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Synthesis of 3-Substituted 2-Aminochromones via Sn(IV)-Promoted Annulation of Ynamides with 2-Methoxyaroyl Chlorides

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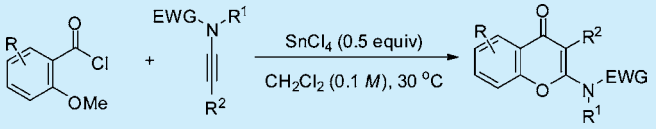
Supporting Information

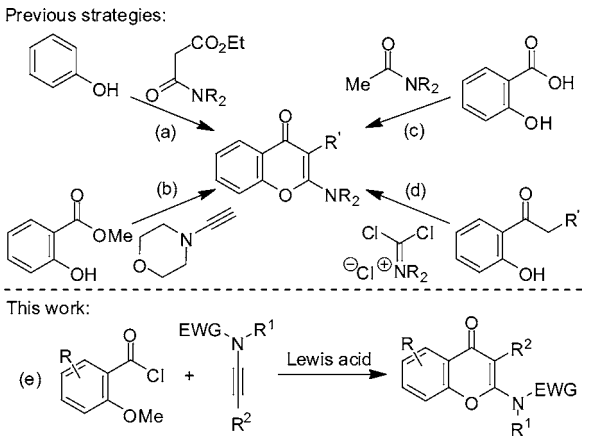
ABSTRACT: A Sn(IV)-promoted annulation reaction of ynamides is described for the efficient synthesis of 3-substituted 2-aminochromones under mild conditions. This novel method allows for a concomitant construction of C−C and C−O bonds between ynamides and 2-methoxyaroyl chlorides by a tandem Friedel−Crafts acylation/oxo-Michael addition/elimination strategy.



2-Aminochromones are the key structural units for pharmaceutical compounds, and this ring system has proven to be a privileged pharmacophore for use in the design of compounds with a diversity of pharmacological properties, such as antiplatelet activity,[1] antiproliferative activity,[2] the inhibition of some kinases,[3] and psychotropic activity.[4]

Although several approaches have been established for the construction of 2-aminochromones,[5] most of them suffer from serious disadvantages such as harsh conditions, low yields, and tedious workup or isolation procedures. In addition, preparation of 2-aminochromones in a one-pot manner is rarely reported in the literature (Scheme 1): Vilsmeier condensation of β-amido ester with phenol (path a)[5a,b] and the reaction of salicylic ester with morpholine ynamine under NEt_3 (path b)[5e] suffer from unacceptably low yields with narrow substrate scopes. Recently, Roma et al. developed a one-pot synthesis of 2-aminochromones starting from acetamides, salicylic acid, and phosphoryl chloride (path c),[5i] but the reaction conditions are harsh, and the only strategy for the construction of 3-substituted 2-aminochromones was reported by the Morris group via the reaction of related Lewis acid complexes of 2′-hydroxyphenones with phosgene iminium chloride (path d).[5h]

Scheme 1. One-Pot Synthesis of 2-Aminochromones[a]



[a]R′ = H in paths a−c; R′ = H, alkyl, aryl in path d.

Ynamides have become an important synthon that has been prominently featured in various synthetic transformations.[6−8] Fueled by preparative access that is efficient and atom-economical,[9,10] the field of ynamide chemistry has rapidly expanded. Various important cyclic systems such as indoles,[11] pyridines,[12] and 2-amidobenzofurans[13] were successfully synthesized from ynamides. Herein, we report a novel synthesis of 3-substituted 2-aminochromones via the annulation reaction of ynamides with 2-methoxyaroyl chlorides under mild conditions (path e). To the best of our knowledge, this annulation of ynamides involving an intermolecular Friedel−Crafts acylation of alkynes[14] followed by intramolecular oxo-Michael addition and elimination reaction has not been described previously.

The feasibility of this annulation reaction was first tested using 2-methoxybenzoyl chloride **1a** and ynamide **2a** (Table 1). No desired product was obtained in the absence of Lewis acid at 16 °C for 5 days with 43% starting material ynamide **2a** recovered (entry 1). Fortunately, we observed the β-chlorovinylogous amide **3a** (the relative stereochemistry of which was assigned using NOE experiments[15]) and 2-aminochromone **4a** under the catalyst ZnI_2 (entry 2). Success in achieving annulation product **4a** led us to examine the effects of reaction time, and we found that only **4a** was afforded when the reaction time was increased to 22.0 h (entry 4). The extent of reaction appears to be closely related to the reaction time used (entries 2−4). We then tried other Lewis acids. Compared with ZnI_2, bidentate Lewis acids $ZnBr_2$, $ZnCl_2$, $Zn(OTf)_2$, and $CuCl_2$ were poor promoters overall (entries 5−8), with $CuCl_2$ appearing to impede the reaction (entry 8), but fortunately, $SnCl_4$ led to **4a** in 94% yield (entry 9). Monodentate Lewis acids $AlCl_3$, $FeCl_3$, and $BF_3{\cdot}OEt_2$ could catalyze the reaction to

