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Palladium catalysed synthesis of pyrroles from enamines

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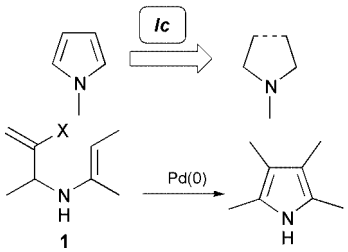
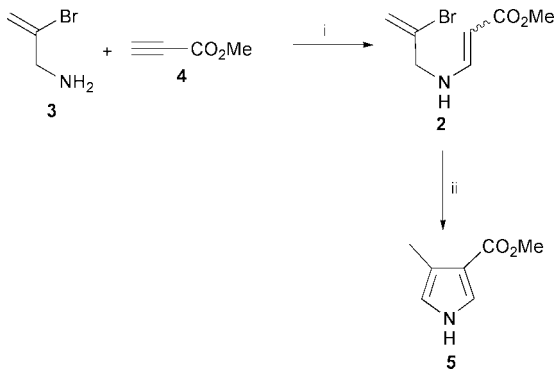
Substituted pyrroles are formed in moderate to good yields by the Pd-catalysed cyclisation of enamines containing β-vinyl bromide functionalities.

Pyrrole and its derivatives feature widely in natural products, drugs, polymers and dyes.[1,2] As a result many efficient synthetic procedures for their preparation have been developed.[3] The synthetic methodology for the preparation of pyrrole and its derivatives can be classified in terms of the number and location of the bonds formed in the reaction.[3a] We are particularly interested in the ***Ic*** approach (Scheme 1) since this approach although frequently used in the synthesis of indoles,[3a,b,4] is quite rare for pyrrole synthesis. It was expected that easily accessible enamines of type **1** would provide access to the desired synthetic procedure ***Ic*** (Scheme 1).



Scheme 1

The results of an initial experiment are shown in Scheme 2. The enamine **2** was prepared in 84% yield by reacting amine **3** and alkyne **4** in DMF at room temperature. The cyclisation step (DMF, 85 °C, oil bath temperature) in the presence of $Pd(OAc)_2$ (10 mol%)/PPh_3 (20 mol%) and K_2CO_3 (2 equiv.) as a base afforded the expected pyrrole **5** but in only 24% yield.

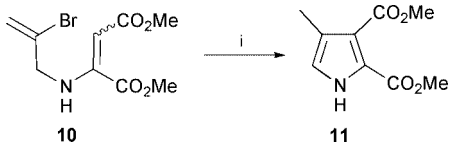


Scheme 2 *Reagents and conditions*: i, DMF, room temp., 84%; ii, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 85 °C, 24%.

Assuming that the low yield of **5** could be caused by instability of the pyrrole product, several other enamines (Table 1) were prepared using similar synthetic procedures in order to further investigate the cyclisation reaction. With bis-substituted alkynes (Table 1, entries c, d and h) the reactions were performed in DMF at 60–65 °C (oil-bath temperature) or in boiling ethanol[5] (Table 1, entry e) producing the required enamines in good yield. Monosubstituted alkynes (Table 1, entries a, f and g) afforded the enamines at room temperature. Enamine **8b** was prepared by addition of propenylamine to the allene in DMF at room temperature. Most of the enamines comprised mixtures of *Z*- and *E*-isomers and these mixtures were used for the cyclisation reactions without attempts to separate the stereoisomers.

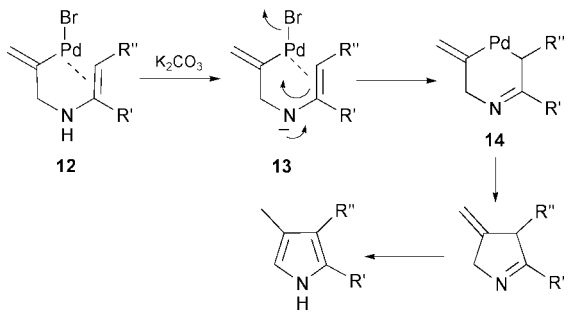
With **8a**–**h** in hand their conversion to the corresponding pyrroles was investigated. The reactions were performed in DMF at 85 °C in the presence of $Pd(OAc)_2/PPh_3$ and K_2CO_3 as already explained affording **9a**–**h** in moderate to good yields. The reaction tolerates a range of functional groups and reaction times are in most cases between 1 and 3 h.

