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Three-component reaction and organocatalysis in one: synthesis of densely substituted 4-aminochromanes

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ABSTRACT

Cyclocondensation of salicylaldehydes with alkyl acetoacetates and 2-aminobenzothiazoles or 2-aminothiadiazole/thiazoles under L-proline catalysis gives 4-hetarylamino substituted chromanecarboxylate derivatives. The mechanism involving the Mannich/hemiketalization cascade reaction and the observed stereoselectivity of the three component process are discussed.

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1. Introduction

The chromane skeleton represents a key structural unit found in a plethora of natural products like flavans and isoflavans.[1] This privileged heterocyclic entity is also an essential feature of more complex compounds including vitamin E, tocopherols and cannabinoids.[2] Among the numerous types of bioactive functionalized chromanes,[3] the 4-amino derivatives have received unusual interest because of their ability to act as ATP-sensitive potassium channel openers.[4] Cromakalim (**1**, Fig. 1) being a lead compound of K_{ATP} activators has had a pivotal influence in the development of new promising cardioprotective agents for myocardial ischemia.[5] Moreover, potassium channels have become attractive pharmacological targets for novel therapeutic strategies in the treatment of hypertension, asthma, urinary incontinence, epilepsy and certain neurodegenerative diseases, glaucoma and diabetes.[5]

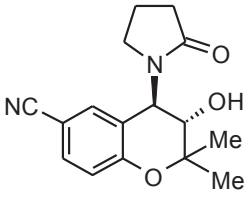

Fig. 1. Pharmacologically valuable cromakalim **1**.

Most of synthetic approaches to the 4-aminochromane framework involve reactions between *o*-hydroxybenzaldimines and electron-rich cyclic or open-chain alkenes catalyzed by several Lewis[6] and Brønsted[7] acids. An alternative route making use of salicylaldehyde Schiff bases consists in their $Sc(OTf)_3$ promoted cyclization with 2,2-dimethoxypropane.[8] Besides, an intramolecular etherification of bromo substituted β-aminoalcohols mediated by CuI/8-hydroxyquinoline constitutes an another preparative protocol.[9] Notably, an adaption of the established imine method for chiral organocatalysts and complexes has permitted development of an enantioselective entry to this molecular architecture.[10]

Recently we have found[11] that the cyclocondensation of salicylaldehydes **2** with alkyl acetoacetates **3** and 2-aminobenzothiazoles **4** or 2-amino-5-methylthiazole **5b** under classical Biginelli reaction conditions (concd HCl catalysis) gave hetarylamino substituted spiroketals **6** (Fig. 2) instead of the expected pyrimidine[12a,b] or oxygen-bridged pyrimidine scaffold.[12a,c] In one case we succeeded in identifying a minor chromane by-product (namely **7b**,

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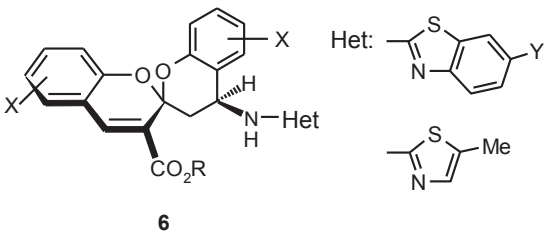
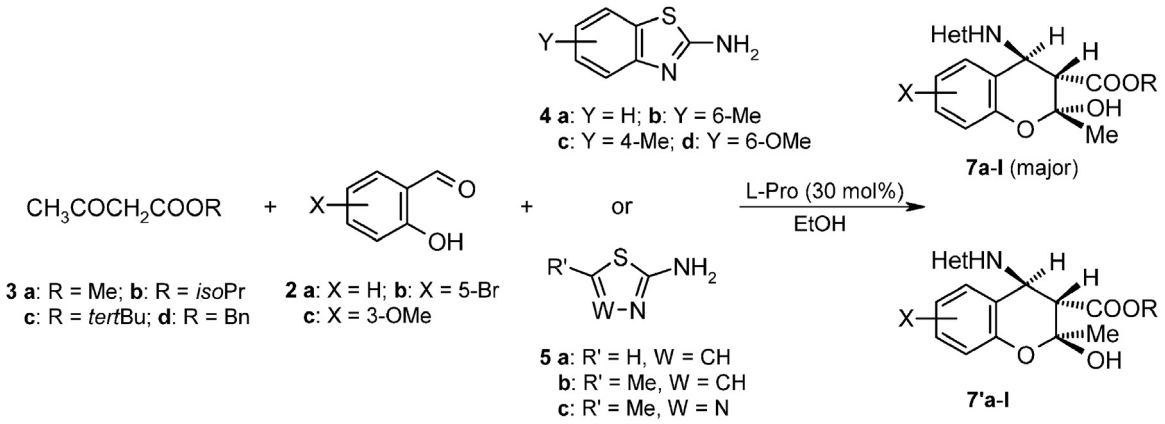
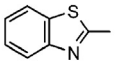
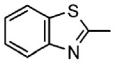
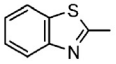
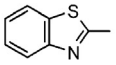
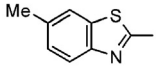
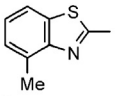
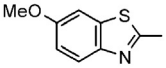
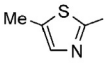
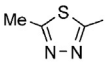
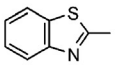
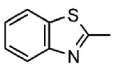


Fig. 2. Spirobischromane product formed under Biginelli conditions.

Scheme 1).[11] It was therefore of interest to study whether a modification of the above experimental procedure might affect the reaction outcome. The widely used organocatalysis by L-proline in diverse multicomponent processes[13] prompted us to examine this amino acid as a promoter for the previously studied transformation. In pursuing our work on the conformationally restricted heterocycles,[11,12] we report here a practical one-pot synthesis of highly substituted 4-aminochromanes. Generally, in this case construction of these bicyclic molecules involves the formation of three new bonds (one C–C, one C–N, and one C–O) and three consecutive stereocenters in one synthetic step.



Product	R	X	Het	Yield[a] [%]	dr[b]
7/7'a	Me	H		45	77:23
7/7'b	*iso*Pr	H		71	82:18
7/7'c	*tert*Bu	H		69	84:16
7/7'd	Bn	H		50	86:14
7/7'e	*tert*Bu	H		57	85:15
7/7'f	*tert*Bu	H		78	84:16
7/7'g	*tert*Bu	H		42	77:23
7/7'h	*tert*Bu	H		53	75:25
7/7'i	*tert*Bu	H		70	80:20
7/7'j	*tert*Bu	H		50	80:20
7/7'k	*tert*Bu	6-Br		63	82:18
7/7'l	*tert*Bu	8-OMe		58	80:20

[a] Isolated yield.

[b] Determined by ^{1}H NMR of the crude product.

Scheme 1. L-Proline catalyzed three-component reaction.

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