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Rapid Synthesis of 3-Amino Isocoumarin Derivatives from Ynamides

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A novel and efficient fast synthesis of 3-amino isocoumarins in good to excellent yields is reported. These interesting scaffolds can be obtained either in a single step from readily available ynamides or in a two-step sequence from the corresponding alkynyl bromide after C-N cross-coupling. This protocol, which only requires Brönsted or Lewis acid as promoter, offers an alternative approach toward 3-substituted isocoumarins in smooth and fast conditions.

Introduction

Lactones encompass a large group of many compounds of biological interest as drugs and biological agents of which isocoumarin is a prominent member. This six-membered lactone derivative is a prevalent structural unit of compounds that exhibit a wide range of potential therapeutic applications including antifungal, antimicrobial, anticancer, antiallergic, anti-inflammatory, anti-HIV, and anticoagulant activities (Figure 1).[1] Among them, 3-substituted variants are significant and in particular, 3-amino isocoumarins are used as safe therapeutic agents for lowering blood cholesterol and as drugs for arteriosclerosis and the like.[2] A plethora of methods are available for the construction of isocoumarin rings involving transition metal-catalyzed coupling, insertion, cyclization and bond cleavage reactions.[3] However, most of the reported procedures have drawbacks, which include the use of expensive catalysts, the need for complex starting materials, and/or drastic conditions. Only two references have reported the synthesis of 3-amino substituted isocoumarins from ynamides: Chang's work described the Pd catalyzed annulation between 2-iodoaromatic acids and alkyl- or aryl-terminated N-sulfonyl substituted ynamides[4] leading to 3,4-disubstituted isocoumarins (scheme 1a); Peng and An[5] reported the synthesis of 3-amino 4-aryl substituted isocoumarin derivatives by a rhodium-catalyzed oxygen mediated annulation (scheme 1b). However, these strategies leading to C3, C4 disubstituted products are not ideal and to the best of our knowledge, no studies have investigated the synthesis from ynamides of 3-amino substituted isocoumarin derivatives with a free 4-position affording thus the possibility to perform further functionalization on this site. Therefore, in view of these limitations, the development of an efficient strategy for their synthesis is highly desirable.

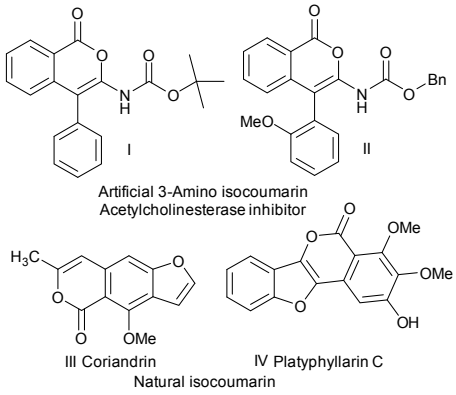

Fig 1. Typical examples of isocoumarins

Results and discussion

Based on this manifold, and to pursue our objective in developing new reactions by employing functionalized ynamides,[6,7] we envisioned that a cycloisomerization reaction can occur from (het)aryl ynamides, bearing an ester function at the *ortho* position, as starting compounds (scheme 1c). While a variety of π-conjugated and benzofused aromatic rings have been prepared from ynamides via cyclization and/or addition reactions induced by Brønsted or Lewis acid,[8] the cycloisomerization of *ortho*-ynamidyl benzoate to 3-amino isocoumarin has never been reported so far. Consequently, we initiated our study by preparing a range of original (het)aryl ynamides **5** starting from readily available *ortho*-halo-substituted benzoate esters **1** with the introduction of the alkyne functional group *via* a Sonogashira cross-coupling reaction. After removal of the trimethylsilyl protecting group, a known two-step method involving alkyne halogenation leading to **4** followed by copper

