Synthesis of α-Amino Acids by Alkylation of Diethyl Acetamidomalonate in the Presence of Palladium Complexes

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The use of diethyl acetamidomalonate (**1a**) and its sodium derivative (**1b**) as nucleophilic reagents toward olefins and diolefins via their π-olefin– and π-allyl–palladium complexes has been studied. In the presence of a palladium catalyst, 1,3-dienes reacted with **1a** to form linear 2,7-alkadienyl derivatives as main products. With the same catalyst, diethyl allylacetamidomalonate was obtained by an intermolecular exchange reaction of the allyl groups of allyl acetate or allyl alcohol. Allylic derivatives of **1a** were also obtained by the stoichiometric reaction of **1b** on isolated π-allyl–palladium complexes. The analogous nucleophilic alkylation of monoolefins is also described. All these condensation products may be further subjected to hydrolysis and decarboxylation to give the corresponding α-amino acids.

The use of (acylamido)malonate derivatives as synthons in the preparation of nonnaturally or naturally occurring α-amino acids is a well-known route for the introduction of a glycine group on various organic substrates.[1] The reactions involving these (acylamido)malonate compounds may be divided in two groups:

(i) the reaction of alkyl halides and related compounds with sodium derivatives, e.g.

$$R^+ + {}^-C(COOR^1)_2 \longrightarrow RC(COOR^1)_2 \xrightarrow[H^+]{H_2O} RCHCOOH$$
$$\qquad\qquad\quad | \qquad\qquad\quad | \qquad\qquad\quad |$$
$$\qquad\qquad NHCOR^2 \qquad\quad NHCOR^2 \qquad\quad NH_2$$

(ii) the addition to activated double bonds (Michael-type reactions), e.g.

$$RCH{=}CH_2 + HC(COOR^1)_2 \xrightarrow{RO^-} RCH_2CH_2C(COOR^1)_2 \xrightarrow[H^+]{H_2O}$$
$$\qquad\qquad\quad | \qquad\qquad\qquad\quad |$$
$$\qquad\qquad NHCOR^2 \qquad\qquad NHCOR^2$$
$$RCH_2CH_2CHCOOH$$
$$\qquad\quad |$$
$$\qquad NH_2$$

These methods have been successfully applied to the synthesis of such α-amino acids as serine, leucine, ornithine, phenylalanine, and tryptophan.

The extension of the use of (acylamido)malonate reagents to stoichiometric or catalytic reactions with transition-metal complexes would considerably enhance the potentiality of the synthesis. In this way, the reactivity of palladium complexes opens large possibilities.

Thus, the formation of a carbon–carbon bond by the reaction of π-allyl–palladium chloride complexes with a malonate anion, first mentioned by Tsuji,[2] proved to be of a general applicability in the synthesis of allylic derivatives since the work of Trost[3] and others. This reaction has recently been extended by Hegedus[4] to the attack of a π-olefin–palladium(II) complex, affording vinyl-substituted compounds.

On the other hand, among the numerous reactions leading to carbon–carbon bond formation catalyzed by palladium complexes, it is worth mentioning the dimerization reaction of conjugated diolefins with the incorporation of nucleophiles such as methylene-active compounds, affording 2,7-octadienyl derivatives,[5] and the allyl group exchange reaction.[6]

Scheme I

$$\mathbf{1a} + CH_2{=}C(R)CH{=}CH_2 \xrightarrow{\text{Pd catalyst}}$$
$$AcNHC(COOEt)_2CH_2C(R){=}CH(CH_2)_3C(R){=}CH_2 \xrightarrow{H_2,\ Pd/C}$$
$$\mathbf{2,\ 5}$$
$$AcNHC(COOEt)_2CH_2CH(R)(CH_2)_4CH(R)CH_3 \xrightarrow[-CO_2]{H_2O,\ H^+}$$
$$\mathbf{3}$$
$$HOCOCH(NH_2)CH_2CH(R)(CH_2)_4CH(R)CH_3$$
$$\mathbf{4}$$

2–4, R = H
5, R = CH_3

With this reactivity in mind, we have studied the behavior of diethyl acetamidomalonate (**1a**) and its sodium derivative (**1b**) (i) with π-olefin– and π-allyl–palladium complexes and (ii) with diolefins or allylic compounds in the presence of palladium species as catalysts.

$$RC(COOEt)_2$$
$$\quad |$$
$$NHAc$$

1a, R = H
b, R = Na

This opens a new route to α-amino acids from readily available unsaturated compounds.

