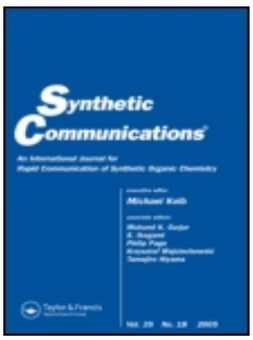

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# AN IMPROVED "ONE-POT" PROCEDURE FOR SYNTHESIS OF FLUORINATED DL-PHENYLALANINES

**Alexander V. Samet,[1,*] Daniel J. Coughlin,[2] A. C. Buchanan III,[1] and Andrei A. Gakh[1,*]**

[1]Chemical and Analytical Sciences Division, Oak Ridge National Laboratory, Oak Ridge, TN 37831-6197, USA
[2]American Cyanamid Co., P.O. Box 400, Princeton, NJ 08543, USA

## ABSTRACT

DL-arylalanines were synthesized from corresponding aromatic aldehydes by an efficient "one-pot" procedure involving Erlenmeyer reaction and subsequent reduction of the resulting oxazolones (without prior isolation) using P/HI.

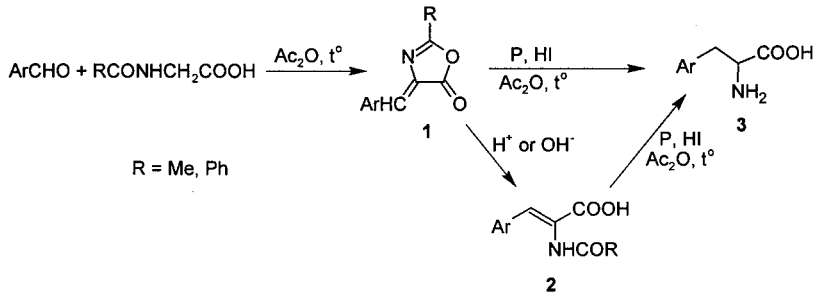
## INTRODUCTION

Fluoro-containing α-amino acids are of significant interest for protein chemistry because fluorinated analogs often possess unique biological properties.[1a,b] Also, the presence of fluorine atom facilitates structural investigations of peptide molecules.[2a–e] Therefore, a search for new synthetic

*Corresponding authors.

approaches to fluoro-containing α-amino acids, and an improvement of the existing ones[2f] are important, especially for parallel high throughput synthesis applications.[2g]

Erlenmeyer azlactone synthesis is a well-known and important approach for preparation of DL-α-amino acids from carbonyl compounds.[3] Optically active amino acids can also be prepared using this procedure.[4,5] However, the synthesis has always been performed as a multi-step procedure, with inevitable losses during isolation and purification of intermediate products. The first step (Erlenmeyer reaction) is a three-component condensation between a carbonyl compound (in most cases, an aromatic aldehyde), *N*-acetyl- or *N*-benzoylglycine, and excess acetic anhydride in the presence of a basic catalyst (usually, NaOAc). The resulting oxazolone **1** ("azlactone") undergoes a reductive ring cleavage (Na/Hg, P/HI or catalytic hydrogenation) to yield the target DL-α-amino acid **3.** This transformation is performed either directly or as a two-step sequence, involving hydrolysis of the azlactone to form a corresponding unsaturated α-acylamino acid **2** and a subsequent reduction of the latter (Scheme).[6] Of the above mentioned reducing agents, red phosphorus in hydroiodic acid is considered to be one of the most versatile.[7] The reaction normally is carried out in acetic anhydride.




***Scheme.***

## RESULTS AND DISCUSSION

During the preparation of fluoro-containing DL-phenylalanines using the P/HI system, we realized that the azlactone did not need to be isolated from the reaction mixture before the reduction. Indeed, yields of azlactones from aromatic aldehydes in Erlenmeyer reaction are usually high, so the only compound present in the mixture in significant amounts by

the end of the reaction (besides azlactone itself) is $Ac_2O$, which serves both as a solvent and as a dehydrating agent. Thus, no other compounds are present to interfere with the subsequent reduction. Moreover, as mentioned above, the reduction is usually performed in $Ac_2O$ as a reaction medium.

