ORGANIC LETTERS

2000
Vol. 2, No. 5
639−642

A Novel and Efficient Synthesis of 3-Fluorooxindoles from Indoles Mediated by Selectfluor

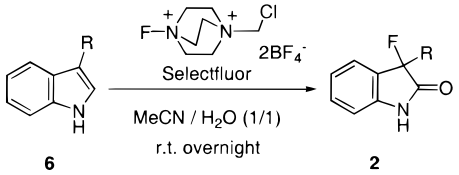
Yoshio Takeuchi,* Takanao Tarui, and Norio Shibata

Faculty of Pharmaceutical Sciences, Toyama Medical & Pharmaceutical University, Sugitani 2630, Toyama, 930-0194 Japan

takeuchi@ms.toyama-mpu.ac.jp

Received December 24, 1999

ABSTRACT



Treatment of several 3-substituted indoles, including derivatives of tryptophan and serotonin, with commercially available Selectfluor in acetonitrile/water furnished 3-substiuted 3-fluorooxindoles in good to high yields. Since 3-fluorooxindoles obtained are sterically similar to both oxindoles and 3-hydroxyoxindoles, they should be useful as probes for investigating the enzymatic mechanism of indole biosynthesis and metabolism.

Oxindole derivatives have received much attention as synthetic intermediates for preparation of biologically active molecules[1] and as useful probes for the study of enzymatic mechanisms involved in indole metabolism and biosynthesis.[2] A variety of oxindoles and 3-hydoroxyoxindoles have been identified as metabolites of biologically active indoles. Oxindole derivatives structurally similar to these metabolites, or similar to intermediates in their formation, are attractive targets in the design of inhibitors of metabolic enzymes and thus of the metabolic pathways of the corresponding indoles.[3,4] For example, oxindolyl-L-alanine (**1a**)[5a] and diox-

(1) (a) Hubacher, M. H.; Doernberg, S.; Horner, A. *J. Am. Pharm. Assoc.* **1953**, *42*, 23−30. (b) Garrido, F.; Ibanez, J.; Gonalons, E.; Giraldez, A. *Eur. J. Med. Chem. Ther.* **1975**, *10*, 143−146. (c) Joshi, K. C.; Pathak, V. N.; Jain, S. K. *Pharmazie* **1980**, *35*, 677−679. (d) Bolotov, V. V.; Drugovina, V. V.; Yakovleva, L. V.; Bereznyakova, A. I. *Khim.-Farm. Zh.* **1982**, *16*, 58−61. (e) Pajouhesh, H.; Parsons, R.; Popp, F. D. *J. Pharm. Sci.* **1983**, *72*, 318−321. (f) Goehring, R. R.; Sachdeva, Y. P.; Pisipata, J. S.; Sleevi, M. C.; Wolfe, J. F. *J. Am. Chem. Soc.* **1985**, *107*, 435−443. (g) Ram, V. J.; Mishra, L.; Pandey, H. N.; Vlietnick, A. J. *J. Heterocycl. Chem.* **1986**, *23*, 1367−1369. (h) Dilber, S.; Saban, M.; Jelaca, J.; Gelineo, A.; Arsenijevic, L.; Bogavac, M. *Pharmazie* **1989**, *44*, 649−650. (i) Gazit, A.; Osherov, N.; Posner, I.; Yaish, P.; Poradosu, E.; Gilon, C.; Levitzki, A. *J. Med. Chem.* **1991**, *34*, 1896−1907.