Results and Discussion

Palladium-Catalyzed Reactions of 1,3-Dienes with 1a. The reaction of **1a** with 1,3-butadiene in the presence of $Pd(OAc)_2$–PPh_3–PhONa as a catalyst produced a 91% yield of diethyl 1-octa-2,7-dienylacetamidomalonate (**2**) as the main product (Scheme I).

The product **2** has been identified by its IR, NMR, and mass spectra. The IR analysis revealed that the internal double bond consists exclusively of the trans form.

It is remarkable that, unlike the case for malonate esters, no byproducts, such as branched isomers, were observed.

Subsequent hydrogenation of **2** with palladium on charcoal gave the saturated compound **3** with 67% yield. The synthesis of α-amino acid **4** was completed by total hydrolysis of **3** with 70% yield. Both **3** and **4** were

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(5) G. Hata, K. Takahashi, and A. Miyake, *Chem. Ind. (London)*, 1836 (1969); G. Hata, K. Takahashi, and A. Miyake, *J. Org. Chem.*, **36**, 2116 (1971).
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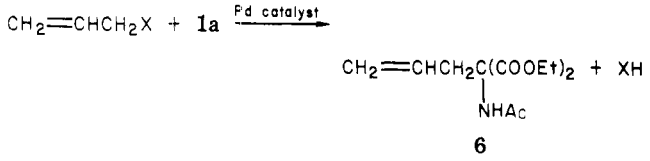
Scheme II



6

X = OH, OAc, Cl

Table I. Palladium-Catalyzed Transfer of Allyl Groups

allylic reagent	solvent	T, °C	time, h	yield,[a] %
allyl chloride	CH_2Cl_2	100	7	5
	DMF	100	8	15
allyl acetate	CH_2Cl_2	90	6	15
	DMF	90	6	32
	neat	90	8	33
allyl alcohol	CH_2Cl_2	100	7	50
	DMF	70	8	60

[a] Determined by VPC and based on 1a. For other operating conditions see the Experimental Section.

identified by IR, NMR, and mass spectra as well as by elemental analysis.

We were unable to obtain the 1:1 adduct diethyl 1-but-2-enylacetamidomalonate by using a chelating diphosphine in the catalytic system, as observed in the case of diethyl malonate.[7]

In order to compare the reactivity of 1a with that of an unsubstituted malonate ester, we have reacted butadiene with diethyl malonate in our experimental conditions. This proved to be roughly 10 times more reactive than 1a, thus indicating a strong deactivating influence of the acetamido substituent.

The similar addition of isoprene to 1a resulted in the selective formation of diethyl 1-(2,7-dimethyl)octa-2,7-dienylacetamidomalonate (5) with 32% yield. This product originates from tail-to-tail dimerization of isoprene.

The NMR and IR spectra indicated that this was indeed the main isomer, the others being present only in trace amounts.

In similar conditions, the reaction of 1,3-pentadiene (mixture of isomers) with 1a did not give the expected product, the pentadiene being recovered essentially unreacted.

The relative order of reactivity butadiene > isoprene > 1,3-pentadiene toward 1a is quite common in these telomerization reactions and is in agreement with the observations of Tsuji.[8]

Palladium-Catalyzed Transfer of Allyl Groups. The reaction of various allylic compounds with 1a in the presence of catalytic amounts of $Pd(OAc)_2$, PPh_3, and PhONa afforded selectively the expected allylation product 6, which was identified by its IR, NMR, and mass spectra (Scheme II).

The results are summarized in Table I. The effect of the solvent on the yield of allylation product appears to be of minor importance. However, dimethylformamide gave slightly better yields than dichloromethane. On the other hand, the reactivity of the allylic compounds increased along the series allyl chloride < allyl acetate < allyl alcohol.

Propyl glycine may be obtained from 6 after hydrogenation and hydrolysis according to Scheme I.

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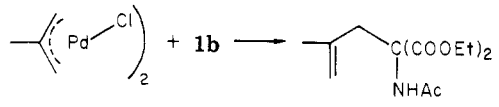
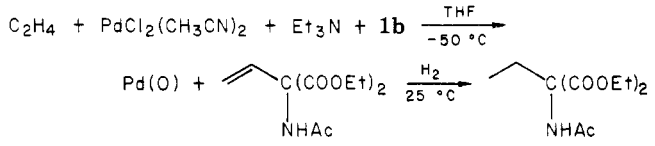
(8) S. Hosaka and J. Tsuji, *Tetrahedron*, **27**, 3821 (1971).

