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Transforming Natural Amino Acids into α-Alkyl-Substituted Amino Acids with the Help of the HOF·CH_3CN Complex

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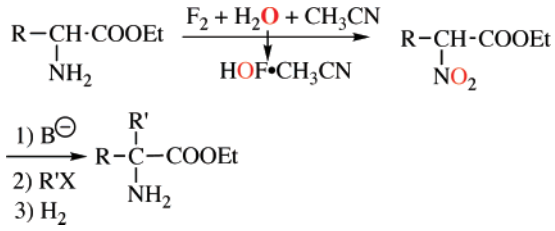

α-Alkyl amino acids can be efficiently prepared in high yields from the respective amino acids themselves. The key step is the oxidation of the amine function to create the corresponding α-nitro acid in a fast and very high yield reaction followed by phase-transfer alkylation and finally reduction to the desired α-alkyl amino acid. Several such acids containing aromatic rings or additional carboxylic groups and acids with steric hindrance at the α-position are suitable substrates. Several alkyl halides were examined as alkylating agents.

Introduction

Unnatural amino acids, especially α-alkylated ones, are of great interest for several reasons. They can act as potential enzyme inhibitors in pharmaceuticals[1] and form peptides resistant to degradation as demonstrated by α-methylphenylalanine, which is much sweeter and more stable than aspartame.[2] Lately, members of this family of compounds emerged as key materials in preventing the ability of amyloidogenic proteins, responsible for diseases such as Alzheimer's and Parkinson's, from adopting a *β*-sheet conformation by interfering with the amyloid self-assembly process.[3] Obviously, diverse synthetic methods for the preparation of amino acids branched at α position are needed, and indeed, some avenues to this end have been devised in the past. These methods are usually based on total syntheses starting with materials such as nitroacetates,[4] oxazinones,[5] or metalated bis-lactam ethers of 2,5-diketopiperazines.[6] Only rarely has an original amino acid been utilized as a starting point.[7] We describe here a general method for constructing α-alkylamino acids starting with the relevant amino acids themselves eliminating the constrains most other methods impose. The key step of the present synthesis is the use of the acetonitrile complex of the hypofluorous acid, HOF·CH_3CN, easily prepared by bubbling dilute fluorine through aqueous acetonitrile at 0 °C.[8]

HOF·CH_3CN has established itself as one of the best oxygen transfer agents organic chemistry has in its arsenal. Earlier processes developed with this reagent are summarized in two reviews describing difficult epoxidations, previously impossible sulfides to sulfone transformations, alkane hydroxylations, vicinal diamino oxidations, α to carbonyl hydroxylations, synthesis of the elusive 1,10-phenanthroline *N*,*N*′-dioxides, and much more.[9,10] Recently, we have also shown that this reagent was able to turn thiazoles and oligothiophenes into the corresponding thiazole *N*-oxides[11] and [all]-*S*,*S*-dioxide oligothiophenes,[12] turn azides into nitro derivatives,[13] convert episulfides to episulfones,[14] quinoxalines to quinoxaline *N*,*N*-

(1) See for example: O'Donnell, M. J. *Tetrahedron* **1988**, *44*, 5389−5401.
(2) Boesten, W. H. J.; Dassen, B. H. N.; Kleijans, J. C. S.; van Agen, B.; van der Wal, S.; de Vries, N. K.; Schoemaker, H. E.; Meijer, E. M. *J. Agric. Food Chem.* **1991**, *39*, 154−158.
(3) Gilead, S.; Gazit, E. *Angew. Chem., Int. Ed.* **2004**, *43*, 4041−4044.
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(5) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276−9286.
(6) Schollkopf, U. *Pure Appl. Chem.* **1983**, *55*, 1799−1806.
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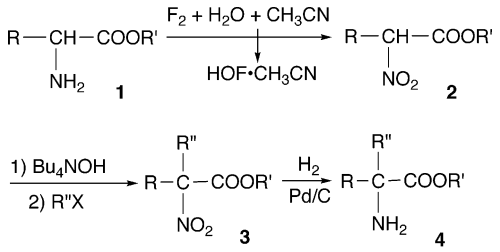
SCHEME 1[a]



a: R = H; R' = Et; R" = C_6H_{13}

b: R = CH_3; R' = R" = Et

c: R = CH_3; R' = Et; R" = C_6H_{13}

d[a]: R = CH_3; R' = Et; R" = $PhCH_2$

e[a]: R = $PhCH_2$; R' = Et; R" = CH_3

f: R = $PhCH_2$; R' = R" = Et

g: R = 4-$MeOC_6H_4CH_2$; R' = Et; R" = CH_3

h: R = Me_2CHCH_2; R' = R" = CH_3

i: R = Me_2CH; R' = R" = CH_3

j: R = $EtOOCCH_2CH_2$; R' = Et; R" = CH_3

[a] **3d** and **3e**, as well as **4d** and **4e**, are identical.

