

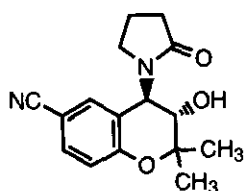
SYNTHESIS OF 2-(BENZOPYRAN-4-YL)PYRIDINE *N*-OXIDE K⁺ CHANNEL OPENER VIA PALLADIUM-CATALYZED CROSS-COUPLING REACTION

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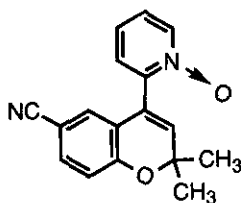
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Abstract- 2-(Benzopyran-4-yl)pyridine *N*-oxide (**3**) was prepared from 2-chlorozincopyridine *N*-oxide and benzopyran-4-yl triflate in the presence of tetrakis(triphenylphosphine)palladium.

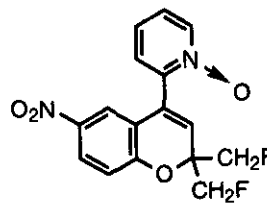
K⁺ channel openers have now received much attention as therapeutic agents for diseases such as hypertension, angina pectoris, asthma, and alopecia.¹ A number of benzopyran derivatives, of which cromakalim (**1**) is the prototype, have been synthesized to find potent K⁺ channel openers, and it has been recently disclosed that a pyridine *N*-oxide derivative (**2**) (Ro 31-6930) is a highly potent agent.² In our search for more promising K⁺ channel openers, we found that the 2,2-bis(fluoromethyl)-6-nitro analogue of **2** (**3**) is more potent than **2**.³



Cromakalim (**1**)



Ro 31-6930 (**2**)

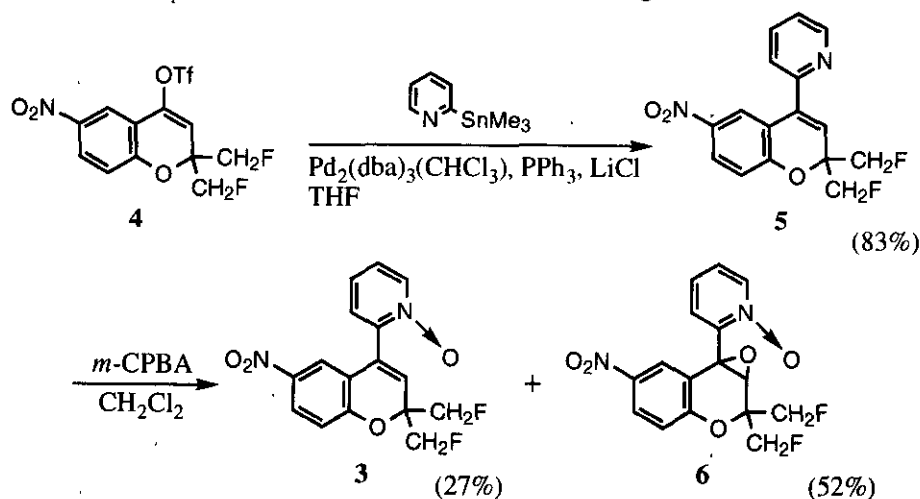


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However, the original procedure for the preparation of **3** (Scheme 1) was very unsatisfactory. Although the transformation of the triflate (**4**) into the 4-(2-pyridyl)benzopyran (**5**) was effected in good yield by treatment with 2-trimethylstannylpyridine in the presence of $\text{Pd}_2(\text{dba})_3(\text{CHCl}_3)\text{-PPh}_3$, the oxidation of **5** with *m*-chloroperbenzoic acid in CH_2Cl_2 resulted in the formation of the desired **3** in poor yield with its epoxide derivative (**6**) being formed as the main product.

These results promoted us to devise an improved preparative procedure of **3**. Herein we wish to report an efficient synthesis of the pyridine *N*-oxide (**3**) by the palladium-catalyzed cross-coupling reaction of the triflate (**4**) with 2-chlorozincipyridine *N*-oxide (**7**).

The palladium-catalyzed cross-coupling reaction of organic halides and sulfonates with organometallic reagents is a well-known effective method for the formation of carbon-carbon bond, such as aryl-alkenyl bond.⁴ While many reports are also available on the application of this method to heteroarylation,⁵ the use of aromatic *N*-oxide derivatives has not been described to our knowledge.



Scheme 1

After some preliminary studies, we found that 2-chlorozincipyridine *N*-oxide (**7**) smoothly reacted with the triflate (**4**) to give **3** in a satisfactory yield. Thus, **7** was prepared by the successive treatment of 2-bromopyridine *N*-oxide hydrochloride (**8**) with *n*-BuLi (2 equiv.) at -78°C in THF and ZnCl_2 (1 equiv.) at $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$, and then, without isolation, was allowed to react with **4** in the presence of $\text{Pd}(\text{PPh}_3)_4$ in THF at room temperature for 21 h. The reaction required an excess of **7**; while the reaction using a 2.5-

washed with saturated NaCl, dried over Na₂SO₄, and the solvent was removed. The crude product was purified by chromatography on silica gel with CH₂Cl₂/MeOH (95:5) as eluent to give 110 mg (64%) of pyridine *N*-oxide (**3**): mp 183-184 °C; ¹H nmr δ: 4.65 (4H, d, *J*=46.2 Hz), 5.95 (1H, s), 7.00 (1H, d, *J*=6.1 Hz), 7.35-7.88 (4H, m), 8.07 (1H, dd, *J*=2.0 Hz and 6.1 Hz), 8.20-8.50 (1H, m). *Anal.* Calcd for C₁₆H₁₂N₂O₄F₂: C, 48.52; H, 3.26; N, 11.32. Found: C, 48.56; H, 3.23; N, 11.34.

ACKNOWLEDGMENTS

The authors are grateful to Dr. M. Hamana, professor Emeritus of Kyushu University, for helpful discussions.

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Received, 24th May, 1995