Palladium-catalysed Cross Double Carbonylation of Amines and Alcohols: Synthesis of Oxamates

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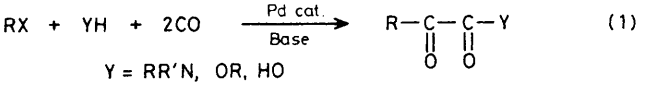
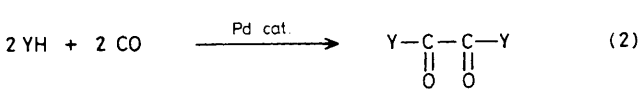
Cross double carbonylation of amines and alcohols in the presence of $PdCl_2(MeCN)_2$/CuI catalyst under CO and O_2 at room temperature gives oxamates efficiently.

Double carbonylation is of importance with respect to mechanistic and synthetic aspects. The double carbonylation of aryl and benzyl halides with amines, alcohols, and water gives the corresponding α-keto acids and their derivatives, equation (1),[1,2] while double carbonylation of amines and alcohols gives amides[3] and esters[4] of oxalic acids, respectively, equation (2). During the course of our study on the activation of amines with transition metal catalysts,[5] we have found that the palladium-catalysed reaction of amines with alcohols in the presence of carbon monoxide proceeds efficiently to give



(1)



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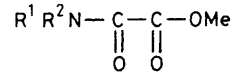
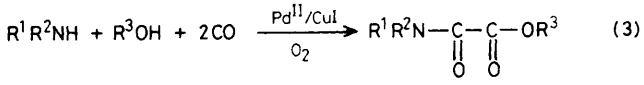
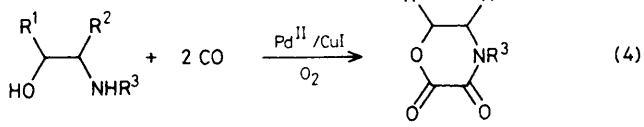


(1)

a; $R^1, R^2 = -[CH_2]_5-$
b; $R^1 = R^2 = Et$
c; $R^1, R^2 = -[CH_2]_4-$
d; $R^1, R^2 = -[CH_2]_2O[CH_2]_2-$



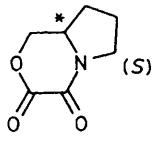
(3)



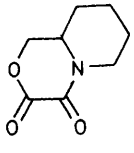
(4)

(2)

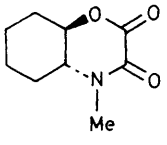
a; $R^1 = R^2 = H$, $R^3 = Et$
b; $R^1 = R^2 = H$, $R^3 = CH_2Ph$
c; $R^1 = Ph$, $R^2 = H$, $R^3 = Me$
d; $R^1 = CH_2NBu_2$, $R^2 = H$, $R^3 = Bu$



(3)



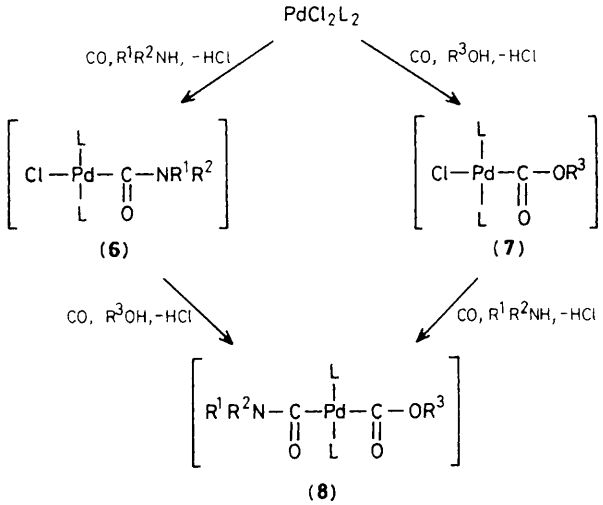
(4)



(5)

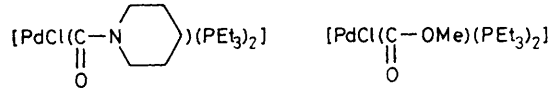
oxamates. This is the first example of cross double carbonylation of amines and alcohols.[6]†

Using a stoicheiometric amount of $PdCl_2(MeCN)_2$ the cross double carbonylation of amines and alcohols proceeds generally in the presence of base. Typically, a mixture of piperidine (1.0 mmol), $PdCl_2(MeCN)_2$ (1.0 mmol), and methanol (100 mmol) was stirred under CO (1 atm) at room temperature for 1 h. Addition of triethylamine (10 mmol) and further stirring at room temperature for 20 h gave 1-methoxalylpiperidine (**1a**) in 90% yield. Similar reactions of diethylamine, pyrrolidine, and morpholine with methanol gave the corresponding double carbonylation products (**1b—d**) in 69, 83, and 59% yields, respectively.‡