dioxides[15] to mention just a few. The ease of transferring oxygen atoms to basic nitrogens in almost any molecule gave us hope that we will be able to manipulate amino acids in preparing some unnatural derivatives as mentioned above.

Results and Discussion

Orthodox oxidation of amino acids invariably result in destroying the substrate through either decarboxylation, deamination, or other pathways mainly because of the harsh conditions which have to be employed. Since HOF·CH_3CN is effective even under very mild conditions, it does not destroy the chemical backbone of the amino acids. Indeed, many natural amino acids could be transformed to the corresponding nitro ones in excellent yields and very short reaction times.[16] An α-alkylation of these products and a subsequent reduction of the nitro moiety back to the parent NH_2 group should produce almost any desired α-alkyl amino acid.

Glycine ethyl ester (**1a**) served as a starting point for this project. We were able to oxidize it in excellent yield and in a matter of seconds to ethyl nitroacetate (**2a**). After several experiments, we found that the best strategy for its alkylation, and for the alkylation of all the α-nitro esters used in this work, was to employ tetrabutylammonium hydroxide as a base under phase-transfer conditions. Thus, treating **2a** with Bu_4NOH and hexyl iodide produced ethyl 2-nitrooctanoate (**3a**)[17] in 80% yield. This α-nitro derivative was then successfully reduced by hydrogenation over Pd/C in higher than 90% yield to form α-hexylglycine ethyl ester (**4a**) (Scheme 1).

Alanine (**1b**) was also successfully oxidized by the HOF·CH_3CN complex to give ethyl 2-nitropropionate (**2b**) in a fast and very high yield reaction. This nitro derivative was alkylated with ethyl iodide to produce ethyl 2-methyl-2-nitrobutyrate (**3b**)[18] in 90% yield and then quantitatively reduced to α-ethylalanine ethyl ester (**4b**).[19] Higher alkyl halides such as hexyl iodide or hexyl bromide could also be used as alkylating agents although the yield of the alkylation process forming ethyl 2-methyl-2-nitrooctanoate (**3c**)[18] (80%) was somewhat lower than in the previous case. Eventually **3c** was converted to α-hexylalanine ethyl ester (**4c**)[7] in very high yield.

Alkylation of **2b** was carried out with benzyl bromide too, and the formed **3d**[20] was again reduced with hydrogen over Pd/C to form α-methylphenylalanine ethyl ester (**4d**).[7] The same compound was also obtained from phenylalanine ethyl ester (**1e**) itself through its oxidation to **2e**,[16] followed by methylation with MeI to **3e** (identical to **3d**) and reduction to **4e** (identical to **4d**). Higher alkyl halides such as ethyl iodide could also react with the nitro derivative **2e** under PTC conditions. The ethyl 2-ethyl-2-nitro-3-phenylpropionate (**3f**) formed in 90% yield was then reduced to α-ethylphenylalanine ethyl ester (**4f**)[19] in similarly high yield.

O-Methyltyrosine ethyl ester (**1g**) successfully followed the above reaction pathway as well, despite the fact that HOF·CH_3CN is capable of transferring oxygen to activated aromatic rings.[21] It turned out that it reacts much faster with the basic amino group than with the anisole derivatives. The ethyl 2-nitro-3-(4-methoxyphenyl)propionate (**2g**) thus obtained was methylated to form **3g** and reduced to α-methyl-*O*-methyltyrosine ethyl ester (**4g**) in nearly quantitative yields.

