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Catalyst-Free Domino Reaction of 1-Acryloyl-1-*N*-arylcarbamylcyclopropanes with Amines: One-Pot Approach to 2,3,6,7-Tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-ones

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Abstract: A facile one-pot, catalyst-free reaction has been developed for the synthesis of 2,3,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-ones from readily available 1-acryloyl-1-*N*-arylcarbamylcyclopropanes and amines using a domino ring-opening/cyclization/aza-addition sequence.

Keywords: catalyst-free conditions; domino reactions; doubly activated cyclopropane; ring-opening; 2,3,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-ones

Introduction

Pyrrolo[3,2-*c*]pyridinone derivatives possess a wide variety of interesting biological activities, and compounds belonging to this class have been reported to behave as CK1γ inhibitors,[1] NAMPT inhibitors,[2] PLK1 inhibitors,[3] Cdc7 kinase inhibitors,[4] ATP-competitive MK2 inhibitors,[5] DP receptor antagonists[6] and CB_2 agonists[7] (Figure 1). Pyrrolo[3,2-*c*]pyridinone derivatives are generally prepared from preformed pyrroles or pyridines.[6,8] However, most of the methods currently available for the synthesis of these compounds require multistep procedures to generate the pyrrole and pyridine rings individually, which can have an adverse impact on their overall efficiency and practicality. In 2004, Xi et al.[9] reported the development of a multi-component domino reaction for the preparation of pyrrolo[3,2-*c*]pyridines, which involved the reaction of Si-tethered diynes with three different organonitriles in the presence of a zirconocene species. In this process, the pyrrolo[3,2-*c*]pyridine products were formed by the cleavage of one of the three C≡N triple bonds and two Si–C bonds. Despite these advances, the development of a one-pot approach for the construction of pyrrolo[3,2-*c*]pyridines in an environmentally benign and economically viable manner with broad substrate scope remains largely unrealized. Herein, we report the results of our recent efforts towards the development of a novel one-pot approach for the synthesis of 2,3,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one derivatives *via* a domino ring-opening/cyclization/aza-addition reaction sequence involving doubly activated cyclopropanes and amines without the need for a catalyst or additives.

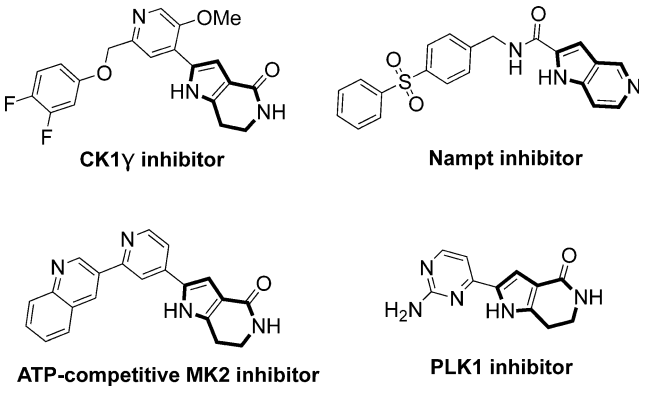
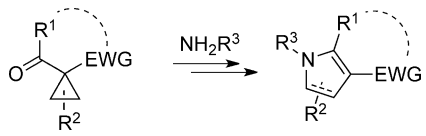


Figure 1. Representative pyrrolo[3,2-*c*]pyridinones possessing bioactivities.

