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Pd Catalysed Intramolecular Coupling Between Tertiary Amines and Allylic Groups; Synthesis of 3-Hydro-1*H*-2-Benzazepinium Salts.

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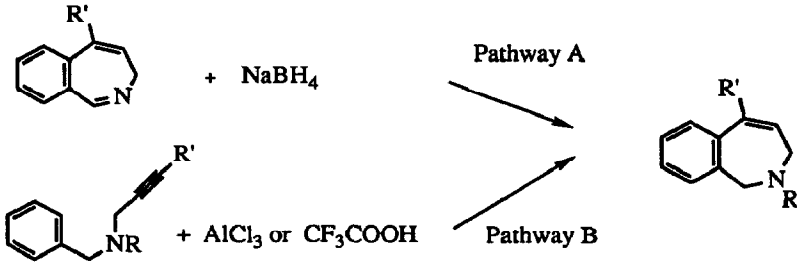
Summary : Tertiary amines have been used as intramolecular nucleophiles in a Pd catalysed allylic substitution reaction leading to benzazepinium salts.

Molecules containing the 2-benzazepine skeleton are known for their antihypertensive, adrenergic blocking, cholinesterase inhibiting and antibiotic activity[1]. The synthesis of partially hydrogenated 2-benzazepine derivatives is an important step in the conception of more complex 2-benzazepine compounds[2] which may be subjected to biological screening processes. There are only two principal routes for the syntheses of 3-hydro-1*H*-2-benzazepines or benzazepinium salts (Scheme 1). One method comprises two key steps, the first involving the formation of 3*H*-2-benzazepines by given routes[3,4] followed by a selective hydrogenation of the imine fragment[4] (Pathway A). The other approach of interest consists of an intramolecular C-C coupling between the ortho aryl carbon and the alkynyl carbon of 1-benzyl amino-2-alkyne derivatives[5] (Pathway B).

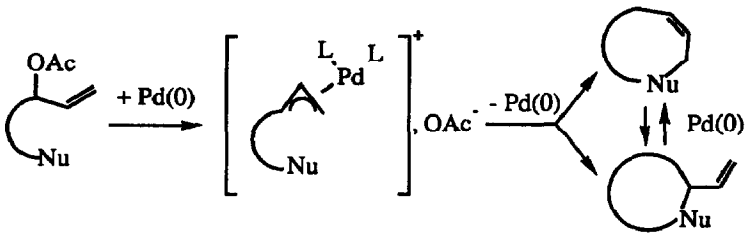
Scheme 1



Moreover, recent work has shown a special interest in 1-benzazepinium salts which have been combined with antibodies in catalysis[6]. This observation has led us to disclose our results on a new efficient method which selectively affords 3-hydro-1*H*-2-benzazepinium compounds in a one-step fashion from N,N-dimethyl 2-(1'-acetoxy-2'-propenyl)-benzylamine derivatives. Our procedure employs a recognised synthetic strategy[7], an intramolecular nucleophilic substitution involving the formation of a η^3-allyl palladium intermediate (Scheme 2). This methodology has been extensively applied elsewhere for the synthesis of N-heterocycles using primary or secondary amines as nucleophiles.

Herein we describe the synthesis of cationic N-heterocycles[8] resulting from the intramolecular addition of tertiary amino groups on allyl-Pd functions[9], generated from allyl acetate derivatives and catalytic amounts of Pd(0).

Scheme 2



In order to determine the most convenient reaction conditions for the synthesis of the 3-hydro-1*H*-2-benzazepinium salts (Scheme 3), $Pd(PPh_3)_4$ was employed as catalyst in combination with different solvents, in the presence or absence of added salt (Table 1).

Scheme 3

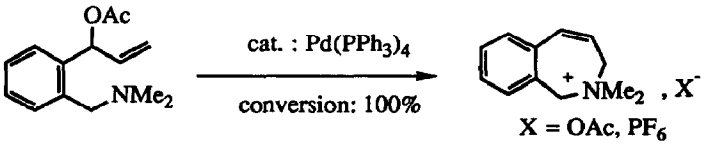


Table 1

Entry	Cat.[a]	Solvent	T°C	Time[b]	Salt[c]	Yield[d]
1	5	THF	70	18	None	60[e]
2	3	MeOH	R.T	18	None	85
3	2	MeOH	R.T	18	$NaPF_6$	86
4	2	MeCN	R.T	1	$NaPF_6$	90
5	2	MeCN	R.T	18	None	90
6	0	MeOH	R.T	24	None	0

a) mol % b) hours c) 1 eq of added salt d) isolated yield e) no reaction is observed at R. T.

With THF (the most frequently used solvent in this type of reaction), we observed the formation of many by-products[10] which explains the moderate yield of the benzazepinium salt (entry 1, table 1) as compared to the other reactions where MeOH and CH_3CN were used as solvents (entries 2-5). It is noteworthy that the introduction of $NaPF_6$ increased the rate of the reaction only when CH_3CN was used (entry 4). This is explained by the fact that acetate can no longer play the role of a competing nucleophile due to the precipitation of NaOAc during the reaction. However, both in MeOH or CH_3CN (entries 2-5), the reaction is regiospecific, no other product being detected by ^1H NMR. For the rest of this study we have thus adopted the conditions corresponding to entry 4, which gave optimal yields.

A study of the influence of various substituents on the allylic chain on the 5- *versus* 7- membered ring formation was also carried out. The determination by ^1H NMR of the ratio between the 7- and the 5-membered cationic heterocycles is reported in Table 2.