The oxidation step of the more sterically hindered leucine methyl ester (**1h**) did not pose a problem, although the alkylation reaction took longer than usual. The reaction led to methyl 2-nitro-4-methylpentanoate (**2h**)[16] in 90% yield, but it took 72 h to methylate it under phase-transfer conditions to methyl 2,4-dimethyl-2-nitro-pentanoate (**3h**) in 85% yield. It should be noted that other then MeI alkylating agents did not work nearly as good due to the steric hindrance exercised by the two *β*-methyl groups on the α position. The hydrogenation step proceeded smoothly and α-methylleucine methyl ester (**4h**)[22] was obtained quantitatively.

The α-position of valine (**1i**) is also quite hindered. This fact does not affect the oxidation step forming the nitro derivative (**2i**)[16] in excellent yield. It affected somewhat the methylation step which needed 72 h to complete, but eventually the methyl 2,3-dimethyl-2-nitrobutyrate (**3i**) was formed in 85% yield. The high steric hindrance on the position α-to the nitro group did affect alkylation process with alkyl halides other than methyl iodide. The reaction of **2i** with hexyl iodide, for example, took 5 days, and even then, the resulting mixture contained little of the desired α-hexyl derivative, large proportion of the starting material and quite a few other byproducts. Following our goal to produce α-alkyl amino acids **3i** was successfully reduced to form α-methylvaline methyl ester (**4i**)[22] in 80% yield.

In order to demonstrate the general nature of the reaction, we also employed the bifunctional glutamic acid (**1j**). The oxygen transfer step performed by the HOF•CH_3CN proceeds

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smoothly forming diethyl 2-nitroglutarate (**2j**)[23] in 85% yield. This derivative was exclusively methylated at the α to the nitro group position forming diethyl 2-methyl-2-nitroglutarate (**3j**)[23] in 90% yield. No alkylation at the 4 position, adjacent to the second carbonyl was observed. The nitro derivative **3j** was eventually reduced almost quantitatively to the desired α-methylglutamic diethyl ester (**4j**).[24]

It should be noted at this stage that although the nitro derivatives could be obtained without much racemization, the present phase-transfer alkylation process results in a full racemization. We are experimenting now with several ideas to avoid the loss of the enantiomeric purity, but of course, there are also well-established orthodox procedures for resolving amino acid racemates.

Conclusion

The need for unnatural amino acids is growing quickly due to their potential biological importance. The method presented above is unique in the sense that it always starts with the corresponding amino acid and is of general nature. The combination of the most reactive element of them all, fluorine, and these delicate transformations is quite interesting.

Experimental Section

General Procedure for Working with Fluorine. This element is a strong oxidant and very corrosive material. It should be used only with an appropriate vacuum line whose detailed description has been documented.[25] For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, simplifying the process. If elementary precautions are taken, work with fluorine is relatively simple and we had no bad experiences working with it.

General Procedure for Producing HOF·CH$_3$CN. Mixtures of 10−20% F_2 with nitrogen were used in this work. The gas mixture was prepared in a secondary container before the reaction was started. It was then passed at a rate of about 400 mL per minute through a cold (−15 °C) mixture of 100 mL of CH_3CN and 10 mL of H_2O in a regular glass reactor.[10] The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.4−0.6 mol/L.

General Procedure for Working with HOF·CH$_3$CN. An appropriate amount of amino acid ester derivative (1−3 g) was dissolved in CH_2Cl_2, and the mixture was cooled to 0 °C. The oxidizing agent was treated with ∼5 g of NaF (a preferable trap for HF which is a byproduct of the HOF·CH_3CN production) until nearly neutral, and then 2 molar equiv of the oxidizing agent was added in one portion to the reaction vessel (1 molar equiv is a source of one oxygen atom). The reaction was usually quenched after a few seconds with saturated sodium bicarbonate until neutral and extracted with $CHCl_3$ (3 × 50 mL), the organic layer was dried over $MgSO_4$, and the solvent was evaporated. The crude product was usually purified by vacuum flash chromatography using increasing portions of EtOAc in PE as an eluent while silica gel 60-H served as the stationary phase. The spectral and physical properties of the known products were compared with those reported in the literature. In every case, excellent agreement was obtained. All known α-nitro esters were referenced throughout this work.

