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Direct access to functionalized 4-nitromethyl-chromenes via a domino reaction under catalyst-free conditions

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A catalyst-free tandem reaction for synthesis of 4-nitromethyl-chromenes has been established from accessible α, β-unsaturated ketones and CH_3NO_2. Target products were obtained in non-toxic solvent under catalyst-free conditions. Especially, the scope of substrates was expanded to tricyclic α, β-unsaturated ketones for the synthesis of tetracyclic heterocompounds in medium to good yields.

Introduction

Functionalized chromenes are the key cores of various natural products and biological heterocyclic compounds.[1] Especially, chromeno[4,3-b]chromene core skeleton as the derivatives of chromenes has significant biological and pharmaceutical activities.[2] For example, racemate dependensin shows potent antimalarial activity (Fig. 1**, A**). Due to their vital biological and pharmacological activities, the development of new and more general synthetic methods for these heterocyclic compounds is of significant interest.[3] Nitro group covered on these heterocyclic compounds is a significant functional group in synthetic chemistry, which can be transformed into nitroso group, amidogen and can be easily removal. Among these significant heterocyclic compounds, chromenes bearing nitrogenous substituent at C-4 position are kinds of potential drugs and drug precursors. For example, **B** was discovered to have potent anti-ischemic properties[4] and **C** is a selective a2-adrenergic antagonist.[5] Therefore, developing an efficient and practical method to build 4-nitromethyl-chromenes is a meaningful work.

To date, lots of methods aimed at synthesizing chromenes bearing nitrogenous substituent at C-4 position have been developed.[6] Ramachary[7] developed a combination of Michael addition and cyclization by using alkyl ketones as nucleophile. Meanwhile, Lu[8] developed a similar route for the synthesis of dihydrocoumarins by using alkyl aldehydes as nucleophile (Scheme 1**,** Path 1). Other approaches using unsaturated aldehyde as nucleophile were developed (Scheme 1**,** Path 2).[9] However, acetophenones were inapplicable in above methods to synthesize 4-nithomethyl chromenes. Later, Choi[10] reported that o-hydroxycinnamaldehydes reacted with nitro methane in 2012 (Scheme 1, Path 3). Despite that further oxidization transforms it into coumarins, this strategy is only appropriate for the o-hydroxycinnamaldehydes. It is obvious that developing more general synthetic methods for functionalized 4-nitromethyl-chromenes and expanding the chromenes family are still big challenges.

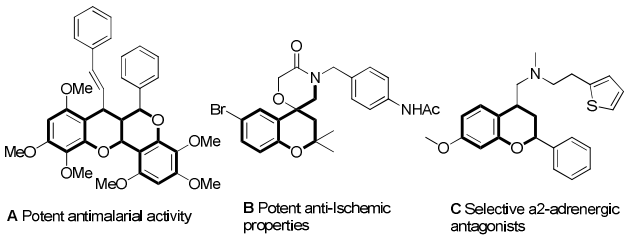
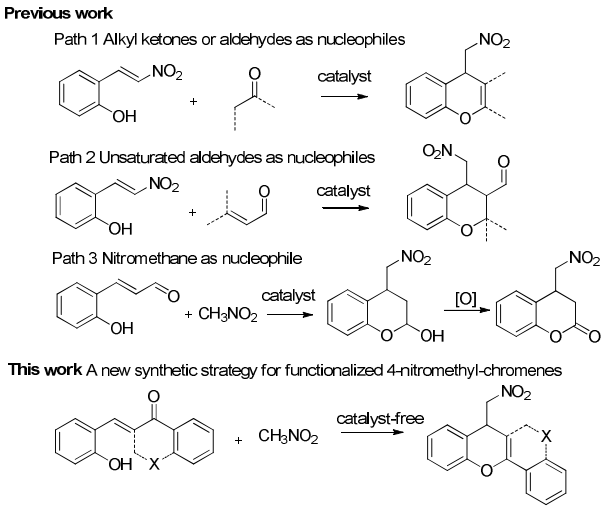


Fig. 1 Biologically important molecules of chromeno[4,3-b]chromene and chromenes with nitrogenous substituent at C-4 position



