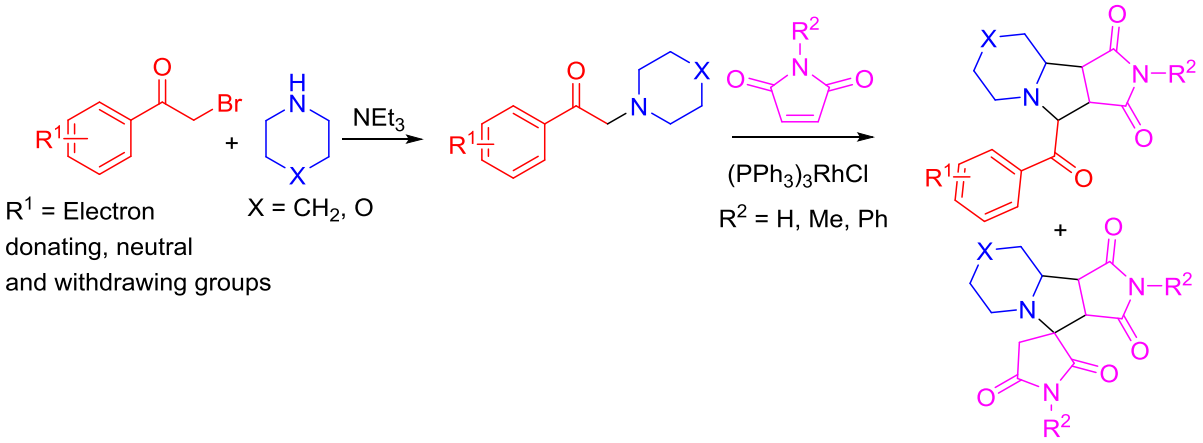
Article:
Allison, M and Sridharan, V (2015) One pot rhodium catalysed three component dehydrogenation route to fused and spiro-heterocycles. Tetrahedron Letters, 56 (47). 6551 - 6555. ISSN 0040-4039

https://doi.org/10.1016/j.tetlet.2015.10.007

One pot rhodium catalysed three component dehydrogenation route to fused and spiro - heterocycles

Matthew Allison and Visuvanathar Sridharan*



Tetrahedron Letters
journal homepage: www.elsevier.com

One pot rhodium catalysed three component dehydrogenation route to fused and spiro - heterocycles

Matthew Allison and Visuvanathar Sridharan*

School of Chemistry, University of Leeds, LS2 9JT , UK

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Rhodium
Dehydrogenation
1,3 Dipolar Cycloaddition
Heterocycles
Multicomponent Reaction

ABSTRACT

A three component rhodium-catalysed dehydrogenation reaction has been used for the synthesis of fused and spiro-heterocycles proceeding in good yields with the formation of three new bonds and four stereo centres

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).

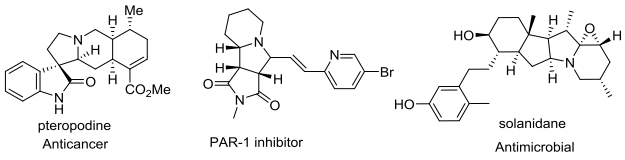
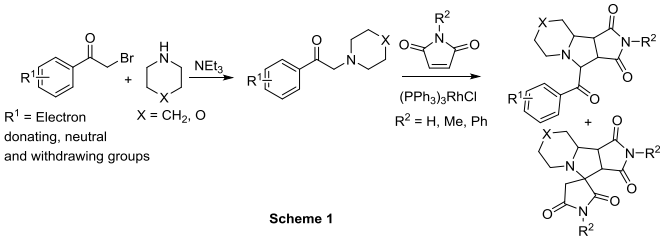


Figure 1

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 an iridium catalysed intramolecular dehydrogenative and dehydartive cross coupling of tertiary amines and ketones.[9-10] Recently Maycock et al. have reported the dehydrogenation of tertiary amines using a copper catalyst.[11] 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).



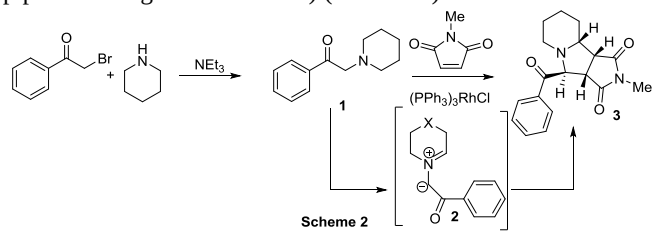
Scheme 1

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 a model e 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 ^oC for 16 h which afforded the fused ring cycloadduct **3** in 46% yield together along with spirocyclic cycloadduct **4** in 44% yield. The relative stereochemistry of