Scheme III



7

Scheme IV



8 9

Nucleophilic Attack on π-Allyl-Palladium Chloride Complexes. The reaction of di-μ-chloro-bis(2-methyl-π-allyl)dipalladium with 1b in the presence of 1,2-bis(diphenylphosphino)ethane in THF led to a smooth alkylation at room temperature with an 82% yield (determined by VPC) of the product 7 (Scheme III).

The structure of 7 has been inferred from its IR and NMR spectra. Compound 7 may be next subjected to hydrolysis to give the corresponding α-amino acid.

Palladium(II)-Assisted Alkylation of Olefins with 1b. The reaction in the cold of 1b with a solution of ethylene in THF, in the presence of $PdCl_2(CH_3CN)_2$ and triethylamine, produced compound 8, which was transformed in situ into 9 by introduction of a hydrogen atmosphere on the reaction mixture and warming to room temperature (Scheme IV).

Compound 9 was obtained in 45% yield based on palladium (determined by VPC) and was compared with an authentic sample prepared by an alternative route.

Similar reaction with propylene gave a very poor yield of products which could not be isolated. The VPC analysis indicated that two compounds were present, which are thought to derive from the reaction at the two different carbon atoms of the double bond.

These results contrast with the reactions involving sodiomalonate esters,[4] where ethylene and propylene exhibit approximately the same reactivity. Moreover, in the reaction with ethylene, 1b is shown to be less reactive than the sodiomalonate esters. These observations may be interpreted in terms of electronic rather than steric effects associated with the nature of the intermediate carbanion.

Experimental Section

All the reactions involving palladium complexes were carried out under an argon atmosphere. Melting points were determined on a hot-stage microscope and are uncorrected. Infrared spectra were measured on a Perkin-Elmer 457 infrared spectrophotometer. Proton magnetic resonance spectra were taken on a Varian CFT 20 spectrometer ($CDCl_3$ solution, Me_4Si standard). Chemical shifts are expressed in δ values (s = singlet, d = doublet, t = triplet, q = quadruplet, m = multiplet). Mass spectra were measured on an AEI MS 12 mass spectrometer. VPC analyses were performed on a Intersmat 120 ML gas chromatograph (4-m Dexsil 300 column, helium flow rate 15 mL/min).

Diethyl acetamidomalonate and allylic compounds were obtained commercially and used as received. Butadiene was dried on molecular sieves and stabilized with di-*tert*-butyl-*p*-cresol on storage. Isoprene and 1,3-pentadiene were distilled over a sodium dispersion under an argon atmosphere. $Pd(OAc)_2$ was prepared according to the literature.[9]

Preparation of Diethyl 1-Octa-2,7-dienylacetamidomalonate (2). In a stainless steel autoclave were introduced 1a

(9) T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, and G. Wilkinson, *J. Chem. Soc.*, 3632 (1965).

(35.2 g, 0.16 mol), $Pd(OAc)_2$ (0.112 g, 0.5 mmol), PPh_3 (0.262 g, 1 mmol), and PhONa (1.75 g, 15 mmol). The autoclave was then closed and 1,3-butadiene (30 mL, 0.34 mol) was injected under vacuum. The mixture was stirred at 110 °C for 2 h. After the mixture had cooled to room temperature, diethyl ether (30 mL) was added to the crude product to obtain a clear solution. This was treated with 10% aqueous KCN (30 mL) and next washed with water. The organic layer was dried over anhydrous sodium sulfate and concentrated to give **2** as a pale yellow oil (47.3 g, 91% yield): IR (neat) 3300, 3080, 1740, 1670, 1540, 970, 910 cm^{-1}; NMR δ 1–2.25 (m, 6 H, $(CH_2)_3$), 1.25 (t, 6 H, $OCH_2\mathbf{CH_3}$), 2.0 (s, 3 H, $COCH_3$), 3.0 (d, 2 H, CH_2), 4.25 (q, 4 H, OCH_2CH_3), 4.75–6.0 (m, 5 H, CH_2=CH and CH=CH), 6.7 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 326 (P + H), 325 (P), 252 (P - COOEt).