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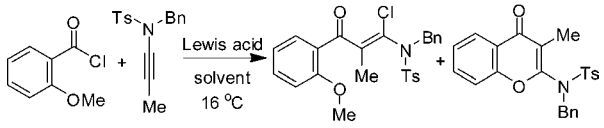
Table 1. Condition Optimization of Annulation Reaction



1a 2a 3a 4a

entry[a]	acid (equiv)	solvent	time (h)	yield of 3a[b] (%)	yield of 4a[b] (%)
1		CH_2Cl_2	120.0	0	0[c]
2	ZnI_2 (1.1)	CH_2Cl_2	0.5	18	48
3	ZnI_2 (1.1)	CH_2Cl_2	9.0	trace	79
4	ZnI_2 (1.1)	CH_2Cl_2	22.0	0	84
5	$ZnBr_2$ (1.1)	CH_2Cl_2	22.0	0	64
6	$ZnCl_2$ (1.1)	CH_2Cl_2	22.0	0	80
7	$Zn(OTf)_2$ (1.1)	CH_2Cl_2	22.0	24	46
8	$CuCl_2$ (1.1)	CH_2Cl_2	22.0	trace	trace
9	$SnCl_4$ (1.1)	CH_2Cl_2	22.0	0	94
10	$AlCl_3$ (1.1)	CH_2Cl_2	22.0	trace	51
11	$FeCl_3$ (1.1)	CH_2Cl_2	22.0	2	45
12	$BF_3{\cdot}OEt_2$ (1.1)	CH_2Cl_2	22.0	19	25
13	$SnCl_4$ (1.1)	toluene	22.0	0	83
14	$SnCl_4$ (1.1)	THF	22.0	trace	trace
15	$SnCl_4$ (1.1)	CH_3CN	22.0	0	36
16	$SnCl_4$ (1.1)	Et_2O	22.0	5	75
17	$SnCl_4$ (0.5)	CH_2Cl_2	22.0	0	91
18	$SnCl_4$ (0.2)	CH_2Cl_2	22.0	6	85
19[d]	$SnCl_4$ (0.5)	CH_2Cl_2	22.0	0	94

[a]Reactions were carried out using **1a** (0.22 mmol) and **2a** (0.20 mmol) with or without Lewis acid in solvent (2 mL) under N_2. [b]Isolated yields. [c]43% of **2a** was recovered. [d]Reaction was carried out at 30 °C.

give the annulation product **4a**, but with low yields (entries 9–12). Brønsted acids such as camphorsulfonic acid (CSA), etc. were attempted but not effective in promoting the annulation of **1a** to **4a**. With the optimized catalyst in hand, solvent screening then revealed that no improvement was made in toluene, THF, CH_3CN, and Et_2O (entries 13–16 vs entry 9). Lowering the amount of $SnCl_4$ to 0.2 equiv could also afford **4a** but with a lower yield (entries 17 and 18), and higher reaction temperature improved the yield to 94% when 0.5 equiv of $SnCl_4$ at 30 °C was used (entry 19). The relative stereochemistry was assigned using the single-crystal X-ray structure of **4a** (Figure 1).

With the optimized reaction conditions in hand, we next turned our attention to assessing the scope of this new annulation reaction (Scheme 2). Initially, ynamides with electron-donating and electron-withdrawing sulfonyl systems