Scheme 1 Methods for the synthesis of 4-nitromethyl-chromenes

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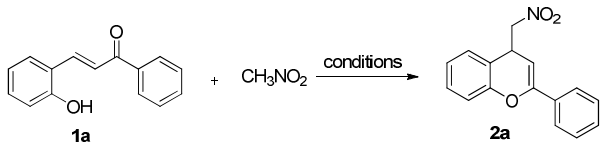
In the past two decades, synthetic chemists have shown great interest in the development of environmentally friendly organic processes involving green chemistry that comprises the use of green solvents, catalysts. Recently, catalyst-free conditions[11] as a powerful strategy get more and more popular. Employing readily available green solvents including water, ethanol, glycerol, polyethylene glycol and lactic acid is also a good strategy. In short, avoiding the use of toxic solvents and minimizing waste generation become a hot research direction in green chemistry.

Herein, we reported a practical and convenient tandem reaction for the synthesis of functionalized 4-(nitromethyl)-2-phenyl-4*H*-chromenes from trans-2-hydroxychalcone and CH_3NO_2. Not only was the tandem reaction catalyst-free in non-toxic solvent which could simplify the treatment after the reaction, but also 7-(nitromethyl)-6,7-dihydrochromeno[4,3-b]chromene as an important structure was easily obtained via this strategy.

Results and discusion

Table 1 Optimization of the reaction conditions[a]



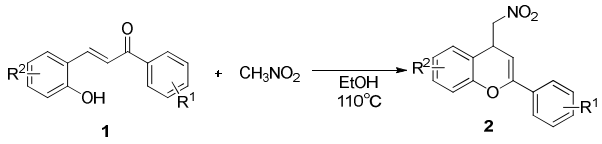
1a **2a**

Entry	Solvent	Additives	Temperature	Yield(%)[b]
1	THF	No	100	Trace
2	CH_3CN	No	100	Trace
3	CH_3NO_2	No	100	Trace
4	H_2O	No	100	51
5	H_2O	$FeCl_3$	100	32
6	H_2O	$CuCl_2$	100	10
7	H_2O	p-TSA	100	Trace
8	H_2O	$NaHCO_3$	100	5
9	H_2O	CH_3COONH_4	100	42
10	CH_3OH	No	100	20
11	CF_3CH_2OH	No	100	36
12	n-tBuOH	No	100	12
13	C_2H_5OH	No	100	90
14	**C_2H_5OH**	**No**	**110**	**96**
15[c]	C_2H_5OH	No	110	93
16[d]	C_2H_5OH	No	110	58

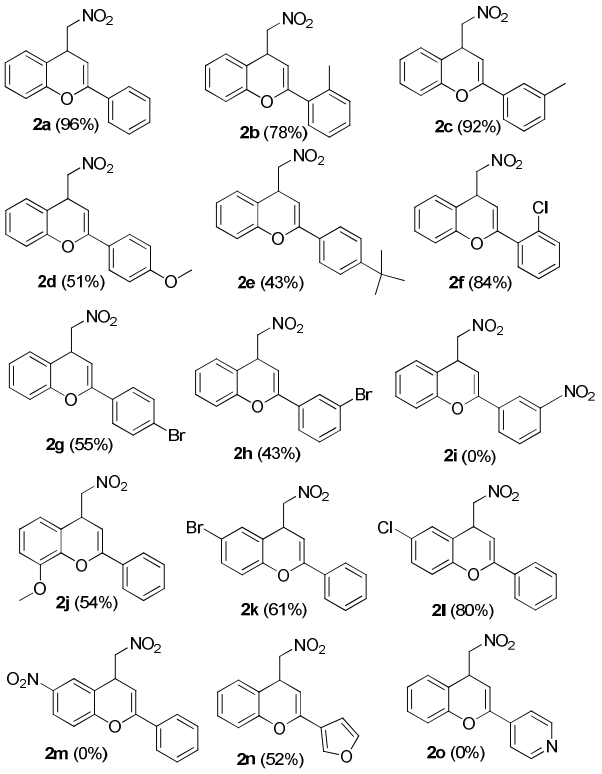
[a]Reaction conditions: **1a**(0.25mmol), CH_3NO_2(18mmol, 1mL), additives(0.025mmol) and 4mL solvent, unless otherwise stated. All reactions were performed under air atmosphere. [b]Isolated yields. [c]9mmol (0.5mL) CH_3NO_2 was added. [d]1.25mmol (70 μL) CH_3NO_2 was added

