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SYNTHESIS OF KEY INTERMEDIATES BENZOPYRAN-4-CARBOXYLIC ACIDS OF NEW POTASSIUM CHANNEL OPENERS BENZOPYRAN-4-AMIDES VIA PALLADIUM-CATALYZED HYDROXYCARBONYLATION

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Abstract: Key intermediates benzopyran-4-carboxylic acids of an important class of potassium channel openers benzopyran-4-amides have been synthesized via palladium-catalyzed hydroxycarbonylation.

Potassium channel openers are a recently discovered and novel class of compounds whose pharmacological action involves the relaxation of smooth muscle by the opening of potassium channels. This pharmacological property suggests a number of therapeutic targets for this class of compounds such as hypertension, angina pectoris, coronary heart disease, asthma, urinary incontinence, and alopecia.[1] Potassium channel openers consist of a group of compounds with a diverse range of chemical structures whose synthetic efforts have been extensively made.[2]

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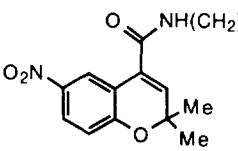

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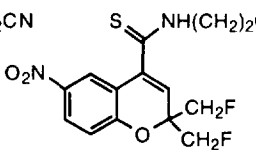

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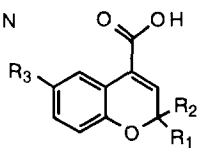

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Previously, we first constructed a pharmacophore model that rationalizes the structure-activity relationships of a chemically diverse and structurally unrelated group of potassium channel openers.[3a] The efforts for designing new potassium channel openers using this model led to some interesting compounds such as compound (**1**) with selective activity to trachea and compounds (**2** and **3**) with highly potent and long-acting antihypertensive effect.[3b-d] Along these lines, we next planned to synthesize 2,2-bis(trifluoromethyl)benzopyran-4-amide derivatives aimed at developing therapeutically more useful potassium channel openers. However, our attempts to prepare these compounds by our earlier methods[3] were unsuccessful, presumably owing to the electronic effect arising from the 2-trifluoromethyl groups.[4] Therefore, we required an efficient synthesis of 2,2-bis(trifluoromethyl)benzopyran-4-amides and the key intermediates benzopyran-4-carboxylic acids **4** ($R_1 = R_2 = CF_3$). In addition, since our earlier routes[3] for the preparation of compounds **1-3** were not readily amenable to large scale work for further biological

evaluation, our goals were also to find a more convenient procedure for their syntheses, especially for the synthesis of the key intermediates benzopyran-4-carboxylic acids **4**.

A cursory search of the literature indicated that more efficient approach to the synthesis of the carboxylic acids **4** would be a palladium-catalyzed hydroxycarbonylation of the benzopyran-4-yl triflates and halides.[5] Herein we report a successful synthesis of the key intermediates benzopyran-4-carboxylic acids **4** of an important class of potassium channel openers benzopyran-4-amide derivatives.

The 2,2-dimethyl and 2,2-bis(fluoromethyl)benzopyran-4-yl triflates **5a** and **5b**, which were prepared from the corresponding benzopyran-4-ones[3d,6] by treatment with triflic anhydride in the presence of 2,6-di-*t*-butyl-4-methylpyridine or 4-dimethylaminopyridine in good yield,[5a,7] were readily converted into the carboxylic acids **4a** and **4b** in the presence of $Pd_2(dba)_3(CHCl_3)$, AcOK, and CO in DMF at room temperature (Table I).[5a,8] In contrast, palladium-catalyzed hydroxycarbonylation of the 2,2-bis(trifluoromethyl)benzopyran-4-yl triflate **5c**[9] using $Pd_2(dba)_3(CHCl_3)$ or $Pd(OAc)_2$-Ph_3P catalyst under these conditions led to only decomposition products, showing the instability of the triflate under these conditions. Thus, although palladium-catalyzed hydroxycarbonylation of the triflates to give the carboxylic acids is a very convenient method for laboratory scale, the triflating agents such as triflic anhydride are very expensive for large scale preparation and the triflates seem to be occasionally unstable. Therefore, we used benzopyran-4-yl bromides instead of the triflates, because the bromides are relatively stable and readily available on a large scale from the corresponding benzopyran-4-ones by reacting the ketones with $POBr_3$, or by the bromination-dehydrobromination reaction of benzopyrans.[3d]

Hydroxycarbonylation of the benzopyran-4-yl bromide **5d**[10] in the presence of $Pd_2(dba)_3(CHCl_3)$ or $Pd(OAc)_2$-Ph_3P catalyst under the Heck reaction conditions[11] gave only a dismal yield (4 or 20%) of the desired product **4a** (Table I). Therefore, we reexamined the reaction conditions. It is known that a catalytic amount of cuprous iodide facilitates the carbon-carbon bond formation of bromoalkenes under the Heck reaction conditions.[5b,12] Some experiments using various amounts of cuprous iodide are shown in Table I and the best results were obtained when the reaction was carried out in the presence of cuprous iodide in amounts equimolar with the bromide **5d**. Other experiments showed that potassium iodide is more efficient. Then, a variety of bromides **5e**-**5h**[9,10] were converted into the corresponding carboxylic acids **4b**-**4e** under the optimum conditions (Table I).

