COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Novel synthesis of fused isoxazolidines *via* a palladium catalysed allene insertion–intramolecular 1,3-dipolar cycloaddition cascade reaction

Tajassas Aftab,[a] Ronald Grigg,*[a] Mark Ladlow,[b] Visuvanathar Sridharan[a] and Mark Thornton-Pett[a]

[a] *Molecular Innovation, Diversity and Automated Synthesis (MIDAS) Centre, School of Chemistry, Leeds University, Leeds, UK LS2 9JT*

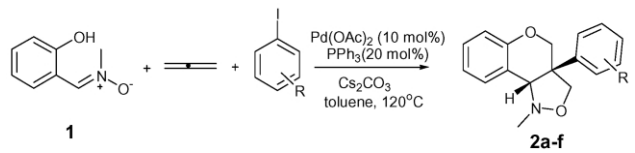
[b] *GlaxoSmithkline, Cambridge Chemistry Unit, Lensfield Road, Cambridge, UK CB2 1EW*

Received (in Cambridge, UK) 27th May 2002, Accepted 2nd July 2002
First published as an Advance Article on the web 11th July 2002

A one pot, three component palladium catalysed allenation of aryl iodides, in combination with a nitrone cycloaddition, leads to formation of fused isoxazolidines, creating two rings, two stereocentres and one tetrasubstituted carbon centre.

The construction of isoxazolidines[1] by 1,3-dipolar cycloaddition (1,3-DC) reactions between nitrones and alkenes, has been used by numerous groups[2] in the total synthesis of alkaloids and other nitrogen containing natural products. As a result of the labile nature of the N–O bond under mildly reducing conditions,[3] isoxazolidines provide an easy entry to a variety of interesting 1,3-difunctional aminoalcohols.

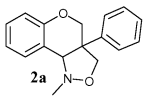
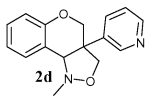
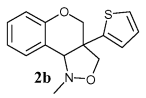
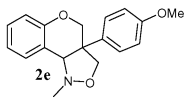
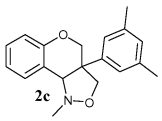
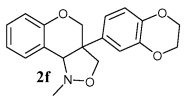
As part of an ongoing research program in developing new cascade reactions, we report here a tactical combination of a palladium catalysed allene insertion coupled with a 1,3-DC, leading to the formation of fused isoxazolidines (Scheme 1).



Scheme 1

A series of aryl iodides were found to react with allene (1 atm) and nitrone **1** in toluene at 120 °C over 48 h in the presence of 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3 and Cs_2CO_3 to afford the corresponding isoxazolidines (**2a**–**f**) in 50–77% yield. The reaction is believed to proceed *via* the catalytic cycle shown in Scheme 2. Initial oxidative addition of the active palladium(0) species into the aryl iodide bond, followed by attack of the arylpalladium(II) species at the centre carbon of the allene, affords the (η^3–η^1) allyl species. Nucleophilic substitution in step 3 regenerates the active palladium(0) species, which restarts the catalytic cycle. Nitrones **3** then undergo an intramolecular 1,3-DC to afford the fused isoxazolidines. A total of four new bonds are created, two C–C and two C–O bonds. Wet toluene was found to be a superior solvent to dry toluene, DMF and acetonitrile. Cs_2CO_3 was the most effective base of those (Cs_2CO_3, Cs_3PO_4, K_2CO_3) tested, and the catalytic system $Pd(OAc)_2$–PPh_3 was superior to $Pd(PPh_3)_4$, $Pd(OAc)_2$–tris(2-furyl)phosphine and $Pd(OAc)_2$–tris(*o*-tolyl)-phosphine. A reaction temperature of 120 °C and a time of 40–48 h were found to be optimum. Lower temperatures and short reaction times lead to incomplete reaction. Initially, when using 1 eq. of nitrone to 1.5 eq. of aryl iodide, 4-iodoanisole afforded the cascade product in 51% yield. However upon reversing the stoichiometry, the reaction yield increased to 63% (Table 1, entry 5). Further increasing the amount of nitrone failed to increase the yield.

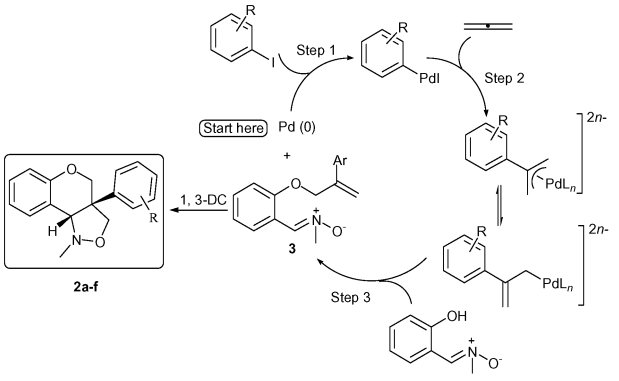
Table 1 Reaction of aryl iodides and **1** to afford **2a**–**f**[a]

Entry	Product	Yield (%)	Entry	Product	Yield (%)
1	 **2a**	50	4	 **2d**	49
2	 **2b**	54	5	 **2e**	63
3	 **2c**	51	6	 **2f**	77

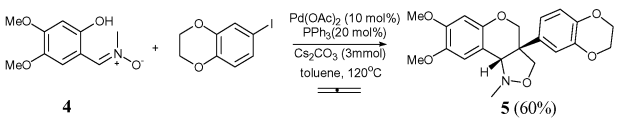
[a] Reactions carried out in toluene employing aryl iodide (1.0 mmol), nitrone **1** (1.5 mmol), allene (1 atm), 10 mol% $Pd(OAc)_2$, 20 mol% PPh_3, Cs_2CO_3 (3 mmol) and heated at 120 °C for 48 h.