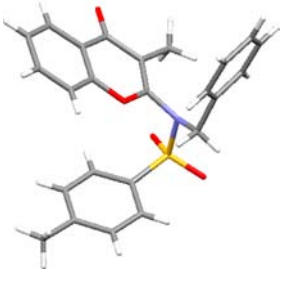
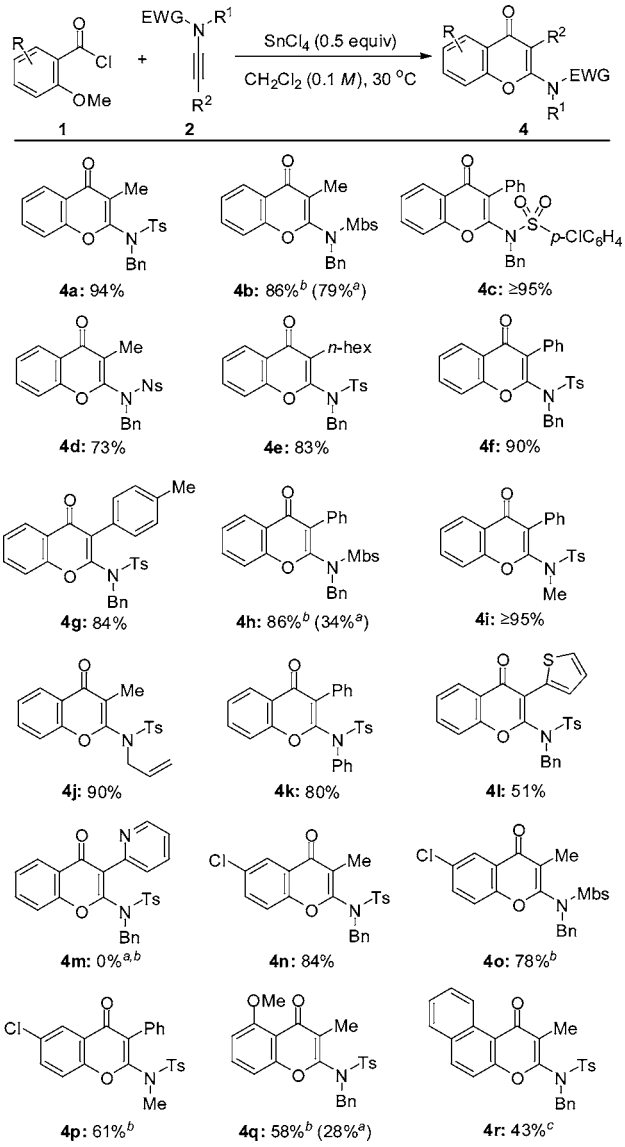


Figure 1. X-ray structure of **4a**.

Scheme 2. Synthesis of 3-Substituted 2-Aminochromones[a]



[a]Unless specified otherwise, reactions were carried out using **1** (0.22 mmol), **2** (0.20 mmol), and $SnCl_4$ (0.10 mmol) in CH_2Cl_2 (2 mL) under N_2. [b]0.5 equiv of ZnI_2 was used. [c]Compound **4r** was prepared from 2-ethoxy-1-naphthoyl chloride. Mbs = *p*-methoxybenzenesulfonyl; Ns = *p*-nitrobenzenesulfonyl.

were examined, the reaction proceeded smoothly to give excellent yields of the desired 2-aminochromones (**4a–c**), and a good yield was obtained for the formation of **4d**, most likely due to the low reactivity of *N*-Ns-substituted ynamide **2d**. We also found an interesting effect on the yield. Most notably, the *p*-anisyl substituent eroded the yield under the catalyst $SnCl_4$ compared with ZnI_2 (see **4b**). This loss of yield is likely due to $SnCl_4$ coordinating to the anisyl group, thereby significantly lowering the effect of the catalyst. A similar phenomenon also occurred for the formation of **4h** and **4q**. Other alkyl- and aryl-terminated ynamides or *N*-alkyl-, alkenyl-, and aryl-substituted ynamides also afforded the desired annulation products (**4e–k**) with high yields even for the bulkier *n*-hexyl- and phenyl-substituted ynamides. For heteroaromatic substituted ynamides, thienyl-terminated ynamide **2l** was also tolerated, giving **4l** in a moderate yield, but no desired product **4m** was isolated for

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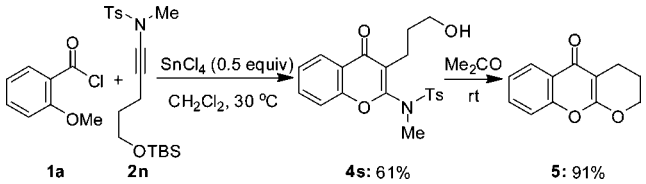
pyridyl-substituted ynamide **2m**. We then explored the electrophilic aryl annulation partner by testing 2-methoxybenzoyl chlorides with electron-withdrawing and electron-donating substitutions. We found that aryl groups displaying a chloride substituent could be transferred, giving good to high yields of the 2-aminochromones (**4n**−**p**), though the yields were slightly diminished compared with 2-methoxybenzoyl chloride, most likely due to the trivial decomposition of **4n**, **4o**, and **4p** in accord with the observed corresponding sulfonamides. 2-Dimethoxybenzoyl chloride **1q**, the reactivity of which is low, could also afford the desired product **4q** in moderate yield, and we were also pleased to find that this annulation was amenable to the synthesis of 2-aminochromone **4r** using 2-ethoxynaphthoyl chloride with ynamide **2a**.