(2) (a) Kato, Y.; Shimokawa, M.; Yokoyama, T.; Mohri, K. *J. Chromatogr. Biomed. Appl.* **1993**, *616*, 67−71. (b) Itakura, K.; Uchida, K.; Kawakishi, S. *Chem. Res. Toxicol.* **1994**, *7*, 185−190. (c) Oestin, A.; Catala, C.; Chamarro, J.; Sandberg, G. *J. Mass Spectrom.* **1995**, *30*, 1007−1017. (d) Thornton-M., J.; Appleton, M. L.; Gonzalez, F. J.; Yost, G. S. *J. Pharmacol. Exp. Ther.* **1996**, *276*, 21−29. (e) Carpenedo, R.; Carla, V.; Moneti, G.; Chiarugi, A.; Moroni, F. *Anal. Biochem.* **1997**, *244*, 74−79. (f) Hu, T.; Dryhurst, G. *J. Electroanal. Chem.* **1997**, *432*, 7−18. (g) Anisimoviene, N. *Biologija* **1997**, 34−39. (h) Yang, Z.; Wrona, M. Z.; Dryhurst, G. *J. Neurochem.* **1997**, *68*, 1929−1941. (i) Mannaioni, G.; Carpenedo, R.; Pugliese, A. M.; Corradetti, R.; Moroni, F. *Br. J. Pharmacol.* **1998**, *125*, 1751−1760. (j) Carpenedo, R.; Mannaioni, G.; Moroni, F. *J. Neurochem.* **1998**, *70*, 1998−2003.

(3) (a) Goddard, C. J.; Schulte, G. R. U. S. US 5064851, 1991; *Chem. Abstr.* **1992**, *116*, 83669. (b) Silvagno, F.; Follenzi, A.; Arese, M.; Prat, M.; Giraudo, E.; Gaudino, G.; Camussi, G.; Comoglio, P. M.; Bussolino, F. *Arterioscler. Thromb. Vasc. Biol.* **1995**, *15*, 1857−1865. (c) Buzzetti, F.; Brasca, M. G.; Longo, A.; Ballinari, D. WO, 9622976, 1996; *Chem. Abstr.* **1996**, *124*, 221574. (d) Licht, D.; Johansen, S. S.; Arvin, E.; Ahring, B. K. *Appl. Microbiol. Biotechnol.* **1997**, *47*, 167−172. (e) Sato, A.; Asao, T.; Hagiwara, Y.; Kitade, M.; Yamazaki, Y. WO 9726242, 1997; *Chem. Abstr.* **1997**, *127*, 161696. (f) Battistini, C.; Ballinari, D.; Ermoli, A.; Penco, S. Vioglio, S. WO 9632380, 1996; *Chem. Abstr.* **1997**, *126*, 18783. (g) Tang, P. C.; Sun, L.; McMahon, G. U.S. US 5883116, 1999; *Chem. Abstr.* **1999**, *130*, 237471. (h) Davis, S. T.; Dickerson, S. H.; Frye, S. V.; Harris, P. A.; Hunter, R. N., III; Kuyper, L. F.; Lackey, K. E.; Luzzio, Michael, J.; Veal, J. M.; Walker, D. H. WO 9915500, 1999; *Chem. Abstr.* **1999**, *130*, 267341.

(4) (a) Kato, T.; Tomita, N.; Hoshikawa, M.; Ehara, K.; Shima, J.; Takahashi, N.; Sugiyama, H. *Heterocycles* **1998**, *47*, 497−500. (b) Hewawasam, P.; Meanwell, N. A.; Gribkoff, V. K.; Dworetzky, S. I.; Boissard, C. G. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1255−1260. (c) Tatsugi, J.; Ikuma, K.; Izawa, Y. *Tetrahedron Lett.* **1995**, *36*, 8611−8612. (d) Hu, T.; Dryhurst, G. *J. Electroanal. Chem.* **1997**, *432*, 7−18. (e) Newlin, W. C., Jr.; Laughlin, S. M. WO 9633701, 1996; *Chem. Abstr.* **1997**, *126*, 37057.

(5) (a) Phillips, R. S.; Miles, E. W.; Cohen L. A. *Biochemistry* **1984**, *23*, 6228−6234. (b) Labroo, R. B.; Cohen, L. A. *J. Org. Chem.* **1990**, *55*, 4901−4904.

