ORGANIC LETTERS

2007
Vol. 9, No. 13
2513−2515

Photoinduced Diastereoselective Addition of Perfluoroalkyl Iodides to Acrylic Acid Derivatives for the Synthesis of Fluorinated Amino Acids

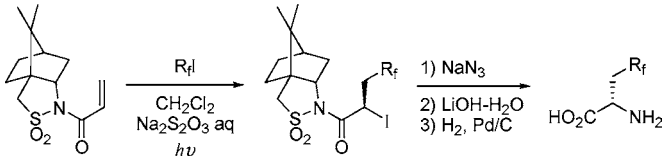
Tomoko Yajima* and Hajime Nagano

Department of Chemistry, Faculty of Science, Ochanomizu University, Otsuka, Bunkyo-ku, Tokyo 112-8610, Japan

yajima.tomoko@ocha.ac.jp

Received March 29, 2007

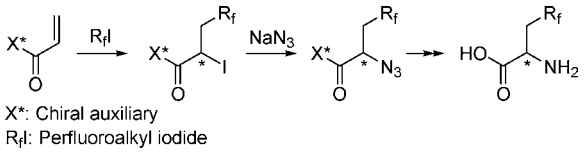
ABSTRACT



Photoinduced diastereoselective addition of perfluoroalkyl iodides in the presence of an aqueous solution of $Na_2S_2O_3$ was an excellent method for iodoperfluoroalkylation of acrylic acid derivatives bearing a chiral auxiliary, with moderate to good stereoselectivities and with no detectable side products. The iodoperfluoroalkylation of *N*-acyloylcamphorsultam provided a convenient route for preparing chiral fluorine-containing amino acids.

Organofluorine compounds have been receiving significant interest in materials science and medicinal chemistry.[1] Addition reactions of perfluoroalkyl iodide to carbon−carbon double bonds are efficient and versatile for the direct introduction of a perfluoroalkyl group onto organic molecules. In particular, the iodoperfluorination of acrylic acid derivatives, followed by nucleophilic substitution of the iodide with a nitrogen nucleophile, gives the corresponding fluorine-containing amino acids[2] (Scheme 1). However, iodofluoroalkylation reactions are limited to electron-rich alkenes.[3] With electron-deficient alkenes, the formation of undesired dimeric, telomeric, or polymeric products is frequently observed, and the desired 1:1 adduct was obtained in low yield.[4] To the best of our knowledge, there are no reports on the asymmetric process. Thus, we investigated the diastereoselective iodoperfluoroalkylation of acrylic acid

Scheme 1



(1) For a review and books, see: (a) Resnati, G. *Tetrahedron* **1993**, *49*, 9385−9445. (b) Uneyama, K. *Organofluorine Chemistry*, Blackwell Pub.: United Kingdom, 2006. (c) Kirsh, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; John Wiley & Sons: New York, 2004. (d) Kitazume, T.; Yamazaki, T. *Experimental Methods in Organic Fluorine Chemistry*; Kodansha Ltd.: Tokyo, 1998. (e) Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; John Wiley & Sons: New York, 1990. (f) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha Ltd.: Tokyo, 1982.

(2) For a review and a book, see: (a) Jäckel, C.; Koksch, B. *Eur. J. Org. Chem*. **2005**, 4483−4503. (b) *Fluorine Containing Amino Acids*; Kukhhar, V. P., Soloshonok, V. A., Eds.; John Wiley & Sons: New York, 1995.

(3) For a review, see: (a) Dolbier, W. R., Jr. *Chem. Rev*. **1996**, *96*, 1557−1584. Photoinduced reactions, see: (b) Tsuchii, K.; Imura, M.; Kamada, N.; Hirao, T.; Ogawa, A. *J. Org. Chem.* **2004**, *69*, 6658−6665.

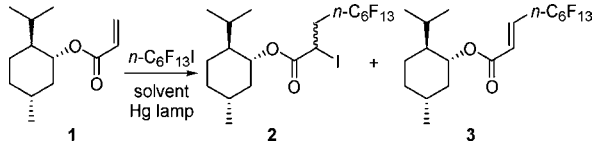
(4) Radical-mediated perfluoroalkylation reactions for α-methylene esters, see: (a) Kamigata, N.; Fukushima, T.; Terakawa, Y.; Yoshida, M.; Iyoda, M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 627−633. (b) Qiu, Z.-M.; Burton, D. J. *J. Org. Chem*. **1995**, *60*, 3465−3472 and references cited therein.

10.1021/ol0707620 CCC: $37.00
Published on Web 06/02/2007

derivatives bearing a chiral auxiliary and report herein that the reaction proceeded smoothly in the presence of an aqueous solution of $Na_2S_2O_3$ under UV irradiation in CH_2Cl_2. We also report that the iodoperfluoroalkylation of an acrylic amide bearing camphorsultam proceeded with high diastereoselectivity, and the adduct was readily converted to the corresponding chiral fluorinated amino acid.