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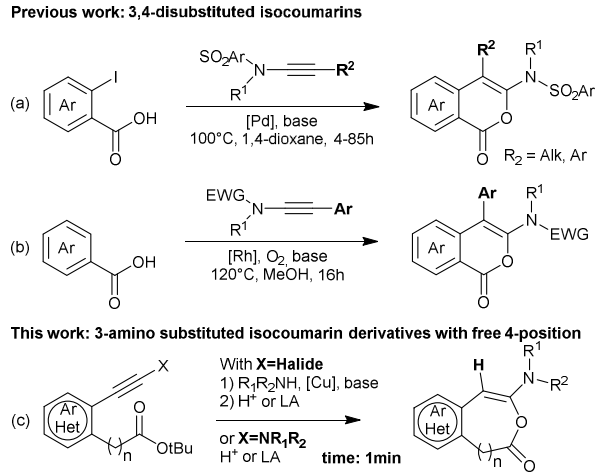
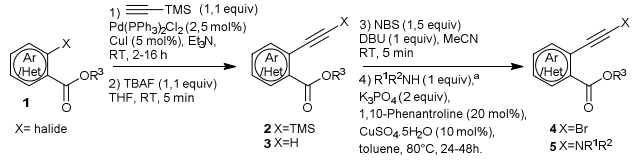
catalyzed C-N cross-coupling was accomplished (see supporting information).[6,9] Gratifyingly, starting from ynamide **5aa**, chosen as a model substrate, upon the use of TFA as a Brønsted acid in stoichiometric amount at room temperature, we found that an ultra-fast reaction took place leading efficiently to the corresponding 3-amino isocoumarin **6aa** (table 1).



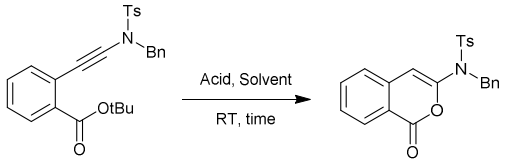
Scheme 1. Background for the study



Scheme 2. General strategy for the synthesis of *ortho*-ynamidyl benzoate **5**. [a]The reaction was carried out with 1 equivalent of R^1R^2NH and 1.1 equivalent of alkynyl bromide **4**.

The reaction proceeded with high selectivity and in nearly quantitative yield in less than one minute (entries 1-5).[10] No trace of isobenzofuranone derivative resulting from a 5-exo-trig cyclization was observed. It is worth noting that keteniminium ions have never been used in the cycloisomerization reaction for isocoumarin synthesis.[11] Besides, this strategy can be considered as a significant achievement in the synthesis of 3-substituted isocoumarin derivatives with a free 4-position because of its performance, simplicity, and low cost. It is also worth mentioning that the annulation was also successfully completed using triflic acid with similar results (entry 3), or in dichloromethane within two weeks without any additional acid (entry 4);[12] however degradation was observed using aqueous hydrochloric acid (entry 6). The annulation can also be advantageously performed in dimethyl carbonate, a green alternative solvent (entry 5). Furthermore, excellent yields were obtained using Lewis acid in catalytic amount. Soft carbophilic Lewis acid such as gold chloride or silver triflate was effective, leading to completion of the reaction with high yield in a very short time (entries 7-9). A lower yield was obtained using aluminium chloride or copper salts (entries 10-12). The ease of implementation, the smooth conditions and the good yields observed suggest that this strategy can be advantageously valorized as it constitutes a powerful, selective and atom-economic strategy to achieve the synthesis of various 3-mono substituted isocoumarins. These encouraging results prompted us to investigate the reaction in more detail. A set of *ortho*-ynamidyl benzoate **5**, readily prepared from ortho-halo-substituted benzoate esters **1** (scheme 2), was studied using optimized acidic conditions based on the use of a stoichiometric amount of trifluoroacetic acid or catalytic Lewis acid, namely silver triflate (scheme 3).

Table 1. Optimization studies of the cycloisomerization of ortho-ynamidyl benzoate **5** to 3-amino isocoumarin **6**.[a,b]



Entry	Acid	Solvent	Time[c]	Yield (%)
1	TFA (1 equiv)	CH_2Cl_2	1min	95
2	TFA (0.5 equiv)	CH_2Cl_2	1min	47
3	TfOH (1 equiv)	CH_2Cl_2	1min	95
4	No acid	CH_2Cl_2	2 weeks	100[(d)]
5	TFA (1 equiv)	DMC	1 min	90
6	HCl (6 M) (1 equiv.)	CH_2Cl_2	1min	degradation
7	AgOTf (5 mol %)	CH_2Cl_2	1min	96
8	AgOTf (5 mol %)	DCE	1min	96
9	$AuCl_3$ (5 mol %)	DCE	1min	96
10	$AlCl_3$ (10 mol %)	DCE	5min	88
11	$Cu(OTf)_2$ (10 mol %)	DCE	1 h	72
12	CuI (10 mol %)	DCE	1h	traces

[a]Isolated yield. [b]Reaction conditions: Ynamide **5aa** (0,2 mmol), solvent (2 mL). [c]The reaction was monitored by TLC. [d]^{1}H-NMR yield. DMC = Dimethyl carbonate; DCE = 1,2-dichloroethane.

