

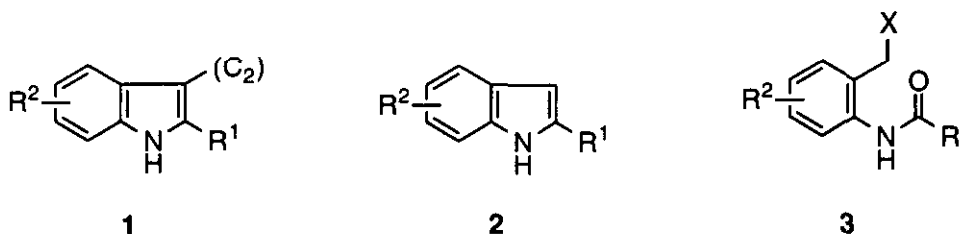
## NOVEL INDOLE-RING CONSTRUCTION METHOD FOR THE SYNTHESIS OF 2-TRIFLUOROMETHYLINDOLES †

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**Abstract** - Novel indole-ring construction method, which is particularly effective for the synthesis of 2-perfluoroalkylindoles, and introduction of a cyanomethyl group at C-3 of 2-perfluoroalkylindoles by means of the Mannich reaction are described.

Because of its specific characters, introduction of a fluorine atom or a perfluoroalkyl group into the lead molecules has been widely used as one of the methods for development of the novel biologically active compounds.<sup>1</sup> Indoles (**1**), especially having a two-carbon unit (2-aminoethyl or carboxymethyl function) at C-3, are attractive compounds from the viewpoint of their various biological activities against the central nervous system<sup>2</sup> or as a plant hormone.<sup>3</sup> However, to our knowledge, no study has been reported concerning the biological activities of their fluorinated or perfluoroalkylated derivatives. We are interested in biological activities of these indoles (**1**, R<sup>1</sup>=perfluoroalkyl), in which both the electron density of the indole ring and the basicity of the nitrogen are expected to be strongly affected.



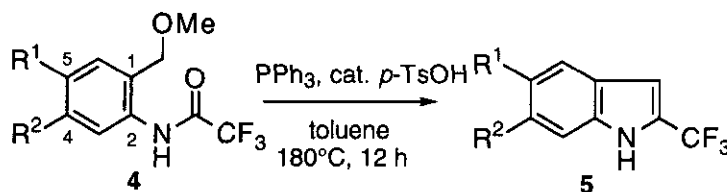
2-Trifluoromethylindole (**2**, R<sup>1</sup>=CF<sub>3</sub>, R<sup>2</sup>=H) was known to be obtained by direct trifluoromethylation of indole<sup>4</sup> or starting from fluorinated material,<sup>5</sup> but there remain problems about the regioselectivity and the number of reaction steps. As another approach to prepare the various 2-trifluoromethylindoles (**2**, R<sup>1</sup>=CF<sub>3</sub>), pyrrole ring formation from 2-(*N*-trifluoroacetyl amino)toluene derivatives (**3**, R<sup>1</sup>=CF<sub>3</sub>) would be suitable. Although available methods for the synthesis of indoles by pyrrole ring formation of

† This paper is dedicated to the memory of the late Professor Yoshio Ban.

**2** are represented by the Madelung reaction<sup>6</sup> and its modified reactions,<sup>7</sup> both of them involve nucleophilic attack of the benzylic carbanion, generated by the action of a strong base, to the amide carbonyl carbon. The base-labile property of the trifluoromethyl group<sup>5</sup> indicates that these methods cannot be employed for our present purpose.

Now we wish to report here a novel method for the synthesis of indoles involving 2-perfluoroalkyl derivatives (**2**, R<sup>1</sup>=perfluoroalkyl), starting from the methyl ether (**3**, X=OMe) or the phosphonium salt (**3**, X=P<sup>+</sup>Ph<sub>3</sub>) and also describe the preparation of **1** (R<sup>1</sup>=perfluoroalkyl) by introduction of a two-carbon unit at C-3 of 2-perfluoroalkylindoles.

On treatment of the methyl ether (**4b**) with triphenylphosphine and a catalytic quantity of *p*-toluene-sulfonic acid in toluene at 180°C (in a sealed tube) for 12 h, 2-trifluoromethylindole derivative (**5b**) was found to be obtained in 44% yield. The same treatment in boiling DMF also gave the product (**5b**) in 36% yield. The results were summarized in Table 1, which shows that this reaction strictly requires an oxygen-substituent at C-4 of the benzene ring in the starting material (Runs 4, 5 in Table 1). This requirement obviously indicates that this reaction proceeds *via* the benzylic cation-intermediate and also suggests a possibility of formation of the phosphonium salt by the subsequent nucleophilic attack of triphenylphosphine, as a crucial step of the reaction.



