Regioselective Palladium-catalysed Amination of 4-Chloroacetoxyalk-2-enoic Esters: Synthesis of Pyrrol-2(5*H*)-ones (4-but-2-enelactams)

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Palladium(0)-catalysed reactions of 4-chloroacetoxyalk-2-enoic esters with amines selectively give 4-aminoalk-2-enoic esters, which are readily converted into pyrrol-2(5*H*)-ones (4-but-2-enelactams).

One of the most synthetically useful reactions involving organopalladium intermediates is the nucleophilic substitution reaction of π-allylic Pd complexes with carbon, nitrogen, and oxygen nucleophiles.[1—3] Pd^0-catalysed exchanges of allylic hydroxy compounds,[4,5] acetates,[4—8] and phenyl ethers[4,5] with primary and secondary amine groups generally proceed in good to excellent yields. Although 1-acetoxy-4-hydroxyalk-2-enes,[8] 1,4-diacetoxyalk-2-enes,[8] and 1-acetoxy-5-methoxycarbonylalk-2-enes[7] are reactive in Pd^0-catalysed aminations, the similar reactions of 1-acyloxyalk-2-enes (**1**) containing an electron-withdrawing group at the conjugated 3-position have not been reported. The introduction of an electron-withdrawing group at the conjugated position would lower the reactivity toward a Pd catalyst, increase the number of positions capable of being attacked by a nucleophile, and favour the deprotonation of an intermediary π-allylic Pd complex.[9,10] We now report that treatment of methyl (*E*)-4-chloroacetoxyalk-2-enoates (**1A**) with an amine in the presence of a Pd^0 catalyst selectively produces methyl (*E*)-4-aminoalk-2-enoates (**2**), which can be transformed into pyrrol-2(5*H*)-ones (4-but-2-enelactams) (**5**).

Simple treatment of aldehydes and methyl *p*-chlorophenylsulphinylacetate with piperidine yielded methyl (*E*)-4-hydroxyalk-2-enoates (**3**),[11] which were converted into the esters (**1**) in excellent yields by employing the appropriate acyl chloride or trifluoroacetic anhydride (TFAA) and 4-dimethylaminopyridine (DMAP). Amination of (**1**) gave (**2**).†

† In a typical amination, to $Pd_2(dba)_3 \cdot CHCl_3$[12] (dba = dibenzylideneacetone) (0.05 equiv.) and Ph_3P (0.05 equiv.) in toluene (85 °C) with stirring under argon were added methyl (*E*)-4-chloroacetoxydec-2-enoate (**1Aa**; $R^1 = Me[CH_2]_4$) (1 equiv.) and Bu^nNH_2 (2 equiv.) at the same time by two syringes, and stirring was continued for 15 min. After cooling the mixture was washed with aqueous NaCl, dried over Na_2SO_4, and evaporated to dryness. Chromatography on silica gel gave methyl (*E*)-4-butylaminodec-2-enoate (**2a**; $R^1 = Me[CH_2]_4$, $R^2 = Bu^n$), the γ-substituted product in 83% yield; the α-substituted ester (**2'a**) and the (*Z*)-isomer of (**2a**) were not obtained.

Table 1. Preparation of (2).

R^1	Y	R^2	Temp./ °C[a]	Yield/ %	Other products (yield/%)
$Me[CH_2]_4$	$COCH_2Cl$	Bu^n	85	83	
$Me[CH_2]_4$	Ac	Bu^n	50[b]	0	(**1Ba**) (90) + (**4a**) (10)
$Me[CH_2]_4$	$COCF_3$	Bu^n	55	54	(**3a**) (28)
$Me[CH_2]_4$	CO_2Et	Bu^n	20	50	(**4a**) (24)
$Me[CH_2]_4$	$COCH_2Cl$	$Me[CH_2]_5$	85	75	
$Me[CH_2]_4$	$COCH_2Cl$	$PhCH_2$	85	76	
$Me[CH_2]_4$	$COCH_2Cl$	Ph	85	77	
Me	$COCH_2Cl$	$Me[CH_2]_5$	85	83	
Me	$COCH_2Cl$	$PhCH_2$	85	86	
Me	$COCH_2Cl$	Pr^iCH_2	85	60	
Me	CO_2Et	Bu^n	20	78	(**4c**) (5)
$CH_2{=}CH[CH_2]_6$	$COCH_2Cl$	Bu^n	85	74	
$MeOCO[CH_2]_2$	$COCH_2Cl$	Bu^n	85	65	

