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Synthesis and biological evaluation of 1-amino isochromans from 2-bromoethyl benzaldehyde and amines in acid medium

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ABSTRACT

We have developed a facile and efficient synthetic route to substituted isochromans for the first time by reacting 2-(2-bromoethyl)benzaldehyde with a variety of aryl, heteroaryl amines in AcOH. The reaction is catalyst/additive free and takes place at reflux conditions with short reaction time to furnish products in good to excellent yields. All the compounds have been characterized by spectral techniques such as IR, ^{1}H NMR and Mass etc. Synthesized compounds were evaluated for antimicrobial activity against specific bacterial like 1) *Staphylococcus* strains *aureus* 2) *Bacillus subtilis* 3) *Escherichia coli* 4) *Pseudomonas aeruginosa*. Compounds **3e, 3n, 3 m, 3 l, 3 k, 3j** and **3b** showed most potent *in vitro* activity against bacterial strains.

Many known biologically active compounds contain heterocyclic core, which is an indispensable element for bio-activity. Among all the aromatic heterocycles, the chemistry of functionalized isochroman and isoquinolone continues to be of great interest because of the industrial and biological importance of these class of compounds. The C-N bond conversions have attracted much interest because nitrogen-containing functional groups that are prevalent in many natural products and pharmaceuticals.[1] Therefore, many remarkable endeavours have been made to develop efficient and general methods for the amination reactions.[2]

Isochroman derivatives generally exhibit various pharmaceutical activities[3] and serve as interesting building blocks in synthetic chemistry.[4] Chiral 1-substituted isochromans constitute the core of many natural products such as cytosporone C–D[5] and synthetic sonepiprazole (U-101387) (Fig. 1), a selective dopamine D4 receptor antagonist.[6] Isochroman-6-carboxamide, (*S*)-(-)-PNU-109291[7] was found to be as a highly selective 5-HT_{1D} agonist for the treatment of migraine headache. Isochromane moieties found in isochromans have shown in Fig. 1.[8]

C-H Bond functionalization[9a] is one of the strategies used for the preparation of 1-substituted isochromans. However formation of substituted isochroman using hypervalent iodine,[9b] metal catalysts,[9c] non-haeme iron mediated amidation,[9d] copper as catalyst and *N*-halosuccinimide as oxidants,[9e] asymmetric catalysis,[9f] Oxa- Pictet-Spengler reaction,[9g] the cyclisation of phenylseleno alcohols,[9h] the addition of *ortho*-lithiated aryl oxiranes to enaminones,[9i] was studied so far.

The isoquinolone ring system is an interesting structural motif not only because of its presence in several natural compounds, but also it is a useful building block in medicinal and organic chemistry.[10] Furthermore, its framework has been found to be a useful chemical scaffold for the synthesis of more elaborate molecules with pharmacological properties.[11] Isoquinolone core is the common structural motif in alkaloids[12] in Fig. 2.

Synthesis of *N*-substituted 4-methylene-3,4-dihydro-1(2*H*)-isoquinolinones[13] involves palladium-catalysed multicomponent processes utilising allenes, with both 2-iodo esters and 2-iodo acyl chlorides. C-H functionalization reaction could be used for the preparation of substituted *N*-aryl tetrahydroquinolines.[14] They are accessible by intramolecular functionalization of benzylic methylene adjacent to the ring nitrogen atom in *N*-aryltetrahydroisoquinoline derivatives.[15]

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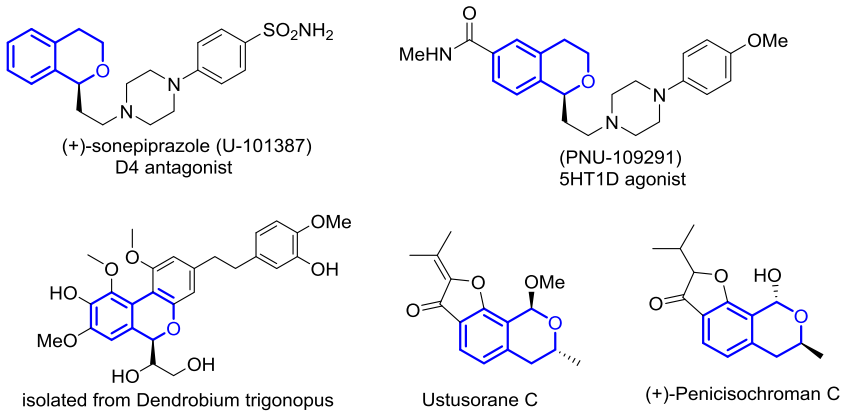


Fig. 1. natural and selected bioactive functionalised isochromans.