* Crossponding Author: V.Sridharan@leeds.ac.uk; Tel +44-1133436520

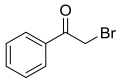
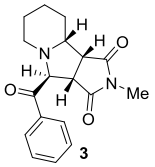
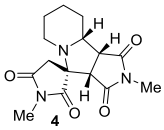
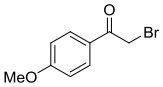
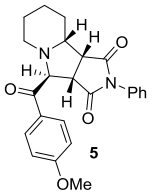
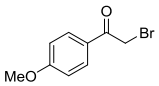
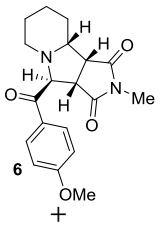
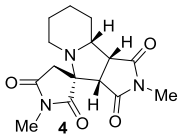
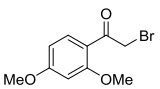
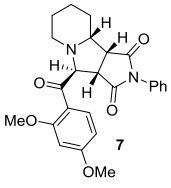
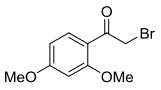
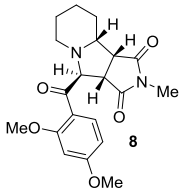
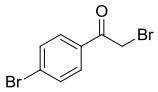
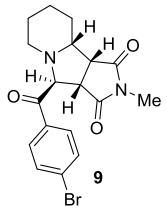
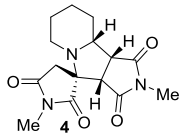
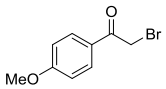
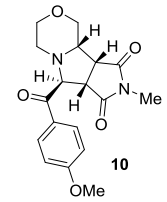
cycloadducts **3** and **4** were assigned using n.O.e studies (see ESI). The cycloaddition was stereoselective and occurred via an endo transition state of the anti dipole **2** (with respect to the piperidine ring and maleimide) (Scheme 2).



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 results in 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).

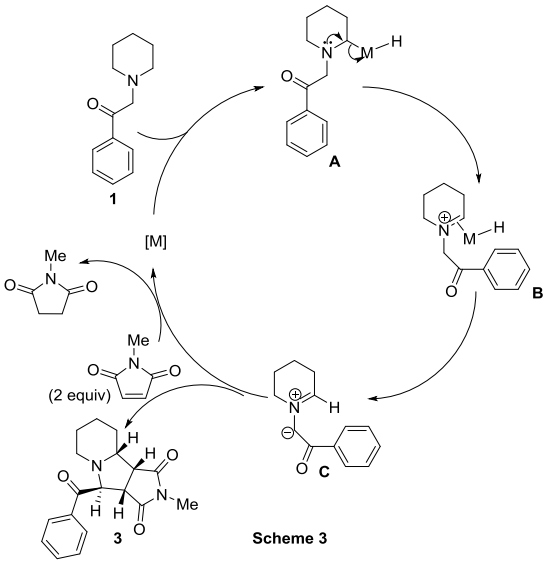
Table1. Rhodium catalysed three component cycloaddition cascade reaction using piperidine and morpholine

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

a.Isolated yield. b. Amine (1 mmol), bromide (1 mmol) and triethylamine (1 mmol) in toluene at room temperature followed by addition of dipolarophile (2 mmol) and Wilkinson catalyst (10 mol%) at 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 reduction of N-phenylmaleimide or cycloaddition occurring faster than the fragmentation of the iminium ion **B** to generate 1-piperideine (Scheme 5). In the case of (Table 1, entry 5) only cycloadduct **8** together with N-methyl succinimide and 2'4' dimethoxyacetophenone were isolated.

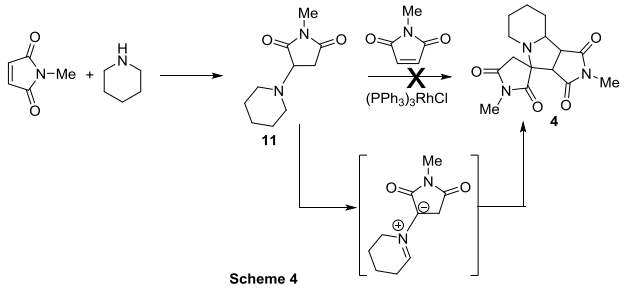
Proposed mechanism for the formation of the fused ring cycloadduct is shown in Scheme 3.



Scheme 3

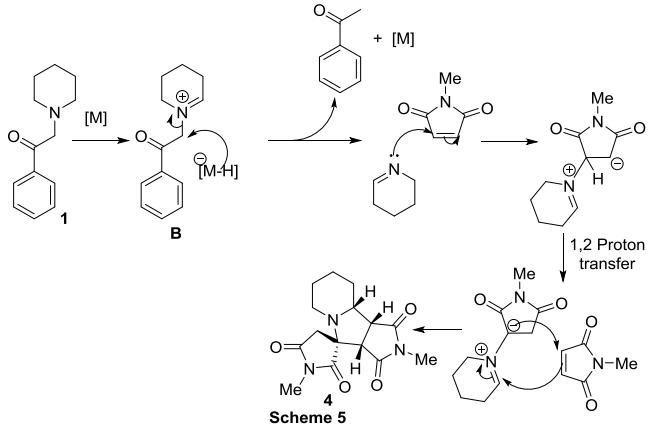
Coordination of the rhodium to the nitrogen atom followed by insertion into the α CH bond generates organometallic species **A**. Iminium complex **B** then undergoes deprotonation furnishing the 1,3-dipole **C** which undergoes the cycloaddition reaction with maleimide.[10,14]

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 the 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 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 reactions to form fused ring heterocycles in good yields.