10.1021/ol991400y CCC: $19.00
Published on Web 02/09/2000

indolyl-L-alanine (**1b**),[5b] which are structurally similar to the proposed intermediate in tryptophan metabolism, were found to be potent competitive inhibitors of both tryptophan synthase and tryptophanase.[5] As a part of our research program involving the design and synthesis of fluorine-containing biologically active compounds,[6] we were interested in the structure of 3-fluorooxindoles **2**. Fluorine most closely resembles the size of hydrogen than does any other substituent, and replacement of hydrogen by fluorine is often regarded as an isosteric substitution.[7] However, recent evidence indicates that fluorine and oxygen, not fluorine and hydrogen, are very nearly isosteric.[8] Further, possible participation of fluorine as a hydrogen bond acceptor suggests that the replacement of hydroxyl group by fluorine would result in production of useful analogues of their parent molecules.[9] Thus, 3-fluorooxindoles **2** are potential mimics both of the corresponding oxindoles and 3-hydoroxyindoles that are often found as metabolites of indoles. In this paper, we wish to report a direct and efficient synthesis of 3-fluorooxindoles **2** from indoles using commercially available Selectfluor, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) (Figure 1).

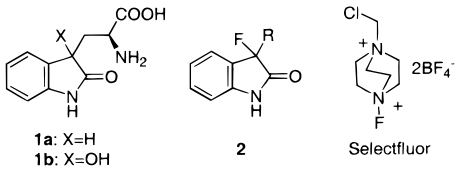


Figure 1.

Although several methods for the synthesis of 3-bromooxindoles have been reported,[10] only a few methods are available for the synthesis of **2**.[11−13] Treatment of isatin with DAST furnishes 3,3-difluorooxindole (**3**).[11] Nucleophilic substitution of the hydroxy group of 3-hydroxyoxindoles **4** by fluoride anion employing DAST seems to be a practical method[12] for the preparation of **2** only if the starting materials **4** are readily available. Successful electrochemical monofluorination of 3-phenylthiooxindoles **5a** has been achieved using Et_4NF to give 3-fluoro-3-phenylthiooxindoles **5b**.[13] This procedure, however, is clearly limited due to the presence of a 3-phenylthio moiety (Figure 2).

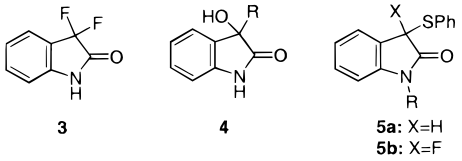
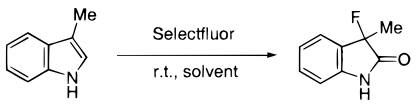


Figure 2.

We first investigated reaction conditions using skatole (**6a**). We found that the choice of solvent and the amount of reagent are important for optimizing the yields. Use of 2 equiv of Selectfluor[14] in acetonitrile gave a complex mixture, whereas reaction in acetonitrile/water (4/1) produced a 45% of 3-fluoro-3-methyloxindole (**2a**) together with a small amount of 3-methyloxindole (**7a**) as a side product. Addition of trifluoroethanol instead of water lowered the yield to 29%. The best result (71% yield) was obtained when the reaction was performed in a 1/1 mixture of acetonitrile/water system with 3 equiv of Selectfluor.[15] Another good solvent system was found to be a 4/1 mixture of acetonitrile/methanol, which produced **2a** in 57%. Lower yields of **2a** were obtained when 1 equiv or more than 3 equiv of Selectfluor was employed for this reaction (Table 1).

To demonstrate the generality of this Selectfluor-mediated fluorination, the procedure was extended to other indoles **6b**−**k** including the derivatives of tryptophan **6i**,**j**, tryptamine **6h**, and serotonin **6k** (Table 2). In all cases, the conversions

Table 1. Reaction of Skatole (**6a**) with Selectfluor[a]



6a **2a**

entry	Selectfluor	solvent	yield (%)*
1	2 eq.	MeCN	complex mixture
2	2 eq.	MeCN / H_2O (4/1)	45
3	2 eq.	MeCN / CF_3CH_2OH (4/1)	29
4	3 eq.	MeCN / H_2O (1/1)	71
5	2 eq.	MeCN / MeOH (4/1)	57
6	1 eq.	MeCN / MeOH (4/1)	18
7	5 eq.	MeCN / MeOH (4/1)	33

[a] Experimental conditions: Selectfluor was added to a solution of **6a**, and the mixture was stirred at rt overnight. *Small to medium amount of 3-methyloxindole (**7a**) was isolated as a side product in all cases.