General Procedure for α-Alkylated Nitro Acids. The nitro amino acid ester derivative (usually 2 g, about 10 mmol) dissolved in 10 mL of CH_2Cl_2 was slowly added over a period of 30 min to a stirred solution of 1 molar equiv of tetrabutylammonium hydroxide, 40 wt % in water. After the mixture was stirred for 10 min, the alkyl halide (5 molar equiv) was added in one portion at room temperature. The mixture was stirred vigorously for 48 h (72 h for the reactions with leucine and valine derivatives), and then the organic layer was separated and washed with water and the aqueous layers were extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, and the solvent was evaporated. Dry ether was added to precipitate the tetrabutylammonium iodide, the filtrate was evaporated, and the desired products were usually purified by vacuum flash chromatography using silica gel 60-H (Merck). Data for the new compounds or for those not well defined in the literature is given below.

General Procedure for α-Alkylated Amino Acids. The nitro alkylated acids were dissolved in methanol, and a catalytic amount of Pd/C (5%) was added. The reaction mixture was stirred for 12 h at room temperature under H_2 (1 atm). The catalyst was removed by filtration, the solvent was evaporated, and the residue was subjected to column chromatography using silica gel Lichroprep NH_2 to afford the corresponding pure amine. Data for some of the new compounds or those not well defined in the literature is given below, while the data for the rest of the compounds can be found in the Supporting Information.

Ethyl 2-ethyl-2-nitrobutyrate (3b):[18] bright yellow oil; 90% yield (from **2b**); IR 1388, 1553, 1747 cm^{-1}; ^{1}H NMR δ 0.93 (3 H, t, J = 7.5 Hz), 1.27 (3 H, t, J = 7.1 Hz), 1.74 (3 H, s), 2.16−2.29 (2 H, m), 4.25 (2 H, q, J = 7.1 Hz); ^{13}C NMR δ 8.1, 13.8, 20.7, 29.7, 62.6, 93.2, 167.5; HRMS m/z calcd for $C_7H_{13}NO_4$ 198.0736 (M + Na)$^+$, found 198.0736.

α-Ethylalanine ethyl ester (4b):[19] colorless oil; 98% yield (from **3b**); IR 1722 cm^{-1}; ^{1}H NMR δ 0.87 (3 H, t, J = 7.4 Hz), 1.28 (3 H, t, J = 7 Hz), 1.32 (3 H, s), 1.57−1.63 (1 H, m), 1.74−1.78 (1 H, m), 1.97 (2 H, broad s), 4.17 (2 H, q, J = 7 Hz); ^{13}C NMR δ 8.4, 14.2, 25.8, 33.7, 58.1, 60.9, 177.4; HRMS m/z calcd for $C_7H_{15}NO_2$ 168.0982 (M + Na)$^+$, found 168.0995.

2-Methyl-2-nitrooctanoate (3c):[18] yellow oil; 80% yield (from **2b**); IR 1386, 1553, 1746 cm^{-1}; ^{1}H NMR δ 0.88 (3 H, t, J = 7 Hz), 1.23−1.35 (11 H, m), 1.63 (3 H, s), 2.12−2.23 (2 H, m), 4.26 (2 H, q, J = 7 Hz); ^{13}C NMR δ 13.8, 14.0, 21.2, 22.4, 23.6, 29.0, 31.4, 36.4, 62.6, 92.8, 167.6; HRMS m/z calcd for $C_{11}H_{21}NO_4$ 254.1349 (M + Na)$^+$, found 254.1362.

α-Hexylalanine ethyl ester (4c):[7] colorless oil; 93% yield (from **3c**); IR 1718 cm^{-1}; ^{1}H NMR δ 0.86−0.89 (3 H, m), 1.21−1.35 (14 H, m), 1.50−1.57 (1 H, m), 1.65−1.73 (1 H, m), 4.16 (2 H, q, J = 7 Hz); ^{13}C NMR δ 14.0, 14.2, 22.5, 24.7, 26.4, 29.5, 31.6, 41.0, 57.7, 60.9, 177.8; HRMS m/z calcd for $C_{11}H_{23}NO_2$ 224.1621 (M + Na)$^+$, found 224.1621.