Donor–acceptor (D–A) cyclopropanes possess an inherent strain energy (27.5 kcal mol^{-1}) that allows them to react as 1,3-dipolar synthons. These compounds are particularly suitable for synthetic applications because of the electronic effects of their substituents, which not only activate the cyclopropanes to

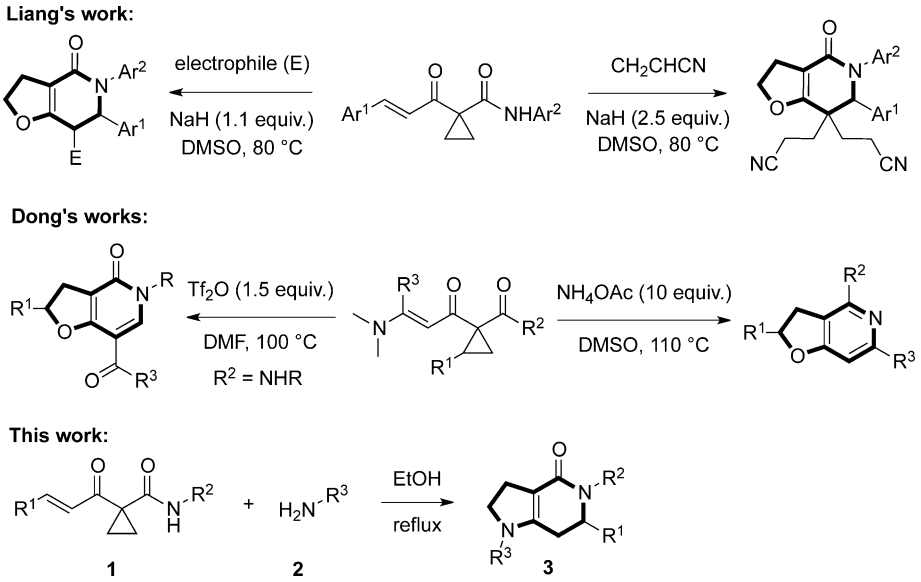


Scheme 1. The synthesis of pyrroles using doubly activated cyclopropanes.

ring-opening reactions but also provide versatile functional groups in the resulting products.[10] Furthermore, the cyclopropane moieties of doubly activated cyclopropanes are more electrophilic than the corresponding singularly activated systems because of the electron-withdrawing effects of the two acceptors.[11] The results of several studies published in the literature have demonstrated that doubly activated 1-alkenoyl-1-carbamoylcyclopropane derivatives are an important class of cyclopropanes, which play an important role in the construction of pyrroles[12] and *N*,*O*-bicyclic dihydrofuro[3,2-*c*]pyridine skeletons (Scheme 1 and Scheme 2). In 2011, Liang et al.[11b] reported the development of an efficient new route for the construction of furo[3,2-*c*]pyridinone skeletons from readily available 1-cinnamoylcyclopropanecarboxamides in a single step. Using 1-cinnamoylcyclopropanecarboxamides generated *in situ* from the reaction of 1-acetylcyclopropanecarboxamides with aldehydes, the same group successfully extended this methodology to achieve the construction of multi-substituted furo[3,2-*c*]-pyridinones *via* a multi-component domino reaction (Scheme 2).[11c] Dong's group developed two new routes for the synthesis of substituted dihydrofuro[3,2-*c*]pyridines, which were reported in 2011 and 2012. The first of these routes involved the Vilsmeier-type reaction of 1-aminoalkenoyl-1-carbamoylcyclopropanes in the presence of Tf_2O in DMF,[11d] whereas the second route used 1-carbamoyl-1-dimethylaminoalkenoylcyclopropanes as the starting materials and ammonium acetate (NH_4OAc) as the ammonia source (Scheme 2).[11e] In 2007, our group established an approach for the divergent construction of γ-iminolactones, dihydroquinolin-2-ones and γ-lactams using three different types of Lewis acid. Notably, all three of these products started from β-hydroxymethylcyclopropanylamides, which were themselves derived from 1-acryloyl-1-*N*-arylcarbamylcyclopropanes *via* a reduction reaction in the presence of $NaBH_4$.[13] Based on a combination of research from the literature[11c–e,12a–h] and our related research towards the synthesis of nitrogen-containing compounds from doubly activated cyclopropane precursors,[11a,12h,14] it was envisioned that novel *N*,*N*-bicyclic 1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one derivatives **3** could be prepared from the reaction of doubly activated cyclopropanes **1** with amines **2** (Scheme 2).

