Tetrahedron Letters,Vol.24,No.42,pp 4573-4576,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

SELENIUM DIOXIDE OXIDATION OF 3-METHYL-4,5,6,7-TETRAFLUOROINDOLES: AN EFFICIENT ROUTE TO TETRAFLUORO ANALOGS OF 3-FORMYL AND 3-ACETOXYMETHYLINDOLE SYSTEMS

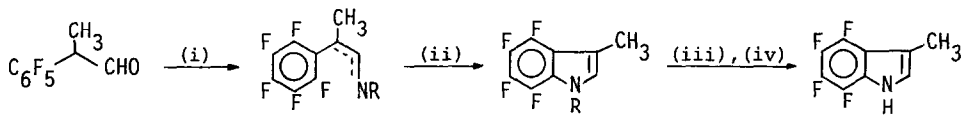
Makoto Fujita and Iwao Ojima*[1]

Sagami Chemical Research Center, Nishi-Ohnuma 4-4-1, Sagamihara, Kanagawa 229, Japan

Summary: Selenium dioxide oxidations of 3-methyl-4,5,6,7-tetrafluoroindoles gave 3-formyl or 3-acetoxymethyltetrafluoroindoles in unexpectedly high selectivities, which turned out to serve as useful intermediates for the syntheses of tetrafluoro analogs of tryptophan, tryptamine and indole acetic acid.

Recently, it has been shown that fluorinated analogs of naturally occurring biologically active compounds often exhibit unique physiological activities.[2] In the course of our study on the synthesis of versatile intermediates for physiologically active organofluorine compounds via functionalizations of readily available starting materials,[3] we were interested in synthesizing tetrafluoro analogs of indoles since indole skeleton is a very important ring system with regard to biologically active compounds such as tryptophan, tryptamine, indole acetic acid and alkaloids. We will describe here convenient routes to 3-formyl- and 3-acetoxymethyl-4,5,6,7-tetrafluoroindoles via novel selenium dioxide oxidations, which serve as useful synthetic intermediates.

We chose 2-pentafluorophenylpropanal (1) as the starting material, which is readily available by the hydroformylation of pentafluorostyrene catalyzed by rhodium complexes such as $Rh_6(CO)_{16}$ and $HRh(CO)(PPh_3)_3$.[3a] The formation of the tetrafluoroindole ring was carried out by reacting 1 with a primary amine followed by cyclization by the action of lithium diisopropylamide (LDA)[4] (eq. 1). For instance, the reaction of 1 with allylamine in the presence of anhydrous magnesium sulfate in chloroform at 0°C gave a mixture of the corresponding Schiff base and enamine (2a) in quantitative yield. Then, 2 thus obtained was treated with 1*M* LDA solution in tetrahydrofuran (THF) at -78°C to give 1-allyl-3-methyl-4,5,6,7-tetrafluoroindole (3a) in 74% yield after purification on silica gel column.[5] In a similar manner, 1-benzyl derivative (3b) was obtained in 79% yield.[5] 3-Methyl-4,5,6,7-tetrafluoroindole (4) was readily obtained through deallylation of 3a with the use of rhodium trichloride catalyzed isomerization followed by acidic hydrolysis (97% yield).



(1)

1

2a: R=Allyl
2b: R=$PhCH_2$

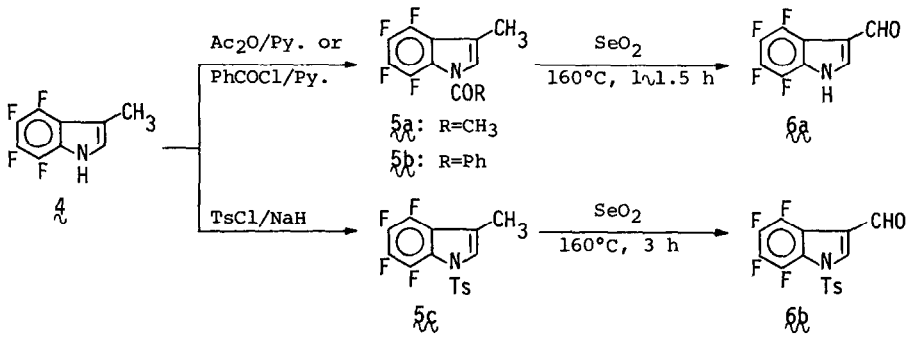
3a: R=Allyl
3b: R=$PhCH_2$

4

(i) RNH_2, $MgSO_4$, $CHCl_3$, 0°C∿r.t., 1 h, (ii) LDA (1 eq.), THF, -78°C, 30 min and -78°C∿r.t., 10 h, (iii) (R=Allyl), $RhCl_3 \cdot 3H_2O$ (1.0 mol%), EtOH, reflux, 14 h, (iv) 6*N* HCl, reflux, 20 min.

Next, we focused on the convenient synthesis of 3-formyl-4,5,6,7-tetrafluoroindoles (6) and 3-acetoxymethyl-4,5,6,7-tetrafluoroindoles (7) through selective oxidation of 3-methyl-4,5,6,7-tetrafluoroindoles since 6 and 7 were well anticipated to be the key-intermediates for the synthesis of tetrafluoro analogs of tryptophan, tryptamine and indole acetic acid.

