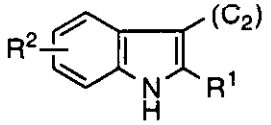
NOVEL INDOLE-RING CONSTRUCTION METHOD FOR THE SYNTHESIS OF 2-TRIFLUOROMETHYLINDOLES ¶

Kazuyuki Miyashita, Katsutoshi Tsuchiya, Katsunori Kondoh, Hideto Miyabe, and Takeshi Imanishi*

Faculty of Pharmaceutical Sciences, Osaka University, 1-6 Yamadaoka, Suita, Osaka 565, Japan

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.[1] 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[2] or as a plant hormone.[3] 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^1=perfluoroalkyl), in which both the electron density of the indole ring and the basicity of the nitrogen are expected to be strongly affected.



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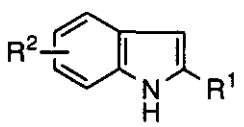

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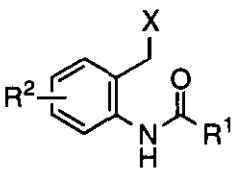

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2-Trifluoromethylindole (**2**, R^1=CF_3, R^2=H) was known to be obtained by direct trifluoromethylation of indole[4] or starting from fluorinated material,[5] but there remain problems about the regioselectivity and the number of reaction steps. As another approach to prepare the various 2-trifluoromethylindoles (**2**, R^1=CF_3), pyrrole ring formation from 2-(*N*-trifluoroacetylamino)toluene derivatives (**3**, R^1=CF_3) 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[6] and its modified reactions,[7] 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[5] 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^1=perfluoroalkyl), starting from the methyl ether (**3** , X=OMe) or the phosphonium salt (**3**, X=P^+Ph_3) and also describe the preparation of **1** (R^1=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*-toluenesulfonic 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.

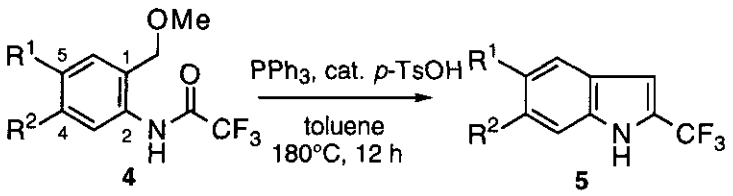


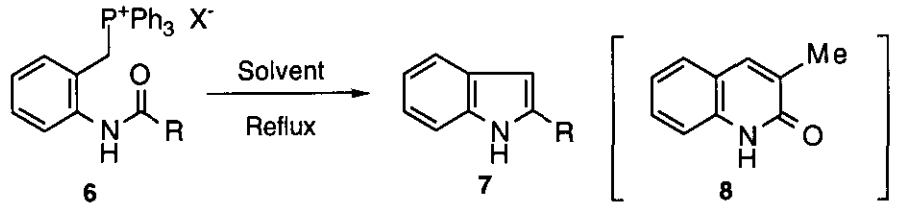
Table 1. Indole-formation reaction of the methyl ether (**4**)

Run	Compd.	R^1	R^2	Yield %	mp °C
1	**a**	H	H	no reaction	-
2	**b**	-OCH_2O-		44 (69)	134-136
3	**c**	MeO	MeO	60 (67)	86-88
4	**d**	H	MeO	48 (52)	89-91
5	**e**	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).

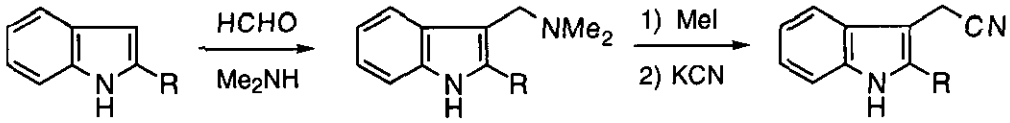


6 **7** **8**

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

Run	Compd.	R	X	Solvent	Time hr	Yield %	mp °C (lit.)
1	**f**	CF_3	Br	DMF	15	82	107-108 (107-108)[4a]
2	**g**	C_2F_5	Br	DMF	12	92	93-94
3	**h**	$PhCH_2$	Cl	*o*-DCB	7	42	80-81 (84-85)[8]
4	**i**	Ph	Cl	*o*-DCB	7.5	29	190-191 (189-190)[7c]
5	**j**	*p*-$NO_2C_6H_4$	Cl	*o*-DCB	8	48	253-255 (249-251)[7c]
6	**k**	MeCO	Cl	*o*-DCB	1	19	154-156 (150)[7d]
7	**l**	EtO_2C	Cl	*o*-DCB	7.5	53	121-123 (123)[7d]

The electrophilic substitution at C-3 of the indole ring is a well-known reaction for the synthesis of the 3-substituted indoles.[9] 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.



7f: R=CF_3
g: R=C_2F_5

9f: R=CF_3, 90%
g: R=C_2F_5, 79%

10f: R=CF_3, 74%
g: R=C_2F_5, 44%

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.

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