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Palladium-Catalysed Synthesis of α-Methylene γ-Butyrolactams via Cyclisation of Homoallylic Chloroformamides[1]

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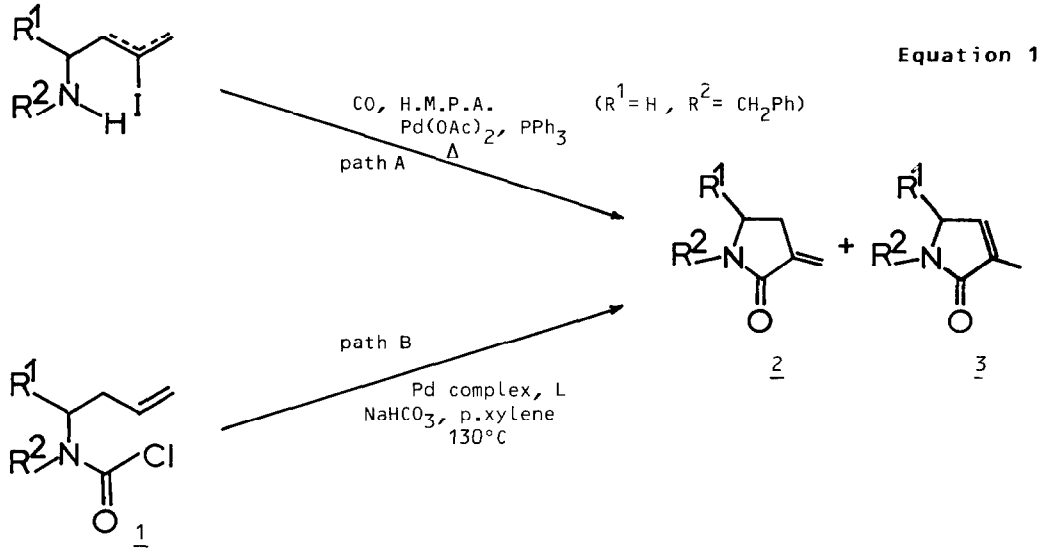
Summary : 3-Methylene 2-pyrrolidinones were prepared by intramolecular cyclisation of homoallylic chloroformamides catalysed by Pd^{II} or Pd° complexes.

The synthesis of α-methylene γ-butyrolactams by Pd^{II}-catalysed carbocyclisation of vinyl iodides bearing an amino group has been reported[2] (eq. 1, path A). This class of compound constitutes potential antitumor agents[3] or their valuable precursors[4] and, in this paper, we describe a different approach to their synthesis by intramolecular cyclisation of homoallylic chloroformamides 1 catalysed by palladium complexes (eq. 1, path B).

Equation 1



Cyclisations were carried out under argon by heating (130°C, 16-20 h) solutions of 1[5] in anhydrous p.xylene containing the palladium catalyst (3-6 mole %), a ligand (2-6 eq. per Pd) and sodium bicarbonate (220 mole %) as base to trap hydrochloric acid formed *in situ*. Representative results, reported in the table, show that satisfactory yields can be obtained not only with Pd° catalysts but also with palladium^{II} acetate. Interestingly, cyclisation of 1 to 2 was also observed, in using the common palladium on charcoal catalyst. From these results, it appears that the ratio 2/3 depends on the nature of both catalyst and substituents R^1 or R^2. We also found that the origin[6] and the age of $Pd(PPh_3)_4$ have a large influence on the regioselectivity and the chemical yields[7].

Table : Intramolecular cyclisation of homoallylic chloroformamides

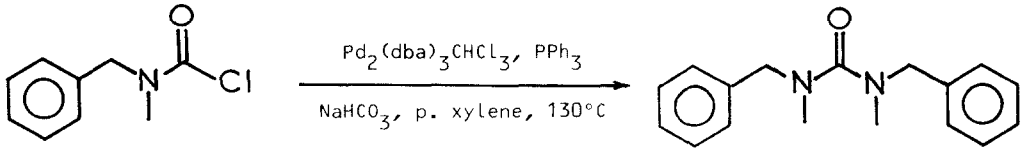
Run	R^1	R^2	Catalyst (mole %)	L (mole %)	Yield % (a)	Ratio 2/3 (b)
1	n.Pr	n.Bu	$Pd(PPh_3)_4$ (6)	PPh_3 (12)	31 to 59	100/0 to 66/34
2			$Pd_2(dba)_3CHCl_3$ (3)	PPh_3 (18)	69	83/17
3			$Pd_2(dba)_3CHCl_3$ (3)	dppe (9)	48	77/23
4			$Pd(OAc)_2$ (3)	PPh_3 (18)	62	67/33
5			Pd/C (6)	PPh_3 (24)	39	97/3
6	n.Pr	$PhCH_2$	$Pd(OAc)_2$ (6)	PPh_3 (36)	76	75/25
7	H	$PhCH_2$	$Pd_2(dba)_3CHCl_3$ (3)	PPh_3 (36)	71	> 95/5
8	n.Hex	$PhCH_2$	$Pd(OAc)_2$ (6)	PPh_3 (36)	75	> 95/5
9	n.Hex	n.Bu	$Pd(OAc)_2$ (6)	PPh_3 (36)	75	98/2

(a) Isolated yields calculated on the quantity of 1 introduced (b) determined by ^1H NMR.

In all cases, the exo-isomer 2 is the preponderant cyclised product. The endo-isomer 3 could result at least in part from isomerisation of 2 in the reaction mixture since formation of 3 (≃ 8%) was observed when pure 2 (R^1 = n.Pr, R^2 = n.Bu) was heated during 13 h under the conditions of run 3.

On the other hand, cyclisation of N-methyl N-benzyl chloroformamide into the corresponding benzolactam was unsuccessful ; instead, the urea derivative was isolated[8] with 39% yield (eq. 2).

Equation 2



References and Notes

1. Presented, in part, at "Congrès national de la Société Française de Chimie", September 9, 1986, Paris" and at "XIIth European Colloquium on Heterocyclic Chemistry" September 29-October 1, 1986, Reims.
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5. The homoallylic chloroformamides are formed at room temperature from corresponding homoallylic amines and phosqen in the presence of pyridin.
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7. Similar methodology has been precedently used for the synthesis of α-methylene γ-butyrolactones : F. HENIN and J.P. PETE, Tetrahedron Lett., 1983, 24, 4687.Variable yields and endo/exo ratios were also observed when using different samples of $Pd(PPh_3)_4$ but the use of $Pd(OAc)_2$ as catalyst was much less efficient (yield ≃ 10%).
8. Under these conditions, the chloroformate analogue led to dibenzylcarbonate.

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