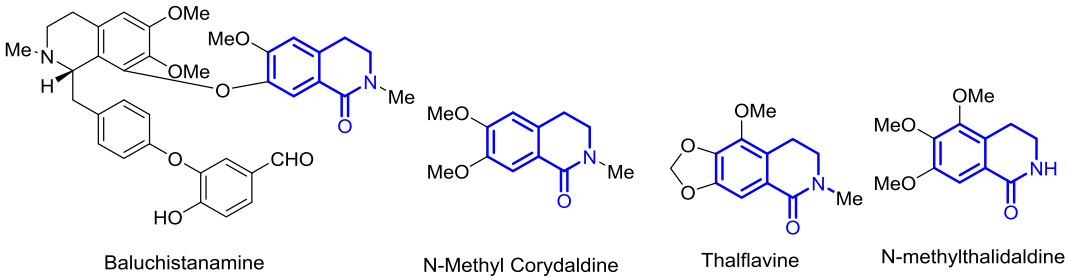
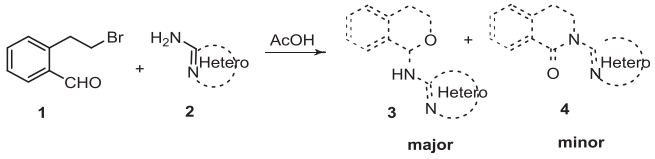
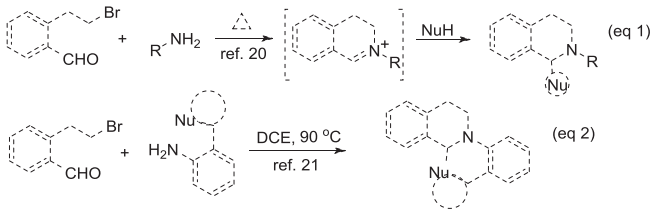


Fig. 2. Naturally occurring 3,4-dihydroisoquinolin-(2H)-one derivatives.



Scheme 1. Synthesis of amino-substituted isochroman.

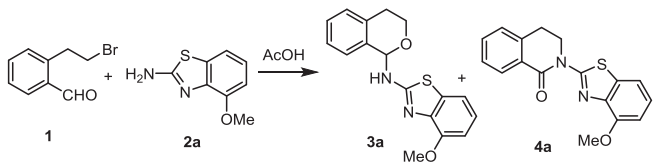


Scheme 2. Previous approaches using 2-(2-bromoethyl)benzaldehyde.

Even though, substituted isochromans are known in the literature, there exists no reports on the synthesis of isochroman-1-amine derivatives. Thus, we became interested to meet this challenge. In connection with our group objective in developing new synthetic strategies for diverse and complex polyheterocycles,[16] herein we report a novel strategy for the rapid access to substituted *N*-aryl, heteroaryl isochromans **3** and *N*-aryl, heteroaryl tetrahydroisoquinolones **4** by using 2-(2-bromoethyl)benzaldehyde **1** as the substrate and a variety of amines **2** (Scheme 1).

In this context, we observed in the literature that 2-(2-bromoethyl)benzaldehyde was explored as a substrate in DCE to access only tetrahydroisoquinolines,[17] and no report exist on the formation of isochromans, either in the presence of external nucleophiles or presence of other nucleophilic group in the amine compound.[18] Further, it was reported that the reaction of 2-(2-bromoethyl)benzaldehyde with aromatic amines generate highly reactive iminium intermediate.

Table 1
Optimization conditions for the synthesis of 1-sustituted isochroman.[a]



Entry	Amines	Temp(°C)/Time	Solvent	Yield[b]
1	4-methoxybenzo[*d*]thiazol-2-amine	r.t/1–24 h	AcOH	[c]
2	4-methoxybenzo[*d*]thiazol-2-amine	40 °C/4 h	AcOH	traces
3	4-methoxybenzo[*d*]thiazol-2-amine	80 °C/4 h	AcOH	73% 3b, 20% 10b

[a] Reaction conditions: 1 (1 eq) and 2b (1.2 eq).
[b] Isolated yields after column chromatography,
[c] No product formation.