(6) (a) Takeuchi, Y.; Shiragami, T.; Kimura, K.; Suzuki, E.; Shibata, N. *Org. Lett*. **1999**, *1*, 1571−1573. (b) Takeuchi, Y.; Kamezaki, M.; Kirihara, K.; Haufe, G.; Laue, K. W.; Shibata, N. *Chem. Pharm. Bull*. **1998**, *46*, 1062−1064. (c) Haufe, G.; Laue, K. W.; Triller, M. U.; Takeuchi, Y.; Shibata, N. *Tetrahedron* **1998**, *54*, 5929−5938. (d) Hayakawa, Y.; Singh, M.; Shibata, N.; Takeuchi, Y.; Kirk, K. L. *J. Fluorine Chem*. **1999**, *97*, 161−164. (e) Yokoyama, H.; Hyodo, R.; Nakada, A.; Yamaguchi, S.; Hirai, Y.; Kometani, T.; Goto, M.; Shibata, N.; Takeuchi, Y. *Tetrahedron Lett*. **1998**, *39*, 7741−7744.

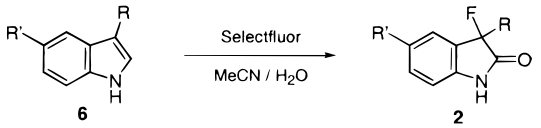
(7) (a) *Biomedical Aspects of Fluorine Chemistry*; Filler, R., Kobayashi, Y., Eds.; Kodansha/Elsevier Biomedical Press: Tokyo, Amsterdam−New York−Oxford, 1982. (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996. (c) Fusso & Yakugaku; Kobayashi, Y., Kumadaki, I., Taguchi, T., Eds.; Hirokawa Publishing Co.: Tokyo, 1992.

(8) Smart, B. E. In *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum Press: New York, 1994; Chapter 3, pp 57−88.

(9) For example Davis, F. A.; Reddy, R. E. *Tetrahedron*: *Asymmetry* **1994**, *5*, 955−960.

(10) For example: (a) Lawson, W. B.; Patchornik, A.; Witkop, B. *J. Am. Chem. Soc*. **1960**, *82*, 5918−5923. (b) Hinman, R. L.; Bauman, C. P. *J. Org. Chem*. **1964**, *29*, 1206−1215. (c) Kornet, M. J.; Thio, P. A.; Malone, N.; Lubawy, W. C. *J. Pharm. Sci*. **1975**, *64*, 639−642. (d) Hino, T.; Tonozuka, M.; Ishii, Y.; Nakagawa, M. *Chem. Pharm. Bull*. **1977**, *25*, 354−358. (e) Szabó-Pusztay, K.; Szabó, L. *Synthesis* **1979**, 276−277.

Table 2. Preparation of 3-Fluorooxindoles **2** from Indoles **6**[a]



entry	indole	R	R'	product[a)]	yield (%)[b)]
1	**6a**	Me	H	**2a**	71
2	**6b**	CH_2CH_2COOMe	H	**2b**	82
3	**6c**	CH_2COOMe	H	**2c**	75
4	**6d**	$CH_2CH_2CH_2COOMe$	H	**2d**	77
5	**6e**	CH_2CH_2OAc	H	**2e**	71
6	**6f**	$CH_2CH_2CH_2OAc$	H	**2f**	69
7	**6g**	$CH_2CH_2CH_2CH_2OAc$	H	**2g**	64
8	**6h**	CH_2CH_2NPhth	H	**2h**	71
9	**6i**	$CH_2CH_2CH(NHAc)COOMe$	H	**2i**	70[c)]
10	**6j**	$CH_2CH_2CH(NHpNB)COOMe$	H	**2j**	92[d)]
11	**6k**	CH_2CH_2NPhth	OAc	**2k**	82