From entries 1-3 (Table 2) it appears that the introduction of a methyl group in position 1' or 2' has no influence on the size of the nitrogen containing heterocycles obtained. When a substituent was introduced on

the terminal olefin carbon of the reagent, the yield of the 2-benzazepinium salt either decreased dramatically (entry 4) or it was not observed at all (entries 5-7).

Scheme 4

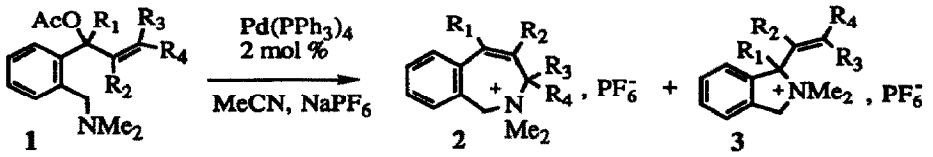
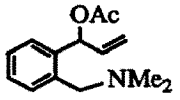
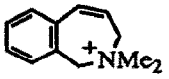
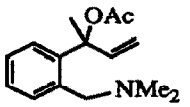
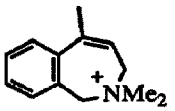
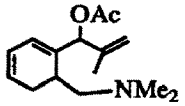
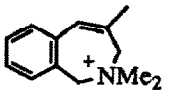
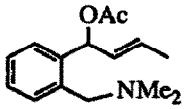
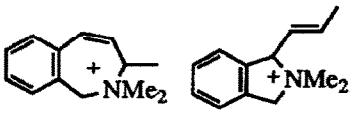
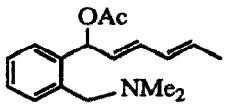
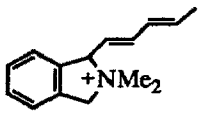
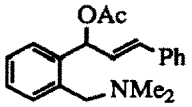
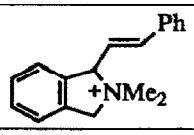
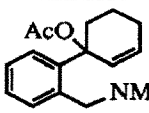
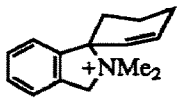


Table 2

Entry	Reagents	Products	2 / 3[a]	Yield[b](%)
1			100 / 0	90
2			100 / 0	85
3			100 / 0	82
4			45 / 55	70
5			0 / 100	60
6			0 / 100	81
7			0 / 100	75

a) Ratio determined by ^1H NMR. b) Isolated Yield. All products gave satisfactory ^1H, ^{13}C NMR and combustion analysis.

The seven-membered ring (entry 4) could be isolated by fractional crystallisation and when redissolved in the presence of a catalytic amount of $Pd(PPh_3)_4$ the reaction afforded the same isomeric mixture as that obtained from the initial reaction. Thus these two regioisomers are in equilibrium with each other. This result eliminates a mechanism that involves kinetic control and it proves that the product formation is under thermodynamic control[9]. One can anticipate that steric interactions between the methyl or vinyl groups and the NMe_2 unit in the

hypothetical seven-membered rings can partly be responsible for their destabilisation. In the last case (entry 7), the benzazepinium salt cannot be obtained because its formation would result in an unfavorable trans-oriented cyclohexene unit.

Conclusion

The present study demonstrates that the intramolecular nucleophilic addition of a tertiary amine to an allylic group can be induced by catalytic amounts of Pd(0), the product formation being under thermodynamic control. Further work to extend this methodology to the synthesis of heterocycles with different ring sizes is underway.

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Experimental:

Synthesis of N,N-dimethyl-3-hydro-1*H*-2-benzazepinium hexafluorophosphate (entry 4, table 1) (in Schlenk tubes under N_2):

A solution of N,N-dimethyl-2-(1'-acetoxy-2'-propenyl)-benzylamine (0.420 g, 1.8 mmol) in CH_3CN (5 ml) was added to a suspension of $Pd(PPh_3)_4$ (0.041 g, 2 mol %) and $NaPF_6$ (0.310 g, 1.84 mmol) in CH_3CN (15 ml). After 1h stirring, the CH_3CN was evaporated and 20 ml of acetone were added to the residue. The mixture was filtered and the solution concentrated *in vacuo*. THF (3 ml) was added followed by a slow addition of diethylether giving a white precipitate. The pure product was isolated by filtration (yield: 0.515 g, 90%).

Anal. Calc. for $C_{12}H_{16}NPF_6$: C, 45.15; H, 5.05; N, 4.39 Found C, 44.98; H, 5.06; N, 4.43. ^1H NMR ($CDCl_3$): δ, 7.67-7.31 (m, 4 H, Ar); 7.21 (d, 1 H, CH, $^3J_{HH}$ = 10.6); 6.27 (td, 1 H, CH, $^3J_{HH}$ = 6.4 and $^3J_{HH}$ = 10.6); 4.37 (s, 2 H, $ArCH_2$); 3.70 (d, 2 H, NCH_2, $^3J_{HH}$ = 6.4); 3.62 (s, 6 H, NMe_2). ^{13}C NMR ($CDCl_3$): δ, 140.3 (ArC=); 137.8, 132.0, 130.4, 129.3, and 129.2 (Ar); 122.5(=C); 65.7 ($ArCH_2$); 60.8 (NCH_2); 51.2 (NMe_2). (Bruker AX 300, 293K, δ in ppm, *J* in Hz).

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10 These compounds have not yet been characterised.

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