Heterocyclization, deprotection and isomerization in an intramolecular palladium-catalysed tertiary amine–allyl coupling reaction

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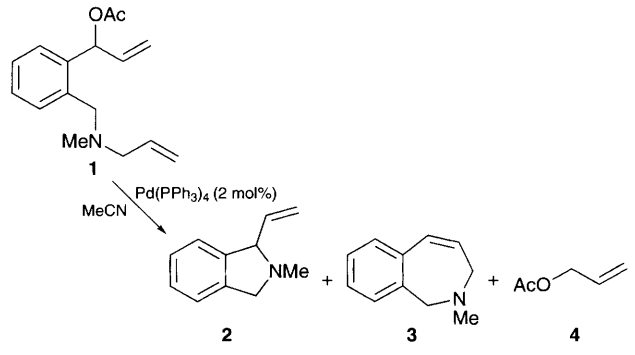
***N*-Methyl-*N*-allyl-2-(1-acetoxyallyl)benzylamine reacts in the presence of tetrakis(triphenylphosphine)palladium to afford a mixture of an isoindole, a 2-benzazepine and allyl acetate; the likely reaction pathway involves a multistep procedure whereby each Pd atom is implicated at least four times, the formation of the isoindole occuring first, followed by an isomerisation to the benzazepine derivative.**

We have recently shown that tertiary amine functions can act as intramolecular nucleophiles towards allylic units η^3-bonded to Pd, thus leading to cationic heterocyclic compounds such as isoindolinium and 2-benzazepinium salts.[1] This methodology would prove, however, more valuable if it could be used for the direct synthesis of the corresponding neutral heterocycles due to the well-known high potential biological activity of these compounds.[2] For example, an *N*-cyclopropylmethyl derivative of 2-benzazepine displayed a high CNS activity, with an eight fold increased of *in vivo* analgesic activity compared to morphine.[3] We have thus embarked on a project aimed at synthesizing such neutral species using our general method by studying the influence of an allylic moiety attached to the nitrogen atom on the course of the reactions studied previously. It has indeed been shown that allyl units on amonium derivatives are efficient leaving groups in the presence of transition metal-based catalysts.[4] In this communication we show that the final product of the reaction is, as expected, a neutral heterocycle, but a close examination of the mechanism involved shows that the reaction is not as straightforward as thought, the palladium atom being part of an unprecedented set of transformations.

In the presence of a catalytic amount of $Pd(PPh_3)_4$, compound **1** led to a high yield of a mixture of isoindole **2** and the benzazepine **3**, together with allyl acetate, after *ca.* 10 h at room temperature (Scheme 1).‡ This reaction was performed in MeCN, but it could be run as effectively without any solvent, since all the compounds involved are liquids in which the palladium catalyst dissolves as the reaction proceeds.

In marked contrast to our previous study, using a dimethylamino derivative, no isoindolinium or benzazepinium salts were formed, *i.e.* the *N*-allyl unit does not prevent the N–C coupling and is readily removed from the reaction product.



Scheme 1

Following the evolution of the products of the reaction with time (Fig. 1) has led us to the conclusion that there are clearly two different processes that have to be considered. The first period of the reaction corresponds to the time during which the disappearance of **1** is concomitant with the formation of the isoindole **2**. After almost all of **1** has reacted, the second period starts during which the only apparent reaction is the one in which **2** isomerizes to **3**. We isolated **2** from the reaction mixture and let it stand in the presence of a catalytic amount of $Pd(PPh_3)_4$ and allyl acetate (1 equiv.) in order to mimic the reaction conditions found during the second period. The isomerization of **2** into **3** did indeed take place (Scheme 2) and after 9.5 h, 66% of the isoindole had isomerized into the 2-benzazepine. Note that the isomerisation of **2** to **3** is almost quantitative since, after 48 h, the yield of **3** is 96%.

As a control we verified that, in the absence of either the palladium catalyst or the allyl acetate, no reaction took place. The reaction is first order in the concentration of **2** and the apparent kinetic constant of the isomerisation was determined by means of ^{1}H NMR spectroscopic methods as being almost identical (within experimental error) to the one found for the second period of reaction. This result clearly demonstrates that the formation of the benzazepine **3** is solely due to the isomerization of **2** formed in the early stage of the reaction. In other words, this is a strong indication that the attack of the nitrogen atom on the allylic group only occurred at the more substituted carbon atom in **1** affording the isoindole **2** as the kinetically controlled product of the reaction. Parallel Pd^0-catalysed rearrangement of allylamines from the kinetic product to the thermodynamic one have been described earlier by Åkermark and Vitagliano.[5] The isomerisation process here must