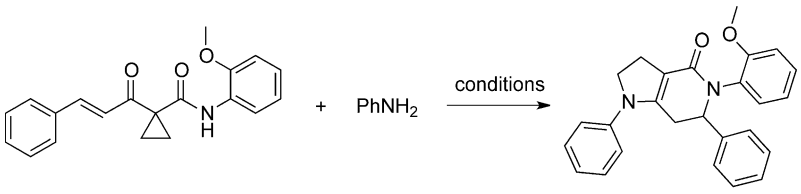
Results and Discussion

With this in mind, 1-cinnamoyl-1-*N*-(2-methoxyphenyl)carbamylcyclopropane (**1a**) was selected as a model substrate and reacted with aniline (**2a**) to optimize the reaction conditions, and the key results of these optimization experiments are summarized in Table 1. Two different bases, including NaOH and pyridine, were initially evaluated for the reaction of **1a** (1.0 mmol) with **2a** (1.2 mmol). The results of these experiments revealed that both bases failed to afford a high yield of the desired compound **3a** when the reaction was conducted in an alcohol solvent in a sealed tube at reflux, although they did allow for a significant reduction in the reaction time, and the simultaneous



Scheme 2. The synthesis of dihydrofuro[3,2-*c*]pyridines using doubly activated cyclopropanes.

Table 1. Survey of the reaction conditions.[a]



1a **2a** **3a**

Entry	Base (equiv)	Solvent	Temperature [°C]	Time [days]	Yield [%][b]
1	NaOH (0.01)	EtOH	reflux	1.5	58
2	NaOH (0.1)	EtOH	reflux	0.75	34
3[c]	NaOH (0.1)	MeOH	reflux	0.2	14
4	pyridine (0.1)	EtOH	reflux	0.7	46
5	–	EtOH	reflux	3.5	89
6[d]	–	EtOH	reflux	5	89
7	–	*i*-PrOH	reflux	3.5	83
8	–	glycol	110	0.8	58

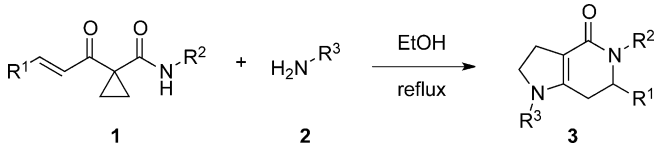
[a] Unless otherwise indicated, all of these reactions were carried out with **1a** (1.0 mmol) and **2a** (1.2 mmol) in solvent (3.0 mL) in a sealed tube.
[b] Isolated yield.
[c] 26% **1a** was recovered.
[d] Reaction was performed under an N_2 atmosphere.

formation of a complex black mixture (Table 1, entries 1–4 *vs.* 5).[15] However, the yield of **3a** was increased significantly to 89% when a mixture of **1a** and **2a** was heated at reflux for 3.5 days in EtOH (3 mL) in a sealed tube (Table 1, entry 5). Further increasing the reaction time, however, did not lead to further increase in the yield of **3a**, even when the reaction was carried out under an atmosphere of nitrogen to prevent the oxidation of the amine (Table 1, entry 6). Several other alcohol solvents, including isopropyl alcohol and glycol were also tested in the reaction, but performed much less effectively than EtOH (Table 1, entries 7 and 8). It is well known that Lewis acids can be beneficial for the ring-opening reaction of D–A cyclopropanes.[10a,e,11a,16] With this in mind, several Lewis acids, including anhydrous $FeCl_3$, $FeCl_3{\cdot}6H_2O$, anhydrous $SnCl_4$, $SnCl_4{\cdot}5H_2O$, $ZnCl_2$, $BF_3{\cdot}Et_2O$ and $TiCl_4$, were evaluated in terms of their ability to catalyze the current reaction. The results of these screening experiments revealed that the addition of a Lewis acid had an adverse impact on the yield of **3a**, with almost all of these reactions resulting in formation of a complex mixture.[17]