Cycloisomerization under both stoichiometric and catalytic conditions proceeded smoothly at room temperature leading to the attempted 3-amino-substituted isocoumarin **6** in a very short time (1 min) with high yields. A variety of protecting groups on the starting ynamide **5** were found to be suitable including sulfonyl,

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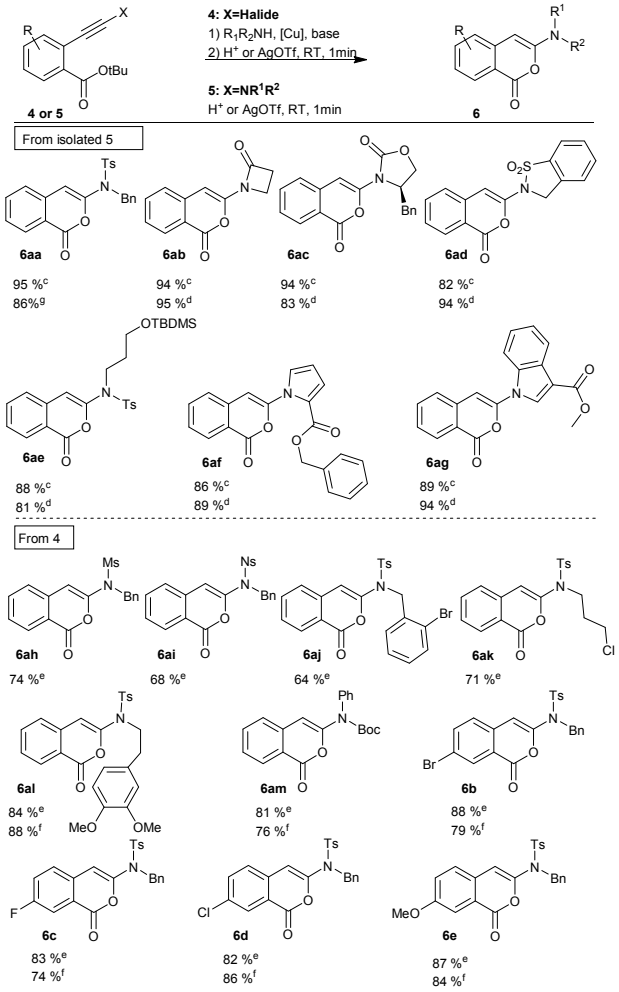
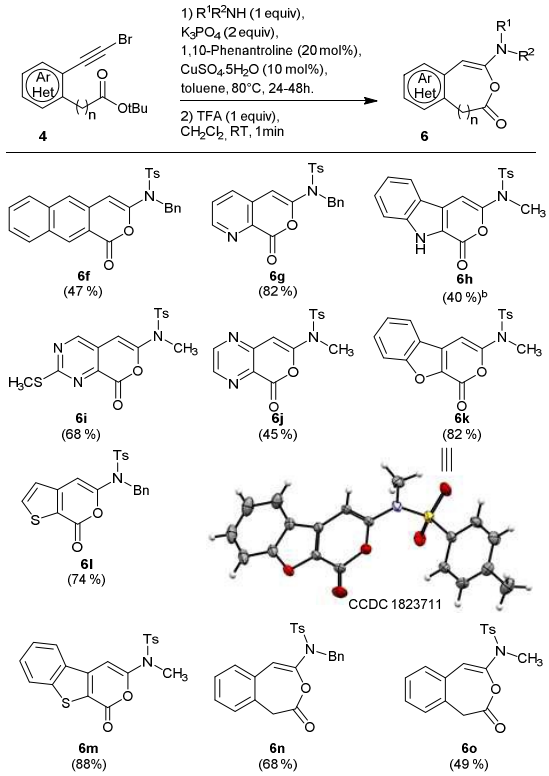
amide or carbamate groups. However, it is worth noting that depending on the nature of the chain present on the nitrogen atom of the ynamide **5**, the copper C-N catalyzed reaction and the acid mediated cycloisomerization were performed either in a two-step (**6aa-6ag**) or a one-step sequence (**6ah-6e**). *N*-Sulfonyl (**5ah-al**, **5b-e**) or *N*-Boc ynamides (**5am**) were not stable enough to be isolated as pure compounds, and a spontaneous cycloisomerization to 3-amino isocoumarins **6** occurred; the crude mixture resulting from the C-N coupling was then directly submitted to acidic conditions leading to the attempted compounds **6ah-6e** with good yields. This result can be explained by the slightly lower stability observed for the latter in the case of the corresponding keteniminium ion **I** and/or the intermediate II/III (scheme 5). Pyrrole- (**6af**) or indole-derived (**6ag**) ynamide also gave good results, demonstrating the broad spectrum of potent applications in medicinal chemistry.