Ethyl 3-(4-methoxyphenyl)-2-methyl-2-nitropropionate (3g): yellow oil; 90% yield (from **2g**); IR 1513, 1555, 1748 cm^{-1}; ^{1}H NMR δ 1.28 (3 H, t, J = 7.1 Hz), 1.66 (3 H, s), 3.37 (1 H, d, J = 14 Hz), 3.56 (1 H, d, J = 14 Hz), 3.78 (3 H, s), 4.27 (2 H, q, J = 7 Hz), 6.80−6.82 (2 H, m), 7.01−7.04 (2 H, m); ^{13}C NMR δ 13.8, 20.8, 41.3, 55.2, 62.9, 93.2, 114.1, 125.0, 131.2, 159.3, 167.4; HRMS m/z calcd for $C_{13}H_{17}NO_5$ 290.1017 (M + Na)$^+$, found 290.0998. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.49; H, 6.30; N, 5.47.

α-Methyl-*O*-methyltyrosine ethyl ester (4g): yellow oil; 100% yield (from **3g**); IR 1725 cm^{-1}; ^{1}H NMR δ 1.27 (3 H, t, J = 7.1 Hz), 1.36 (3 H, s), 1.62 (2 H, broad s), 2.73 (1 H, d, J = 13.3 Hz), 3.07 (1 H, d, J = 13.3 Hz), 3.78 (3 H, s), 4.15 (2 H, q, J = 7.1 Hz), 6.80−6.82 (2 H, m), 7.06−7.26 (2 H, m); ^{13}C NMR δ 14.2, 26.6, 45.9, 55.2, 58.7, 61.0, 113.7, 128.6, 131.0, 158.6, 177.2; HRMS m/z calcd for $C_{13}H_{19}NO_3$ 238.1457 (M + H)$^+$, found 238.1437. Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90. Found: C, 65.98; H, 8.17; N, 5.91.

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Methyl 2,3-dimethyl-2-nitrobutyrate (3i): yellow oil; 85% yield (from **2i**); IR 1398, 1552, 1756 cm^{-1}; ^1H NMR δ 0.97−1.01 (6 H, m), 1.69 (3 H, s), 2.77−2.80 (1 H, m), 3.80 (3 H, s); ^{13}C NMR δ 17.7, 17.8, 18.2, 34.2, 53.6, 96.8, 167.9; HRMS *m*/*z* calcd for $C_7H_{13}NO_4$ 198.0741 $(M + Na)^+$, found 198.0736. Anal. Calcd for $C_7H_{13}NO_4$: C, 47.99; H, 7.48; N, 8.00. Found: C, 47.90; H, 7.42; N, 8.27.

α-Methylvaline methyl ester (4i):[22] colorless oil; 80% yield (from **3i**); IR 1733 cm^{-1}; ^1H NMR δ 0.86 (3 H, d, $J = 7$ Hz), 0.91 (3 H, d, $J = 7$ Hz), 1.26 (3 H, s), 1.58 (2H, broad s), 1.94−2.02 (1 H, m), 3.71 (3 H, s); ^{13}C NMR δ 16.3, 17.4, 23.5, 35.7, 51.9, 60.7, 178.3; HRMS *m*/*z* calcd for $C_7H_{15}NO_2$ 146.1164 $(M + Na)^+$, found 146.1175.

Diethyl 2-methyl-2-nitroglutarate (3j):[23] brown oil; 90% yield (from **2j**); IR 1387, 1555, 1741 cm^{-1}; ^1H NMR δ 1.21−1.30 (6 H, m), 1.80 (3 H , s), 2.35−2.57 (4 H, m), 4.15 (2 H, q, $J = 7$ Hz), 4.28 (2 H, q, $J = 7$ Hz); ^{13}C NMR δ 14.2, 14.5, 22.0, 29.3, 31.9, 61.3, 63.4, 92.1, 167.3, 172.0; HRMS *m*/*z* calcd for $C_{10}H_{17}NO_6$ 248.1146 $(M + H)^+$, found 248.1128.

α-Methylglutamic diethyl ester (4j):[24] colorless oil; 95% yield (from **3j**); IR 1734 cm^{-1}; ^1H NMR δ 1.15−1.24 (9 H, m), 1.78−1.82 (1 H, m), 2.02−2.07 (1 H, m), 2.21−2.44 (2 H, m), 4.02−4.15 (4 H, m); ^{13}C NMR δ 14.5, 19.8, 29.1, 29.3, 61.0, 61.5, 65.3, 174.4, 175.2; HRMS *m*/*z* calcd for $C_{10}H_{19}NO_4$ 240.1195 $(M + Na)^+$, found 240.1206.

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Supporting Information Available: General experimental conditions, as well as complete characterization, including NMR spectra of all compounds described in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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