

## 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  $\pi$ -allylic Pd complexes with carbon, nitrogen, and oxygen nucleophiles.<sup>1-3</sup> Pd<sup>0</sup>-catalysed exchanges of allylic hydroxy compounds,<sup>4,5</sup> acetates,<sup>4-8</sup> and phenyl ethers<sup>4,5</sup> with primary and secondary amine groups generally proceed in good to excellent yields. Although 1-acetoxy-4-hydroxyalk-2-enes,<sup>8</sup> 1,4-diacetoxyalk-2-enes,<sup>8</sup> and 1-acetoxy-5-methoxycarbonylalk-2-enes<sup>7</sup> are reactive in Pd<sup>0</sup>-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  $\pi$ -allylic Pd complex.<sup>9,10</sup> We now report that treatment of methyl (*E*)-4-chloroacetoxyalk-2-enoates (**1A**) with an amine in the presence of a Pd<sup>0</sup> 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**),<sup>11</sup> 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**).<sup>†</sup>

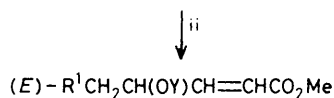
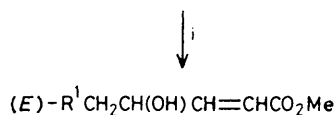
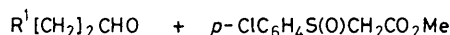
<sup>†</sup> In a typical amination, to Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub><sup>12</sup> (dba = dibenzylideneacetone) (0.05 equiv.) and Ph<sub>3</sub>P (0.05 equiv.) in toluene (85 °C) with stirring under argon were added methyl (*E*)-4-chloroacetoxydec-2-enoate (**1Aa**; R<sup>1</sup> = Me[CH<sub>2</sub>]<sub>4</sub>) (1 equiv.) and Bu<sup>n</sup>NH<sub>2</sub> (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<sub>2</sub>SO<sub>4</sub>, and evaporated to dryness. Chromatography on silica gel gave methyl (*E*)-4-butylaminodec-2-enoate (**2a**; R<sup>1</sup> = Me[CH<sub>2</sub>]<sub>4</sub>, R<sup>2</sup> = Bu<sup>n</sup>), the  $\gamma$ -substituted product in 83% yield; the  $\alpha$ -substituted ester (**2'a**) and the (*Z*)-isomer of (**2a**) were not obtained.

Table 1. Preparation of (2).

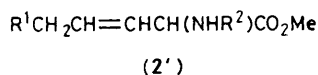
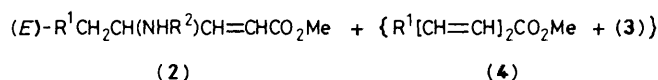
R <sup>1</sup>	Y	R <sup>2</sup>	Temp./ °C <sup>a</sup>	Yield/ %	Other products (yield/%)
Me[CH <sub>2</sub> ] <sub>4</sub>	COCH <sub>2</sub> Cl	Bu <sup>n</sup>	85	83	
Me[CH <sub>2</sub> ] <sub>4</sub>	Ac	Bu <sup>n</sup>	50 <sup>b</sup>	0	(1Ba) (90) + (4a) (10)
Me[CH <sub>2</sub> ] <sub>4</sub>	COCF <sub>3</sub>	Bu <sup>n</sup>	55	54	(3a) (28)
Me[CH <sub>2</sub> ] <sub>4</sub>	CO <sub>2</sub> Et	Bu <sup>n</sup>	20	50	(4a) (24)
Me[CH <sub>2</sub> ] <sub>4</sub>	COCH <sub>2</sub> Cl	Me[CH <sub>2</sub> ] <sub>5</sub>	85	75	
Me[CH <sub>2</sub> ] <sub>4</sub>	COCH <sub>2</sub> Cl	PhCH <sub>2</sub>	85	76	
Me[CH <sub>2</sub> ] <sub>4</sub>	COCH <sub>2</sub> Cl	Ph	85	77	
Me	COCH <sub>2</sub> Cl	Me[CH <sub>2</sub> ] <sub>5</sub>	85	83	
Me	COCH <sub>2</sub> Cl	PhCH <sub>2</sub>	85	86	
Me	COCH <sub>2</sub> Cl	Pr <sup>i</sup> CH <sub>2</sub>	85	60	
Me	CO <sub>2</sub> Et	Bu <sup>n</sup>	20	78	(4c) (5)
CH <sub>2</sub> =CH[CH <sub>2</sub> ] <sub>6</sub>	COCH <sub>2</sub> Cl	Bu <sup>n</sup>	85	74	
MeOCO[CH <sub>2</sub> ] <sub>2</sub>	COCH <sub>2</sub> Cl	Bu <sup>n</sup>	85	65	

