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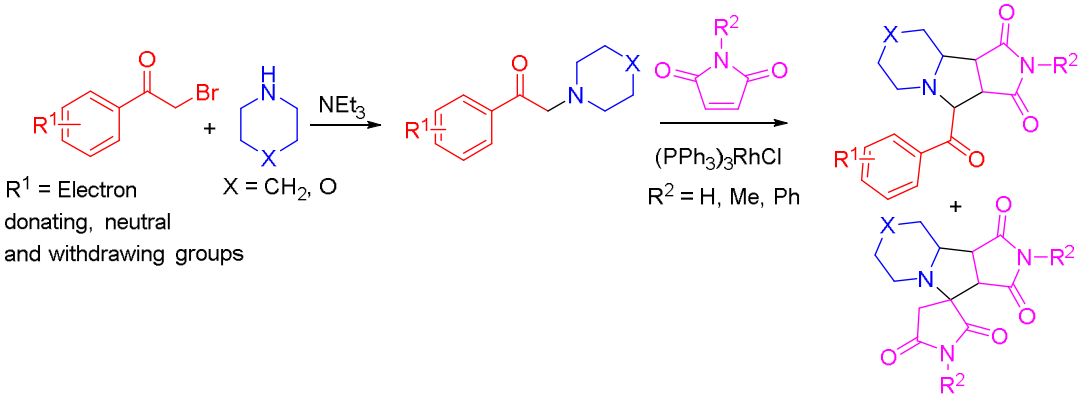

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ABSTRACT

A three component rhodium-catalysed dehydrogenation reaction has been used for the synthesis of fused and spiro-heterocycles. The reaction proceeds in good yields with the formation of three new bonds and four stereocentres

Indolizidines are important heterocyclic structural motifs and form the backbone of naturally abundant bioactive compounds possessing a wide range of medicinal properties such as anticancer,[1] treatment for thrombotic disease,[2] anti-inflammatory and antimicrobial[3] (Fig. 1).

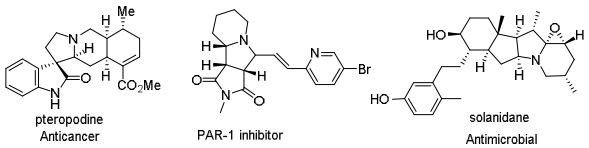

Figure 1

Figure 1. Indolizidines bioactive compounds

It is critical to the drug discovery process that synthetic chemists develop new methods for the formation of indolizidine heterocycles to increase their molecular complexity, whilst at the same time reducing the need for numerous reaction steps, reagents, solvent use, time and energy.[4] In recent years, the catalytic dehydrogenation of tertiary amines has emerged as a novel synthetic method to generate heterocyclic scaffolds. Functionalisation of sp^3 C-H bonds, adjacent to the nitrogen atom, can be achieved utilising transition metal catalysts such as Ru,[5] Rh[6] and V[7] with cooxidants to generate iminium ion species, which in turn react with various nucleophiles.[8]

Liang *et al.* have reported the platinum catalysed Michael addition cyclisation reaction of *N*-aryl piperidines with nitrovinyl phenols for the synthesis of heterocycles whilst Xiao *et al.* have reported the iridium catalysed intramolecular dehydrogenative and dehydrative cross coupling of tertiary

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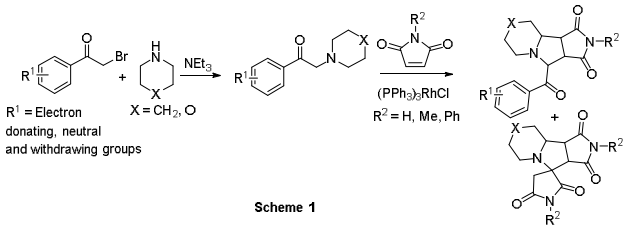
amines and ketones.[9-10] Recently Maycock *et al.* have reported the dehydrogenation of tertiary amines using a copper catalyst.[11] Additionally, we have been involved in generating azomethine ylides *via* catalytic dehydrogenation of tertiary benzylic amines utilising palladium black.[12]

In this communication we report a novel one pot, three component rhodium catalysed dehydrogenation/1,3-dipolar cycloaddition reaction utilising piperidine or morpholine to generate fused and spiro- heterocycles proceeding with the formation of three new bonds and four stereocentres (Scheme 1).

