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PALLADIUM(II)-MEDIATED ROUTES TO FUNCTIONALISED HETEROCYCLES

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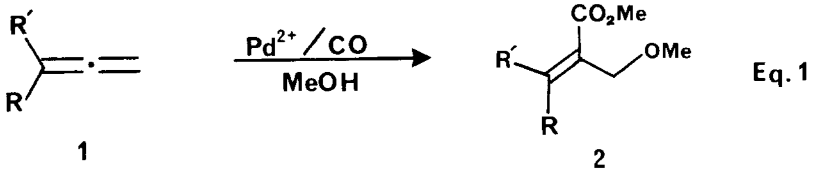
Summary. A series of allenic amines/amides **3** have been prepared and shown to undergo a palladium(II)-catalysed cyclisation, in the presence of carbon monoxide and methanol, to give α-(heterocyclic) acrylates **4**.

The use of palladium(II) to activate alkenes towards attack by nucleophiles, such as alcohols, amines and carbanions, is a process that has shown considerable synthetic potential over recent years.[1] A significant feature of this reaction is the flexibility inherent in the initial product of nucleophilic attack on the alkene, namely a σ-alkyl palladium complex. This species may undergo, for example, CO or olefin insertion thus providing a range of functionalised products.

Extension of this reactivity to π-systems other than alkenes is attractive and Alper has recently reported that allenes **1** undergo a facile Pd(II)-catalysed alkoxy-alkoxycarbonylation to give acrylates **2** (Equation 1)[2].



The obvious synthetic potential of allenes in this process prompted us to examine the intramolecular version of the reaction shown in Equation 1, although with an emphasis on the use of a nitrogen rather than an oxygen nucleophile i.e. Equation 2.[3,4]

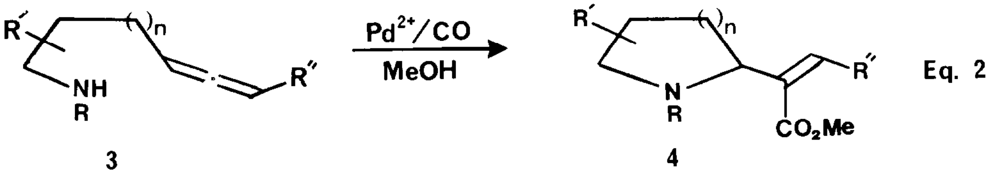
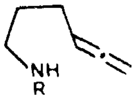
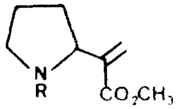
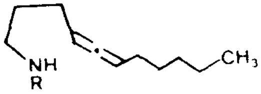
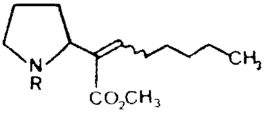
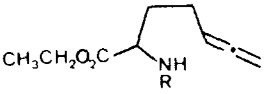
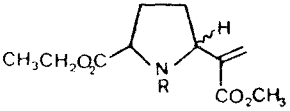
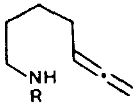
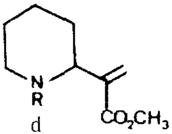
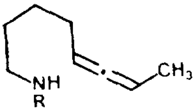
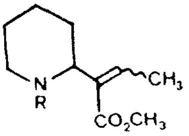


TABLE 1

3	4[a]	yield
		
a R=CH$_2$Ph	a R=CH$_2$Ph	67%
b R=SO$_2$pTol	b R=SO$_2$pTol	57%
c R=CO$_2$Me	c R=CO$_2$Me	56%
		
d R=CH$_2$Ph	d R=CH$_2$Ph (E/Z 1:1)	86%
		
e R=CH$_2$Ph	e R=CH$_2$Ph[c]	55%
f R=SO$_2$pTol[b]	f R=SO$_2$pTol[c]	68%
		
g R=H	g R=H[d]	
h R=CH$_2$Ph	h R=CH$_2$Ph	42%
i R=SO$_2$pTol[b]	i R=SO$_2$pTol	20%
j R=CO$_2$Me	j R=CO$_2$Me[d]	
		
k R=CH$_2$Ph	k R=CH$_2$Ph (E/Z 6:1)	52%

a. Yields represent isolated and purified material and have not been optimised.

b. Cyclisation was effected in the presence of either Na$_2$CO$_3$ or Et$_3$N.

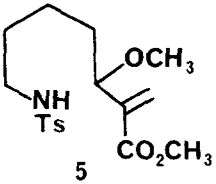
c. Both **4e** and **4f** were isolated as a 3:1 mixture of isomers with the <u>trans</u>-isomer predominating. Assignment of configuration is based on ^{1}H n.m.r. studies.

d No cyclisation was observed.