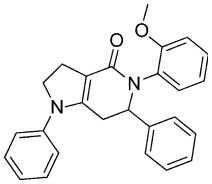
The optimal conditions for this transformation were finally identified as heating a mixture of **1** (1.0 mmol) and **2** (1.2 mmol) in EtOH at reflux in a sealed tube (Table 1, entry 5). With the optimized conditions in hand, we proceeded to explore the scope and limitations of this reaction using a range of doubly activated cyclopropanes **1** and substituted aniline derivatives **2**. The results of these experiments are summarized in Table 2.

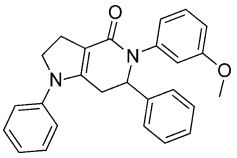
The influence of the R^2 substituent on the amide of the cyclopropane substrate **1** was evaluated in terms of its impact on the outcome on this domino reaction. The results of these experiments revealed that the electronic nature (i.e., electron-donating or electron-withdrawing) and the position (i.e., *ortho*-, *meta*- or *para*-position) of the substituents (e.g., OMe, Cl and CO_2Et) on the phenyl ring had very little impact on the yields of the corresponding products **3a–h** (80–94%). It is noteworthy that **1i** (R^2 = benzyl group) reacted smoothly to give the desired compound **3i** in 60% yield. Unfortunately, however, it was not possible to synthesize starting material **2j** or any of its analogues (such as R^2 = methyl, isopropyl and cyclohexyl) because of limitations posed by the existing synthetic methods.[18] For this reason, it was not possible to assess the universal applicability of this approach with this type of compound. These scoping experiments showed that a variety of aryl groups could be tolerated at the R^1 position of the cyclopropane starting material, with the corresponding products **3k–s** being isolated in 64–90% yields, regardless of the electronic nature and the position of the substituents on the phenyl ring. Changes to the nature of the amine **2** (R^3) were also well tolerated, with 4-methoxyaniline and ethyl 4-aminobenzoate both reacting smoothly to give the corresponding products **3t** and **3u** in 70% yield, respectively. It is noteworthy, however, that the reaction time required by the former of these two anilines was much shorter than that required by the latter. Interestingly, the reaction afforded **3v** in 80% yield after 2 days when benzylamine was employed as the amine in the reaction. However, the use of aliphatic amines, such as *tert*-butylamine and cyclohexylamine resulted in much lower yields of the desired fused cyclic compounds **3w** and **3x** in 17% and 34% yields, respectively.

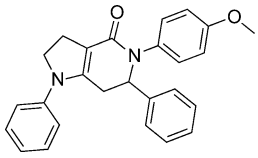
Table 2. Evaluation of the reaction scope.[a,b]

