A Convenient Route to Substituted Phenylalanines

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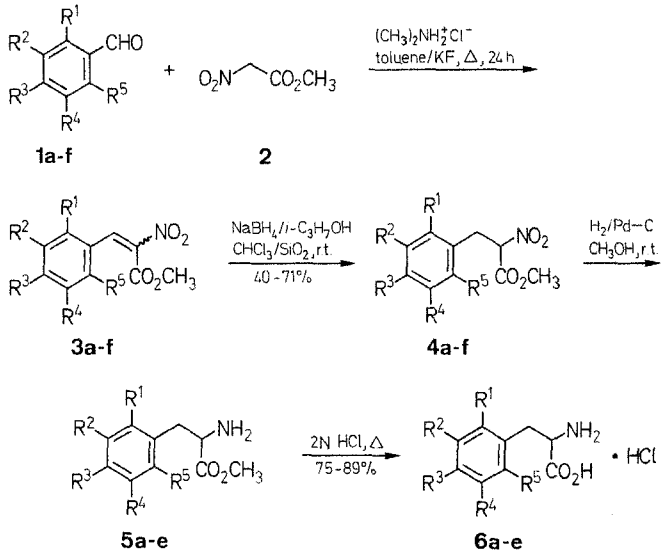
A four-step route to phenylalanines substituted on the aryl moiety is reported starting from aromatic aldehydes. Some novel methyl 2-nitro-3-arylpropionates have been isolated as intermediates in the synthesis and are described.

Although a number of methods are available for synthesizing α-amino acids and their derivatives,[1-6] the preparation of these compounds is a topic of continuing interest owing to their fundamental biological properties. Among the amino acids, those bearing an aromatic group are particularly important as they are specifically involved in various metabolic and biosynthetic pathways.[7] In this context, we describe here an efficient four-step procedure leading to substituted phenylalanines hydrochlorides.

Substituted benzaldehydes **1** are reacted with methyl nitroacetate **(2)** in the presence of dimethylammonium chloride and a small amount of potassium fluoride in refluxing toluene to give a *E*/*Z*-mixture of the α-nitrocinnamic esters **3**. By adapting a method recently described for reducing nitrostyrenes,[8] these crude unsaturated compounds **3** are then easily converted into the methyl 2-nitro-3-arylpropionates **4** (Table). Subsequent catalytic reduction of nitro derivatives **4** with palladium-on-charcoal furnishes the amino esters **5**, which are directly hydrolyzed with diluted hydrochloric acid to give the substituted phenylalanines hydrochlorides **6** (Table).

Except for **6a**, which has already been prepared by other routes,[9,10] we have chosen to apply the present method to the synthesis of hitherto unknown amino acids hydrochlorides **(6b–e)**.



The key step in the above synthetic sequence is the preparation of the α-nitrocinnamic esters **3**, since several previously attempted condensations of nitroacetic esters with aldehydes have been reported to give mainly bis-adducts.[11-13] This drawback is partially overcome by using the system potassium fluoride/dimethylammonium chloride as condensation agent though, in certain cases such as that of **3d** or **3e**, the formation of the by-products remains appreciable.

It must also be pointed out that the hydrogenation of these α-nitrocinnamic esters **3** to the amino esters **5** must be carried out in two successive stages, because their direct reduction in alcoholic solutions leads to unwanted products resulting from side-reactions (especially addition to the double bond), similar in type to those already described in comparable cases.[14,15]

This route to substituted phenylalanines is versatile, but does have limitations in that undesirable reactions sometimes occur in the catalytic hydrogenation step. Thus, in the case of the benzofuran **4e**, the double bond of the furan ring is reduced and the final amino acid hydrochloride obtained is the 2,3-dihydrobenzofuran **6e**. In the case of **4f**, on the other hand, a complete debromination takes place. The *in situ* produced hydrobromic acid inhibits the reduction, and the sole product, obtained quantitatively, is the methyl 2-nitro-3-(3,4-dimethoxyphenyl)-propionate **7**.

