Bioorganic & Medicinal Chemistry Letters, Vol.2, No.5, pp. 381-382, 1992
Printed in Great Britain

0960-894X/92 $5.00 + .00

A NEW EFFICIENT SYNTHESIS OF Ro-31-6930, A POTENT POTASSIUM CHANNEL ACTIVATOR, AND ITS ANALOGS

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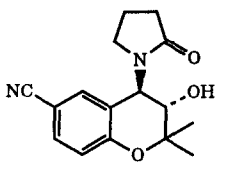
(*Received* 10 *December* 1991)

Abstract ; *A potent potassium channel activator, Ro-31-6930 and its analogs were prepared efficiently by employing Pd(O) mediated coupling of the appropriate enol triflates and pyridine (tributyl) tin.*

Since the discovery of cromakalim **1**,[1] a prototypic agent of a class of potassium channel activators by the research group at SmithKline & Beecham and Roche, and its potential therapeutic applications for the treatment of hypertension, peripheral vascular disease, angina, incontinence, asthma and so on, enormous synthetic efforts in numerous laboratories have been carried out. Recently, it has been disclosed that pyridine N-oxide derivative (Ro-31-6930) **2**[2] by Roche was found to be 10 fold more potent than cromakalim.



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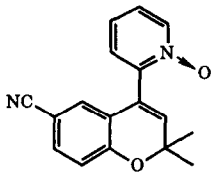

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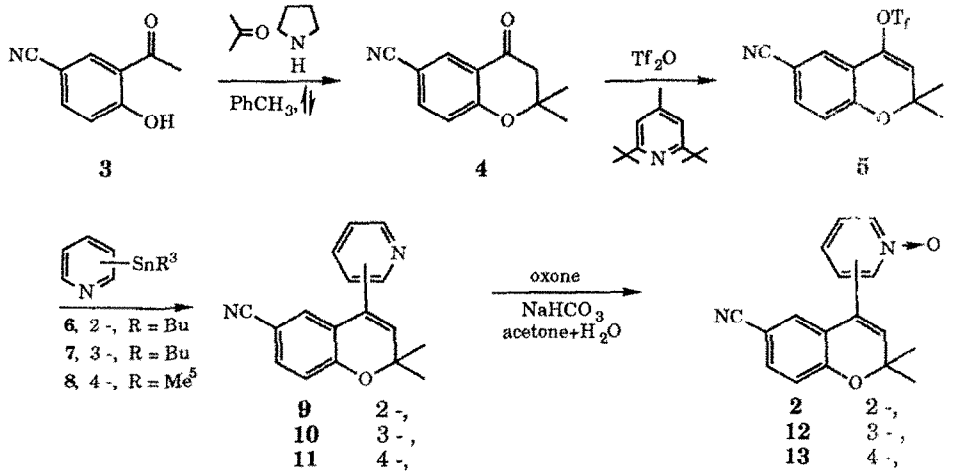
A good biological activity and the structural uniqueness of a N-oxide unit in **2** prompted us to devise a general and efficient synthesis for the purpose of a structure-activity relationship study of this class of compounds. The original synthesis of this compound employed a Claisen rearrangement of pyridylpropargyl phenyl ether. This synthesis was associated with a serious intrinsic problem to yield a benzopyran along with a benzofuran as a side product, which was solved lately[3] by fine tuning the concentration of the reaction mixture.

Herein, we would like to provide a new efficient synthetic pathway to Ro-31-6930 as well as its analogs from the common intermediate.

Our synthesis started with 4-cyano-2-acetyl phenol **3**, which was obtained by Fries rearrangement of 4-cyano-1-acetoxy benzene.[4] Condensation of **3** with acetone in the presence of pyrrolidine in toluene provided chromanone **4** in 80% yield. The requisite enol-triflate **5** was obtained in 85% yield by treating **4** with triflic anhydride in the presence of 2,6-di-t-butyl-4-methylpyridine in dichloromethane. The key coupling reaction of **5** and **6** was best effected by refluxing for 10 hr with a catalytic amount of $Pd_2(dba)_3(CHCl_3)$ (5 ~ 10%), tris(2-furyl) phosphine



(10 ~ 20%) and LiCl (8eq) in THF to give **9** in 80% yield.[6,7]

Analogs **10** and **11**[5] were obtained in uniformly high yield (72% and 75%, respectively) under the same conditions as described above. A selective oxidation of pyridines **9**, **10** and **11** was realized to give **2**, **12** and **13**, respectively by oxone and $NaHCO_3$ in H_2O-acetone.[8] (70%, 67% and 68%, respectively) Bioassays for **12** and **13** are underway and the results will be published in due course.

In conclusion, a coupling of the enol-triflate and trialkyl pyridyl tin (a variation of Stille's chemistry) mediated by Pd(O) in the presence of LiCl provided Ro-31-6930 and its analogs efficiently.

References and Notes

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