Initially, trans-2-hydroxychalcone (**1a**, 0.25mmol) was chose as the model substrate to react with CH_3NO_2 (18mmol, 1mL) for the synthesis of desired product under catalyst-free conditions. Preliminary experiment showed that no product was observed in THF, CH_3CN, and CH_3NO_2 (Table 1, entries 1-3). Interestingly, when water was used as solvent, product could be obtained in 51% yield (Table 1, entry 4). And this possibly indicated protonic solvents may be beneficial to the reaction. While additives were added into the reaction, yields have no obvious improvement (Table 1, entries 5-9). In view of such situation, we chose other protonic solvents instead of water. Lower product yields were got in CH_3OH, CF_3CH_2OH and n-tBuOH (Table 1, entries 10-12). Excitingly, great conversion occurred in C_2H_5OH at 110°C while lower temperature resulted in lower yield (Table 1, entries 13-14). Decreasing the dosage of CH_3NO_2 reduced the yield (Table 1, entry 15 and 16). Accordingly, we chose the best condition to be identified as 0.25mmol **1a** and 18mmol CH_3NO_2 in 4mL C_2H_5OH at 110°C.

Table 2 Exploring generality and scope of the novel reaction[a, b]



1 **2**



[a]Reaction conditions: **1** (0.25mmol), 18mmol (1mL) CH_3NO_2 and 4mL C_2H_5OH at 110°C. [b]Isolated yields.

With the optimized reaction conditions in hand, the scope and generality of the novel reaction were investigated. The results which are summarized in Table 2 demonstrated that the corresponding target products could be obtained in medium to excellent yields for various substrates except substrates bearing nitro group. The reactions of the substrates bearing electron-donating groups (-CH_3, -OCH_3, -$C(CH_3)_3$ on the phenyl ring (R^1) proceeded smoothly to give the corresponding products in 43-92% yields (Table 2, **2b**-**2e**). In addition, the substrates bearing halogen can also be transformed into desired products (Table 2, **2f**-**2h**). And the reaction of **1i** bearing nitro group, a strong electron-withdrawing group, didn't afford product. Investigating the substituent effect of the phenyl ring (R^2), similar results emerged (Table 2, **2j**-**2m**). Remarkably, this strategy was further applied to

heterocyclic substrates to synthesize corresponding product. 4-(nitromethyl)-2-(thiophen-3-yl)-4*H*-chromene was successfully obtained in 52% yield (Table 2, **2n**). However, the reaction with pyridyl didn't deliver target product (Table 2, **2o**). This might be caused by alkaline pyridine ring.

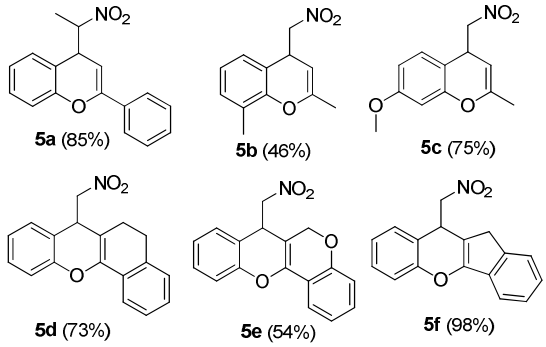
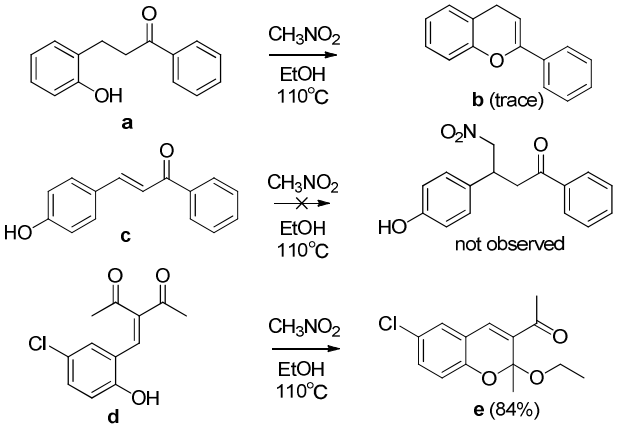