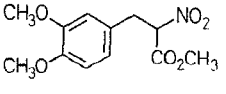


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Table. Methyl 2-Nitro-3-arylpropionates **4** Prepared from Aromatic Aldehydes **1**[a] and Substituted Phenylalanine Hydrochlorides **6** Prepared

Product	R^1	R^2	R^3	R^4	R^5	Yield (%)	m.p.[b] (°C) (solvent) or b.p./torr (°C)	Molecular Formula[c] or Lit. m.p. (°C)	MS *m/e* (MH^+)[d]	^{1}H-NMR (solvent/TMS)[e] δ (ppm)
4a	H	OCH_3	OCH_3	OCH_3	H	58[f]	129–130 (2-propanol)	$C_{13}H_{17}NO_7$ (299.3)	–	3.32–3.67 (AB part of ABX system, 2H, $\delta_A = 3.43$, $J_{AX} = 3.2$ Hz, $J_{AB} = 14.7$ Hz, $\delta_B = 3.48$, $J_{BX} = 11.9$ Hz); 3.80 (s, 3H); 3.83 (s, 9H); 5.23–5.43 (X part of ABX system, 1H); 6.40 (s, 2H)
4b	OCH_3	H	OCH_3	H	OCH_3	65[f]	84–85 (2-propanol)	$C_{13}H_{17}NO_7$ (299.3)	–	3.26–3.76 (AB part of ABX system, 2H, $\delta_A = 3.41$, $J_{AX} = 7.3$ Hz, $J_{AB} = 15$ Hz, $\delta_B = 3.60$, $J_{BX} = 8.8$ Hz); 3.76 (s, 3H); 3.78 (s, 6H); 3.79 (s, 3H); 5.30–5.51 (X part of ABX system, 1H); 6.09 (s, 2H)
4c	H	H	$CH(CH_3)_2$	H	H	40[f]	118–121/0.06	$C_{13}H_{17}NO_4$ (251.3)	–	1.21 (d, 6H, $J = 6.8$ Hz); 2.86 (hept, 1H, $J = 6.8$ Hz); 3.33–3.70 (AB part of ABX system, 2H, $\delta_A = 3.45$, $J_{AX} = 2.7$ Hz, $J_{AB} = 14.7$ Hz, $\delta_B = 3.50$, $J_{BX} = 12$ Hz); 3.80 (s, 3H); 5.20–5.42 (X part of ABX system, 1H); 7.12 (s, 4H)
4d	$-(CH=CH)_2-$		H	H	OCH_3	71[f]	oil	$C_{15}H_{15}NO_5$ (289.3)	–	3.68 (s, 3H); 3.94 (s, 3H); 3.75–4.20 (AB, part of ABX system, 2H);[h] 5.45–5.67 (X part of ABX system, 1H); 7.12–8.04 (m, 6H)
4e	$-CH=CHO-$		OCH_3	H	H	41[f]	61–63 (ether/pentane)	$C_{13}H_{13}NO_6$ (279.3)	–	3.57–3.92 (AB part of ABX system, 2H, $\delta_A = 3.68$, $J_{AX} = 3.8$ Hz, $J_{AB} = 14.7$ Hz, $\delta_B = 3.73$, $J_{BX} = 11.3$ Hz); 3.80 (s, 3H); 3.98 (s, 3H); 5.27–5.50 (X part of ABX system, 1H); 6.65–6.83 (m, 2H); 6.99 (d, 1H, $J = 8.3$ Hz); 7.67 (d, 1H, $J = 2.3$ Hz)
4f	H	Br	OCH_3	OCH_3	H	52[f]	81–83 (ether/hexane)	$C_{12}H_{14}BrNO_6$ (348.2)	–	3.30–3.66 (AB part of ABX system, 2H, $\delta_A = 3.42$, $J_{AX} = 3.3$ Hz, $J_{AB} = 14.7$ Hz, $\delta_B = 3.46$, $J_{BX} = 11.4$ Hz); 3.84 (s, 3H); 3.85 (s, 6H); 5.21–5.44 (X part of ABX system, 1H); 6.69 (d, 1H, $J = 2.1$ Hz); 7.00 (d, 1H, $J = 2.1$ Hz)
6a	H	OCH_3	OCH_3	OCH_3	H	89[g]	242–244 (dec.)	242 (dec.)[9] 243–244[10]	256	3.12 (br. d, 2H, $J = 6$ Hz); 3.65 (s, 3H); 3.77 (s, 6H); 4.13 (br. t, 1H, $J = 6$ Hz); 6.63 (s, 2H); 7.70–9.40 (4H[j])
6b	OCH_3	H	OCH_3	H	OCH_3	76[g]	216–219[i] (dec.)	$C_{12}H_{18}NO_5Cl$ (291.7)	256	2.95–3.13 (m, 2H); 3.65–3.88 (m, 1H); 3.77 (s, 6H); 3.79 (s, 3H); 6.17 (s, 2H); 7.40–9.20 (4H[j])
6c	H	H	$CH(CH_3)_2$	H	H	80[g]	270–272 (dec.)	$C_{12}H_{18}NO_2Cl$ (243.7)	208	1.19 (d, 6H, $J = 7.2$ Hz); 2.88 (hept., 1H, $J = 7.2$ Hz); 3.14 (br. d, 2H, $J = 6$ Hz); 4.08 (br. t, 1H, $J = 6$ Hz); 7.21 (s, 4H); 7.80–9.90 (4H[j])
6d	$-(CH=CH)_2-$		H	H	OCH_3	75[g]	241–245 (dec.)	$C_{14}H_{16}NO_3Cl$ (281.7)	246	3.57 (br. d, 2H, $J = 7$ Hz); 3.77–3.98 (m, 1H); 3.90 (s, 3H); 7.25–8.20 (m, 6H); 8.20–9.70 (4H[j])
6e	$-CH_2CH_2O-$		OCH_3	H	H	76[g]	237–241 (dec.)	$C_{12}H_{16}NO_4Cl$ (273.7)	238	2.92–3.42 (m, 4H); 3.73 (s, 3H); 3.97 (br. t, 1H, $J = 6$ Hz); 4.50 (br. t, 2H, $J = 9$ Hz); 6.70 (s, 2H); 7.70–9.60 (4H[j])