Attempted oxidation of 3b by using CrO_3-acetic anhydride-H_2SO_4 (Thiele reagent)[6] resulted in the formation of complex mixture. However, selenium dioxide oxidation[7] of 3b in refluxing diglyme brought about an unexpectedly high yield (92%) production of 1-benzyl-3-formyl-4,5,6,7-tetrafluoroindole (6c).[8,5] As the direct oxidation of 4 with selenium dioxide resulted in the decomposition of indole skeleton, 1-position of 4 was protected by acetyl, benzoyl or tosyl group, (5a-c), and submitted to the selenium dioxide oxidation. The oxidation of 5a and 5b gave 3-formyl-4,5,6,7-tetrafluoroindole (6a) in 86% and 74% yields, respectively (eq. 2)[8,5]: the acetyl and benzoyl protecting groups were removed during the reaction. In contrast with this, the reaction of 5c gave 1-tosyl-3-formyl-4,5,6,7-tetrafluoroindole (6b) in 81% yield (eq. 3)[8,5]: 1-tosyl group is tolerant of the reaction.

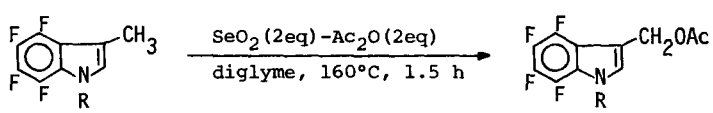


(2)

(3)

It should be noted that the selective oxidation of a methyl group attached to indole nucleus to the corresponding formyl group is successfully performed in good yield by using selenium dioxide as specific oxidant since it has been shown that in general the oxidation of this type is very difficult and selenium dioxide oxidation of methyl groups attached to arenes only gives a mixture of the corresponding aldehyde and carboxylic acid in low yield.[7] It is also noteworthy that tetrafluoroindole skeleton is tolerant of the selenium dioxide oxidation.

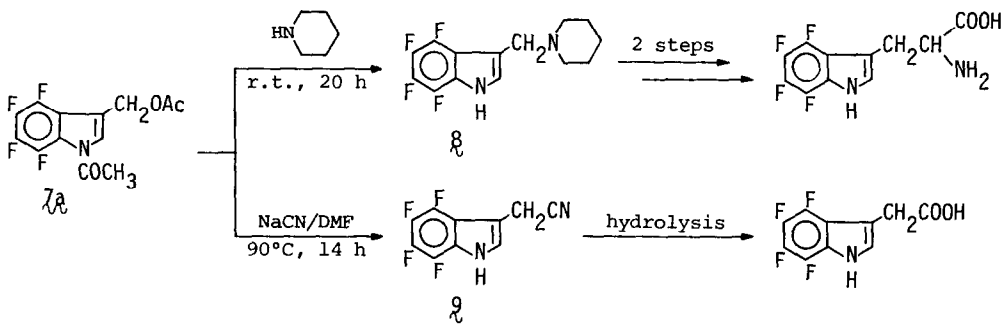
When the oxidation of 5a was carried out in the presence of acetic anhydride, another unique reaction took place, viz., 1-acetyl-3-acetoxymethyl-4,5,6,7-tetrafluoroindole (7a) was obtained in 60% yield after purification on silica gel column; similarly, 1-benzoyl, 1-tosyl and 1-benzyl derivatives (7b-d) were obtained in 40-60% yields (eq. 4)[9,5]. In these reactions, it turned out that 6 was formed as side product, which was separated by a column chromatography on silica gel.



(4)

