

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

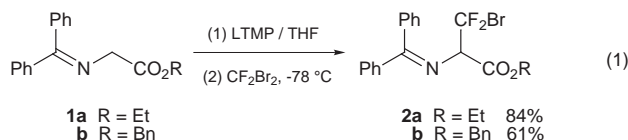
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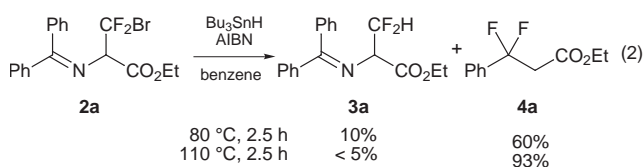
3-Bromo-3,3-difluoroalanine Schiff bases are synthesized by bromodifluoromethylation of the corresponding glycine Schiff bases with CF_2Br_2 ; their intramolecular rearrangement involving radical *ipso*-substitution at the aromatic ring of the imine moiety provides 3,3-difluoro-3-arylpropanoates in good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

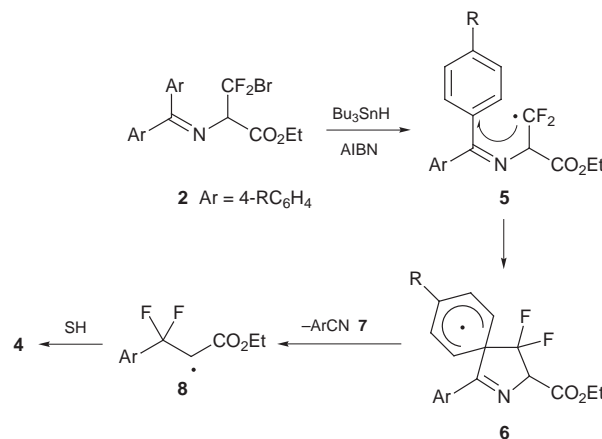


3-Bromo-3,3-difluoroalanine Schiff bases **2** are interesting fluorinated synthetic building blocks, and their transformations were examined next. Firstly, we explored $\text{Bu}_3\text{SnH}/\text{AIBN}$ mediated radical cleavage of the carbon–bromine bond in **2**. Treatment of **2a** with $\text{Bu}_3\text{SnH}/\text{AIBN}/\text{benzene}$ at 80°C for 2.5 h gave not only the reduction product **3a** (10%), but also unexpectedly gave ethyl 3,3-difluoro-3-phenylpropanoate⁵ **4a** (60%) as the major product [eqn (2)]. Raising the reaction



temperature ($> 110^\circ\text{C}$) favoured the rearrangement (**2a**→**4a**). The formation of **4a** can be explained by assuming the pathway pictured in Scheme 1. Initially, $\text{Bu}_3\text{SnH}/\text{AIBN}$ 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

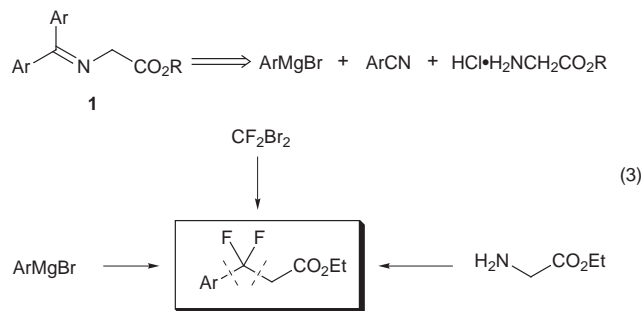
Other examples of selective formation of **4** are given in Table 1. The Schiff bases **2** which possess either electron-donating or -withdrawing substituents on the aryl ring of the imine moiety provide **4** in high yields. It is noted that the reactions of **2c** and **2d**, which have electron-donating 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	$T/^\circ\text{C}$	t/h	Product	Yield ^b (%)
1	Ph	110	2.5	4a	93
2	4-MeC ₆ H ₄	130	7.0	4c	90
3	4-MeOC ₆ H ₄	130	7.0	4d	99
4	4-FC ₆ H ₄	110	1.5	4e	80 (99) ^c
5	4-CF ₃ C ₆ H 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



achieved by the coupling of three components, *i.e.* ArMgBr, CF₂Br₂ 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.

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Notes and References

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‡ Representative 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, CF₂Br₂ (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. NH₄Cl, and the organic layer was washed with brine and dried over Na₂SO₄. Purification of the products by recrystallization from hexane gave colorless plates. (ii) A solution of **2a** (19.9 mg, 0.05 mmol), Bu₃SnH (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.

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