(6) (7) (8) (9)

Scheme 1



(10) (11)

Importantly, the cross double carbonylations can be performed catalytically using molecular oxygen and CuI as oxidant and co-catalyst, respectively, equation (3). Typically, when a mixture of piperidine (1.0 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol), and CuI (0.15 mmol) in methanol (50 mmol) was stirred in the presence of dehydrating reagent $CH(OMe)_3$ (2.0 mmol) under CO (80 kg/cm^2) and O_2 (5 kg/cm^2), oxamate (**1a**) and 1,1′-oxalyldipiperidine were obtained in 29% and 44% yields, respectively. As a co-catalyst, CuI gives the best results. The use of an excess of alcohol increases the amount of cross double carbonylation products. It is noteworthy that when the same mixture was reacted under the 1 : 1 mixture of CO and O_2 (1 kg/cm^2), monocarbonylation products, 1-methoxycarbonylpiperidine (43%) and 1,1′-carbonyldipiperidine (33%) were obtained exclusively.

When the catalytic reaction is applied to β-aminoalcohols, intramolecular double carbonylation proceeds highly efficiently, giving the corresponding cyclic oxamates (**2**), equation (4). In this case, the addition of dehydrating reagent $CH(OMe)_3$ is not necessary. Typically, into a 10 ml autoclave were placed 2-(ethylamino)ethanol (1.0 mmol), $PdCl_2(MeCN)_2$ (0.05 mmol), CuI (0.25 mmol), and acetonitrile (2 ml). The autoclave was charged with CO (80 kg/cm^2) and O_2 (5 kg/cm^2), and the mixture was stirred at room temperature for 20 h. Filtration and subsequent chromatography on Florisil gave 4-ethylmorpholine-2,3-dione (**2a**) (m.p. 70.0—70.5 °C), in 86% yield. The representative results of the intramolecular double carbonylation of aminoalcohols are summarized in Table 1.

Cyclic oxamates are excellent protecting compounds of aminoalcohols and important precursors for biologically active compounds, particularly β-adrenergic blocking agents.

† Quite recently, a du Pont chemist reported double carbonylation of aminoalcohols using a stoicheiometric amount of $PdCl_2$ and NaOAc in less than 57% yields (ref. 6).

‡ The structure of the products were determined on the basis of analytical, and i.r. and n.m.r. spectral data.

Table 1. Palladium-catalysed carbonylation of aminoalcohols.[a]

Oxamate[b]	% Isolated Yield
(**2a**)	86
(**2b**)	85
(**2c**)	82
(**2d**)	84[c]
(**3**)	67
(**4**)	76
(**5**)	70

[a] The reaction was carried out according to the procedure described in the text. [b] The structures of the products were determined on the basis of analytical and i.r., n.m.r., and mass spectral data. [c] Monocarbonylation product, 3-butyl-5-(dibutylamino)methyl-1,3-oxazolidine-2-one was obtained in 5% yield.

For example, 4-butyl-6-(dibutylamino)methylmorpholine-2,3-dione (**2d**) is an active local anaesthetic and analgesic agent.[7] Furthermore, the oxamates derived from optically active aminoalcohols which are readily prepared by either reduction of amino acids or amination of asymmetric epoxides would be potential precursors for further asymmetric inductions.

The reaction can be rationalized by assuming the pathway shown in Scheme 1. The amine or alcohol attacks the carbon monoxide which co-ordinates to PdX_2L_2 to give the carbamoylpalladium complex (**6**) or alkoxycarbonylpalladium complex (**7**).[8] Further co-ordination of carbon monoxide to (**6**) or (**7**) and the subsequent nucleophilic attack of alcohol or amine gives the alkoxycarbonylcarbamoylpalladium complex (**8**). Reductive elimination of oxamate (**9**) gives PdL_2 which is readily oxidized with O_2–CuI–HCl to complete the catalytic cycle. Using a stoicheiometric amount of a palladium(II) phosphine complex, intermediate complexes were isolated. The reaction of piperidine with $PdCl_2(PEt_3)_2$ (1 equiv.) in methanol (100 equiv.) under CO (1 kg/cm^2) gave the carbamoyl complex (**10**) and alkoxycarbonyl complex (**11**) in 6% and 57% yields, respectively,‡ but these yields do not necessarily indicate directly whether the reaction proceeds mainly *via* (**6**) or *via* (**7**).

In summary palladium-catalysed cross double carbonylation of amines and alcohols proceeds efficiently to give oxamates, particularly synthetically versatile cyclic oxamates.

Received, 9th September 1986; Com. 1297

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