Table 1 summarizes the initial studies using perfluorohexyl iodide and menthyl acrylate **1**,[5] which are easy to handle compared with simple volatile acrylates. All reactions were carried out under photoirradiation with a Hg lamp in a Pyrex tube. In the absence of solvent, the reaction gave the desired product **2**, formed by the attack of a perfluoroalkyl radical on the β-carbon of the acrylate as reported by Qiu et al.,[4b] in 22% yield (entry 1). Benzotrifluoride (BTF), benzene, and CH_2Cl_2 were used as solvents, and the best yield was obtained in CH_2Cl_2 (entries 2−4). Dilute reaction conditions gave higher yields, but longer reaction times gave olefinic side product **3** (entries 5 and 6). A large excess of perfluorohexyl iodide increased the yield of **2** up to 83% (entries 7−10). From the experimental observations: (1) the reaction slowed as time passed, and the starting material was recovered, even when a large excess of iodide was used; and (2) the reaction mixture became pink after irradiation, and it is thought that iodine, which is a byproduct, retarded the addition reaction. Thus, to trap the iodine, an aqueous solution of $Na_2S_2O_3$ was added to the reaction mixture, and the reaction was completed within 1 h to give a 91% yield without any side products (entry 11). However, in all cases, the reactions were nondiastereoselective.

Table 1. Screening of Iodoperfluorohexylation Reaction Conditions Using Substrate **1**[a]

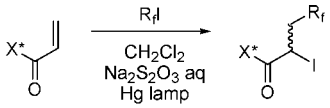


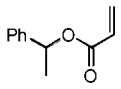
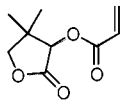
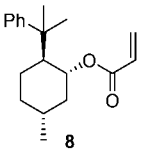
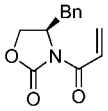
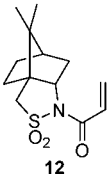
entry	n-$C_6F_{13}I$ (equiv)	time (h)	solvent (mol/L)[c]	**2**[b] (%)	**3** (%)
1	1.2	6	neat	22	−
2	1.2	6	BTF (1.0)	13	−
3	1.2	6	benzene (1.0)	4	−
4	1.2	6	CH_2Cl_2 (1.0)	37	−
5	1.2	24	CH_2Cl_2 (0.1)	32	19
6	1.2	24	CH_2Cl_2 (0.04)	40	21
7	2.0	24	CH_2Cl_2 (0.04)	68	14
8	5.0	6	CH_2Cl_2 (0.04)	56	8
9	5.0	24	CH_2Cl_2 (0.04)	76	13
10	10.0	24	CH_2Cl_2 (0.04)	83	8
11[d]	10.0	1	CH_2Cl_2 (0.04)	91	−

[a] The reaction was carried out under irradiation with a Hg lamp in a Pyrex tube at rt. [b] Diastereomer ratio of **2a** was 50:50. [c] Molarity in **1**/solvent. [d] In the presence of a solution of $Na_2S_2O_3$ (5 equiv) in water (0.01 mol/L).

We next investigated the iodoperfluoroalkylations of acrylic acid derivatives bearing chiral auxiliaries (**4**,[6] **6**,[7] **8**,[8] **10**,[9] and **12**,[10] shown in Table 2) under the same conditions as entry 11 in Table 1[11] (Table 2). All of the substrates smoothly reacted with perfluorohexyl iodides to give the corresponding iodoperfluorohexyl products in good yields. Acrylates **4** gave no diastereoselectivity, and **6** gave low diastereoselectivity (entries 1 and 2). Both **8** and **10** gave a diastereoselectivity of 76:24 (entries 3 and 4). Although the chelation controlled reaction of **10** using $Mg(ClO_4)_2$ as a

Table 2. Iodoperfluoroalkylation of Acrylic Acid Derivatives Bearing Chiral Auxiliaries[11]



entry	substrate	R_fI	time (h)	product	yield (%)	dr[a]
1	 **4**	n-$C_6F_{13}I$	1	**5**	80	50:50
2	 **6**	n-$C_6F_{13}I$	1	**7**	82	60:40
3	 **8**	n-$C_6F_{13}I$	1	**9**	87	76:24
4	 **10**	n-$C_6F_{13}I$	1.5	**11**	69	76:24
5	 **12**	n-$C_6F_{13}I$ n-C_3F_7I i-C_3F_7I C_2F_5I CF_3I	1.5 2.5 2.0 2.5 5.0	**13** **14** **15** **16** **17**	73 73 75 68 63	77:23 81:19 83:17 79:21 80:20

[a] Diastereoselectivities were determined by ^1H NMR. The relative configurations of products **5**, **7**, **9**, and **11** were not determined. The stereochemistries of the major diastereomer of **13**−**17** were (2*S*) (see ref 13).