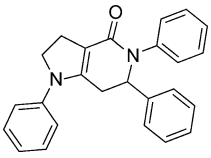


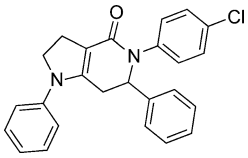
1 2 3

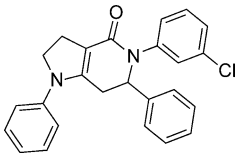

3a: 3.5 d, 89%

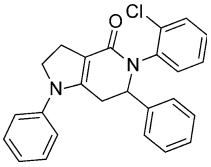

3b: 2 d, 83%

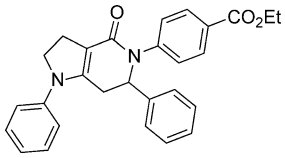

3c: 3 d, 94%

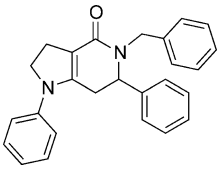

3d: 3 d, 91%

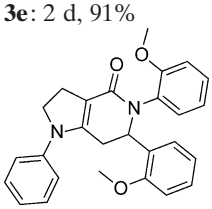

3e: 2 d, 91%

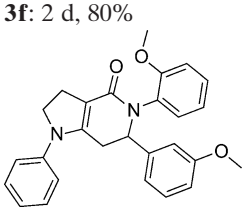

3f: 2 d, 80%

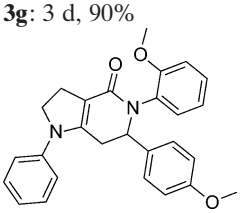

3g: 3 d, 90%

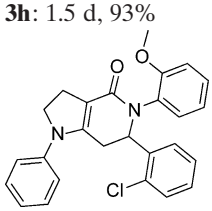

3h: 1.5 d, 93%

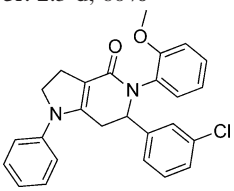

3i: 2.5 d, 60%[c]

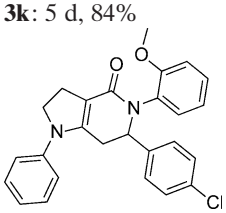

3k: 5 d, 84%

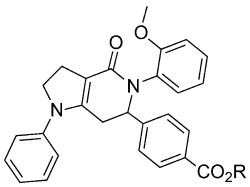

3l: 4 d, 90%

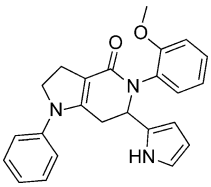

3m: 5.5 d, 87%

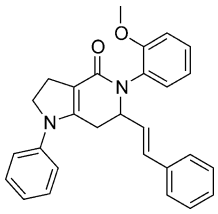

3n: 6 d, 84%

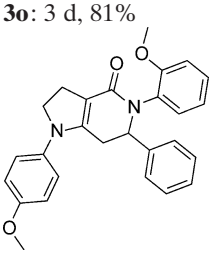

3o: 3 d, 81%

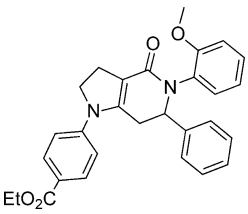

3p: 6.5 d, 75%

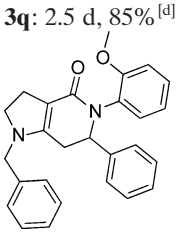

3q: 2.5 d, 85%[d]

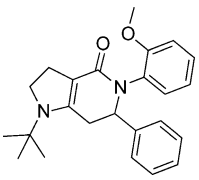

3r: 2 d, 64%[e]

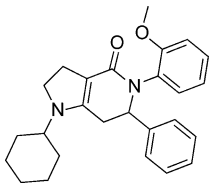

3s: 5 d, 89%


3t: 2 d, 70%


3u: 9 d, 70%[f]

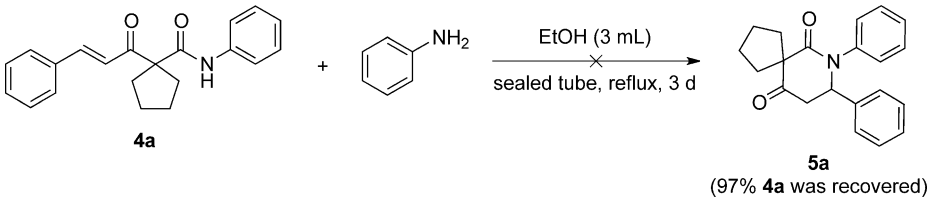

3v: 2 d, 80%


3w: 4 d, 17%[c]

