Novel intramolecular rearrangement of 3-bromo-3,3-difluoroalanine Schiff bases *via* radical *ipso*-substitution at the aromatic ring

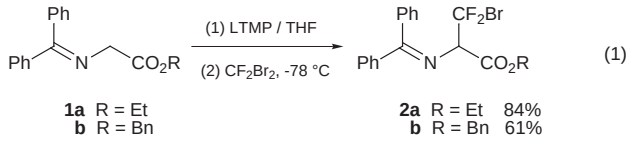
Hideki Amii, Susumu Kondo and Kenji Uneyama*†

Department of Applied Chemistry, Faculty of Engineering, Okayama University, Tsushimanaka 3-1-1, Okayama 700-0082, Japan

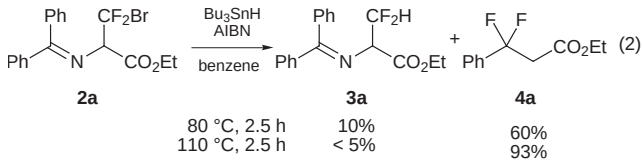
3-Bromo-3,3-difluoroalanine Schiff bases are synthesized by bromodifluoromethylation of the corresponding glycine Schiff bases with CF_2Br_2; their intramolecular rearrangement involving radical *ipso*-substitution at the aromatic ring of the imine moiety provides 3,3-difluoro-3-arylpropanoates in good yields.

Organofluorine compounds are receiving increasing attention in the medicinal, agricultural, and material sciences. In particular, interest in fluorine-containing amino acids and their derivatives has existed for many years, since they have potentially unique biological activities and thus are a current synthetic target.[1] Herein we report a new approach to the preparation of 3-bromo-3,3-difluoroalanine Schiff bases **2** and their intramolecular rearrangement *via* radical *ipso*-substitution at the aromatic ring, which provides β,β-difluoroalkanoates.[2,3]

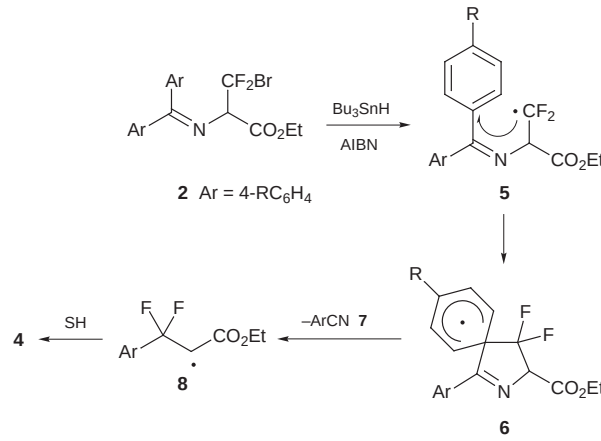
3-Bromo-3,3-difluoroalanine Schiff bases **2** are synthesized using commercially available CF_2Br_2, the simplest CF_2 unit.[4] Appropriate choice of reaction conditions was essential to avoid the decomposition of the bromodifluoromethyl moiety of **2** due to nucleophilic attack of the bases, such as NaH and even LDA. When Schiff base **1** was treated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) in THF at −78 °C followed by CF_2Br_2, difluoromethylene compounds **2** were obtained in good yields [eqn (1)].



3-Bromo-3,3-difluoroalanine Schiff bases **2** are interesting fluorinated synthetic building blocks, and their transformations were examined next. Firstly, we explored Bu_3SnH/AIBN mediated radical cleavage of the carbon–bromine bond in **2**. Treatment of **2a** with Bu_3SnH/AIBN/benzene at 80 °C for 2.5 h gave not only the reduction product **3a** (10%), but also unexpectedly gave ethyl 3,3-difluoro-3-phenylpropanoate[5] **4a** (60%) as the major product [eqn (2)]. Raising the reaction



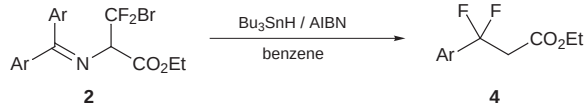
temperature (> 110 °C) favoured the rearrangement (**2a**→**4a**). The formation of **4a** can be explained by assuming the pathway pictured in Scheme 1. Initially, Bu_3SnH/AIBN mediated homolytic fission of the C–Br bond in **2** generates α,α-difluoroalkyl radical species **5**. The resultant α-fluorinated carbon radical **5** undergoes intramolecular *ipso* attack to the aromatic group[6–10] of the imine moiety of **5**, forming the spiro cyclohexadienyl radical **6**. Extrusion of aromatic nitrile **7** from **6** then occurs to furnish the carbon radical **8**.[11] Subsequent hydrogen abstraction gives rise to β,β-difluorocarboxylic acid ester **4** as the final product.



Scheme 1

Other examples of selective formation of **4** are given in Table 1. The Schiff bases **2** which possess either electron-donating or -withdrawing substituents on the aryl ring of the imine moiety provide **4** in high yields. It is noted that the reactions of **2c** and **2d**, which have electron-donating substituents, required more forcing conditions (entries 2 and 3), whereas electron-withdrawing substituents enhanced the reaction rates (entries 4 and 5).