We were especially excited by the discovery that ynamide **2n** bearing a terminal TBS ether moiety participated in the annulation with 2-aminochromone **4s** bearing a free hydroxyl group formed (Scheme 3). The resulting highly functionalized

Scheme 3. Annulation of Ynamide 2n Bearing Terminal TBS Ether and Synthesis of Chromone 5



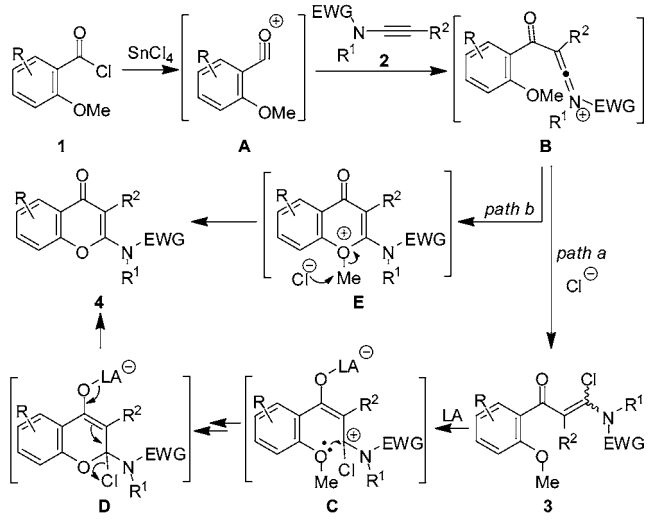
product offers many opportunities for chemical transformations. For example, 2-aminochromone **4s** was further transformed into tricyclic chromone **5** in 91% yield.

Possible pathways leading to the annulation product are proposed as shown in Scheme 4. The reaction would be initiated by formation of acylium ion **A** via the chloride anion released by 2-methoxybenzoyl chloride **1a** under the Lewis acid. Then electrophilic addition of the in situ generated acylium ion **A** with ynamide **2** gives the keteniminium ion **B**. The following nucleophilic attack of intermediate **B** has two possible pathways: trapping the keteniminium ion by the chloride anion affords β-chlorovinylogous amide **3** (path a), which undergoes oxo-Michael addition, demethylation, and dechlorination to furnish the final product **4**; the other optional path for the intermediate **B**, subsequent cyclization, occurs to afford intermediate **E** (path b), which is demethylated by a chloride anion to achieve the desired product **4**; and an inverse demand hetero-[4 + 2] cycloaddition pathway is also possible (path c): an α-acyl ketene **F** could be formed from acylium ion **A** and then undergo [4 + 2] cycloaddition with ynamide **2** to give 2-aminochromone **4**. However, we observed the β-chlorovinylogous amide **3** and obtained **3a** by chromatographic separation, which clearly implies that path a should be the necessary process, and paths b and c are the possible concomitant ways.

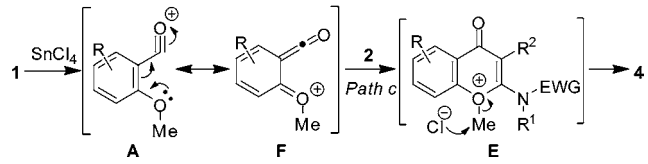
In conclusion, a novel and highly efficient Sn(IV)-promoted annulation reaction of ynamides with 2-methoxyaroyl chlorides has been developed. This reaction provides a general and straightforward way to construct 3-substituted 2-aminochromones under mild conditions and tolerates a wide range of functional groups. More importantly, this is the first example of acylium ion-induced annulation of ynamides by a tandem Friedel−Crafts acylation/oxo-Michael addition/elimination strategy. A plausible mechanism of the reaction has been

Scheme 4. Proposed Mechanism for the Annulation of Ynamides with 2-Methoxyaroyl Chlorides

Friedel-Crafts acylation initiating annulation pathways:



An α–acyl ketene [4+2] annulation pathway:



proposed. Further investigation for the construction of other heterocyclic and carbocyclic systems via this acylium ion induced annulation reaction is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02137.

Detailed experimental procedures (PDF)
^{1}H and selected ^{13}C NMR spectra (PDF)
X-ray crystallographic data of **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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