Fig. 2 Further investigation on the scope of the novel reaction

Further investigation on the scope indicated that nitro ethane could be suitable for this reaction system (Fig. 2, **5a**). In addition, substituted (E)-4-(2-hydroxyphenyl)but-3-en-2-one could react smoothly with nitro methane in middle yield (Fig. 2, **5b, 5c**).

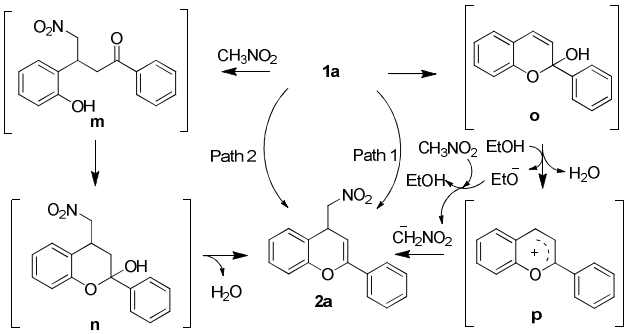
What's more, we looked forward to applying this practical procedure to synthesis chromeno[4,3-b]chromene structure and its analogues (Fig. 2, **5d-5f**). To our delight, chromeno[4,3-b]chromene could be obtained in 54% yield via this strategy and The other two tetracyclic heterocompounds both were prepared in good yields.



Scheme 2 Control experiments

To understand the mechanism, we carried out several control experiments shown in Scheme 2. Because the possible vital intermediate 3-(2-hydroxyphenyl)-4-nitro-1-phenylbutan-1-one (Scheme 3, **m**) can't be obtained, 3-(2-hydroxyphenyl)-1-phenylpropan-1-one (Scheme 2, **a**) was employed instead of that possible intermediate and an unexpected result emerged. Even increasing temperature to 120°C, trace cyclized product (Scheme 2, **b**) was observed. On the other hand, (E)-3-(4-hydroxyphenyl)-1-phenylprop-2-en-1-one (Scheme 2, **c**) as an analogue was tested, and no Michael addition product was observed. So we were glad to accept that Michael addition did not occur in the reaction. Based on previous work, trans-2-hydroxychalcone can be transformed into flavylium ion by acids.[12] Due to high temperature and protonic EtOH, there may be a similar process in this reaction. Moreover, during exploring the substrate scope, 1-(6-chloro-2-ethoxy-2-methyl-2H-chromen-3-yl)ethanone (Scheme 2, **e**) was obtained through intramolecular cyclization under standard conditions and it didn't further react with CH_3NO_2. This might be owed to the acetyl which can stabilize the intermediate through its' electronic effect.

Accordingly, using the process for preparing **2a** as model, a probable mechanism was proposed (Scheme 3). Intramolecular cyclization of trans-2-hydroxychalcone proceed firstly (Scheme 3, path 1). Then, the generation of cationic species **P** results in the formation of a water molecule and ethoxide ion which can take a proton from CH_3NO_2 to generate the carbanion. This carbanion can reacts with **P** to give the desired product. Another way is via intramolecular cyclization after Michael addition (Scheme 3, path 2). But from the observation of control experiments, the first way forming **2a** was more receivable.



Scheme 3 Plausible mechanism

Conclusions

In summary, this paper described a simple and practical method for the synthesis of 4-nitromethyl-chromenes under catalyst-free and non-toxic solvent conditions via tandem reaction. Most 4-nitromethyl-chromenes are prepared in acceptable to good yields. And an important structure, chromeno[4,3-b]chromene core was easily obtained through this strategy. Further experiments are underway in our laboratory.

Acknowledgements

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