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Facile synthesis of densely substituted chroman derivatives through Brønsted acid ionic liquid catalyzed three-component reactions of aromatic aldehydes, 1,1-diarylethylenes and nucleophiles

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ABSTRACT

By using a sulfone-containing Brønsted acid ionic liquid as catalyst, various densely substituted chroman derivatives were synthesized through hitherto unreported three-component reactions of aromatic aldehydes, 1,1-diarylethylenes and nucleophiles. The representative reactions involve (i) condensation of benzaldehyde, 2-naphthol and 1,1-diphenylethylene and (ii) selective assembly of salicylaldehyde, indole and 1,1-diphenylethylene. The reactions were performed under solvent-free conditions, and the only by-product was water. The Brønsted acid ionic liquid could be recovered and reused without significant loss of its activity.

1. Introduction

Multicomponent reactions (MCRs) are powerful tools in modern drug discovery and allow fast, automated and high throughput synthesis of diverse structural scaffolds required in the search of novel therapeutic and pharmacologically active molecules.[1] Electrophilic reaction of aldehyde with two different nucleophiles is well known, which has been widely applied in organic synthesis through the established MCRs.[2] Although many successful examples have been reported, developing new MCRs based on this strategy often encountered a notorious difficulty in controlling the reaction selectivity. To address this issue, various approaches have been developed to prevent the side reaction, condensation reaction of aldehyde with the same nucleophile.[3] An elegant one is to use bifunctional aldehyde or nucleophile as substrate, which has multiple reactive sites enabling further intramolecular reaction.[4] With this strategy, the assembly reaction will occur in favor of forming a stable product, which is generally associated with multiple interactions of two different substrates. Therefore, the reaction selectivity of MCRs is maximized.[5]

Chromans (dihydrobenzopyrans) are important and ubiquitous structural motifs found in a variety of important biologically active natural products such as vitamin E and flavonoids.[6] The significance of these heterocyclic motifs has led to a demand for efficient synthetic methods. Metal complexes or acids catalyzed addition or cyclization reactions of phenols and dienes were often used to synthesize chromans.[7] A sequential ring-closing metathesis-transfer hydrogenation sequence has been used to synthesize chromanes.[8] Recently, intramolecular *oxo*-Michael addition reaction was also employed to construct this scaffold.[9] Although there are myriad methods known to accomplish the synthesis of these privileged molecules and their derivatives, sustained efforts have been paid to developing efficient synthetic methods under user-friendly conditions.

Recently, styrene derivatives were used as π-type nucleophiles in many organic transformations.[10] Particularly, in electrophilic reaction of aldehyde, 1,1-diphenylethylene has been demonstrated to be a very active nucleophile.[11] We have recently investigated three-component reactions of aldehyde with two different nucleophiles.[12] However, to the best of our knowledge, in this type of MCRs, the styrenyl system-based π-type nucleophiles have been rarely reported.[13] Considering the fact that 1,1-diphenylethylene contains a C—C double bond, which is quite reactive upon addition of hydroxyl group,[14] it is not unreasonable to expect that this type of compound can act as a bifunctional nucleophile in establishing some three-component reaction of aldehyde. Out of these considerations, we started some time ago, a research program on this topic.

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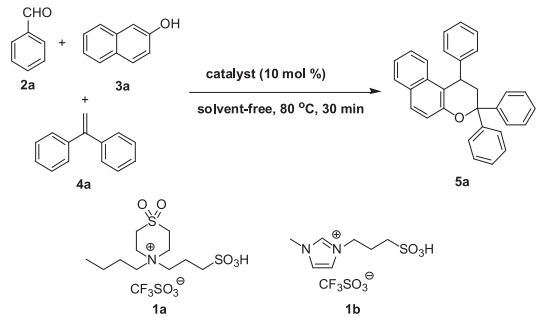
Brønsted acid ionic liquids have been widely used in synthesis and catalysis.[15] Particularly, these ILs have also been proved to be effective for promoting many MCRs.[16] Herein, we report for the first time the use of 1,1-diphenylethylene as a bifunctional nucleophile in establishing three-component reactions. The aim of this work is to show that a combination of styrenyl system-based π-type nucleophile with aldehyde may provide a promising scenario where three-component assembly occurs selectively, providing various densely substituted chroman derivatives in an expedient way. The use of a Brønsted acid ionic liquid is the key to make MCRs possible.