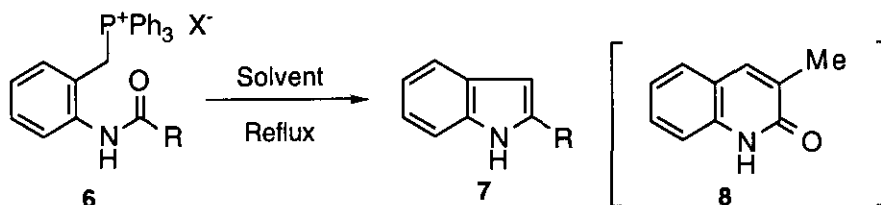
**Table 1.** Indole-formation reaction of the methyl ether (**4**)

Run	Compd.	R <sup>1</sup>	R <sup>2</sup>	Yield %	mp °C
1	<b>a</b>	H	H	no reaction	-
2	<b>b</b>	-OCH <sub>2</sub> O-		44 (69)	134-136
3	<b>c</b>	MeO	MeO	60 (67)	86-88
4	<b>d</b>	H	MeO	48 (52)	89-91
5	<b>e</b>	MeO	H	no reaction	-

Yield in the parenthesis is based on the consumed starting material.

Next, the conversion of the phosphonium salts (**6**) into indoles (**7**) was tried. The salts (**6**), easily obtained by acylation of the 2-aminobenzylphosphonium salt, were heated under reflux in *o*-dichlorobenzene (*o*-DCB) or *N,N*-dimethylformamide (DMF) to afford the desired indoles (**7**) and the results were summarized in Table 2. The thermal conversion of **6f** into **7f** does not demand any oxygen function on the benzene ring in the starting material, differently from the method from the methyl ethers (**4**). This fact would inform that the phosphonium salt is an actual intermediate for both routes. Reactions of the phosphonium salts (**6h-l**) bearing other acyl groups than fluorinated acyl group also

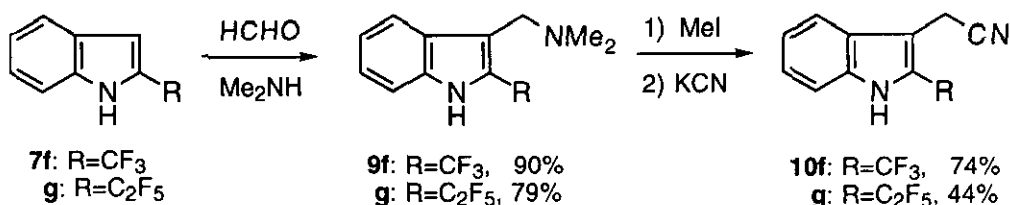
proceeded under the same conditions to afford the indole derivatives (**7h-l**) (Runs 3-7). Interestingly, the pyruvinamide derivative (**6k**) afforded the quinolone derivative (**8**) in 62% yield accompanied with the indole (**7k**) (Run 6).



**Table 2.** Indole-formation reaction of the phosphonium salt (**6**)

Run	Compd.	R	X	Solvent	Time hr	Yield %	mp °C (lit.)
1	<b>f</b>	$\text{CF}_3$	Br	DMF	15	82	107-108 (107-108) <sup>4a</sup>
2	<b>g</b>	$\text{C}_2\text{F}_5$	Br	DMF	12	92	93-94
3	<b>h</b>	$\text{PhCH}_2$	Cl	<i>o</i> -DCB	7	42	80-81 (84-85) <sup>8</sup>
4	<b>i</b>	Ph	Cl	<i>o</i> -DCB	7.5	29	190-191 (189-190) <sup>7c</sup>
5	<b>j</b>	<i>p</i> - $\text{NO}_2\text{C}_6\text{H}_4$	Cl	<i>o</i> -DCB	8	48	253-255 (249-251) <sup>7c</sup>
6	<b>k</b>	MeCO	Cl	<i>o</i> -DCB	1	19	154-156 (150) <sup>7d</sup>
7	<b>l</b>	$\text{EtO}_2\text{C}$	Cl	<i>o</i> -DCB	7.5	53	121-123 (123) <sup>7d</sup>