Diethyl Octylacetamidomalonate (3). Compound **2** (24.15 g, 75 mmol), 10% palladium on charcoal (2 g), and pentane (30 mL) were charged in a stainless steel autoclave. This was then purged and filled with hydrogen (3 MPa). The mixture was stirred at 50 °C until hydrogen uptake ceased, the hydrogen pressure being maintained at 3 MPa by further additions. After the mixture was cooled and filtered, the pentane was removed in vacuo leaving **3** as a white solid (16.4 g, 67% yield): mp 40–43 °C; IR (Nujol mull) 3300, 1740, 1670, 1540 cm^{-1}; NMR δ 0.75–2.5 (m, 17 H), 1.35 (t, 6 H, $OCH_2\mathbf{CH_3}$), 2.1 (s, 3 H, $COCH_3$), 4.3 (q, 4 H, $\mathbf{OCH_2}CH_3$), 6.8 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 328 (P - H), 256 (P - COOEt).

Octyl Glycine (4). Compound **3** (10 g, 30 mmol) was refluxed for 3 h in 20% aqueous sodium hydroxide (25 mL). The solution was then cooled, and 20 mL of 50% hydrochloric acid was added giving a white precipitate which was redissolved by addition of 25 mL of water. The mixture was refluxed for 8 h and then chilled until white crystals appeared. This crystalline solid was collected by filtration and washed sequentially with water, ethanol, pyridine to pH 6, and water. The octyl glycine **4** was recovered after drying (4 g, 70% yield): mp 239 °C; IR (Nujol mull) 1660, 1580, 1510 cm^{-1}; mass spectrum (70 eV) *m/e* 187 (P), 142. Anal. Calcd for $C_{10}H_{21}O_2N$: C, 64.17; H, 11.20; N, 7.49. Found: C, 64.20; H, 11.20; N, 7.10.

Preparation of Diethyl 1-(2,7-Dimethyl)octa-2,7-dienylacetamidomalonate (5). The reaction was carried out by using the same procedure as described for **2**, charging $Pd(OAc)_2$ (0.037 g, 0.165 mmol), PPh_3 (0.071 g, 0.33 mmol), PhONa (0.380 g, 5 mmol), **1a** (11.73 g, 0.054 mol), and isoprene (11.2 mL, 0.112 mol). The mixture was stirred at 100 °C for 4 h. After treatment with 10% aqueous KCN and extraction of the organic product with diethyl ether, the solvent was removed in vacuo to give **5** as a yellow oil (6.25 g, 32% yield): IR (neat) 3300, 3080, 1740, 1670, 885 cm^{-1}; NMR δ 1.0–2.2 (m, 6 H, $(CH_2)_3$), 1.25 (t, 6 H, $OCH_2\mathbf{CH_3}$), 1.55 (s, 3 H, CH_2=C$\mathbf{CH_3}$), 1.7 (s, 3 H, CH=C$\mathbf{CH_3}$), 1.95 (s, 3 H, $COCH_3$), 3.0 (s, 2 H, CH_2), 4.2 (q, 4 H, $\mathbf{OCH_2}CH_3$), 4.7 (s, 2 H, CH_2=C), 5.2 (t, 1 H, CH=C), 6.75 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 354 (P + H), 280 (P - COOEt).

General Procedure for the Preparation of Diethyl Allylacetamidomalonate (6). In a stainless steel autoclave were placed **1a** (11.5 g, 0.053 mol), $Pd(OAc)_2$ (0.037 g, 0.165 mmol), PPh_3 (0.071 g, 0.33 mmol), and PhONa (0.38 g, 5 mmol). The autoclave was closed and 20 mL of the solvent containing 0.060 mol of the allylic compound was introduced by means of a syringe. The mixture was stirred at the desired temperature for 6–8 h. After filtration of the reaction mixture, the solvent was removed in vacuo to give a heavy oil. This was found to contain the initial compound **1a** and the allylation product **6**. The yield of **6** was determined on the basis of the VPC analysis. A pure sample of **6** was obtained by crystallization from a benzene–pentane mixture: mp 43–45 °C; IR (KBr) 3240, 3080, 1740, 1670, 920 cm^{-1}; NMR δ 1.25 (t, 6 H, $OCH_2\mathbf{CH_3}$), 2.0 (s, 3 H, $COCH_3$), 3.1 (d, 2 H, CH_2), 4.25 (q, 4 H, $\mathbf{OCH_2}CH_3$), 4.9–5.6 (m, 3 H, CH_2=CH), 6.8 (s, 1 H, NH); mass spectrum (70 eV) *m/e* 258 (P + H), 257 (P), 184 (P - COOEt). The reagent, the solvent, and the temperature as well as the corresponding yield are given in Table I.