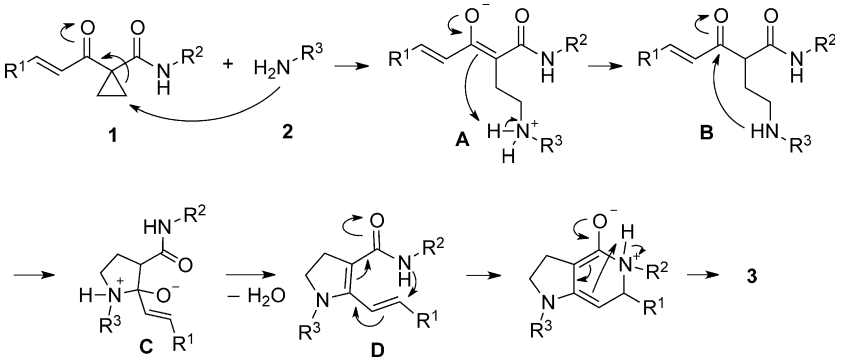

3x: 2.5 d, 34%[c]

[a] Unless otherwise indicated, all of these reactions were carried out with **1** (1.0 mmol) and **2** (1.2 mmol) in EtOH (3.0 mL) at reflux.
[b] Isolated yield.
[c] Formed as part of a complex mixture.
[d] The reaction was performed with the methyl formate substitute **1q**, with R = Et or Me in the final product **3q**, and the ratio of the two compounds was approximately 2:1, as determined by ^{1}H NMR.
[e] 22% **1r** was recovered and the yield of **3r** could not be increased by prolonging the reaction time.
[f] 26% **1u** was recovered and the yield of **3u** could not be increased by prolonging the reaction time.

A controlled experiment was conducted to get a deeper understanding of the mechanism of this domino reaction. Compound **4a** was reacted with aniline under the standard reaction conditions for 3 days. The results of this experiment revealed that the desired compound **5a** was not isolated following the quenching of the reaction, and that compound **4a** was recovered instead in 97% yield (Scheme 3). Taken together with the results of similar studies from the literature, this result allowed us to propose a possible



Scheme 3. A controlled experiment.



Scheme 4. Proposed mechanism.

mechanism for the current reaction, which is shown in Scheme 4.[11c–e,12a] According to this mechanism, amine **2** would initially attack the doubly activated cyclopropane **1** to generate the quaternary ammonium analogue **A**, which would undergo a cyclization reaction through intermediate **B** to give the multi-substituted dihydropyrrole **D**.[12a] Finally, pyrrole **D** would give the 1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one **3** *via* an intramolecular aza-addition reaction.[19]

Conclusions

In summary, a facile and efficient, one-pot, catalyst-free domino reaction has been developed for the synthesis of 2,3,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one derivatives from doubly activated cyclopropanes and amines. This domino procedure involves a contiguous bond cleavage/formation process. Furthermore, this protocol uses readily available starting materials, has a broad substrate scope and provides good to excellent yields of the desired products with dense and flexible substitution patterns. The products themselves could be used as important building blocks for the synthesis of complex products.[20]

Experimental Section

Typical Procedure for the Synthesis of 3 (3a as an Example)

To a solution of 1-cinnamoyl-*N*-(2-methoxyphenyl) cyclopropanecarboxamide (**1a**) (321 mg, 1.0 mmol) in EtOH (4.0 mL) at room temperature was added aniline (**2a**) (0.109 mL, 1.2 mmol) in a sealed tube at reflux. Then the mixture was well stirred under reflux for 3.5 days (the whole process was closely monitored by TLC). After cooling off, the mixture was added water (5.0 mL), and the aqueous phase was extracted with ethyl acetate (20 mL × 3). The combined organic layer was dried over sodium sulfate. The solvent was evaporated, and the residue was purified by a short flash silica gel column chromatography (eluent: ethyl acetate/petroleum ether = 4/5) to give 5-(2-methoxyphenyl)-1,6-diphenyl-2,3,6,7-tetrahydro-1*H*-pyrrolo[3,2-*c*]pyridin-4(5*H*)-one (**3a**) as yellow solid; yield: 352.6 mg (89%).

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