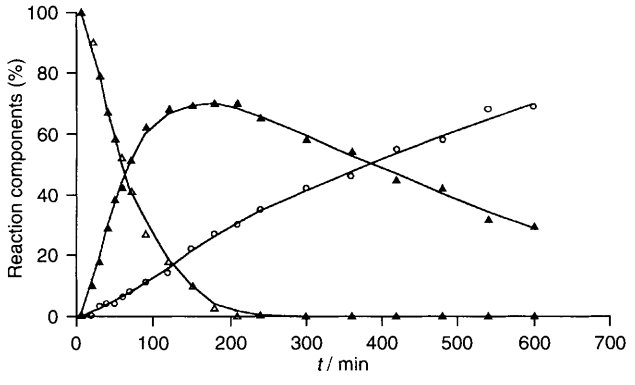
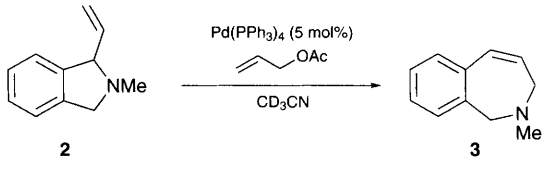


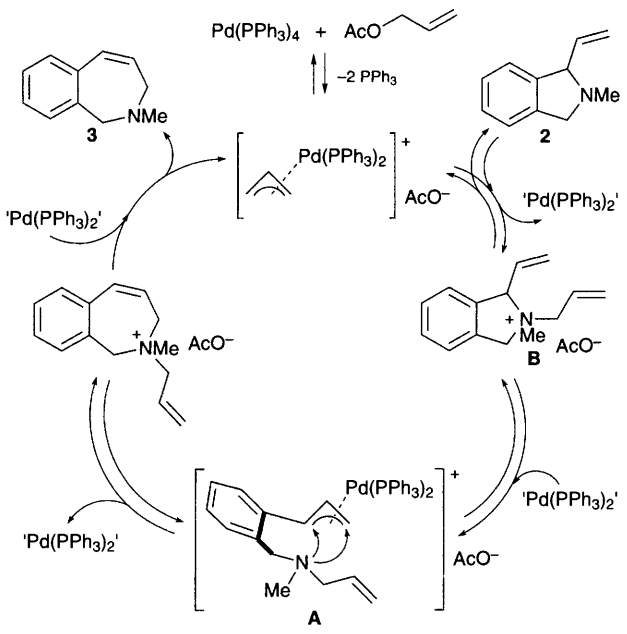
Fig. 1 Reaction of benzylamine **1**(△) to give **2**(▲) and **3**(○)



Scheme 2

imply an intermolecular attack of the isoindole at the allyl group of $[(\eta^3\text{-allyl})Pd(PPh_3)_2]^+$ to afford the intermediate [**B**] (Scheme 3). Related intermolecular additions of tertiary amines have been recently disclosed.[6] Note however that there is so far little evidence, if any, for the formation of such a cationic intermediate.

A likely reaction pathway for the isomerization (Scheme 3) can now be drawn from these observations. The intermediate marked [**A**] should lead to the benzazepine **3** *via* intramolecular attack of the amino group in the position opposite to the $Pd(PPh_3)_2$ moiety with respect to the allyl fragment after the *syn–anti* isomerisation of the latter has taken place.[1] We have indeed shown in our previous related heterocyclisation of dimethylbenzylamine derivatives that the formation of the seven-membered ring is thermodynamically favoured. The present result now sheds some light upon the mechanism of this reaction, since the presence of an allyl unit on the N atom allows the observation of the kinetically controlled product **2**. Thus the cleavage of the exocyclic *N*-allyl moiety in [**B**] should be very fast relative to the ring opening reaction leading to [**A**].



Scheme 3

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Footnotes

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‡ *Selected NMR data* for 2,3-dihydro-1-vinyl-*N*-methyl-1*H*-isoindole **2**: ^{1}H NMR ($CDCl_3$): 5.80 (ddd, 1 H, –CH=, $^3J_{HHtrans}$ 17.1, $^3J_{HHcis}$ 9.9, $^3J_{HH}$ 8.4), 5.40–5.31 (m, 2 H, $=CH_2$), 4.26 (dd, 1 H, $ArCH_2N$, $^2J_{HH}$ 12.6 $^4J_{HH}$ 1.4), 3.98 (large d, 1 H, ArCH), 3.67 (dd, 1 H, $ArCH_2N$, $^4J_{HH}$ 2.9), 2.54 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): 118.4 ($=CH_2$), 74.5 (ArCH), 60.4 ($ArCH_2N$), 39.8 (NCH_3). For 2,3-dihydro-*N*-methyl-1*H*-2-benzazepine **3**: ^{1}H NMR ($CDCl_3$): 6.46 (dt, 1 H, ArCH, $^3J_{HH}$ 12.3, $^4J_{HH}$ 2.1), 5.78 (dt, 1 H, $=CH–CH_2$, $^3J_{HH}$ 3.9), 3.82 (s, H, $ArCH_2$), 3.54 (dd, 2 H, $NCH_2CH=$), 2.41 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$): 61.6, 60.3 (2 C, $ArCH_2$ and NCH_2CH), 43.5 (1 C, CH_3).

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