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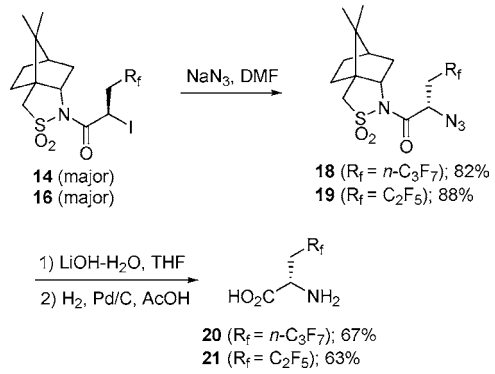
(10) Clark, W. M.; Bender, C. *J. Org. Chem.* **1998**, *63*, 6732−6734.

Lewis acid[12] was attempted, the stereoselectivity did not increase. *N*-Acyloylcamphorsultam **12** gave a diastereoselectivity of 77:23, and the diastereomers were easily separated by column chromatography (entry 5). Then, reactions of **12** with various perfluoroalkyl iodides were performed, and easily separable diastereomer mixtures of **14**−**17** were obtained, respectively.[13]

Finally, we synthesized fluorine-containing amino acids **20** and **21** using the major diastereomers of products **14** and **16**, respectively, as starting materials (Scheme 2). Azide

Scheme 2



displacement proceeded with inversion of configuration,[14] and the azides **18** and **19** were obtained in good yields without any loss of stereochemical purity. The removal of the sultam auxiliary via hydrolysis[15] afforded α-azidocarboxylates. Finally, hydrogenation of the azide group by a standard method[16] gave (*S*)-4,4,5,5,6,6,6-heptafluoronorleucine (**20**)[14b] in 67% yield and (*S*)-4,4,5,5,5-pentafluoronorvaline (**21**)[14b] in 63% yield for two steps. The absolute configurations were determined by comparing the specific rotations of the α-azidocarboxylates with the reported values.[14b] The enantiomeric excesses of **20** and **21** were determined to be 94% ee and 92% ee, respectively, by analyzing the ^{1}H NMR spectrum of the Mosher amide of the corresponding amino acids.[14b]

In conclusion, we reported the diastereoselective iodoperfluoroalkylation of acrylic acid derivatives and the asymmetric synthesis of fluorine-containing amino acids. In the presence of an aqueous solution of $Na_2S_2O_3$, the iodoperfluoroalkylation proceeded with excellent yield and with moderate to good stereoselectivities. (*S*)-4,4,5,5,6,6,6-Heptafluoronorleucine (**20**) and (*S*)-4,4,5,5,5-pentafluoronorvaline (**21**) were synthesized on the basis of the diastereoselective iodoperfluoropropylation of *N*-acyloylcamphorsultam **12**. This route is a new and efficient asymmetric method for the synthesis of fluorinated amino acids, and the synthesis of various fluorinated amino acids is currently in progress.

Supporting Information Available: General experimental procedures and characterization data for compounds **2**, **3**, **5**, **7**, **9**, **11**, and **13**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0707620

(11) General procedure for the photoinduced addition reaction is as follows: In a Pyrex glass tube were placed the olefin (0.2 mmol), perfluoroalkyl iodide (2.0 mmol), and CH_2Cl_2 (5 mL). Then, $Na_2S_2O_3$ (158 mg, 1 mmol) and water (1 mL) were added. After sealing the tube, the mixture was mixed by shaking and then irradiated with a Hg lamp at room temperature. After the reaction was completed, the products were extracted with CH_2Cl_2. The extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by silica gel column chromatography to afford pure product.

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(13) The absolute configurations of **14** and **16** were determined after being transformed into the corresponding known α-azidocarboxylates and comparing the specific rotations with the reported values.[14b] The stereochemistries of **13**, **15**, and **17** were determined by comparing the chemical data with those of **14** and **16**. The stereochemical feature of the reaction of **12** can be rationalized in terms of the stereoselectivities of the radical allylation reactions of **12**. See: Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.* **1990**, *112*, 6738−6740.

(14) Azide displacement of the halogen attached to the α-carbon to the carbonyl proceeded with inversion of configuration. See: (a) Labelle, M.; Morton, H. E.; Guindon, Y.; Springer, J. P. *J. Am. Chem. Soc.* **1988**, *110*, 4533−4540. (b) Larsson, U.; Carlson, R.; Leroy, J. *Acta Chem. Scand.* **1993**, *47*, 380−390.

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