme 4. Cyclisation of pyrrole-2-carbaldehyde radical precursors **7** using a CO atmosphere.

The logic of our results suggests that the protocol could be used to add CO to an intermediate alkyl radical **9a** to yield the acyl radical **8a** with subsequent cyclisation to **14a**. This reaction has been reported in the literature but with an 80 atm pressure of CO.[13] A reaction was attempted using our protocol with 1-(2-bromoethyl)-1*H*-pyrrole-2-carbaldehyde but gave only 1-ethyl-1*H*-pyrrole-2-carbaldehyde **11a** (32%) with only traces of cyclisation. Clearly the high pressure of CO is required for the carbonylation of **9a** even though favoured thermodynamically.

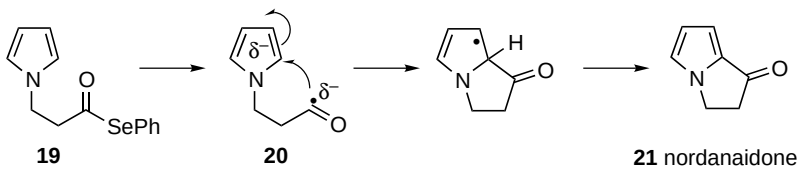
The analogous 1*H*-pyrrole-3-carbaldehyde reactions were also investigated with a view to the synthesis of target pyrrolizidine natural products. 1*H*-Pyrrole-3-carbaldehyde was synthesised from *N*-(triisopropylsilyl)-pyrrole using a Vilsmeier reaction with oxalyl chloride and DMF in 65% yield.[16] The synthesis of the precursors was carried out as for the corresponding 1*H*-pyrrole-2-carbaldehydes (Scheme 5). The acyl selenides were formed in high yield but were unstable to chromatography resulting in lower yields than for the corresponding pyrrole-2-carbaldehydes. The cyclisations were carried out using the CO atmosphere and two-phase solution protocol to give the predicted cyclised compounds **4a**–**c** in moderate yields. No reduced uncyclised aldehydes [1-(3-oxoalkyl)-1*H*-pyrrole-3-carbaldehydes] were formed in any of the reactions but 1-ethyl-1*H*-pyrrole-3-carbaldehyde (17%) was formed in the reaction of **1a**. A cyclised product **18c** ($n=2$) (54%), resulting from decarbonylation, was isolated for the reaction of **1c**. The six-membered ring cyclisation from **1b** to yield **4b** did not yield any products resulting from decarbonylation showing that the rate of cyclisation (**2b** to **3b**) is faster than the corresponding rates for the five- and seven-membered ring cyclisations, i.e. cyclisation of **2b** to **3b** is faster than loss of CO under the reaction conditions. Five-membered ring cyclisation onto heteroarenes is known to be strained.[2] The cyclisations proceeded with complete regioselectivity to the 2-position on the pyrrole. The structures of **4b** and **4c** have been confirmed by X-ray crystallography.

Our synthetic protocol has been used to prepare a natural product pyrrolizine, which is a pheromone from the Lepidoptera family, Danainae genus. The synthesis of other pyrrolizidine natural products is underway. We tested whether cyclisation would take place without an electron withdrawing group present on the pyrrole ring in order to prepare nordanaidone **21**.[17] The radical precursor **19** was synthesised using the methods in Scheme 2 and reacted using our protocol to yield nordanaidone **21** (23%, 16% from pyrrole) (Scheme 6). Although the yield was low, cyclisation of the nucleophilic acyl radical **20** onto an electron rich pyrrole ring is possible.

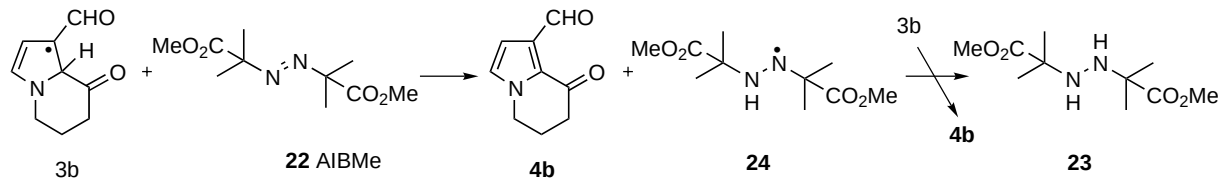
The mechanism of cyclisation is shown in Schemes 1 and 3. S_H2 Abstraction of the selenyl group with $Bu_3Sn^\bullet$ radicals to form acyl radicals **2** (or **8**) and cyclisation to the π-radical intermediates **3** (or **13**) is



Scheme 5. Synthesis and cyclisation of pyrrole-3-carbaldehyde radical precursors. (i) NaH, DMF; (ii) $BrCH_2(CH_2)_nCO_2Me$; (iii) LiOH, $EtOH/H_2O$: **17a**, $n=1$ (69%); **17b**, $n=2$ (90%); **17c**, $n=3$ (89%); (iv) Bu_3P, CH_2Cl_2, NPSP: **1a**, $n=1$ (40%); **1b**, $n=2$ (40%); **1c**, $n=3$ (35%); (v) Bu_3SnH (1.8 equiv.) in a solution of cyclohexane was added by syringe pump over 7 h and AIBN (for **1a**) or AIBMe (for **1b**,**c**) (1.8 equiv.) added portion-wise over 5 h under an atmosphere of CO to a solution of **1** in acetonitrile under reflux: **4a**, $n=1$ (32%); **4b**, $n=2$ (50%); **4c**, $n=3$ (38%).



Scheme 6. Synthesis of the pyrrolizine insect pheromone, nordanaidone.



Scheme 7. Role of 'initiator' in the oxidative step of the oxidative cyclisation. Bu_3SnH (1.5 equiv.) and AIBMe (2.0 equiv.) were added by syringe pump to a solution of **1b** under reflux and an atmosphere of CO over 5 h and refluxed for further 3 h.

clear cut. The mechanism of rearomatisation is still unclear and is discussed in Ref. 11. In the Bu_3SnH mediated oxidative cyclisations reported in the literature, greater than one equivalent of AIBN is required suggesting that AIBN is involved with a H-abstraction mechanism for this step. Azo compounds are known to act as oxidants and therefore dihydro-AIBN would be expected as a product, but is unstable to the reaction conditions and cannot be isolated. Therefore, in initial studies, AIBMe **22** [azobisisobutyrate methyl ester, or by IUPAC nomenclature, 2-(1-methoxycarbonyl-1-methyl-ethylazo)-2-methyl-propionic acid methyl ester] was used (Scheme 7). Cyclisation of **1b** gave the cyclised product **4b** (30%) and dihydro-AIBMe **23** (17%) (analysis by ^1H NMR spectroscopy using an internal standard) indicating that AIBMe is responsible for the oxidative step. The relative yields indicate the intermediate radical **24** oxidises a second equivalent of the π-radical intermediate **3b** to **4b**. Alternatively, **24** is reduced by Bu_3SnH to complete a chain reaction by generating $Bu_3Sn^{\bullet}$ radicals.

The products and yields (e.g. cyclisation of **13b** to **14b** and **15**) differ depending on the conditions used, e.g. the use of syringe pump addition or sealed tubes, rate of Bu_3SnH addition, presence or absence of CO and the amount of radical initiator (or oxidant). Further study is underway to optimise reaction conditions, determine the mechanism and to develop the protocol for natural product synthesis.

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