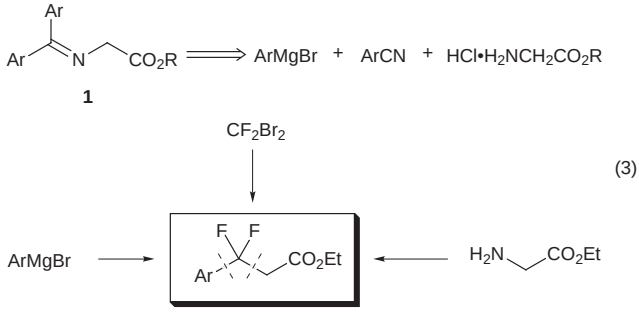
Table 1 Radical rearrangement of Schiff base **2**[a]



Entry	Ar	*T*/°C	*t*/h	Product	Yield[b] (%)
1	Ph	110	2.5	**4a**	93
2	4-MeC_6H_4	130	7.0	**4c**	90
3	4-$MeOC_6H_4$	130	7.0	**4d**	99
4	4-FC_6H_4	110	1.5	**4e**	80 (99)[c]
5	4-$CF_3C_6H_4$	110	2.0	**4f**	90

[a] All reactions were carried out in sealed glass tubes containing **2**, Bu_3SnH (2 equiv.) and AIBN (0.1 equiv.). After the reactions were completed, an equimolar amount of aromatic nitrile was generated (90–95% isolated yield in each case). [b] Reported yields are isolated yields unless specified. [c] The number in parentheses is the yield determined by ^{19}F NMR analysis.

The Schiff bases **1** are easily synthesized in one pot from the corresponding arylmagnesium bromides, aryl cyanides and glycine ethyl ester hydrochloride [eqn (3)].[12] In the net transformation to **4**, aryl cyanides were regenerated after completion of the intramolecular radical rearrangement, as shown in Scheme 1. Thus, the construction of **4** was formally



(3)

achieved by the coupling of three components, *i.e.* ArMgBr, CF_2Br_2 and glycine derivatives.

In conclusion, the synthesis and a novel reaction of 3-bromo-3,3-difluoroalanine Schiff bases were developed, which provide a new route to difluoromethylene compounds *via* intramolecular rearrangement involving radical *ipso*-substitution at the aromatic ring.

We thank to the SC NMR laboratory of Okayama University for ^{19}F NMR analyses and the Ministry of Education, Science, Sports and Culture of Japan for financial support (Grant-in-Aid for scientific research, No. 09305058).

Notes and References

† E-mail: uneyamak@cc.okayama-u.ac.jp

‡ Representive experimental procedures. (i) To a solution of 2,2,6,6-tetramethylpiperidine (106 mg, 0.75 mmol) in freshly distilled THF (1 ml) cooled down to 0 °C under argon atmosphere, 1.53 M BuLi in hexane (0.50 ml, 0.75 mmol) was added dropwisely and then stirred for an additional 30 min. The LTMP solution was cooled to −78 °C, and the solution of glycine Schiff base (0.5 mmol) in THF (1 ml) was added dropwisely to the LTMP solution. After 1 h, CF_2Br_2 (525 mg, 2.5 mmol) was added, and the mixture was stirred at −78 °C for a further 5 h. The reaction mixture was quenched with aq. NH_4Cl, and the organic layer was washed with brine and dried over Na_2SO_4. Purification of the products by recrystalization from hexane gave colorless plates. (ii) A solution of **2a** (19.9 mg, 0.05 mmol), Bu_3SnH (34.9 mg, 0.12 mmol) and AIBN (1.0 mg, 6.0 mmol) in benzene (2 ml) was heated at 110 °C in a sealed glass tube for 2.5 h. The reaction mixture was cooled, reduced in volume, and purified by chromatography on silica gel (hexane–EtOAc) to afford **4a** (10.0 mg, 93%) as a colorless oil.

1 V. P. Kukhar' and V. A. Soloshonok, *Fluorine-containing Amino Acids*, Wiley, Chichester, UK, 1995.
2 A [3,3]-sigmatropic rearrangement route to β,β-difluoro-carbonyl compounds has been reported: see S. T. Patel, J. M. Percy and R. D. Wilkes, *Tetrahedron*, 1995, **51**, 11 327.
3 T. Takagi, N. Okikawa, S. Johnoshita, M. Koyama, A. Ando and I. Kumadaki, *Synlett*, 1996, 82.
4 Reaction of an alanine Schiff base with CF_2Br_2 in the presense of LDA has been reported: see P. Bay and J. P. Vevert, *Tetrahedron Lett.*, 1978, **14,** 1215.
5 Compound **4a** was identified by comparison with an authentic sample synthesized by difluorination of ethyl benzoylacetate using DAST, see S. C. Sondej and J. A. Katzenellenbogen, *J. Org. Chem.*, 1986, **51**, 3508.
6 L. Benati, P. Spagnolo, A. Tundo and G. Zanardi, *J. Chem. Soc., Chem. Commun.*, 1979, 141.
7 J. Grimshaw, R. Hamilton and J. Trocha-Grimshaw, *J. Chem. Soc., Perkin Trans. 1*, 1982, 229.
8 J. Aubé, X. Peng, Y. Wang and F. Takusagawa, *J. Am. Chem. Soc.*, 1992, **114**, 5466.
9 E. Lee, H. S. Whang and C. K. Chung, *Tetrahedron Lett.*, 1995, **36**, 913.
10 M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137 and 141.
11 An equimolar amount of aromatic nitrile was isolated and identified by GC, NMR and IR analysis and comparison with authentic material.
12 M. J. O'Donnell and R. L. Polt, *J. Org. Chem.*, 1982, **47**, 2663.

Received in Cambridge, UK, 27th May 1998; 8/03944E