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REGIOSPECIFIC SYNTHESIS OF α-METHYLENE-β-LACTAMS BY A HOMOGENEOUS PALLADIUM CATALYZED RING EXPANSION-CARBONYLATION REACTION

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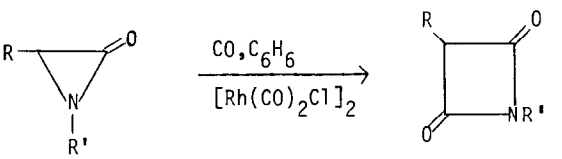
Summary: Tetrakis(triphenylphosphine)palladium(0) [or palladium acetate and added triphenylphosphine] catalyzes the carbonylation of methyleneaziridines to α-methylene-β-lactams at room temperature and one atmosphere.

Three membered ring compounds undergo some fascinating ring expansion reactions with metal complexes. For example, treatment of diaziridines with cobalt carbonyl results in a novel ring expansion to oxazolines [2]. Rhodium(I) catalyzed carbonylation of aziridines affords β-lactams with the carbon monoxide insertion occurring into the most substituted carbon-nitrogen bond [3]. Metal complex catalyzed carbonyl insertion of α-lactams also occurs into the saturated carbon-nitrogen rather than the carbonyl carbon-nitrogen bond of the reactant (eq. 1) [4]. It was anticipated that replacement of the carbonyl function of an α-lactam by a carbon-carbon double

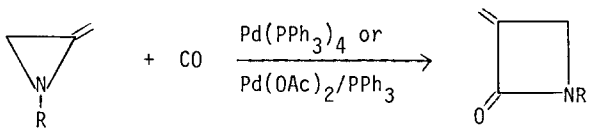


(eq. 1)

bond, i.e. a methyleneaziridine, would alter the regiochemistry of the ring expansion-carbonylation reaction since the unsaturated moiety, being a stronger donor than a carbonyl group, could π-complex to the metal. The latter would also be coordinated to the nitrogen atom (by means of the lone pair) and therefore carbonyl insertion, should it occur, would take place into the unsaturated carbon-nitrogen bond. We now wish to report that the metal complex catalyzed carbonylation reaction of methyleneaziridines indeed does proceed as

anticipated, affording α-methylene-β-lactams in good yields.

Treatment of N-n-butylmethyleneaziridine [1,R=n-C_4H_9], readily prepared from 2,3-dibromopropene and n-butylamine[5], with carbon monoxide and a catalytic quantity of tetrakis(triphenylphosphine)palladium(0), in



(1) (2)

methylene chloride for 40 hours at room temperature and one atmosphere, afforded pure 1-n-butyl-3-methyleneazetidin-2-one [2,R=n-C_4H_9] in 79 % yield. The ratio of substrate to catalyst used was 10:1. The structure of the product was determined on the basis of analytical[6] and spectral data. A carbonyl stretching band was observed at 1740 cm^{-1}(neat), consistent with an α-methylene-β-lactam [7] and distinct from the isomeric 4-methyleneazetidin-2-one [ν_{CO} 1775-1780 cm^{-1}] [8]. The proton magnetic resonance spectrum ($CDCl_3$) displayed signals at δ 0.86(CH_3), 1.42(CH_2CH_2), 3.28(NCH_2), 3.67(CH_2(ring)), 5.08, and 5.62 (vinyl protons) ppm while a molecular ion appeared in the mass spectrum at m/e 139. While palladium(0) catalysts containing bidentate ligands such as bis(1,2-bisdiphenylphosphino)ethane or bis(dibenzylideneacetone)palladium were not useful, palladium acetate with added triphenylphosphine is a viable catalytic system. Triphenylphosphite can be used instead of triphenylphosphine, but product yields are lower.

The palladium catalyzed carbonylation and ring expansion reaction is applicable to a variety of methyleneaziridines, and the results are given in Table 1. Good yields were realized with methyleneaziridines containing alkoxy and acetal units. The latter, of course, is convertible to the aldehyde.

The following general procedure was used: carbon monoxide was bubbled through a methylene chloride (4 ml) solution containing palladium acetate or $Pd(PPh_3)_4$ [0.135 mmol]. After two minutes triphenylphosphine [0.54 mmol - if added] in methylene chloride (2 ml) was added followed, two minutes later, by 1 in CH_2Cl_2 (2 ml). After stirring at room temperature (see Table 1 for reaction times), the solvent was removed by rotary evaporation and the residue was subjected to thin-layer chromatography (silica gel) using 8:1 hexane-ethyl acetate to give pure 2.

TABLE 1

Palladium Catalyzed Carbonylation of Methyleneaziridines [a]

1, R=	Reaction time, hr	Catalyst	Yield of 2, %[b]
$n\text{-}C_4H_9$	40	$Pd(PPh_3)_4$	79
	40	$Pd(dba)_2$	10
$n\text{-}C_6H_{13}$	21	$Pd(OAc)_2,4PPh_3$	72
	20	$Pd(OAc)_2,4P(OPh)_3$	44
1-adamantyl	90[c]	$Pd(PPh_3)_4$	55
	40	$Pd(OAc)_2,4PPh_3$	43
$CH_2CH_2CH_2OCH_3$	21	$Pd(OAc)_2,4PPh_3$	75
$CH_2CH(OCH_3)_2$	21	$Pd(OAc)_2,4PPh_3$	83
	20	$Pd(PPh_3)_4$	75

[a]conditions - see general procedure. [b]Yields are of analytically pure products. [c]48°C, 1,2-dichloroethane as the solvent.

In conclusion, α-methylene-β-lactams, an important class of compounds [7], can be isolated in good yields by the palladium catalyzed carbonylation of methyleneaziridines. The reaction is regiospecific, proceeds under exceptionally mild conditions, and is simple in execution and workup. It compares favorably with other metal mediated routes to such heterocycles including the palladium catalyzed carbonylation of 2-bromoalkylamines which requires temperatures of 80-120° and pressures of 1-4 atmospheres [9], and the use of chromium carbene [10] or cationic iron vinylidene complexes [11] - elegant methods which, however, are stoichiometric with respect to the metal complex.

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