[a] Reaction time 15 min. [b] Reaction time 5 h.

The allylic acetate (**1B**), although in general widely used, scarcely reacted in the presence of a Pd^0 catalyst. The allylic trifluoroacetate (**1C**) reacted easily, but competitive amination occurred at CF_3CO to give (**3**). Amination of the π-allylic Pd complexes readily formed from the allylic carbonates (**1D**) was accompanied by deprotonation yielding methyl alka-2,4-dienoates (**4**)[9] probably owing to the formation of the basic ^-OEt. Amination of the π-allylic Pd complex generated from (**1A**) occurred with satisfactory results, because $^-OCOCH_2Cl$ is a better leaving group than ^-OAc, and less basic than ^-OEt. Similar yields of (**2**) were obtained by use of $Pd(Ph_3P)_4$ instead of $Pd_2(dba)_3{\cdot}CHCl_3$. Results are given in Table 1 (Scheme 1).

$R^1[CH_2]_2CHO + p\text{-}ClC_6H_4S(O)CH_2CO_2Me$

↓ i

$(E)\text{-}R^1CH_2CH(OH)CH{=}CHCO_2Me$

(**3**)

↓ ii

$(E)\text{-}R^1CH_2CH(OY)CH{=}CHCO_2Me$

(**1A**); Y = $COCH_2Cl$
(**1B**); Y = Ac
(**1C**); Y = $COCF_3$
(**1D**); Y = CO_2Et

↓ iii

$(E)\text{-}R^1CH_2CH(NHR^2)CH{=}CHCO_2Me$ + $\{R^1[CH{=}CH]_2CO_2Me$ + (**3**)$\}$

(**2**) (**4**)

$R^1CH_2CH{=}CHCH(NHR^2)CO_2Me$

(**2'**)

Scheme 1. *Reagents:* i, piperidine; ii, YCl or TFAA, DMAP; iii, R^2NH_2, $Pd_2(dba)_3{\cdot}CHCl_3{+}Ph_3P$ or $Pd(Ph_3P)$.

(**2**) —i→ PhS, R^1CH_2, N, O, Bu^n (**6**) —ii, iii→ R^1CH_2, N, O, Bu^n

(**5a**); $R^1 = Me[CH_2]_4$
(**5b**); $R^1 = Me$
(**5c**); $R^1 = CH_2{=}CH[CH_2]_6$

Scheme 2. *Reagents:* i, PhSH, 80 °C; ii, MCPBA; iii, benzene, 80 °C.

Compounds (**2**) were readily converted into the lactams (**5**) in reasonable yields by the following procedure: (i) cyclization to the 3-phenylthiopyrrolidinones (**6**) by treatment with benzenethiol at 80 °C,[13] (ii) oxidation with *m*-chloroperbenzoic acid (MCPBA) (1 equiv.) to give the corresponding sulphoxides, and (iii) elimination of benzenesulphenic acid by refluxing in benzene (Scheme 2). The total yields of (**5a**), (**5b**), and (**5c**) based on (**2**) were 64, 63, and 61%, respectively. The butenolide unit is widely found in naturally occurring compounds with physiological activity and a variety of methods are available for the preparation of butenolides. Compounds (**5**) and (**6**) are versatile synthetic intermediates for preparing the nitrogen analogues of butenolides which may show interesting physiological activities.

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