[a]Isolated yield. [b]Reaction conditions: 1) *Cu-catalyzed C-N cross-coupling*: R^1R^2NH (1 equiv), K_3PO_4 (2 equiv), 1,10-Phenantroline (20 mol%), $CuSO_4.5H_2O$ (10 mol%), toluene, 80°C, 24h-48h. 2) *Acid-mediated cycloisomerization*: TFA (1 equiv) or AgOTf (5 mol%), ynamide (0.2 mmol), CH_2Cl_2, RT, 1 min. [c]From isolated **5** using TFA (1 equiv). [d] From isolated **5** using AgOTf (5 mol%). [e] From **4** using TFA (1 equiv). [f] From **4** using AgOTf (5 mol%). [g]Reaction carried out from the corresponding benzyl ester compound.

Scheme 3. Fast synthesis of mono-substituted 3-amino isocoumarins **6**[a,b]

Encouraged by this successful acid-mediated cycloisomerization of ynamides, we then tested the possibility of increasing the level of structural complexity by introducing various chains on the nitrogen atom (**6aj-al**) that could be used for further functionalization. Different substitution patterns on the aryl ring of *ortho*-ynamidyl benzoate **5** were also well tolerated under the reaction conditions, including electron-withdrawing (**6b-d**) or electron-donating methoxy groups (**6e**). Importantly, the cyclization was not limited to the small scale used for the scope and limitation studies as it was also conveniently performed on a 2.7 mmol scale from **4b** in 88% yield in a two-step sequence using a stoichiometric amount of TFA. Pivotal to our synthetic strategy was the possible introduction of molecular diversity early into the route depending on the nature of starting compounds and the very short reaction time.



[a]Isolated yields. [b]Completion of the reaction in 30 min after addition of TFA (3 equiv).

Scheme 4. Acid mediated cycloisomerization from *ortho*-ynamidyl (het)aryl ester[a]

Hence, given the prevalence of heterocycles in medicinal chemistry, we were pleased to observe that the desired cycloisomerization process could straightforwardly be extended to various ynamidyl hetaryl derivatives (scheme 4). Various heteroaryl motifs were suitable in this reaction, which only required trifluoroacetic acid as promoter, and afforded an efficient entry to original structurally diverse series of original heteroaryl-fused dihydro-2H-pyran-2-ones **6f-6m**.[13] Indole derivative **6h** required 30 minutes for completion. The

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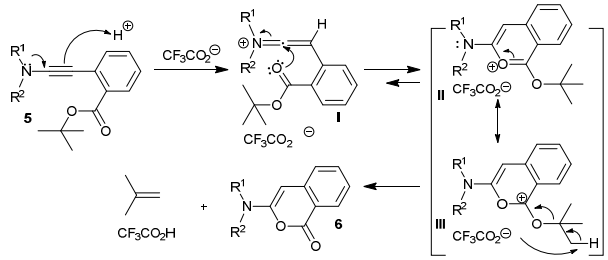
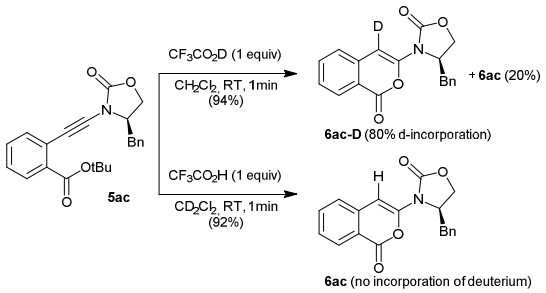
structure of **6k** was confirmed by single-crystal X-ray diffraction.[14] The preparation of 4-oxo-4,5-dihydro-3-benzoxepine **6n-o** was carried out from the corresponding not isolated *tert*-butyl acetate ester derivatives **5n-o** (n=1) *via* a 7-endo-trig cyclization in good to moderate yields. Unfortunately, a complex mixture was observed from the corresponding *tert*-butyl propanoate ester derivative (n=2) to yield the corresponding eight-membered ring compound.