The electrophilic substitution at C-3 of the indole ring is a well-known reaction for the synthesis of the 3-substituted indoles.<sup>9</sup> However it has not been reported concerning the same reaction of the indoles having an electron-withdrawing group such as a trifluoromethyl group at C-2. We examined the Mannich reaction for the perfluoroalkyl derivatives (**7f** and **g**) and found that the reaction proceeds in good yield to afford the dimethylaminomethyl derivatives (**9**). After quaternization of **9** with methyl iodide, the substitution reaction with cyanide anion smoothly took place to afford 2-perfluoroalkylindole-3-acetonitrile (**10**). These results show that this indole-formation reaction can be a versatile one for the synthesis of various 2-trifluoromethylindole derivatives by combination with the Mannich reaction.



Characteristic feature of this novel indole-ring formation reaction is that this method is especially useful for the synthesis of the 2-perfluoroalkylindole derivatives, which are difficult to be prepared by the other methods, and, furthermore, the source of the trifluoromethyl group is a trifluoroacetyl group that is safe and easy to handle. Although the detail of this indole-formation mechanism is not clear, both reactions, starting from the methyl ether and the phosphonium salt, seem to proceed *via* a common intermediate. Further mechanistic study and synthetic study of the 2-trifluoromethyl derivatives of biologically active indoles by use of this methodology are under way.

## REFERENCES

1. R. Filler and Y. Kobayashi, 'Biomedical Aspects of Fluorine Chemistry,' Kodansha, Tokyo, 1982; R. Filler, in 'Fluorine, the First Hundred Years,' ed. by R. E. Banks, D.W. A. Sharp, and J. C. Tatlaw, Elsevier, New York, 1986, p. 361; N. Ishikawa, 'Biologically Active Organofluorine Compounds,' CMC, Tokyo, 1990.
2. J. E. Saxton, 'The Alkaloids,' Vol. 8, ed. by R. H. F. Manske, Academic Press, New York, 1965, p. 1; R. A. Glennon, *J. Med. Chem.*, 1986, **30**, 1.
3. L. J. Audus, 'Plant Growth Substances,' Leonard Hill, London, 1959; T. C. Moore, 'Biochemistry and Physiology of Plant Hormones,' Springer-Verlag, New York, 1979.
4. a) M. Yoshida, T. Yoshida, M. Kobayashi, and N. Kamigata, *J. Chem. Soc., Perkin Trans. 1*, 1989, 909; b) Y. Girard, J. G. Atkinson, P. C. Bélanger, J. J. Fuentes, J. Rokach, C. S. Rooney, D. C. Remy and C. A. Hunt, *J. Org. Chem.*, 1983, **48**, 3220; Q.-Y. Chen and Z.-T. Li, *J. Chem. Soc., Perkin Trans. 1*, 1993, 645.
5. Y. Kobayashi, I. Kumadaki, Y. Hirose, and Y. Hanzawa, *J. Org. Chem.*, 1974, **39**, 1836.
6. W. Madelung, *Ber.*, 1912, **25**, 1128.
7. Following derivatives of **1** were employed under basic conditions: X=H, a) W. J. Houlihan, V. A. Parrino, and Y. Uike, *J. Org. Chem.*, 1981, **46**, 4511; X=P<sup>+</sup>R<sub>3</sub>, b) M. Le Corre, A. Hercouet, and H. Le Baron, *J. Chem Soc., Chem. Commun.*, 1981, 14; c) M. Le Corre, A. Hercouet, T. Le Stanc, and H. Le Baron, *Tetrahedron*, 1985, **41**, 5313; d) L. Capuano, A. Ahlhelm, and H. Hartmann, *Chem. Ber.*, 1986, **119**, 2069; X=SiMe<sub>3</sub>, e) G. Bartoli, M. Bosco, R. Dalpozzo, and P. E. Todesco, *J. Chem. Soc., Chem. Commun.*, 1988, 807; G. Bartoli, G. Palmieri, M. Petrini, M. Bosco, and R. Dalpozzo, *Tetrahedron*, 1990, **46**, 1379.
8. J. P. Li, K. A. Newlander, and T. O. Yellin, *Synthesis*, 1988, 73.
9. W. A. Remers, in 'Indoles Part One, The Chemistry of Heterocyclic Compounds,' ed. by Houlihan, Wiley-Interscience, New York, 1972, p. 1.

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