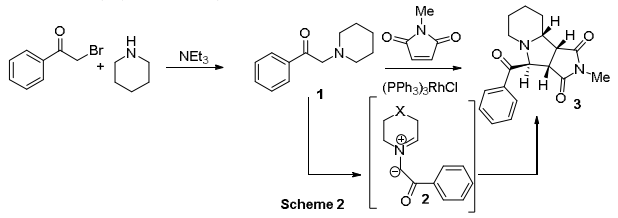


Scheme 1

We initially surveyed a range of catalysts based on Pd, Ru, Rh and identified $Rh(PPh_3)_3Cl$ as an effective catalyst for this transformation.[13]

Initially, we carried out the model reaction of 2-bromoacetophenone (1 mmol) with piperidine (1 mmol) and triethylamine (1 mmol) in toluene (20 mL) at room temperature. When alkylation was complete (TLC), *N*-methylmaleimide (2 mmol) and $(PPh_3)_3RhCl$ (10 mol%) were added and the reaction heated at 110 °C for 16 h to afford the fused ring cycloadduct **3** in

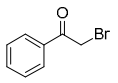
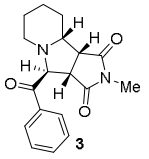
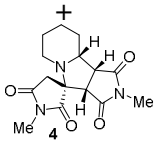
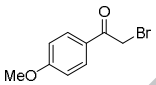
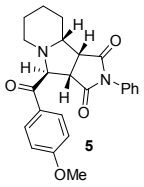
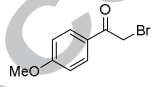
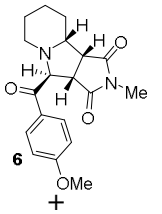
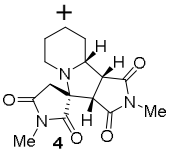
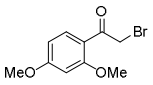
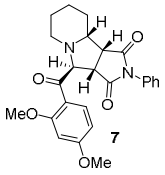
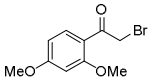
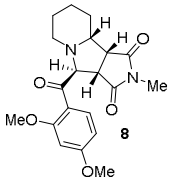
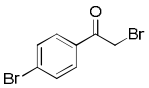
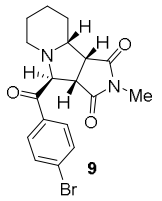
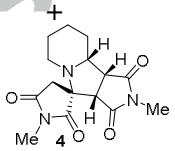
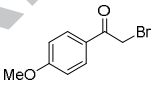
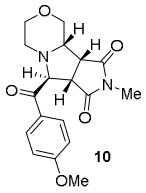
46% yield along with spirocyclic cycloadduct **4** in 44% yield. The relative stereochemistry of cycloadducts **3** and **4** were assigned using n.O.e studies (see ESI). The cycloaddition reaction was stereoselective and occurred *via* an *endo* transition state of the *anti* dipole **2** (with respect to the piperidine ring and maleimide) (Scheme 2).



Scheme 2

Two equivalents of maleimide were used to regenerate the active rhodium catalyst by acting as a recipient for the hydrogen removed from **1** during the dehydrogenation process. Dehydrogenation resulted in the stereoselective formation of **2**. Next, we explored the effects of substitution on the benzene ring of 2-bromoacetophenone during the multicomponent reaction. Thus, electron donating groups resulted in good yields of the fused ring cycloadducts (Table 1 entries 2-5). However, using an electron withdrawing group *e.g.* 2,4'-dibromoacetophenone resulted in low yield of the fused ring cycloadduct (Table 1 entry 6).

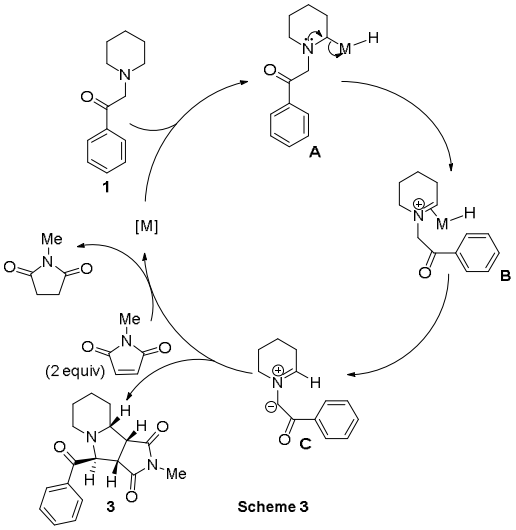
Table 1. Rhodium catalysed three component cycloaddition cascade reaction using piperidine and morpholine

Entry	Alkylbromide	Product	Yield (%)[a,b]
1		 **3** +  **4**	46 + 44
2		 **5**	51
3		 **6** +  **4**	61 + 37
4		 **7**	50
5		 **8**	55
6		 **9** +  **4**	35 + 40
7		 **10**	45

[a]Isolated yield. [b]Amine (1 mmol), bromide (1 mmol), triethylamine (1 mmol), toluene, room temperature followed by the addition of dipolarophile (2 mmol), Wilkinson catalyst (10 mol%), 110 °C, overnight.