<sup>a</sup> Reaction time 15 min. <sup>b</sup> Reaction time 5 h.

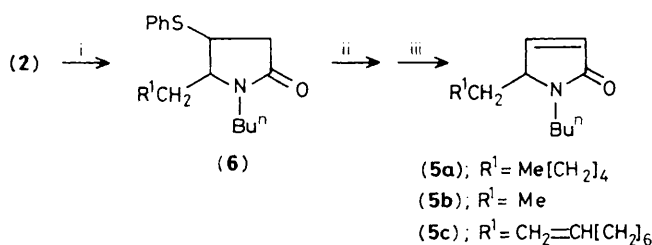
The allylic acetate (1B), although in general widely used, scarcely reacted in the presence of a Pd<sup>0</sup> catalyst. The allylic trifluoroacetate (1C) reacted easily, but competitive amination occurred at CF<sub>3</sub>CO to give (3). Amination of the π-allylic



- (1A); Y = COCH<sub>2</sub>Cl  
 (1B); Y = Ac  
 (1C); Y = COCF<sub>3</sub>  
 (1D); Y = CO<sub>2</sub>Et



Scheme 1. Reagents: i, piperidine; ii, YCl or TFAA, DMAP; iii, R<sup>2</sup>NH<sub>2</sub>, Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> + Ph<sub>3</sub>P or Pd(Ph<sub>3</sub>P).



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

Pd complexes readily formed from the allylic carbonates (1D) was accompanied by deprotonation yielding methyl alka-2,4-dienoates (4)<sup>9</sup> 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<sub>2</sub>Cl is a better leaving group than -OAc, and less basic than -OEt. Similar yields of (2) were obtained by use of Pd(Ph<sub>3</sub>P)<sub>4</sub> instead of Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub>. Results are given in Table 1 (Scheme 1).

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,<sup>13</sup> (ii) oxidation with *m*-chloroperbenzoic acid (MCPBA) (1 equiv.) to give the corresponding sulphoxides, and (iii) elimination of benzenesulphonic 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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## References

- B. M. Trost, *Tetrahedron*, 1977, **33**, 2615.
- J. Tsuji, 'Organic Synthesis with Palladium Compounds,' Springer-Verlag, Berlin, 1980.
- R. F. Heck, 'Palladium Reagents in Organic Syntheses,' Academic Press, London, 1985.
- K. E. Atkins, W. E. Walker, and R. M. Manyik, *Tetrahedron Lett.*, 1970, **11**, 3821.
- K. Takahashi, A. Miyake, and G. Hata, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 230.
- B. M. Trost and J. P. Genêt, *J. Am. Chem. Soc.*, 1976, **98**, 8516.
- B. M. Trost and E. Keinan, *J. Org. Chem.*, 1979, **44**, 3451.
- J. P. Genêt, M. Balabane, J. E. Bäckvall, and J. E. Nyström, *Tetrahedron Lett.*, 1983, **24**, 2745, and references cited therein.
- T. Sakai, K. Seko, A. Tsuji, M. Utaka, and A. Takeda, *J. Org. Chem.*, 1982, **47**, 1101.
- B. M. Trost, M. Lautens, and B. Peterson, *Tetrahedron Lett.*, 1983, **24**, 4525.
- R. Tanikaga, Y. Nozaki, T. Tamura, and A. Kaji, *Synthesis*, 1983, 134.
- T. Ukai, H. Kawazura, Y. Ishii, J. J. Bonnet, and J. A. Ibers, *J. Organomet. Chem.*, 1974, **65**, 253.
- R. Tanikaga, H. Yamashita, and A. Kaji, *Synthesis*, 1986, 416.