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SYNTHESIS OF DEHYDROPHENYLALANINE DERIVATIVES BY PALLADIUM CATALYZED ARYLATION OF 2-ACETAMIDOACRYLIC ACID

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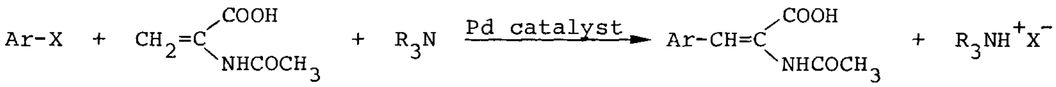
Summary: Arylation of 2-acetamidoacrylic acid using $Pd(OAc)_2/PPh_3$ or $PdCl_2(PPh_3)_2$ as catalytic systems leads to α-acetamidocinnamic acids of Z configuration.

The application of rhodium complexes with chiral phosphines as homogeneous catalysts for the hydrogenation of N-acylaminoacrylic acids has permitted the enantioselective synthesis of α-aminoacids with a high degree of stereospecificity and in high yields.[1] Most frequently substituted and unsubstituted α-acylaminocinnamic acids are used as prochiral substrates. These are prepared according to the Plöchl-Erlenmeyer method, which involves reaction between an aldehyde and acetylglycine followed by hydrolysis of the resulting azlactones.[2]

In principle, α-acylaminocinnamic acids could be prepared by palladium catalyzed arylation of the readily available α-acylaminoacrylic acid according to the Heck procedure, which provides a very convenient method for forming C-C bonds at vinylic positions.[3,4]



$$Ar\text{-}X + CH_2{=}C\begin{matrix}COOH\\ NHCOCH_3\end{matrix} + R_3N \xrightarrow{\text{Pd catalyst}} Ar\text{-}CH{=}C\begin{matrix}COOH\\ NHCOCH_3\end{matrix} + R_3NH^+X^-$$

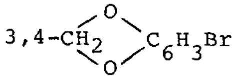
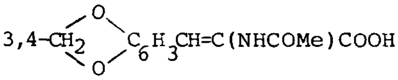
However, unsuccesfull attempts toward this direction have been reported by Ziegler and Heck.[5]

Due to our interest in the area of C-C bond formation using organic halides and transition metal compounds[4,6] we undertook an investigation of the above arylation and now we wish to report that under suitable conditions the process can be performed in a satisfactory manner. Palladium acetate in the presence of triphenylphosphine or dichlorobis(triphenylphosphine)palladium were used as catalysts. Triethylamine, tetramethylethylenediamine or tri-n-butylamine were required as organic base. The obtained results are reported in the Table.

In a typical procedure, bromobenzene (1.9 g, 12 mmol), 2-acetamidoacrylic acid (1.8 g, 14 mmol), tetramethylethylenediamine (TMED, 3.2 g, 28 mmol), $Pd(OAc)_2$ (0.026 g, 0.12 mmol) and PPh_3 (0.13 g, 0.48 mmol) were stirred by means of a magnetic bar in a 25 ml round-bottomed flask. The mixture was heated at 110°C under a reflux condenser in a N_2 atmosphere for 24 h. After this time GLC analysis showed that all the bromide had reacted. The cooled reaction mixture was stirred with

TABLE

Palladium catalyzed arylation of 2-acetamidoacrylic acid.[a]

Aryl Halide	Catalyst[b]	Base	Time (h)	Product[c]	%Yield[d]
C_6H_5Br	$Pd(OAc)_2/PPh_3$	TMED	24	$C_6H_5CH{=}C(NHCOMe)COOH$[e]	70
C_6H_5Br	$PdCl_2(PPh_3)_2$	TMED	37	$C_6H_5CH{=}C(NHCOMe)COOH$[e]	57
C_6H_5Br	$Pd(OAc)_2/PPh_3$	Et_3N	11	$C_6H_5CH{=}C(NHCOMe)COOH$[e]	62
$4\text{-}ClC_6H_4Br$	$Pd(OAc)_2/PPh_3$	TMED	45	$4\text{-}ClC_6H_4CH{=}C(NHCOMe)COOH$	40
$4\text{-}ClC_6H_4Br$	$Pd(OAc)_2/PPh_3$	Et_3N	22	$4\text{-}ClC_6H_4CH{=}C(NHCOMe)COOH$	76
$4\text{-}MeOC_6H_4Br$	$PdCl_2(PPh_3)_2$	TMED	38	$4\text{-}MeOC_6H_4CH{=}C(NHCOMe)COOH$	45
$4\text{-}MeOC_6H_4Br$	$Pd(OAc)_2/PPh_3$	Et_3N	20	$4\text{-}MeOC_6H_4CH{=}C(NHCOMe)COOH$	75
$3,4\text{-}(MeO)_2C_6H_3Br$	$Pd(OAc)_2/PPh_3$	TMED	42	$3,4\text{-}(MeO)_2C_6H_3CH{=}C(NHCOMe)COOH$	60
 $3,4\text{-}CH_2{<}^{O}_{O}{>}C_6H_3Br$	$Pd(OAc)_2/PPh_3$	Et_3N	8	 $3,4\text{-}CH_2{<}^{O}_{O}{>}C_6H_3CH{=}C(NHCOMe)COOH$	53
$2\text{-}MeC_6H_4Br$	$Pd(OAc)_2/PPh_3$	Et_3N	30	$2\text{-}MeC_6H_4CH{=}C(NHCOMe)COOH$[f]	52
$1\text{-}C_{10}H_7Br$	$Pd(OAc)_2/PPh_3$	Et_3N	22	$1\text{-}C_{10}H_7CH{=}C(NHCOMe)COOH$[f]	60
$4\text{-}PhCOOC_6H_4Br$	$Pd(OAc)_2/PPh_3$	$\underline{n}\text{-}Bu_3N$	36	$4\text{-}PhCOOC_6H_4CH{=}C(NHCOMe)COOH$[f,g]	25