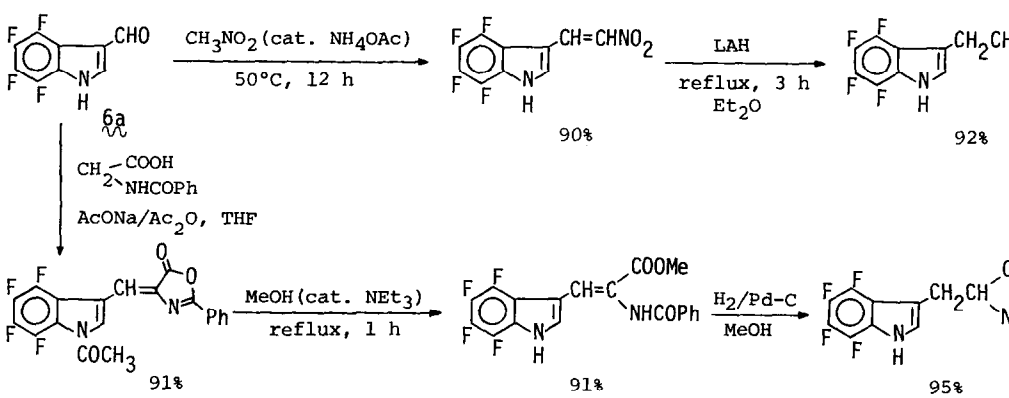
a: R=CH_3CO; b: R=PhCO; c: R=tosyl

The anticipated usefulness of 6 and 7 thus obtained was proved by the following examples: (i) the reaction of 7a with piperidine (large excess) at room temperature for 20 h gave 3-piperidinomethyl-4,5,6,7-tetrafluoroindole (8) in 97% yield, which is a known key-intermediate[10] for the synthesis of 4,5,6,7-tetrafluorotryptophan (eq. 5), (ii) the reaction of 8 with sodium cyanide (5 eq.) in dimethylformamide at 90°C for 14 h gave 3-cyanomethyl-4,5,6,7-tetrafluoroindole (9) in 41% yield, which is also known to be an excellent precursor[10a] of 4,5,6,7-tetrafluoroindole acetic acid (eq. 6), (iii) 4,5,6,7-tetrafluorotryptamine was obtained from 6a through condensation with nitromethane followed by lithium aluminum hydride reduction in 83% overall yield and (iv) N-benzoyl-4,5,6,7-tetrafluorotryptophan methyl ester was obtained from 6a through Erlenmeyer's azlactone method[11] in 79% overall yield.



(5)

(6)



(7)

(8)

As it is known that 4,5,6,7-tetrafluorotryptophan exhibits strong activities in the inhibition of both the tryptophanyl hydroxamate and aminoacyl *t*-RNA formation,[12] tetrafluoro analogs of tryptamine, indole acetic acid and other indole derivatives are expected to have some unique physiological activities.

Further investigations along this line are currently underway.

References and Notes

1. Present Address: Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794, U. S. A.
2. For example, (a) R. Filler and Y. Kobayashi (Eds.), "Biomedical Aspects of Fluorine Chemistry", Elsevier Biomedical Press, Amsterdam, 1982; (b) F. A. Smith, CHEMTECH, 422 (1972); (c) R. Filler, ibid., 752 (1974).
3. (a) T. Fuchikami and I. Ojima, J. Am. Chem. Soc., 104, 3527 (1982); (b) T. Fuchikami, M. Yatabe and I. Ojima, Synthesis, 365 (1981); (c) I. Ojima, M. Yatabe and T. Fuchikami, J. Org. Chem., 47, 2051 (1982); (d) T. Fuchikami and I. Ojima, Tetrahedron Lett., 23, 4099 (1982).
4. It was found that NaOH, NaOMe, KH and DBU were ineffective for this cyclization. Although KF turned out to be effective (2b→3b: 45%), the reaction required rather drastic conditions (150°C, 8 h in DMF).
5. All the new compounds obtained here gave satisfactory elemental analyses and spectral data.
6. (a) T. Nishimura, Org. Syn., Coll. Vol. 4, 713 (1963); (b) J. Thiele and E. Winter, Ann., 311, 353 (1900). This reagent is known to convert $ArCH_3$ into $ArCH(OAc)_2$ which gives ArCHO on hydrolysis.
7. For a review on selenium dioxide oxidation, see N. Rabjohn, Org. React., 24, 261 (1976).
8. Typical procedure is as follows. A mixture of 5a (8.58 g, 35.0 mmol) and selenium dioxide (7.77 g, 70 mmol) in diglyme (35 ml) was heated under reflux for 1.5 h with stirring. After the filtration of metal and the removal of solvent, the reaction mixture was submitted to a short column chromatography on silica gel (CH_2Cl_2) to give 6a as colorless crystals (6.54 g, 86.1%): mp. 182-5°C (sublim.). 6b: mp. 180-1°C. 6c: mp. 112-3°C.
9. Typical procedure is as follows. A mixture of 5a (247 mg, 1.01 mmol), selenium dioxide (222 mg, 2.00 mmol) and acetic anhydride (0.2 ml) in diglyme (1.0 ml) was sealed in a Pyrex tube and heated at 160°C for 2 h (4 h for 5c) with stirring. Then, water (3 ml) was added and the reaction mixture was extracted with ether, dried over anhydrous magnesium sulfate. After the solvent was removed, the reaction mixture was submitted to a column chromatography on silica gel to give 7a as pale yellow crystals (182 mg, 60%): mp. 131-3°C. 7b: mp. 112-3°C. 7c: mp. 120-2°C.
10. (a) T. D. Petrova, T. I. Savchenko, T. F. Ardyukova and G. G. Yakobson, Khim. Geterotsikl. Soedin., 213 (1971); (b) H. M. Rajh, J. H. Uitzetter, L. W. Westerhuis, C. L. van den Dries and G. I. Tesser, Int. J. Peptide Protein Res., 14, 68 (1979).
11. For example, R. M. Herbst and D. Shemin, Org. Syn., Coll. Vol. 2, 1 (1943).
12. (a) D. G. Knorre, O. I. Lavrik, T. D. Petrova, T. I. Savchenko and G. G. Yakobson, FEBS Letters, 12, 204 (1971); (b) G. A. Nevinsky, O. O. Favorova, O. I. Lavrik, T. D. Petrova, L. L. Kochkina and T. I. Savchenko, ibid., 43, 135 (1974).

(Received in Japan 30 June 1983)