Spirocycle formation was not observed when *N*-phenylmaleimide was used as a dipolarophile (Table 1, entries 2 and 4). Only fused-ring cycloadducts **5**, **7** and *N*-phenyl succinimide were isolated indicating either the reduction of *N*-phenylmaleimide or cycloaddition occurred faster than fragmentation of the iminium ion **B** to generate 1-piperideine (Scheme 5). In the case of Entry 5 only cycloadduct **8** together with *N*-methyl succinimide and 2'4' dimethoxyacetophenone were isolated.

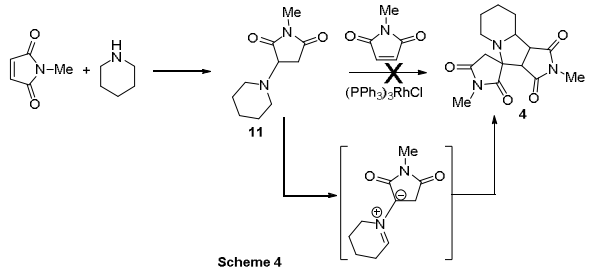
The proposed mechanism for the formation of the fused ring cycloadduct is shown in Scheme 3.



Scheme 3

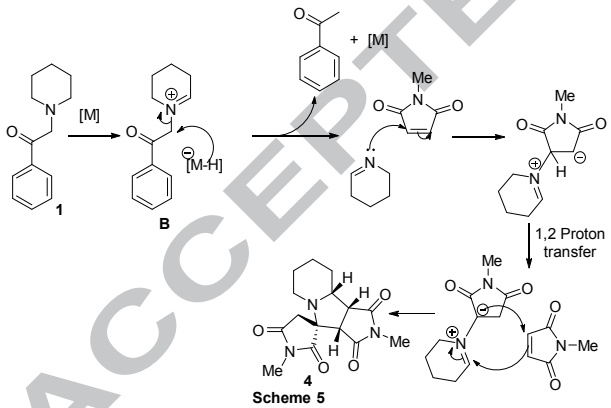
Coordination of rhodium to the nitrogen atom followed by insertion into the α CH bond generates organometallic species **A**. Iminium complex **B** then undergoes deprotonation furnishing the 1,3-dipole **C** which undergoes the cycloaddition reaction with maleimide.[10,14]

We further probed the formation of spirocycle **4**. Initially it was thought that spirocyclic product **4** could arise from the Michael addition of piperidine with *N*-methylmalemide followed by rhodium catalysed cycloaddition with *N*-methylmalemide (Scheme 4). To test this hypothesis piperidine (1 mmol) and *N*-methylmalemide (1 mmol) were reacted in toluene (15 ml) for 16 hours to produce Michael product **11**. *N*-methylmalemide (2 mmol), triethylamine (10 mol%) and $RhCl(PPh_3)_3$ (10 mol%) were then added to the reaction vessel and heated to 110˚C for a further 16 hours which failed to provide the spirocyclic cycloadduct **4.** Only staring materials were recovered, probably due to strong chelation between the piperidine nitrogen and the imide carbonyl group to rhodium.



Scheme 4

Another proposed mechanism for the formation of spirocyclic cycloadduct **4** is shown in Scheme 5. At this stage, it must be emphasised that the proposed mechanism is merely tentative and is the subject of ongoing research.



Scheme 5

Metal catalysed insertion into the α–CH bond generates the iminium ion species **B** and metal hydride. The metal hydride can act as a nucleophile to produce acetophenone and 1-piperideine. 1-Piperideine then undergoes Michael addition with *N*-methyl maleimide to form a zwitterionic species which undergoes 1,2-proton transfer to generate the 1,3-dipole which reacts with *N*-methyl maleimide to produce spirocyclic cycloadduct **4**. 1-Piperideine could also arise *via* the metal catalysed dehydrogenation of piperidine. However, this possibility was ruled out by using preformed staring material **1** in the above process. Further evidence to support the above mechanism was the isolation of acetophenone during the above process (Scheme 5).

In summary we have successfully carried out a one-pot, three component rhodium catalysed dehydrogenation/1,3-dipolar cycloaddition reaction to form fused ring heterocycles in good yields.

Acknowledgments

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