[a] Aldehydes **1a–d** are commercially available. Compound **1e** was prepared according to Ref 17. Aldehyde **1f** was synthesized according to Ref 18.
[b] Melting points are uncorrected.
[c] The microanalyses showed the following maximum deviations from the calculated values: for **4** C ±0.21, H ±0.09, N ±0.11; for **6**: C ±0.27, H ±0.09, N ±0.19, Cl ±0.25.
[d] The mass spectra were determined with a Nermag Ribermag R10-10C spectrometer using the chemical ionization method (NH_3).
[e] The ^{1}H-NMR spectra were recorded at 90 MHz using a Varian EM 390 spectrometer: solvent for **4**: $CDCl_3$; for **6**: DMSO-d_6.
[f] Yield of distilled or recrystallized product except for **4d** which has been purified by chromatography.
[g] Yield of product purified as described in the experimental part.
[h] In this case, the calculation is impracticable because most of the AB lines are overlapped by the signal of the methyl group.
[i] Allotropic change at 175–180°.
[j] Exchangeable with D_2O.

In this context, we have confirmed in separate experiments that the nitro group of **4a**, **4b** or **4c** remains unreacted when a small amount of hydrobromic acid is added to the reaction medium.

The end products **6a–e** as well as the rigorously purified intermediates **4a–f** and compound **7** have been fully characterized on the basis of their microanalytical and spectral data.

Methyl nitroacetate (2):
Compound **2** is commercially available (Fluka AG), but expensive. Therefore, it has been prepared on a large scale (2.5 mol) starting from methyl acetoacetate according to a previously reported procedure for ethyl nitroacetate,[16] but using methanol instead of ethanol in the second step of the reaction; yield: 72%; b.p. 69.5–71.5°C/3.5 torr.