This approach proved to be quite successful. Thus, DL-phenylalanine **3a** was obtained from benzaldehyde in 48% isolated yield starting from *N*-acetylglycine and in 51% isolated yield starting from hippuric acid (*N*-benzoylglycine) compared to 39–43% total yield described previously[5] for a 2-step sequence (starting from hippuric acid). The results for fluorinated DL-phenylalanines are summarized in table.

Both *N*-acetyl- and *N*-benzoylglycines could be successfully used in the reaction. However, in some cases yields with hippuric acid are markedly lower. This difference is probably due to a higher stability of phenyl-substituted azlactones towards acidic hydrolysis compared to the methyl-substituted ones.[2,6] Indeed, ether extracts from the reaction work-up (see Experimental) contained largely unreacted azlactones; their amounts being higher for the reactions with hippuric acid. Therefore, we used *N*-acetylglycine as a starting compound in most cases.

In summary, we have developed an efficient one-pot procedure for the preparation of fluorinated DL-phenylalanines. The yields for known compounds are comparable or higher than those achieved by known multistep procedures involving the Erlenmeyer reaction. We expect that this method could also be successfully employed for the synthesis of other substituted DL-phenylalanines.

***Table.*** Yields and M.P. of Fluorinated Phenylalanines **3b–i**

| Compound | Ar | Yield (%)[a] |
|---|---|---|
| **3b**[b] | 2-$FC_6H_4$ | 42 (B) |
| **3c**[c] | 4-$CF_3C_6H_4$ | 32 (A) |
| **3d**[d] | 4-$CF_3OC_6H_4$ | 44 (A) |
| **3e** | 3-$CF_3OC_6H_4$ | 52 (A), 20 (B) |
| **3f** | 2-F-4-$CF_3C_6H_3$ | 44 (A), 23 (B) |
| **3g** | 3-F-4-$ClC_6H_3$ | 62 (A) |
| **3h** | 2-F-4-$BrC_6H_3$ | 43 (A) |
| **3i** | 2-F-5-$BrC_6H_3$ | 36 (A) |

[a]A—starting from *N*-acetylglycine; B—starting from hippuric acid.
[b]Literature yield 21% (3-step procedure, starting from hippuric acid).[8]
[c]Literature yield 20% (4-step procedure, starting from *N*-acetylglycine).[9]
[d]Reported in 1990,[10] no details presented.

## EXPERIMENTAL

**General procedure.** A mixture of hippuric acid (0.90 g, 5 mmol) or *N*-acetylglycine (0.60 g, 5 mmol), aromatic aldehyde (10% molar excess), and NaOAc (0.3 g) in $Ac_2O$ (1.5 ml) was heated for 30 min at 110–115°C. Red phosphorus (0.4 g) and more $Ac_2O$ (1 ml) were added to the reaction mixture, followed by a dropwise addition of 47% HI (2.5 ml). The resulting suspension was refluxed for 3.5 h with stirring, then filtered (still hot), and the precipitate washed on the filter with AcOH (1 ml). The filtrate was evaporated to dryness in vacuo, and the residue was taken into a mixture of water (7 ml) and ether (5 ml). The water layer was separated, extracted once more with ether (5 ml) and evaporated to dryness again. The residue was dissolved in 1–2 ml of water, and pH was adjusted to 5–6 with aqueous $NH_3$. The resulting white precipitate of amino acid was filtered off, washed with 1 ml of an ice-cold water, and dried.

$^1$H NMR spectra (400 MHz, DMSO-$d_6$) and m.p. of DL-phenylalanines **3b-i**.

**DL-2-Fluorophenylalanine 3b.** M.p. 254–256°C (decomp.) (lit.[11] m.p. 258.5–259°C (decomp.). $^1$H NMR: δ 2.77 (dd, $J = 13.5$ Hz, $J = 8.8$ Hz, 1H); 3.21 (br.d, $J = 13.5$ Hz, 1H); 3.39 (br.s, 1H); 7.1–7.2 (m, 2H); 7.25 (m, 1H), 7.34 (m, 1H).