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[a] All reactions were carried out at 110°C (oil bath temperature). [b] 1 mole% of $Pd(OAc)_2$ or $PdCl_2(PPh_3)_2$ and 2-4 mole % of PPh_3. [c] Z-configuration (see text). [d] Yields are of isolated purified products. [e] Obtained as dihydrate. [f] These new compounds had satisfactory ^1H and ^{13}C NMR and mass spectra. [g] Lower yields were obtained with other bases.

dilute HCl and the insoluble product was filtered and washed with water. Crystallization of the almost pure product from water gave α-acetamidocinnamic acid dihydrate (70% yield) m.p. 185-6 °C.[7]

The same procedure was followed when tri-n-butylamine was used, but, after reaction completion, a solution of $NaHCO_3$ was added to the mixture. Stirring for 1-2 hours was followed by separation and acidification of the aqueous phase. Furthermore, the reactions with triethylamine were carried out in capped heavy walled Pyrex flasks filled with nitrogen. Vigorous stirring was required and the work up was similar to that used with TMED.

The isolated α-acetamidocinnamic acid as well as the 4-chloro-,[8] 4-methoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxy-derivatives[9] had m.p.s which did not differ significantly from those of compounds obtained via the azlactone route. Furthermore, the IR and NMR spectroscopic features of commercial sample of α-acetamidocinnamic acid and of the 3,4-dimethoxy-derivative prepared independently by the Plöchl-Erlenmeyer method, were identical to those presented by the products of our investigation. Compounds obtained by the azlactone route are usually considered to have Z-configuration.[10] However, the actual determination of the geometry has been mainly performed, sometimes controversially,[11] on the parent azlactones, on esters, or on the benzamido-derivatives rather than on the acetamidocinnamic acids themselves.[12] Only recently the molecular structure of a commercial sample of α-acetamidocinnamic acid dihydrate was determined by three-dimensional X-ray data and the Z configuration was shown to be valid.[13] On the other hand ^{13}C NMR spectroscopy has proved to be a powerful tool for establishing the configuration of similar compounds[14,15] and we decided to apply this technique to all the products of our investigation with the aim of assigning the double bond geometry.

^{13}C NMR single resonance spectra of the reaction products showed two closely spaced carbonyl resonances (three for the benzoxy-derivative). As suggested by available data,[15] an unambiguous assignment of the resonance to the amide and carboxylic carbonyl can be made only on the basis of the long-range ^1H, ^{13}C couplings. Therefore, the spectra of the carbonyl region were expanded and both resonances appeared as multiplets originating from coupling to the olefinic and methyl proton as well as to the N-H proton, which undergoes exchange at a rate low enough to give rise to observable coupling.

Low power selective irradiation of the methyl protons and deuterium exchange experiments allowed the assignments of the resonances and of all the ^1H, ^{13}C coupling constants for the carbonyl carbons. Furthermore, the spectra indicated that only a single isomer was present in the isolated products. The values of the $^1H\text{-}C{=}C\text{-}^{13}COOH$ coupling costants were in the range 4.7-5.2 Hz.[16] Therefore they are consistent with a cis arrangement of the coupled nuclei and the assignment of the Z configuration can be considered unambiguous for all the products obtained.

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16) Other coupling constants were in the following ranges: $^{2}J_{^{1}HC^{13}C}$, 5.9-6.3 Hz; $^{2}J_{^{1}HN^{13}C}$, 2.8-3.0 Hz; $^{3}J_{^{1}HNC^{13}C}$, 1.6-2.1 Hz. Chemical shifts (relative to internal TMS) were in the ranges 168.1-170.2 δ for $-NH-^{13}CO-CH_3$ and 165.2-166.5 δ for $-^{13}COOH$. ^{13}C NMR spectra were recorded on a Varian XL-200 (DMSO, 20°C). Digital resolution was 0.50 Hz per point and the FID was not weighted by mathematical functions.

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