Having demonstrated the efficiency of our original cycloisomerization reaction starting from *ortho*-ynamidyl (het)aryl ester, we next focused on gaining insight into its mechanism. The reaction was presumably initiated by protonation of the electron-rich alkyne of the starting ynamide **5**, due to the electron-donating ability of the nitrogen, yielding a highly reactive keteniminium ion **I** (scheme 5).[15] Then a 6-endo-trig cyclization may generate pyrylium salt **II** in resonance with the carbocationic form **III**. Trapping of the proton from the *tert*-butyl group by the released carboxylate can lead to the formation of the isocoumarin cycle **6**. Pyrylium salts **II** are predicted to be strain-free compounds whose energy decreases due to π-delocalization which explains why weakly nucleophilic counter-ions did not trap this intermediate.[16]



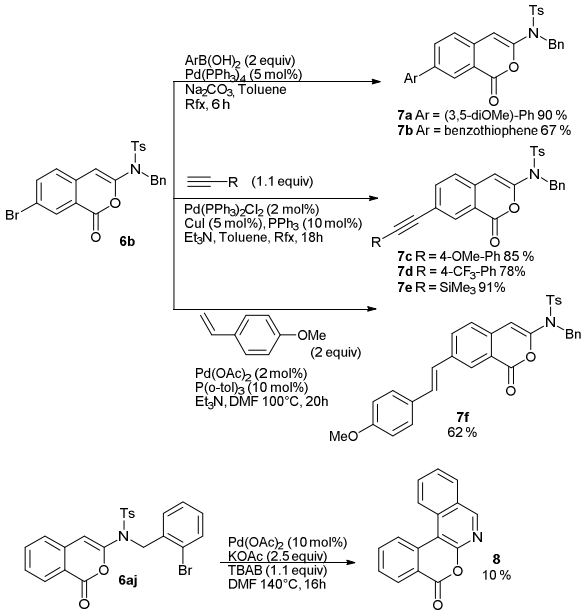
Scheme 5. Proposed mechanism

In addition, a series of experiments shown in scheme 6 were performed starting from deuterated acid or solvent. Upon treatment of **5ac** with one equivalent of CF_3CO_2D, the resulting 3-amino isocoumarin **6ac-D** was shown to incorporate a deuterium atom on the enamide in 80% yield which is coherent with the mechanism proposed above (scheme 5). The remaining **6ac** likely comes from protonation by non-deuterated TFA derived from a *tert*-butyl group proton carboxylate trap. The use of one equivalent of CF_3COOH in CD_2Cl_2 resulted in no incorporation of deuterium in 3-amino isocoumarin **6ac**, demonstrating first the role of the acid and second that this transformation is not solvent-dependent.



Scheme 6. Deuteration study

The resulting isocoumarins were also further diversified by derivatization of the bromine group (scheme 7). To include diverse functionalities, Sonogashira, Suzuki-Miyaura, and Heck reactions were applied to **6b**, leading to a diverse set of new 3-amino isocoumarins **7a-f** with good yields. In addition, 5H-isochromeno[3,4-c]isoquinolin-5-one **8** was isolated from **6aj**, albeit in low yield; along with the intramolecular Heck reaction, a concomitant removal of the *N*-Tosyl group was observed. This isoquinolinone derivative is found in many natural products and/or pharmacologically relevant therapeutic agents.[17]



[a]Isolated yields.

Scheme 7. Post-functionalization *via* Pd catalyzed cross-coupling reactions[a]

Conclusions

In summary, we have successfully developed an efficient method to synthesize original 3-amino isocoumarins and derivatives bearing a free 4-position using smooth and fast conditions with good yields. This process uses the readily accessible *ortho*-ynamidyl benzoate ester in presence of an acid promoter and can be successfully extended to the *ortho*-ynamidyl (het)aryl ester. We believe that this work represents an easy and straightforward access to a range of isocoumarins likely to find applications in medicinal chemistry.

Conflicts of interest

The authors declare no competing financial interest.

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