Acknowledgments

We thank Leeds University for support.

Notes and references

1 Zhao, Y.; Liu, L.; Sun, W.; Lu, J.; McEachern, D.; Li, X.; Yu, S.; Bernard, D.; Ochsenbein, P.;. Ferey, V.; Carry, J. C.: .Deschamps, J. R.; Sun, D.: Wang, S. J. Am. Chem. Soc. **2013**, 135, 7223-7234.

2 Schoenafinger, K.; Steinhagen, H.; Scheiper, B.; Heinelt, U.; Wehner, V.; Herrmann, M. PCT Int. Appl. **2010**, 65pp, CODEN:PIXXD2; WO2011128421

3 Torres, M. C. M.; Pinto, F. L.; Braz-Filho, R.; Silveira, E.R.; Pessoa, O. L. P.; Bezerra Jorge, R. J.; Ximenes, R. M.; Monteiro, H. S. A.; Evangelista, J. S. A. M.; Diz-Filho, E. B.S.; Toyama,M. H. J. Nat. Prod. **2011**, 74, 2168-2173.

4 Tietze, L. F. Chem. Rev. **1996**, 96, 115-136.

5 (a) Murahashi, S. I.; Zhang, D., Chem. Soc. Rev., **2008**, 37, 1490-1501; (b) Rueping, M.; Vila, C.; Koenigs, R. M.; Poscharny, K.; Fabry, N. D. C. Chem. Commun. **2011**, **47**, 2360-2362; (c) Freeman, D. B.; Furst, L.; Condie, A. G.; Stephenson, C. R. J. Org. Lett., **2012**, 14, 94-97.

6 Catino, A. J.; Nichols, J. M.; Nettles, B. J.; Doyle, M. P. J. Am. Chem. Soc. **2006**, 128, 5648-5649.

7 a) Singhal, S.; Jain, S. L.; Sain, B. Chem. Commun. **2009**, 2371-2372; (b) Sud, A.; Sureshkumar, D.; Klussmann, M. Chem. Commun. **2009**, 3169-3171; (c) Boess, E.; Sureshkumar, D.; Sud, A.; Wirtz, C.; Fares, C.; Klussmann, M. J. Am. Chem. Soc. **2011**, 133, 8106-8109.

8 (a) Campos, K. R. Chem. Soc. Rev. **2007**, 36, 1069-1084; (b) Jones, K.M.; Klussmann, M. Synlett **2012**, 23, 159-162; (c) Yeung, C. S.; Dong, V. M. Chem. Rev. **2011**, 111 , 1215-1292; (d) Blacker, A. J.; Sitrling, M. J.; Page, M. I. Org. Process Res. Dev. **2007**, 11, 642-648; (e) Hollmann, D.; Bain, S.; Tillack, A.; Beller, M., Angew. Chem. Int. Ed. **2007**, 46, 8291-8294.

9 Xai,X. F.; Shu, X. Z.; Ji, K.G.; Yang, Y. F.; Shaukat, A.; Liu, X. Y.; Liang, Y. M. J. Org. Chem. **2010**, **75**, 2893-2902.

10 Nie, S. Z.; Sun, X.; Wei, W. T.; Zhang, X. J.; Yan, M.; Xiao, J. L. Org. Lett. **2013**, 15, 2394-2397.

11 Deb, M. L.; Dey, S. S.; Bento, I.; Barros, M. T.; Maycock,C. D. Angew. Chem. Int. Ed. **2013**, 52**,** 9791-.

12 Grigg,R.; Somasundrem, A.; Sridharan, V. Synlett **2009**, **1**, 97-99.

13 (a) Gorman, R. M.; Little, M. A.; Morris, J. A.; Sridharan, V. Chem. Commun. **2012**, 48, 9537-9539; (b) Windle, J.; Allison, M.; Shephered, H.; Sridharan, V. RSC Adv. **2014**, 4, 2624-2627.

14 (a) Grigg, R.; Heaney, F.; Idle, J.; Somasundram, A. Tetrahedron Letters **1990**, 31 , 2767-2770; (b) Anguille, S.; Brunet, J. J.; Chu, N. C.; Diallo, O.; Pages, C.; Vincendeau, S. Organometallics **2006**, 25, 2943-2948.