Tetrahedron Letters Vol. 21, pp 3593 - 3594 0040-4039/80/0908-3593$02.00/0

STEREOSELECTIVE SYNTHESIS OF ERYTHRO-3-FLUOROPHENYLALANINE

Tadahiko Tsushima,* Junko Nishikawa, Tomohiro Sato, Hiroshi Tanida,
Kazuo Tori and Teruji Tsuji

Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

and

Susumu Misaki* and Masahiro Suefuji

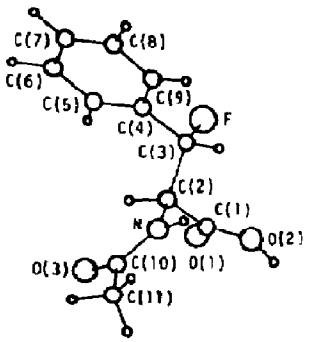
Daikin Kogyo Co., Ltd., Research Department, Chemical Division,
700-1 Hitotsuya, Settsu, Osaka 564, Japan

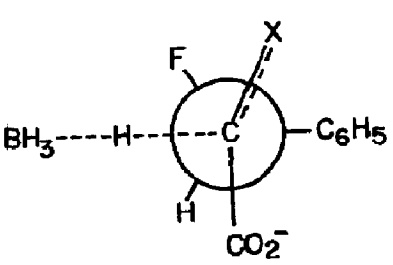
Summary: Reductive amination of 3-fluorophenylpyruvic acid was found to give erythro-3-fluorophenylalanine with high selectivity.

Our previous paper[1] reported the elucidation of threo and erythro configurations of 3-fluorophenylalanine based on chemical transformation and X-ray analysis. According to that study, the aziridine ring opening reaction recently reported by Wade et al.[2] was found to be a highly stereoselective reaction producing the threo diastereoisomer in a yield higher than 90%. We herein report a stereoselective synthesis of the erythro diastereoisomer by reductive amination of 3-fluorophenylpyruvic acid.

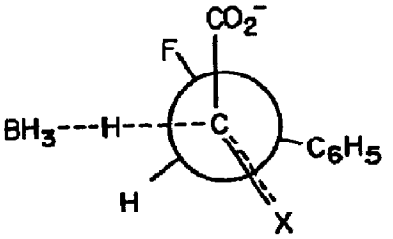
Treatment of β-phenylpyruvic acid esters with molecular fluorine in an inert solvent [CH_3CN-$CF_2ClCFCl_2$] gave the desired starting material, 3-fluorophenylpyruvic acid esters, in fairly good yield [65-70%].[3] This reaction proceeded satisfactorily with α-keto acid derivatives which predominantly exist in the enol form but not with derivatives in the keto form which gave complex mixtures of products. In the latter case, various side reactions by fluorine such as hydrogen abstraction, carbon-carbon bond breaking, and addition to the carbonyl group, may have occurred before the rate-determining enolization step and caused the unsatisfactory results. Thus, the desired results can probably be obtained by completing this step in advance as in the former case or facilitating it by choosing proper reaction conditions. Methyl 3-fluorophenylpyruvate thus obtained was then converted into sodium 3-fluorophenylpyruvate under mild alkaline hydrolysis conditions [50% aq. 2-PrOH/$NaHCO_3$], which prevent defluorination, and subsequently subjected to reductive amination using $NaBH_4$-NH_4OH or $NaBH_3CN$-NH_4Br according to reported methods.[4] Both reductive amination procedures gave a fluorinated amino acid in an isolation yield ranging from 40% to 20%, the former being superior to the latter. The ^1H and ^{19}F NMR spectra of the amino acid clearly showed that this compound was identical to isomer B[1] which was obtained together with isomer A[1] in fluorodehydroxylation of 3-phenylserine and was identified as the erythro isomer: m.p. 168-170°C (dec.): MS (m/e) 184 (M^++H), 163 (M^+-HF), 109 (C_7H_6F), etc.: ^1H NMR in D_2O (int. DSS) 4.33 (1H, dd, $J(H_\alpha F)$ 16, $J(H_\alpha H_\beta)$ 3.4 Hz, H_α), 6.17 (1H, dd, $J(H_\beta F)$ 44 Hz, H_β), ~7.4 (5H, m, arom. H); ^{19}F NMR in D_2O(ext. C_6F_6) -21.3 (J 46, 16 Hz).

In order to unambiguously confirm the erythro configuration of the product, it was acetylated and recrystallized [CH_3OH] to afford fine crystals for X-ray analysis (see figure);[5] m.p. 167-169°C. Therefore, the present reaction was highly stereoselective and the threo isomer yield was not more than 5%.





I



II

For the mechanistic interpretation of this reaction, an imine intermediate and two reactant-like transition states I and II were invoked. According to the explanations[6] of asymmetric induction hitherto proposed for the reduction of carbonyl compounds, transition state I satisfactorily accounts for the preferable formation of the erythro isomer and transition state II explains the formation of the threo isomer. The latter transition state was proposed by Cornforth et al. for the reduction of α-halo ketones.[6] Our present result favors transition state I, making a striking contrast to the case of α-halo ketone reduction. After the completion of this work, we found a similar report published by Pandit et al.[7] this year. They proposed that transition state I was also favored over transition state II in the synthesis of erythro-3-fluoroaspartic acid ester. We emphasize here the importance of stabilization interactions (Coulombic attraction and/or hydrogen bonding) between fluorine and the NH group in the choice of the transition state I, because it was found by us in the NMR spectroscopic study[8] of rotamers of both diastereoisomers of 3-fluorophenylalanine that these interactions bring about stronger effects on equilibria of rotational conformations than do steric factors of the functional groups involved.

We thank Dr. K. Kawada for his help with the synthetic work.

REFERENCES AND NOTES

1. T. Tsushima, T. Sato and T. Tsuji, Tetrahedron Lett. the preceding paper.
2. T. N. Wade, F. Gaymard and R. Guedj, Tetrahedron Lett. 2681 (1979).
3. All the fluorination products obtained were converted into the corresponding trimethylsilyl ether derivatives by treatment with BSA, which gave, after fractional distillation, satisfactory physical and analytical data confirming monofluorination. These trimethylsilyl ethers were easily hydrolyzed in aqueous methanol under the nitrogen atmosphere to afford pure 3-fluoro-2-keto esters such as methyl 3-fluorophenylpyruvate (existing in the enol form) which were fully characterized on the basis of physical and analytical data. Experimental details will be reported elsewhere in the near future.
4. U.-H. Dolling, A. W. Douglas, E. J. J. Grabowski, E. F. Schoenewaldt, P. Sohar, and M. Sletzinger, J. Org. Chem. 43, 1634 (1978); R. F. Borch, M. D. Bernstein and M. D. Durst, J. Am. Chem. Soc. 93, 2897 (1971).
5. T. Sato and T. Tsushima, Acta Cryst. submitted for publication.
6. See references and arguments cited in H. O. House, "Modern Synthetic Reactions," ed. R. Breslow, W. A. Benjamin, Menlo Park, Calif., 1972, Second ed., pp 54-58.
7. M. J. Wanner, J. J. M. Hageman, G.-J. Koomen and U. K. Pandit, J. Med. Chem. 23, 85 (1980).
8. K. Tori et al. to be published elsewhere.

(Received in Japan 30 May 1980)