Mechanistically the cyclisation step can be rationalised in several ways. It is possible that Pd(II) acts as a Lewis acid by coordinating either the enamine double bond or the electron withdrawing group (CO_2Me, $SO_2C_6H_4Me$-*p*) lowering the pK_a of the N–H group. This would facilitate the formation of the corresponding anion leading to cyclisation *via* nucleophilic attack on the vinyl bromide moiety. Interestingly we observed that for enamine **10**, where the pK_a of the N–H group is sufficiently low to allow deprotonation by K_2CO_3, the Pd-catalyst is not required (Scheme 3). The expected product **11** was formed by heating **10** in DMF (85 °C) in the presence of only K_2CO_3. The reaction with other enamines used in this study without the Pd-catalyst but in the presence of K_2CO_3 resulted in recovery of the starting materials. ^{1}H NMR spectroscopy of the crude reaction mixtures indicated the presence of a small amount of product only in the case of enamine **8e** after a significantly longer reaction time than for reaction performed in the presence of Pd-catalyst (6 *cf.* 1 h).



Scheme 3 *Reagents and conditions*: i, K_2CO_3, DMF, 85 °C, 53%.

Another mechanistic rationalisation of the reaction is shown in Scheme 4. This involves the oxidative addition of Pd(0) into the C–Br bond followed by coordination to the enamine double bond to form **12**. Formation of the anion **13** and nucleophilic substitution of bromide at the Pd[7] leads to palladacycles **14**



Scheme 4

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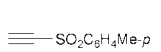
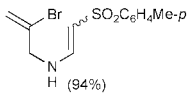
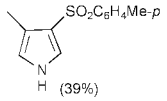
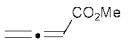
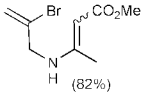
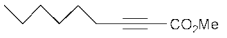
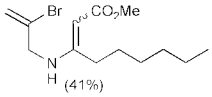
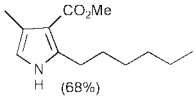
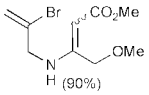
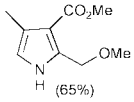
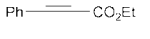
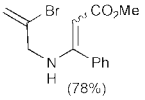
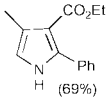
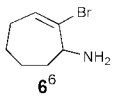
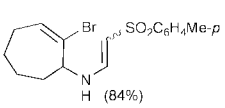
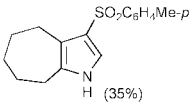
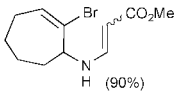
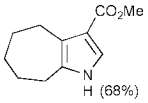
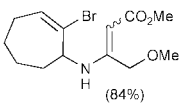
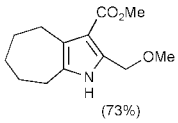
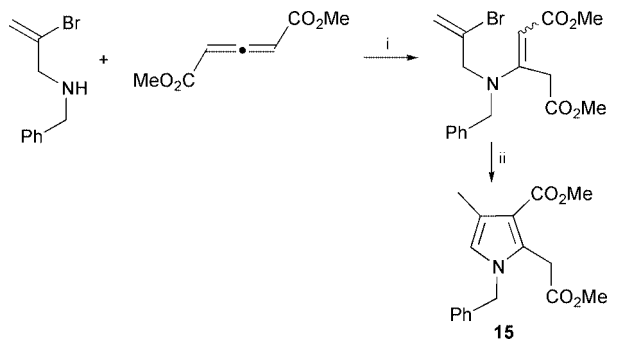
Table 1

Entry	Amine	Alkyne/allene **7**	Enamine **8** (yield)	Pyrrole **9** (yield)
a	**3**		 (94%)	 (39%)
b	**3**		 (82%)	 (41%)
c	**3**		 (41%)	 (68%)
d	**3**		 (90%)	 (65%)
e	**3**		 (78%)	 (69%)
f	 **6**[6]		 (84%)	 (35%)
g	**6**		 (90%)	 (68%)
h	**6**		 (84%)	 (73%)

which after reductive elimination and isomerisation produces the pyrroles.

Nucleophilic substitution at Pd(II) followed by reductive elimination is a process well known in the literature[7] and in the current reactions more likely than disfavoured 5-*endo* cyclisation. Some related synthesis of pyrrolidine[8] and pyrroline[9] derivatives that involve nucleophilic substitution at Pd(II) are known.

The same approach was applied for the synthesis of **15**, a potentially important pyrrole for the preparation of compounds with anti-inflammatory activity[10] (Scheme 5). Performing the cyclisation reaction in the presence of a Pd-catalyst afforded the desired pyrrole in 94% yield. In this case the anion is formed by deprotonation at the methylene group adjacent to the ester functionality.



Scheme 5 *Reagents and conditions*: i, DMF, room temp., 86%; ii, $Pd(OAc)_2$, PPh_3, K_2CO_3, DMF, 85 °C, 94%.

In conclusion, we report a novel synthetic route for the preparation of substituted pyrroles. The two step procedure involving enamine formation followed by Pd-catalysed cyclisation produces pyrroles in good yields.

We thank the EPSRC and Leeds University for support.

Notes and references

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