[a] Experimental conditions: Selectfluor (3 equiv) was added to a solution of **6** in $MeCN/H_2O$ (1/1), and the mixture was stirred at rt overnight. *p*NB: *p*- nitrobenzoyl. (a) Corresponding oxindoles **7** were isolated as side products in all cases. (b) Isolated yield after silica gel column chlomatography. (c) Mixture of diastereoisomers (46% de). (d) Mixture of diastereoisomers (5% de).

to 3-fluorooxindoles **2** proceeded in good to high yields. It is of interest to note that, with *N*-Ac-Trp-OMe (**6i**) as a substrate, the corresponding fluorooxindole **2i** was obtained with 46% de, whereas no diastereoselectivity was observed in the case of *N*-*p*NB-Trp-OMe (**6j**). A typical experimental procedure is as follows. Selectfluor (3.0 equiv) was added to a stirred solution of indoles **6** (0.2−0.4 mmol) in actonitrile/water (1/1, 2 mL) at room temperature. After overnight stirring, the reaction mixture was diluted with ethyl acetate (50 mL), washed with water (10 mL), 4% HCl (10 mL), a saturated solution of sodium bicarbonate (10 mL), and brine (10 mL), and dried over Na_2SO_4. The solvent was removed under reduced pressure to give a residue that was purified by column chromatography on silica gel eluting with ethyl acetate/hexane to furnish **2** in a pure state. Identification of the products was achieved by ^1H and ^{19}F NMR, IR, mass spectrometry, and elemental analysis. The characteristic ^{19}F NMR (254 MHz, $CDCL_3$) peaks appear around at δ−155 ppm for all fluorooxindoles **2**.[16]

(11) (a) Middleton, W. J.; Bingham, E. M. *J. Org. Chem.* **1980**, *45*, 2883−2887. (b) Torres, J. C.; Garden, S. J.; Pinto, A. C.; da Silva, F. S. Q.; Boechat, N. *Tetrahedron* **1999**, *55*, 1881−1892.

(12) Labroo, R. B.; Labroo, V. M.; King, M. M.; Cohen, L. A. *J. Org. Chem.* **1991**, *56*, 3637−3642.

(13) Hou, Y.; Higashiya, S.; Fuchigami, T. *J. Org. Chem.* **1997**, *62*, 8773−8776.

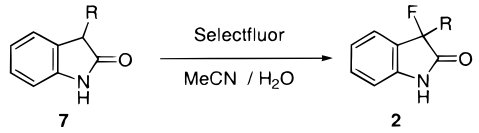
(14) (a) Banks, R. E. *J. Fluorine Chem.* **1998**, *87*, 1−17. (b) Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737−1755.

(15) Since Selectfluor seems to decompose slowly in water, 3 equiv of reagent (not 2 equiv) was used when the reaction was performed in aqueous media just in case.

(16) ^{19}F NMR (254 MHz, $CDCL_3$) δ: **2a** −153.7 ppm (q, J = 22.2 Hz); **2b**, −159.6 ppm (br dd J = 12.9 Hz, 14.8 Hz); **2c**, −153.6 ppm (t, J = 10.2 Hz); **2d**, −156.7 ppm (t, J = 14.8 Hz); **2e**, −155.3 ppm (t, J = 13.9 Hz); **2f**, −157.8 ppm (t, J = 15.7 Hz); **2g**, −156.7 ppm (t, J = 14.8 Hz); **2h**, −154.8 ppm (t, J = 13.9 Hz); **2i**, −152.4 ppm (t, J = 17.8 Hz), −152.6 ppm (t, J = 13.4 Hz); **2j**, −154.1 ppm (t, J = 16.6 Hz), −155.0 ppm (br d J = 16.5 Hz); **2k**, −156.8 ppm (t, J = 15.7 Hz).

Finally, we examined the direct Selectfluor fluorination at the C-3 position of the oxindoles **7** in order to gain mechanistic information. Treatment of oxindoles **7** with 1 equiv of Selectfluor in acetonitrile/water (1/1) system furnished **2**, although the yields were much lower than those observed in the fluorination of indoles (Table 3).