**DL-4-(Trifluoromethyl)phenylalanine 3c.** M.p. 228–231°C (decomp.) (lit.[12] m.p. 222°C (decomp.). $^1$H NMR: δ 2.94 (dd, $J = 14.0$ Hz, $J = 8.5$ Hz, 1H); 3.17 (dd, $J = 14.4$ Hz, $J = 5.0$ Hz, 1H); 3.44 (dd, $J = 8.5$ Hz, $J = 5.0$ Hz, 1H) ; 7.46 (d, $J = 7.8$ Hz, 2H); 7.62 (d, $J = 7.8$ Hz, 2H).

**DL-4-(Trifluoromethoxy)phenylalanine 3d.** M.p. 257–259°C (decomp.). $^1$H NMR: δ 2.90 (dd, $J = 14.2$ Hz, $J = 7.9$ Hz, 1H); 3.13 (dd, $J = 14.2$ Hz, $J = 4.4$ Hz, 1H); 3.42 (dd, $J = 7.9$ Hz, $J = 4.4$ Hz, 1H); 7.246 (d, $J = 8.3$ Hz, 2H); 7.37 (d, $J = 8.3$ Hz, 2H).

**DL-3-(Trifluoromethoxy)phenylalanine 3e.** M.p. 241–244°C (decomp.). Calculated for $C_{10}H_{10}F_3NO_3$, %: H, 4.04; N, 5.62. Found, %: H, 3.76; N, 5.22. $^1$H NMR: δ 3.04 (dd, $J = 14.2$ Hz, $J = 8.6$ Hz, 1H); 3.21 (dd, $J = 14.2$ Hz, $J = 4.8$ Hz, 1H); 3.75 (m, 1H); 7.37 (m, 3H); 7.44 (t, $J = 8.1$ Hz, 1H).

**DL-2-Fluoro-4-(trifluoromethyl)phenylalanine 3f.** M.p. 260–262°C (decomp.). Calculated for $C_{10}H_9F_4NO_2$, %: H, 3.61; N, 5.58. Found, %: H, 3.63; N, 5.56. $^1$H NMR: δ 2.90 (dd, $J = 13.9$ Hz, $J = 8.1$ Hz, 1H); 3.35 (dd, $J = 13.9$ Hz, $J = 5.3$ Hz, 1H); 3.46 (dd, $J = 8.1$ Hz, $J = 5.3$ Hz, 1H); 7.50–7.65 (m, 3H).

**DL-4-Chloro-3-fluorophenylalanine 3g.** M.p. 243–245°C (decomp.). Calculated for $C_9H_9ClFNO_2$, %: H, 4.17; N, 6.44. Found, %: H, 4.00; N, 6.42. $^1$H NMR: δ 2.80 (dd, $J = 14.0$ Hz, $J = 8.2$ Hz, 1H); 3.16 (br.d,

$J = 14.0$ Hz, 1H); 3.43 (br.d, $J = 8.5$ Hz, 1H); 7.13 (d, $J = 8.3$ Hz, 1H); 7.32 (d, $J = 10.3$ Hz, 1H); 7.50 (m, 1H).

**DL-4-Bromo-2-fluorophenylalanine 3h.** M.p. 265–267°C (decomp.). Calculated for $C_9H_9BrFNO_2$, %: H, 3.46; N, 5.34. Found, %: H, 3.78; N, 5.15. $^1$H NMR: δ 2.78 (dd, $J = 14.2$ Hz, $J = 8.5$ Hz, 1H); 3.20 (dd, $J = 14.2$ Hz, $J = 4.0$ Hz, 1H); 3.44 (dd, $J = 8.5$ Hz, $J = 4.0$ Hz, 1H); 7.34 (m, 2H); 7.48 (d, $J = 9.1$ Hz, 1H).

**DL-5-Bromo-2-fluorophenylalanine 3i.** M.p. 261–264°C (decomp.). Calculated for $C_9H_9BrFNO_2$, %: H, 3.46; N, 5.34. Found, %: H, 3.48; N, 5.28. $^1$H NMR: δ 2.77 (dd, $J = 14.3$ Hz, $J = 8.8$ Hz, 1H); 3.25 (dd, $J = 14.3$ Hz, $J = 5.2$ Hz, 1H); 3.39 (dd, $J = 8.8$ Hz, $J = 5.2$ Hz, 1H); 7.14 (t, $J = 9.2$ Hz, 1H); 7.47 (m, 1H); 7.56 (dd, $J = 6.3$ Hz, $J = 2.2$ Hz, 1H).

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