In most cases, cyclisation was effected by treating the amine (or derivative)[5] (0.1 M solution in methanol) with palladium(II) chloride(0.1 equiv.) and cupric chloride (3 equiv.) under an atmosphere of carbon monoxide. These reactions were conducted at room temperature and were generally complete within 4-8 hours. The product(s) was isolated by flash chromatography, following work-up with a 10% solution of ethanolamine in water. The results of this study, using a range of allenic amine derivatives, are shown in Table 1. For **3f** and **3i** the cyclisation reaction was most effectively accomplished when carried out in the presence of an added base (Na_2CO_3 or Et_3N).

Some interesting comparisons can be made between this work and earlier studies of the palladium(II)-catalysed cyclisation/carbonylation of amino alkenes. We find that a relatively basic nitrogen function (N-benzyl) can be tolerated. Such groups tend to have been avoided in the alkene series although our attempts to carry out the cyclisation of primary amine **3g** were unsuccessful[6]. Although six-membered rings could be obtained, we have found, in agreement with the earlier observations made by Hegedus[1], that a relatively nucleophilic amine is most efficient at producing a ring of this size.

Sulfonamide **3i** underwent cyclisation only when in the presence of a base (Na_2CO_3 or Et_3N). In the absence of a base, products **5** and **6**, resulting from simple alkoxy (or chloro)-alkoxy carbonylation of the allenic residue, were observed.[7] Carbonate **3j** could not be induced to cyclise under any conditions. Products analogous to **5** and **6** were isolated from **3f** when a base was omitted, although some cyclisation (20%) was also observed.



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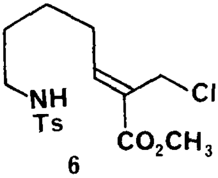

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Studies in our laboratory are currently underway to extend this methodology to include (a) the control of the absolute stereochemistry of the heterocyclic product and (b) to exploit the reactivity of the acrylate function in the synthesis of neurotoxic alkaloids.

Acknowledgement

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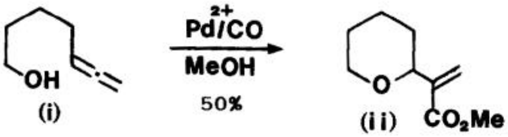
References and Notes

1. For a review of the mechanistic and synthetic aspects of this reaction see L.S. Hegedus *Tetrahedron*, 40, 2415, (1984). For examples of more recent work in this area see H. Alper, J.B. Woell, B. Despeyroux and D.J.H. Smith, *J.C.S. Chem.Commun.*, 1983, 1270; M.F. Semmelhock and C. Bodurow, *J.Am.Chem.Soc.*, 106, 1496, (1984); A.S. Kende and D.J. Wustrow, *Tetrahedron Letters*, 26, 5411, (1985) and references therein; Y. Tamaru, T. Kobayashi, S. Kawamura, H. Ochiai, and Z. Yosida, *Tetrahedron Letters*, 26, 4479, (1985); H. Alper and D. Leonard, *J.C.S. Chem. Commun.*, 1985, 511.

2. H. Alper, F.W. Hartstock and B. Despeyroux, *J.C.S. Chem. Commun.*, 1984, 905.

3. Intermolecular amination of allenes, in the presence of Group VIII metals, results in the formation of dimers. D.R. Coulson, *J. Org. Chem.*, 38, 1483, (1973). See also I. Shimizu and J. Tsuji, *Chem. Lett.*, 1984, 233 and L.S. Hegedus, N. Kambe, R. Tamura, P.D. Woodgate, *Organometallics*, 2, 1658, (1983).

4. We have also examined briefly the cyclisation of allenic alcohols e.g. (i)→(ii). Details will be published in due course.



5. Most of the substrates used were prepared by conventional methods from readily available allenes, L. Brandsma and H.D. Verkrkuijsse, *"Synthesis of acetylenes, allenes and cumulenes"* Studies in Organic Chemistry, Elsevier, 1981, 8. The amino acids **3e** and **3f** were prepared by alkylation of glycine (G. Stork, A.W. Leong, and A.M. Touzin, *J. Org. Chem.*, 41, 3491, (1976)) with 5-bromopenta-1,2-diene. This was followed by either reduction ($NaBH_4$) to give **3e** or hydrolysis followed by reaction with TsCl/pyridine to give **3f**.

6. This was an attempt to prepare a bicyclic α-methylene-β-lactam, see M. Mori K. Chiba, M. Okita and Y. Ban, *J.C.S. Chem. Commun.*, 1979, 698 and references therein.

7. Analogous products have been observed with allene under similar conditions. R.G. Schultz, *Tetrahedron*, 20, 2809, (1964) and M.S. Lupin, J. Powell and B.L. Shaw, *J. Chem. Soc.(A)*, 1966, 1687.

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