The reason for this is not yet fully understood. However, a possible rationalization is that the phenolic OH group of **1** could undergo a double allene insertion under the reaction conditions leading to dienyl ethers as by-products.[4] It was found that electron rich aryl iodides (Table 1, entries 5 and 6) gave the highest yields. Moderate yields were obtained with electronically neutral aryl iodides, whilst aryl iodides with electron withdrawing substituents (*p*-nitro and methyl *p*-iodobenzoate) gave only traces of product. Based on this trend nitrone **4** was prepared and evaluated in the cascade. However studies of the cascade employing **4** and *p*-nitroiodobenzene and *p*-iodoacetophenone failed to yield significant amounts of the desired product, whilst reaction of nitrone **4** with 3,5-ethylenedioxyiodobenzene yielded the corresponding isoxazolidine **5** in 60% yield (Scheme 3).

Literature rate data[5] for the 1,3-DC of *N*-methyl-*C*-phenylnitrone to various dipolarophiles indicate that the presence of



Scheme 2



Scheme 3

DOI: 10.1039/b205069b

electron withdrawing substituents on the aryl group of nitrones **3** should facilitate the cycloaddition as well as accelerating the initial oxidative addition of palladium(0) to aryl iodide. Thus the failure of *p*-nitroiodobenzene and *p*-iodoacetophenone to deliver products **2** is puzzling and suggests intervention of side reactions at step 3 in Scheme 2.

The expected *cis*-ring junction stereochemistry of **2a**–**f** and **5** was confirmed by several X-ray structures, one of which, **2e** is shown in Fig.1.†

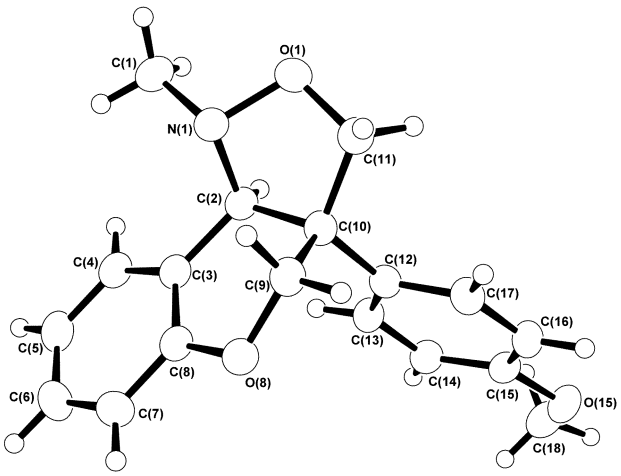


Fig. 1 X-Ray structure of **2e**.

Further studies involving microwave irradiation to help reduce reaction time/temperature are currently being considered and investigations into making the process general for all aryl iodides are being performed.

We thank the EPSRC, University of Leeds and GlaxoSmithKline for support.

Notes and references

† *Crystal data* for **2e**: $C_{18}H_{19}NO_3$, M = 297.34, monoclinic, space group $P2_1/c$, a = 12.6825(3), b = 11.2067(2), c = 11.1528(2) Å, α = 90°, β = 106.9260(10)°, γ = 90°, U = 1516.47(5) Å^3, Z = 4, T = 150(2) K, μ = 0.089 mm^{-1}, 24778 reflections collected, 2950 independent reflections (R_{int} = 0.0758), R_1 = 0.0433, wR_2 = 0.108 (all data). CCDC 183955. See http://www.rsc.org/suppdata/cc/b2/b205069b/ for crystallographic files in CIF or other electronic format.

1 P. Grunanger and P. Vita-Finzi, *Isoxazoles*, Wiley, New York, 1991.
2 Luciduline: W. Oppolzer and M. Petrizilka, *Helv. Chim. Acta*, 1978, **61**, 2755; J. J. Cocaine G. B. Tufariello, J. J. Mullen, E. J. Tegeler, S. C. Trybulski, S. Wong and A. Ali, *J. Am. Chem. Soc.*, 1978, **101**, 2435; Chanoclavine: W. Oppolzer and J. I. Grayson, *Helv. Chim. Acta*, 1980, **63**, 1706; Daunosamine: P. M. Wovkulich and M. R Uskokovic, *J. Am. Chem. Soc.*, 1981, **103**, 3956.
3 M. Frederickson, *Tetrahedron*, 1997, **53**, 403.
4 R. Grigg, N. Kongkathip, B. Kongkathip, S. Luangkamin and H. A. Dondas, *Tetrahedron*, 2001, **57**, 7965.
5 H. Basu and H. Schlenk, *Chem. Phys. Lipids*, 1971, **6**, 266; N. A. Akmanova, Y. M. Shaul'skii and Y. V. Svetkin, *Zh. Org. Chem.*, 1976, **12**, 88.