Table 3. Fluorination of Oxindoles **7**[a]

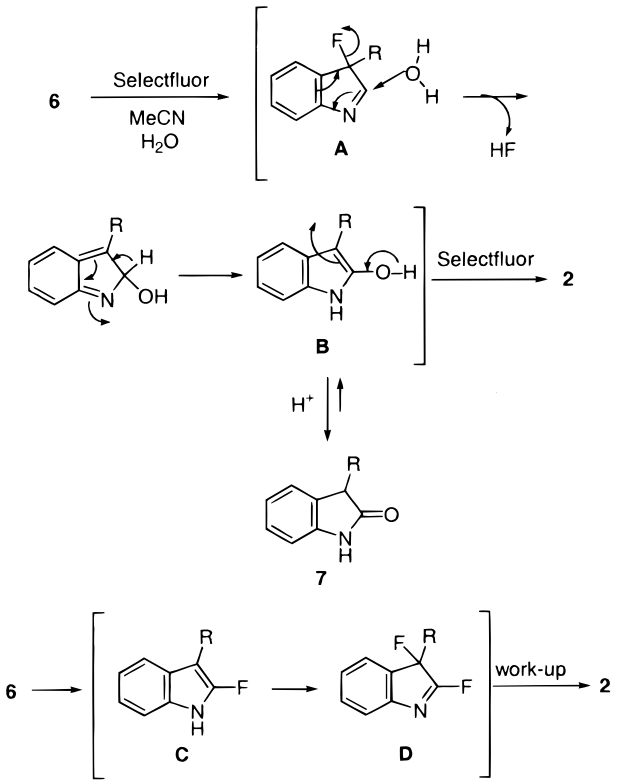


entry	7	R	product	yield (%)[a)]
1	**7a**	Me	**2a**	48
2	**7b**	CH_2CH_2COOMe	**2b**	25

[a] Experimental conditions: Selectfluor (1 equiv) was added to a solution of **7** in $MeCN/H_2O$ (1/1), and a mixture was stirred at rt overnight. (a) Isolated yield after silica gel column chlomatography.

On the basis of the above results and on information from the literature,[10a,b] we propose the reaction mechanism outlined in Scheme 1. According to this proposal, reaction of **6** with Selectfluor yields the unstable 3-fluoroindolenine **A**, which undergoes loss of HF by addition of water. A subsequent 1,5-prototopic shift gives the enol **B**. Finally, fluorination

Scheme 1. Proposed Reaction Mechanism from **6** to **2**



of **B** with additional Selectfluor yields **2**. Formation of the oxindole **7** as a side product could be explained by tautomerization of the enol **B** catalyzed by solvent water. The lower yield of **2** from **7** may be due to the difficulty of the tautomerization from keto-form **7** to enol-form **B** under the reaction conditions (Scheme 1). Another pathway[10a,b] considerable from **6** to **2** via 2-fluoroindole **C** and 2,3-difluoroindolenine **D** especially in nonaqueous media such as in methanol/acetonitrile cannot be ruled out as well, though we did not detect **C** nor **D** in the reaction mixture. Trapping the proposed initial adducts is now in progress.

In summary, we have developed a novel and efficient synthesis of 3-fluorooxindoles. Although there are two reports of the reaction of indoles with fluorinating reagents, including Selectfluor, in the literature,[17,18] these reactions do not furnish any 3-fluorooxindoles. To our knowledge, this transformation represents the first reported example of direct synthesis of 3-fluorooxindoles **2** from indoles.

Acknowledgment. This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture of Japan. N.S. wishes to thank the Nissan Science Foundation for support. Y.T. thanks the Asahi Glass Foundation.

OL991400Y

(17) (a) Barton, D. H. R.; Hesse, R. H.; Jackman, G. P.; Pechet, M. M. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2604−2608. (b) Hodson, H. F.; Madge, D. J.; Slawin, A. N. Z.; Widdowson, D. A.; Williams, D. J. *Tetrahedron* **1994**, *50*, 1899−1906.

(18) It is of particular interest to note that 3-fluorooxindoles **2** are solely produced in our system, while 3-fluoro-2-methoxyindoline is the product in the reaction of *N*-tosylindole with Selectfluor. See ref 17b.