Methyl 2-Nitro-3-arylpropionates (4a–f); General Procedure:
Dimethylammonium chloride (8.15 g, 0.1 mol), toluene (250 ml), aldehyde (**1a–f**; 0.05 mol), methyl nitroacetate (**2**; 7.14 g, 0.06 mol) and potassium fluoride (435 mg, 0.0075 mol) are placed in a one-necked 500 ml conical flask equipped with a Dean-Stark water separator (capacity ca. 20 ml). The mixture is refluxed with stirring for 24 h, then allowed to cool to room temperature. Direct rotary evaporation of the toluene from the reaction vessel under reduced pressure leaves a residue which is taken up with water (40 ml) and dichloromethane (160 ml). The organic layer is separated and the aqueous phase is extracted with dichloromethane (3 × 50 ml). The organic extracts are combined, dried with magnesium sulfate, filtered, and evaporated to give a crude *E*/*Z*-mixture of the α-nitrocinnamic ester (**3a–f**). This material is dissolved without further purification in a mixture of chloroform (625 ml) and isopropyl alcohol (185 ml). Maintaining vigorous stirring, silica gel (200–400 mesh ASTM; 100 g) is then poured into the flask and powdered sodium borohydride (9.46 g, 0.25 mol) is added portionswise over a period of 5 min. The slurry is stirred for an additional 2 h, then acetic acid (15 ml) is carefully added. The insoluble material is filtered by suction, and the solvent is evaporated *in vacuo* (the recovered solvents are used to thoroughly rinse the silica gel). The resulting crude product is taken up with water (50 ml) and dichloromethane (200 ml). The organic phase is separated and the aqueous layer is extracted with dichloromethane (3 × 60 ml). The combined extracts are dried with magnesium sulfate, filtered, and evaporated to dryness to give a residue, which is column-chromatographed on silica gel (300 g, eluent dichloromethane). Removal of the solvent followed by recrystallization (**4a**, **4b**, **4e**, **4f**) or distillation (**4c**) affords analytically pure compounds in the reported yields (Table).

In the case of **4d**, the attempted distillations of the oily product led to complete decomposition. However, the chromatographed material proved satisfactorily pure as judged by NMR spectroscopy and microanalytical results.

$C_{15}H_{15}NO_5$	calc.	C 62.28	H 5.23	N 4.84
(289.3)	found	62.49	5.32	4.79

Phenylalanines Hydrochlorides (6a–e); General Procedure:
Palladium-on-charcoal (2 g, 10%) is placed in a 250 ml two-necked round bottomed flask, covered with methanol (80 ml), and efficiently stirred whilst hydrogen is bubbled through this suspension (flow rate: 35 ml/min). After 15 min, the methyl 2-nitro-3-arylpropionate (**4a–f**) is added in one portion and bubbling with stirring is continued for 5 additional hours. The insoluble material is then filtered by suction through a short pad of Celite, rinsed with methanol and the filtrate evaporated under reduced pressure. The residue is dissolved in dichloromethane (100 ml) then filtered if a light insoluble material is present. Removal of the solvent leaves the amino ester (**5a–e**) as a colorless oil, which is directly treated with 2 normal hydrochloric acid (60 ml). This mixture is heated in an oil bath with stirring for 5 h (105°C for **5a–c**, 70°C only for **5d** and **5e** in order to avoid a partial decomposition of the product). Evaporation to dryness *in vacuo* from the reaction flask yields a material that is taken up with water (40 ml), then evaporated again (this operation is repeated three times). The crude product is treated with anhydrous acetone (35 ml). After gentle refluxing with stirring for 40 min, the resultant suspension is allowed to cool to ambient temperature. Filtration of the solid provides analytically pure **6a–e** in the reported yields (Table).

With regard to **4f**, the above-described hydrogenation procedure induces a complete removal of bromine from the aromatic ring without reduction of the nitro group. The crude material obtained after evaporation of the solvent is chromatographed on a silica gel column (100 g, eluent dichloromethane) to give **7** (2.55 g) which is further purified by recrystallization (ether/hexane); yield 2.05 g (76%), m.p. 53–54.5°C.

$C_{12}H_{15}NO_6$	calc.	C 53.53	H 5.62	N 5.20
(269.3)	found	53.48	5.70	5.14

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.33–2.68 (AB part of ABX system, 2 H, δ_A = 3.44, J_{AX} = 3.8 Hz, J_{AB} = 14.4 Hz, δ_B = 3.49, J_{BX} = 11.2 Hz); 3.83 (s, 3 H); 3.86 (s, 6 H); 5.20–5.42 (X part of ABX system, 1 H); 6.65–6.88 (m, 3 H).

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