Diethyl (2-Methylallyl)acetamidomalonate (7). The complex di-μ-chloro-bis(2-methyl-π-allyl)dipalladium was prepared in water in the presence of ethylene as described in the literature.[10] A solution of **1b** was prepared by reacting sodium hydride (0.072 g, 3 mmol) with **1a** (0.651 g, 3 mmol) in 15 mL of freshly distilled THF and stirring 1 h at room temperature. The π-allyl–palladium complex prepared above (0.330 g, 0.837 mmol) and 1,2-bis(diphenylphosphino)ethane (0.479 g, 0.12 mmol) were stirred in freshly distilled THF (15 mL) at room temperature for 1 h. This clear orange solution was added in one portion to the THF solution of **1b**. The resulting mixture was then stirred at room temperature for 2 h. After that time, it was concentrated to half volume and 60 mL of water was added. After filtration of the black suspension, the mixture was extracted with diethyl ether (four 40-mL portions). These combined extracts were dried over anhydrous sodium sulfate, and the solvent was removed under vacuum. VPC analysis of a solution of this crude product with tetradecane as internal standard indicated an 82% yield of **7**, which could be further purified by crystallization from water: mp 91 °C; IR (KBr) 3240, 3080, 1740, 1640, 1520, 920 cm^{-1}; NMR δ 1.25 (t, 6 H, $OCH_2\mathbf{CH_3}$), 1.65 (s, 3 H, CH_2=C$\mathbf{CH_3}$), 2.0 (s, 3 H, $COCH_3$), 3.1 (s, 2 H, CH_2), 4.25 (q, 4 H, $\mathbf{OCH_2}CH_3$), 4.7 and 4.85 (2 s, 2 H, CH_2=C), 6.7 (s, 1 H, NH).

Diethyl Ethylacetamidomalonate (9). Anhydrous $PdCl_2$ (1.5 g, 8.5 mmol) was refluxed in 20 mL of anhydrous acetonitrile for 30 min to give an orange crystalline solid, which was collected by filtration, washed with pentane, and dried, giving an 85% yield of dichlorobis(acetonitrile)palladium. A solution of **1b** in THF was prepared as described in the synthesis of **7**, starting from 3 mmol of **1a**. On the other hand, ethylene (15 mmol) was added to a suspension of the palladium–acetonitrile complex (0.778 g, 3 mmol) in 60 mL of THF. The resulting solution was cooled to −78 °C, and triethylamine (0.84 mL, 6 mmol) was added dropwise. After 15 min of stirring, the THF solution of **1b** was added slowly. The mixture was stirred at −50 °C for 1 h, and then the argon atmosphere was flushed and replaced by hydrogen, while the flask was allowed to warm to room temperature. After filtration of the resulting black suspension, the solution was passed through a short silica gel column and the solvent evaporated to give 1.2 g of a pale yellow oil. This crude product was found by VPC analysis, with tetradecane as internal standard, to contain 0.326 g of **9** (45% yield). The pure product could not be isolated and the NMR spectrum was recorded from the crude yellow oil: NMR δ 0.75 (t, 3 H, $\mathbf{CH_3}CH_2C$), 1.25 (t, 6 H, $OCH_2\mathbf{CH_3}$), 2.0 (s, 3 H, $COCH_3$), 2.3 (q, 2 H, $CH_3\mathbf{CH_2}C$), 4.25 (q, 4 H, $\mathbf{OCH_2}CH_3$), 6.7 (s, 1 H, NH).

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Registry No. **1a**, 1068-90-2; **1b**, 30412-43-2; **2**, 70562-45-7; **3**, 5440-55-1; **4**, 17702-88-4; **5**, 70562-46-8; **6**, 14109-62-7; **7**, 37944-29-9; **8**, 70562-47-9; **9**, 32819-24-2; 1,3-butadiene, 106-99-0; isoprene, 78-79-5; ethylene, 74-85-1; allyl chloride, 107-05-1; allyl acetate, 591-87-7; allyl alcohol, 107-18-6.

(10) F. R. Hartley and S. R. Jones, *J. Organomet. Chem.*, **66**, 465 (1974).