2. Results and discussion

Initially, three-component reaction of benzaldehyde **2a**, 2-naphthol **3a** and 1,1-diphenylethylene **4a** was investigated, and the results are listed in Table 1. The reaction was performed under solvent-free conditions at 80 °C. The expected product was chroman **5a**. In the presence of strong Brønsted acids, such as toluenesulfonic acid and triflic acid, the three-component reaction proceeded, but **5a** was obtained only in moderate yields after 30 min of reaction (entries 1 and 2). Trifluoroacetic acid was proved to be ineffective for this reaction (entry 3). The performance of Lewis acids, such as $Sc(OTf)_3$, $Fe(OTf)_3$ and $ZnCl_2$, was also examined in the three-component reactions, and the yield reached only to 30% in the best case (entries 4 to 6). Although the yields are not satisfactory, these preliminary results demonstrated that synthesis of chroman through 1,1-diphenylethylene-participated three-component reaction of aldehyde and a OH-containing counter nucleophile is indeed possible. In order to find a suitable catalyst for this three-component reaction, we then turned to a sulfonyl-containing Brønsted acid ionic liquid **1a**, which has displayed remarkable catalytic activity in various organic reactions.[17] To our great delight, the three-component reaction proceeded very well over ionic liquid **1a**, and 93% of yield was obtained under the identical conditions (entry 7). A conventional SO_3H-functionalized Brønsted acid ionic liquid, Forbes's ionic liquid **1b**, was also examined, however, the yield obtained is inferior as compared with **1a** (entry 8). These results give us impetus to investigate the effects of other parameters on the performance of the model three-component reaction, such as temperature, reaction time and catalyst amount (entries 9 to 11). Finally, the optimal conditions were confirmed as follows: 80 °C, 30 min and 5 mol % of ionic liquid **1a**. It should be noted that, at the end of the reaction, the formed product could be easily isolated with ionic liquid catalyst by means of extraction using dichloromethane. The recovered ionic liquid **1a** could be reused in the next run after 20 min of treatment under vacuum conditions at 80 °C (20 mmHg). Its catalytic activity in the model reaction keeps unchanged in at least six runs.

To extend the scope of the reaction, other substrates were submitted to the condensation under the conditions of entry 7. The relevant results are reported in Fig. 1. First, various benzaldehydes were examined by using 2-naphthol and 1,1-diphenylethylene as counter substrates. In all cases, good to excellent yields were obtained, whatever the nature of the substituent present on the aldehyde (electron-donating or electron-withdrawing). An aliphatic aldehyde, 3-phenylpropanal, was also used, and the result obtained was as competent as in the case of the aromatic aldehyde. Some other phenols, such as 6-bromo-2-naphthol, trimethylhydroquinone and sesamol, were also submitted to the condensation. And all these phenols afforded the corresponding adducts in good yields under the conditions of entry 7. Proceeding on the same line, we finally extended our strategy to more complex substrates in order to determine the scope of our methodology. Remarkably, as shown in Fig. 1, 4-hydroxycoumarin 2-hydroxy-1,4-naphthoquinone, 4-hydroxy-6-methyl-2-pyrone and dimedone also selectively reacted with 2-naphthol and 1,1-diphenylethylene, affording a diverse array of valuable and complex chroman derivatives. Di(4-chlorophenyl)ethylene can also be used in this three-component reaction. However, attempts to use simple styrene and its substituted counterparts, such as 4-methylstyrene and α-methylstyrene, failed to afford the desired product. It may result from the poor nucleophilicities of these styrenes.[13]

Table 1
Three-component reaction of benzaldehyde **2a**, 2-naphthol **3a** and 1,1-diphenylethylene **4a**[a]



Entry	Catalyst	Yield (%)
1	PTSA	54
2	TfOH	45
3	CF_3CO_2H	Trace
4	$Sc(OTf)_3$	30
5	$Fe(OTf)_3$	15
6	$ZnCl_2$	Trace
7	**1a**	93
8	**1b**	60
9[b]	**1a**	61
10[c]	**1a**	49
11[d]	**1a**	73
12[f]	**1a**	92

[a] Reaction conditions: **2a**, 0.5 mmol; **3a**, 0.5 mmol, **4a**, 0.5 mmol; catalyst, 0.025 mmol; 80 °C, 30 min.
[b] **1a**, 0.0125 mmol.
[c] 50 °C.
[d] 15 min.
[f] **1a** was reused in the fifth run.

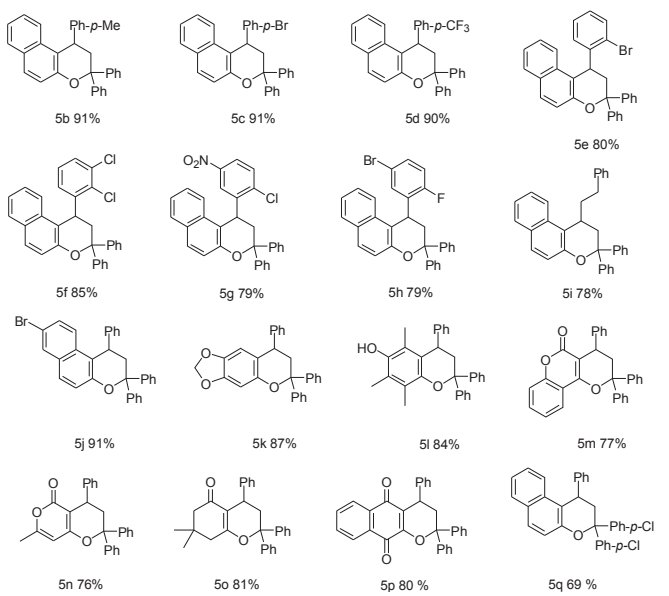


Fig. 1. Scope of three-component reaction of aldehyde, phenol and 1,1-diphenylethylene.

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