These benzopyran-4-carboxylic acids **4a**-**4e** were easily converted to the benzopyran-4-amide derivatives such as **1**-**3** as previously reported.[3]

Thus, this palladium-catalyzed hydroxycarbonylation provides a more convenient procedure for preparing the important class of potassium channel openers benzopyran-4-amide derivatives.

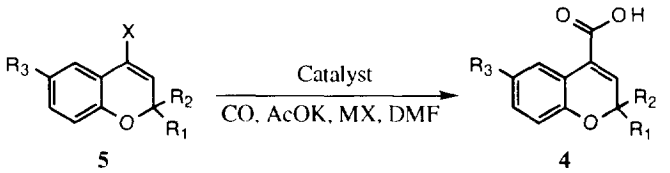

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Table I. Palladium-Catalyzed Hydroxycarbonylation of Benzopyran-4-yl Triflates and Bromides[a]

5[b]	R_1 (=R_2)	R_3	X	Catalyst (mol %)	MX (mol %)	Reaction temp, °C	Reaction time, h	4[b,c] (% yield)
5a	Me	NO_2	OTf	$Pd_2(dba)_3(CHCl_3)$ (5)	-	room temp.	1	**4a** (85)
5b	CH_2F	NO_2	OTf	$Pd_2(dba)_3(CHCl_3)$ (5)	-	room temp.	3	**4b** (63)
5c	CF_3	NO_2	OTf	$Pd_2(dba)_3(CHCl_3)$ (5)	-	- 10	2	-[d]
5d	Me	NO_2	Br	$Pd_2(dba)_3(CHCl_3)$ (5)	-	100	20	**4a** (4)[e]
5d	Me	NO_2	Br	$Pd_2(dba)_3(CHCl_3)$ (5)	CuI (20)	100	20	**4a** (35)[f]
5d	Me	NO_2	Br	$Pd_2(dba)_3(CHCl_3)$ (5)	CuI (100)	100	20	**4a** (88)
5d	Me	NO_2	Br	$Pd_2(dba)_3(CHCl_3)$ (1)	CuI (100)	130	6	**4a** (94)
5d	Me	NO_2	Br	$Pd_2(dba)_3(CHCl_3)$ (1)	KI (100)	130	6	**4a** (99)
5d	Me	NO_2	Br	$Pd(OAc)_2$ (1), Ph_3P (2)	-	100	20	**4a** (20)[g]
5d	Me	NO_2	Br	$Pd(OAc)_2$ (1), Ph_3P (2)	CuI (100)	130	6	**4a** (79)
5d	Me	NO_2	Br	$Pd(OAc)_2$ (1), Ph_3P (2)	KI (100)	130	6	**4a** (92)
5e	CH_2F	NO_2	Br	$Pd(OAc)_2$ (1), Ph_3P (2)	KI (100)	130	6	**4b** (95)
5f	CH_2F	CN	Br	$Pd(OAc)_2$ (1), Ph_3P (2)	KI (100)	130	6	**4c** (98)
5g	CH_2F	C_2F_5	Br	$Pd(OAc)_2$ (1), Ph_3P (2)	KI (100)	130	6	**4d** (89)
5h	CF_3	NO_2	Br	$Pd(OAc)_2$ (5), Ph_3P (10)	KI (100)	130	6	**4e** (87)

[a]Reactions were carried out under a CO balloon in the presence of catalyst and AcOK (4 equiv) in DMF with or without metal halide. [b]All new compounds were adequately characterized spectroscopically. [c]**4a**, see reference 3c. **4b**, see reference 3d. **4c**, mp 165-167 °C. **4d**, mp 173-174 °C. **4e**, mp 96-97 °C. [d]Only decomposition products were isolated. [e]93% of starting material was recovered. [f]62% of starting material was recovered. [g]75% of starting material was recovered.

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9. The triflate **5c** (mp 61-62 °C) was prepared from 3,4-dihydro-6-nitro-2,2-bis(trifluoromethyl)-2*H*-1-benzopyran-4-one (mp 109-110 °C) by the reaction with triflic anhydride and 4-dimethylaminopyridine in CH_2Cl_2 at room temperature in 97% yield. The bromide **5h** (mp 93-94 °C) was obtained by reacting the benzopyran-4-one with $POBr_3$ at 150 °C in 52% yield. The benzopyran-4-one was prepared by treating 2'-fluoro-5'-nitroacetophenone with hexafluoroacetone trihydrate in the presence of pyrrolidine in benzene in moderate yield, because the established synthetic routes[3d,6] that include the reaction of 2'-hydroxyacetophenones with carbonyl compound in the presence of a base were problematic.
10. The benzopyranyl bromides **5d-5g** were prepared from the corresponding benzopyran-4-ones by treatment with $POBr_3$ at 130 °C, or from the corresponding benzopyrans by bromination followed by treatment with sodium hydroxide in good yield.[3d]
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