# New Efficient Route to α-Nitro Acids. Oxidation of Amino Acids with HOF·$CH_3CN$

Shlomo Rozen,* Arie Bar-Haim, and Eyal Mishani

*School of Chemistry, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel-Aviv University, Tel-Aviv 69978, Israel*

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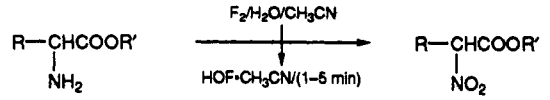
The family of α-nitro acid derivatives is useful as a starting point for various reactions, and thus several synthetic methods have been devised for the preparation of its members. Most of these methods, however, are based on a combination of two fragments such as nitroacetate and an alkyl group or a carboxylic acid derivative and a nitro compound.[1] These procedures are usually characterized by long reaction times with yields rarely exceeding 70%. When amino acids were directly oxidized, the products were usually ammonia or its salts and a nitrogen-free organic residue.[2]

In the last few years we have developed a new and powerful oxygen transfer agent, the HOF·$CH_3CN$ complex, which does not contain any polluting heavy metals usually associated with strong oxidizers. This reagent, made easily by bubbling $F_2$ through aqueous acetonitrile, is able to hydroxylate tertiary deactivated C–H bonds,[3] epoxidize practically any olefin,[4] and oxidize aromatic rings,[5] alcohols, ketones,[6] and amines[7] all under very mild reaction conditions. The last reaction prompted us to examine whether α-nitro esters can be made directly from the corresponding amino acid derivative without the usual oxidative deamination resulting when other oxidants are used.

Reacting ethyl glycine (1) with HOF·$CH_3CN$ for 1 min at room temperature produced ethyl nitroacetate (2) in quantitative yield, an overall performance difficult to beat. Esters of alanine (3), valine (4), and leucine (5) behaved very similarly and produced benzyl 2-nitropropanoate (6), methyl 2-nitro-3-methylbutanoate (7),[8] and methyl 2-nitro-4-methylpentanoate (8)[1b] in 95, 85, and 80% yields, respectively, with reaction times of around 5 min. The dicarboxylic amino acids dimethyl aspartate (9) and glutamate (10) did not behave differently, and dimethyl 2-nitrosuccinate (11) and nitroglutarate (12)[8] were formed within less than 5 min with higher than 80% yields (eq 1).

Despite the fact that the HOF·$CH_3CN$ complex was able to oxidize various aromatic rings and especially activated ones,[7] the short reaction times with the amino group enabled us to selectively oxidize it without affecting the



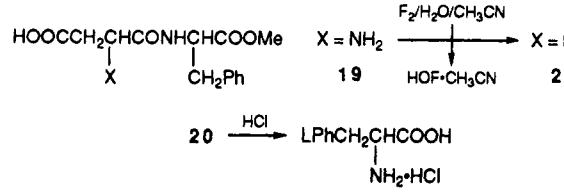

(1)

| | | |
|---|---|---|
| 1 | R = H; R' = Et | 2 |
| 3 | R = $CH_3$; R' = $CH_2Ph$ | 6 |
| 4 | R = *i*-Pr; R' = Me | 7 |
| 5 | R = *i*-Pr$CH_2$; R' = Me | 8 |
| 9 | R = MeOOC$CH_2$; R' = Me | 11 |
| 10 | R = MeOOC$(CH_2)_2$; R' = Me | 12 |
| 13 | R = Ph$CH_2$; R' = Me | 15 |
| 14 | R = *p*-HO$C_6H_4CH_2$; R' = Me | 16 |
| 17 | R = HO$CH_2$; R' = Et | 18 |

aromatic ring. Both the methyl ester of phenylalanine (13) and of tyrosine (14) were converted to the corresponding nitro derivatives 15[8] and 16[9] in 85 and 95% yields, respectively.

It was of special interest to see if the free hydroxyl group of serine ethyl ester (17) would also survive this reaction. We found that in this case the oxidation of the amino group took about 30 s, and this short reaction time ensured the survival of the primary hydroxyl moiety. Ethyl 2-nitro-3-hydroxypropanoate (18)[1] was formed in 70% yield.

While it was obvious that the 2-nitrocarboxylate derivatives would not retain their chirality because of the considerable acidity of the hydrogen adjacent to the nitro and carboxylic groups, it was of interest to determine if other chiral centers in a molecule would be affected by the reagent. Another question was whether the carboxylic acid has to be protected as an ester and whether an amide moiety would be preserved under the reaction conditions. Answers were found in the short (4 min) reaction of the dipeptide aspartame (19) with the oxidizing HOF·$CH_3CN$ complex (eq 2). The corresponding nitro derivative




20 was obtained as a diastereoisomeric mixture in 85% yield, $[\alpha]_D$ ($CHCl_3$; $c = 0.1$) = 50°. While the chiral center of the aspartic acid segment around which the oxidation took place was racemized, the phenylalanine part remained intact as is evident from the HCl hydrolysis of 20. The $[\alpha]_D$ of the resulting phenylalanine hydrochloride was found to be −9°, similar to an authentic phenylalanine·HCl sample. It was also clear that the free carboxylic acid would not interfere with the oxidation of the adjacent amino group. However, it was convenient to work with esters which are more soluble in organic solvents.

