Synthesis of N-Acyl Aromatic α-Amino Acids

Bonchul Ku and Dong Young Oh*

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 131-650

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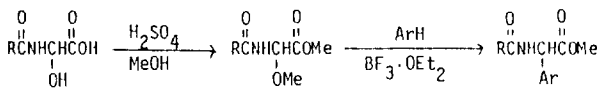
Aromatic amino acids of the phenylglycine type have found wide applications in the synthesis of semisynthetic penicillins and cephalosporins (e.g. ampicillin)[1]. These amino acids that are also present in the cyclic depsipeptides Enduracidin A and B[2] are generally prepared from the corresponding aldehydes by Strecker synthesis[3] and from 5-methoxyhydantoins[4] by the amidoalkylation of aromatic compounds. As a part of our synthetic approaches directing toward synthetic amino acids we report here that N-acyl aromatic α-amino acids (**5-10**) were readily synthesized from methyl α-methoxyhippurate (**3**)[5] and methyl α-methoxy-N-benzoyloxycarbonylglycinate (**4**) by the aromatization of various aromatic compounds. The starting materials were prepared from α-hydroxyhippuric acid (**1**) and α-hydroxy-N-benzoyloxycarbonylglycine (**2**) by treatment with methanolic sulfuric acid.



1; R = Ph **3**; R = Ph **5-10**
2; R = $PhCH_2O$ **4**; R = $PhCH_2O$

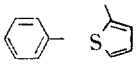
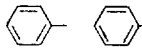
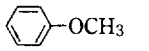
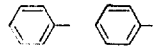
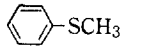
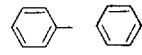
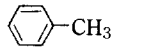
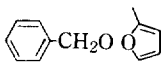
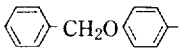
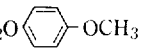
The compounds **1** and **2** could also be converted into the aromatic α-amino acids only in lower yields and under the heterogeneous reaction conditions resulting from the sparing solubility of the compounds in organic solvent and strong acids such as sulfuric acid, which could not be compatible with acid sensitive aromatic compounds (e.g. furane, thiophene), were used for the amidoalkylation[6].

Thus **3** and **4** were the substrates of choice which were amidoalkylated under the mild Lewis acid (BF_3·OEt_2) to give the desired aromatic α-amino acids in excellent yields.

In a typical experiment, to a stirred solution of **1** (1 mmol) and thioanisole (2 mmol) in CH_2Cl_2 (3 m*l*) was added dropwise freshly distilled BF_3·OEt_2 (1.2 mmol) at −10°C under nitrogen, followed by warming up to rt. When the reaction was completed (2-4 hr, TLC), the solution was poured into a cold $NaHCO_3$ solution (10 m*l*). Extraction with ether (3 × 20 m*l*), washing with water (10 m*l*), drying over $MgSO_4$ and removal of the solvent gave the crude products. Pure samples were obtained by chromatography (EtOAc/n-Hex) and recrystallization.

As shown in Table I, the reaction was clean and completed within a few hours, during that time the starting material disappeared on TLC. In the case of the monosubstituted aromatic compounds the crude products were, according to the nmr spectrum. a mixture of ortho and para isomers. The chemical shifts of the methine hydrogens in the ortho isomers are more shifted to down field (0.2-0.6 ppm) than in the para isomers. The para isomers which predominated were obtained pure on careful recrystallization. The intermediate immonium[6] ions were assumed as the reactive species resulting from the primary reaction of the substrates and boron trifluoride etherate.

Table 1. N-Acyl Aromatic α-Amino Acids 5-10 Prepared

Run	R	Ar	Reaction time(hr)	Product[7]	Yield (%)
1			8	**5**	91
2			2	**6**	85(p/o = 92:8)[a]
3			3	**7**	92(p/o = 87:13)[a]
4			2	**8**	79(p/o = 72:28)[a]
5			5	**9**	69
6			3	**10**	82(p/o = 82/18)[a]

[a] Determined by nmr.

References

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2. H. A. James, Amino Acids, Peptides and Related Compounds., Butterworths, 1973.
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4. D. Ben-Ishai, G. Ben-Et and A. Warshawsky, *J. Heter. Chem.,* 1970, **7,** 1289.
5. U. Zoller and D. Ben-Ishai, *Tetrahedron,* 1975, **31,** 863.
6. H. E. Zaugg and W. B. Martin, *Synthesis,* 1970, 49.
7. Characterization of **5-10**; **5**; mp; 104-105°C, nmr($CDCl_3$, δ); 7.4(m, 9H), 5.98(d, 1H), 3.64(s, 3H), 3.62(s, 3H), ir (KBr, Cm^{-1}); 1770, 1651. **6**(para isomer); mp; 123-124°C, nmr($CDCl_3$, δ); 7.2(m, 10H), 5.70(d, 1H), 3.64(s, 3H), 3.62 (s, 3H), ir(KBr, Cm^{-1}); 1759, 1655. **7**(para isomer); mp; 121-122°C, nmr($DCDl_3$, δ); 7.2(m, 10H), 5.75(d, 1H), 3.72 (s, 3H), 2.41(s, 3H), ir(KBr, Cm^{-1}); 1754, 1652. **8**(para isomer); mp; 103-104°C, nmr($CDCl_3$, δ); 7.1(m, 10H), 5.74(d, 1H), 3.71(s, 3H), 2.31(s, 3H), ir(KBr, Cm^{-1}); 1771, 1650. **9**; mp; 79-80°C, nmr($CDCl_3$, δ); 7.4(m, 7H), 6.34(d, 2H), 5.50(d, 1H), 5.12(s, 2H), 3.35(s, 3H), ir(KBr, Cm^{-1}); 1740, 1720. **10**(para isomer); mp; 95-96°C, nmr($CDCl_3$, δ); 7.1(m, 9H), 5.78(d, 1H), 5.30(d, 1H), 3.80(s, 3H), 3.64 (s, 3H), ir(KBr, Cm^{-1}); 1758, 1724.