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

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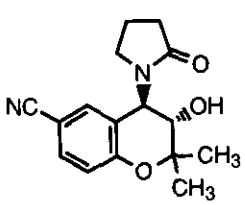
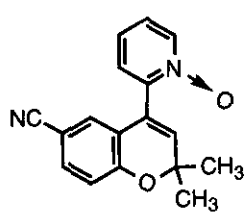
Abstract- 2-(Benzopyran-4-yl)pyridine *N*-oxide (**3**) was prepared from 2-chlorozinciopyridine *N*-oxide and benzopyran-4-yl triflate in the presence of tetrakis(triphenylphosphine)palladium.

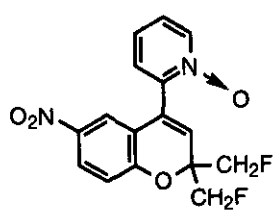
K^+ channel openers have now received much attention as therapeutic agents for diseases such as hypertension, angina pectoris, asthma, and alopecia.[1] A number of benzopyran derivatives, of which cromakalim (**1**) is the prototype, have been synthesized to find potent K^+ channel openers, and it has 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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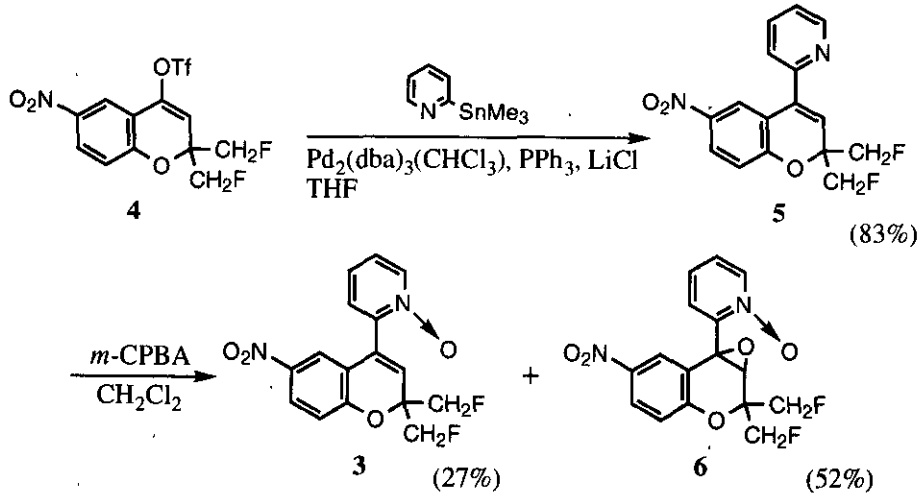
However, the original procedure for the preparation of **3** (Scheme 1) was very unsatisfactory. Although the transformation of the triflate (**4**) into the 4-(2-pyridyl)benzopyran (**5**) was effected in good yield by treatment with 2-trimethylstannylpyridine in the presence of $Pd_2(dba)_3(CHCl_3)$-PPh_3, 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-chlorozinciopyridine *N*-oxide (**7**).

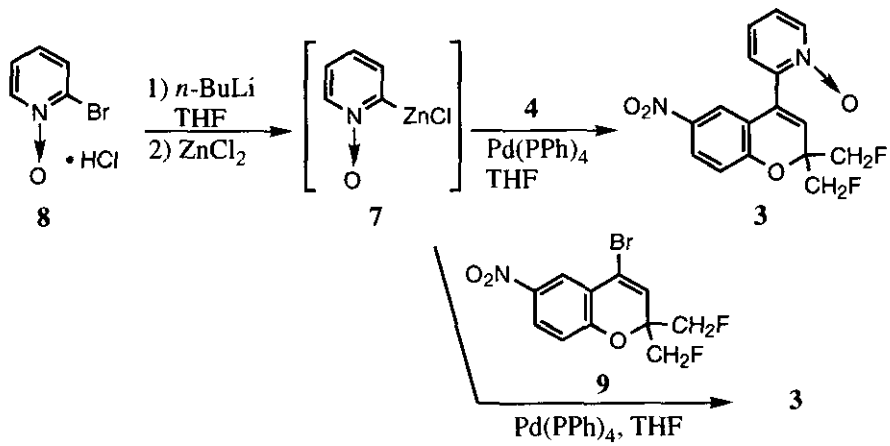
The palladium-catalyzed cross-coupling reaction of organic halides and sulfonates with organometallic reagents is a well-known effective method for the formation of carbon-carbon bond, such as aryl-alkenyl bond.[4] While many reports are also available on the application of this method to heteroarylation,[5]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



Scheme 1

After some preliminary studies, we found that 2-chlorozinciopyridine *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 °C →0 °C, and then, without isolation, was allowed to react with **4** in the presence of $Pd(PPh_3)_4$ in THF at room temperature for 21 h. The reaction required an excess of **7**; while the reaction using a 2.5-

fold excess **7** gave a low yield of **3** (35%, recovered **4** in 55%), the yield of **3** increased to 64% (recovered **4** in 17%) by the reaction with a 5.1-fold excess **7** (Scheme **2**).



Scheme 2

The reaction of **7** (2.5 equiv.) with the 4-bromobenzopyran analogue (**9**)[6] also proceeded under similar conditions to give **3**, though in a lower yield (18%). These results demonstrate that metallic derivatives of aromatic *N*-oxide have considerable promise as components of the palladium-catalyzed cross-coupling reactions.

Further studies are in progress to extend the scope of this type of reaction.

EXPERIMENTAL SECTION

^{1}H Nmr spectrum was recorded on a Hitachi R-24B 60-MHz spectrometer in $CDCl_3$ in the case with tetramethylsilane as internal standard, and is reported in δ.

COUPLING PROCEDURE:

To a suspension of 564 mg (2.68 mmol) of 2-bromopyridine *N*-oxide hydrochloride (**8**) in 6 ml of THF at -78 °C, 5.66 mmol of *n*-BuLi was added dropwise. After 30 min of stirring, a solution of 5.18 ml (2.59 mmol) of $ZnCl_2$ in 5 ml of THF was added to the mixture, then the reaction was stirred for 15 min, and the reaction was allowed to warm to 0 °C (15 min). To the mixture, 39 mg (0.034 mmol) of $Pd(PPh_3)_4$ in 3 ml of THF and 200 mg (0.51 mmol) of the triflate (**4**) in 2 ml of THF were added. After 21 h stirring at room temperature, the mixture was diluted with water and extracted with ethyl acetate. The extract was

washed with saturated NaCl, dried over Na_2SO_4, and the solvent was removed. The crude product was purified by chromatography on silica gel with CH_2Cl_2/MeOH (95:5) as eluent to give 110 mg (64%) of pyridine *N*-oxide (**3**): mp 183-184 °C; ^{1}H 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 $C_{16}H_{12}N_2O_4F_2$: C, 48.52; H, 3.26; N, 11.32. Found: C, 48.56; H, 3.23; N, 11.34.

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