## Experimental Section

$^1H$ NMR spectra were recorded with a Bruker AC-200 with $CDCl_3$ as solvent and $Me_4Si$ as an internal standard. The proton broad band decoupled $^{13}C$ NMR spectra were recorded at 50.3 MHz. Here too, $CDCl_3$ served as a solvent and TMS as internal

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0022-3263/94/1959-1208$04.50/0 

Table 1

| entry[a] | $^1$H NMR ($CHNO_2$) | $^{13}$C NMR ($CHNO_2$) | IR ($cm^{-1}$) | MS ($m/e$) |
|---|---|---|---|---|
| 6 | 5.24 (q, $J$ = 7.1 Hz) | 83.09 | 1361, 1561, 1753 | 163 $(M - NO_2)^+$ |
| 7 | 4.92 (d, $J$ = 8.1 Hz) | 93.33 | 1561, 1756 | 115 $(M - NO_2)^+$ |
| 8 | 5.22 (dd, $J_1$ = 9.9, $J_2$ = 5.2 Hz) | 86.54 | 1374, 1563, 1757 | 129 $(M - NO_2)^+$ |
| 11 | 5.59 (dd, $J_1$ = 9.0, $J_2$ = 4.8 Hz) | 82.95 | 1378, 1569, 1730–1760[b] | |
| 12 | 5.34 (dd, $J_1$ = 5.1, $J_2$ = 4.9 Hz) | 86.40 | 1374, 1566, 1730–1760[b] | 174 $(M - OMe)^+$; 159 $(M - NO_2)^+$ |
| 15 | 5.36 (dd, $J_1$ = 9.3, $J_2$ = 6.2 Hz) | 88.90 | 1370, 1563, 1755 | 209 $(M)^+$; 163 $(M - NO_2)^+$ |
| 16[c] | 5.32 (dd, $J_1$ = 9.0, $J_2$ = 6.3 Hz) | 89.27 | 1376, 1561, 1763 | 225 $(M)^+$; 179 $(M - NO_2)^+$ |
| 18 | 5.29 (dd, $J_1$ = 5.8, $J_2$ = 4.4 Hz) | 88.40 | 1566, 1752, 3600 | 117 $(M - NO_2)^+$ |
| 20[d] | 5.5 (1H, m) | 83.68 | 1561, 1686, 1741, 3600 | 324 $(M)^+$ [e] |

[a] Unless otherwise stated, all products are oils. [b] A wide band due to the two carbonyls. [c] Anal. Calcd for $C_{10}H_{11}NO_5$: C, 53.33; H, 4.92; N, 6.22. Found: 53.01; H, 4.77; N, 6.20. [d] Anal. Calcd for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 51.65; H, 5.20; N, 8.24. [e] By chemical ionization.

standard. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films in $CHCl_3$ solution or in KBr pellets on a Nicolet 205 FTIR spectrophotometer.

**General Procedure for Working with Fluorine.** Fluorine is a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or monel in a well-ventilated area should be constructed for working with this element. For more experimental details see, for example, ref 10. For the occasional user, however, various premixed mixtures of $F_2$ in inert gases are commercially available, simplifying the whole process. The reactions themselves can be carried out in glass vessels. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no bad experiences working with it.

**General Procedure for Producing the Oxidizing HOF·$CH_3CN$.** Mixtures of about 10% $F_2$ with nitrogen were used in this work. The gas mixture was prepared in a secondary container before the reaction was started. This mixture was then passed at a rate of about 400 mL/min through a cold (−15 °C) and vigorously stirred mixture of 400 mL of $CH_3CN$ and 40 mL of $H_2O$. The formation of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was titrated with thiosulfate. It is thus possible to achieve concentrations of more than 1 mol/L of the oxidizing reagent which at room temperature has a half-life time of about 3–4 h.

**General Oxidation Procedure.** About 10 mmol of an amino acid derivative was dissolved in 10–20 mL of $CH_2Cl_2$. The mixture was then added to the glass reactor containing 5 g of NaF and 30–50 mmol of the oxidizing HOF·$CH_3CN$ in aqueous $CH_3CN$ (150 mL). The reaction was allowed to proceed at room temperature for about 5 min, neutralized with saturated sodium bicarbonate solution, poured into 1500 mL of water, extracted with $CH_2Cl_2$, and washed with $NaHCO_3$ and water until neutral. The organic layer was dried over $MgSO_4$ and the solvent evaporated. The oily products were usually purified either by vacuum flash chromatography using silica gel 60-H (Merck) or low-pressure distillation. The spectral and physical properties of the known products thus obtained were compared with those reported in the literature. In every case excellent agreement was obtained. Ethyl nitroacetate (2) is the only commercial nitro derivative obtained in this work. Some spectral data for new compounds or for ones which have not been well defined in the literature are given in Table 1.

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