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Phase Transfer Reagent Promoted Tandem Ring-Opening and Ring-Closing Reactions of Unique 3-(1-Alkynyl) Chromones

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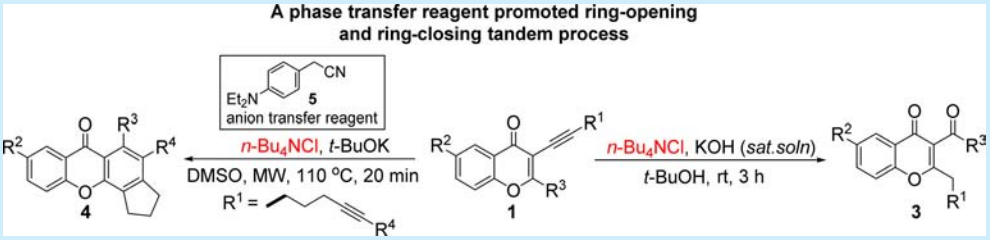
Supporting Information

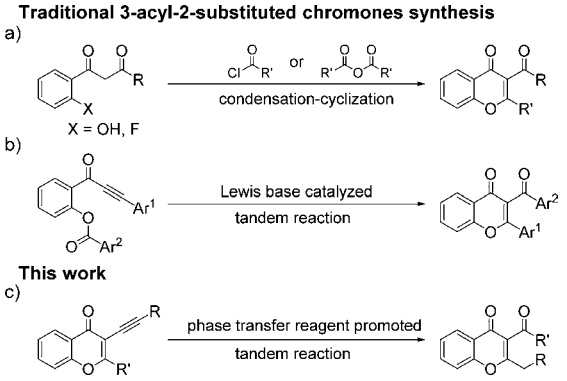


ABSTRACT: A phase transfer reagent promoted tandem ring-opening and ring-closing reaction of 3-(1-alkynyl) chromones has been developed. This process remarkably generates functionalized 3-acyl-2-substituted chromones. Interestingly, when 3-(hepta-1,6-diyn-1-yl)chromone derivatives are applied, a novel tetracyclic chromone scaffold can be obtained by a further intramolecular 4 + 2 cyclization.

A chromone fragment is a ubiquitous structure that occurs in a wide variety of naturally occurring[1] and synthetic compounds exhibiting various important biological activities.[2] Among the chromone derivatives reported, 3-acyl-2-substituted chromone derivatives display several biological activities such as antimalarial, anticytochrome P450, and anti-HIV activities.[3] Besides, 3-acyl-2-substituted chromones with good photochromic properties have also been reported.[4] However, only a few synthetic approaches have been investigated.[5] The 3-acyl-2-substituted chromone derivatives can usually be prepared in the conventional synthesis from 2-fluoride or 2-hydroxyacetophenones by a tandem condensation and cyclization reaction at high temperature[5a,c−e] (Scheme 1a) with limited functional derivatives. Recently, Doi and co-workers reported a concise synthesis of diverse 3-aroylflavones (3-benzoyl-2-phenylchromones) via Lewis base catalyzed tandem acyl transfer−cyclization[5b] (Scheme 1b). Our research group has focused on the functionalized 3-(1-alkynyl)chromones to generate diversified natural-product-like scaffolds through cascade reactions.[6] Herein, we describe novel phase transfer reagent promoted tandem ring-opening and ring-closing reactions of unique 3-(1-alkynyl)chromones with water to construct diversified 3-acyl-2-benzyl or alkyl chromones with a more broad scope under mild reaction conditions in good to excellent yields (Scheme 1c).

In our earlier studies of the phenylacetonitrile modulated cyclization with 3-(1-alkynyl)chromones (Scheme 2),[6b] we found the desired product **2** in 10% yield with 3-acetyl-2-(4-cyanobutyl) chromone **3g** in 62% yield while phenylacetonitrile was replaced by *n*-Bu_4NCl (TBAC). We envisioned that the

Scheme 1. Strategies for the Synthesis of 3-Acyl-2-substituted Chromones



formation of **3g** involves a domino process as depicted in Scheme 2. First, M1 could be generated by a Michael addition of H_2O with compound **1g** under phase transfer conditions, along with the pyrone ring-opening to form M2. Subsequently, the OH anion of M2 can recyclize with the allene bond which was formed via an alkyne isomerization to produce the intermediate M3. The protonation of M3 finally leads to the formation of the 3-acetyl-2-(4-cyanobutyl) chromone **3g**. Notably, with only the *n*-Bu_4NCl additive this tandem process does not precede the known cyclization to form a furan,

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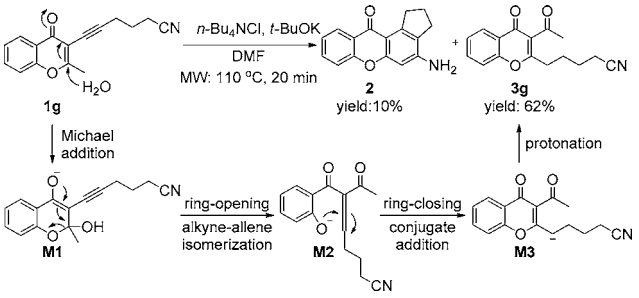
Scheme 2. Plausible Mechanism for the Formation of 3g

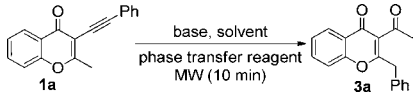


furocoumarin, or xanthone scaffold as reported before.[6] This is a novel efficient synthetic approach to generate functional 3-acyl-2-substituted chromone derivatives via a tandem reaction of 3-(1-alkynyl)-chromones.

Based on the above results, we examined this tandem reaction with 2-methyl-3-(phenylethynyl) chromone **1a** using different conditions (Table 1). When the reaction was carried out in the presence of 2.0 equiv of *t*-BuOK and *n*-Bu_4NCl (TBAC) in DMF at 110 °C for 10 min under microwave irradiation, the desired product **3a** was isolated in 40% yield (Table 1, entry 1). When 10 equiv of H_2O were added, the yield of the reaction increased to 63% (Table 1, entry 2). This result supports our proposed mechanism that H_2O is involved in the Michael addition with **1a**. In the presence of water, *t*-BuOK could be converted to KOH. When using 2 equiv of saturated solution of KOH instead of 2 equiv of *t*-BuOK and 10 equiv of H_2O (Table 1, entry 3), the desired product **3a** was obtained in 33% yield. By changing the solvent to *t*-BuOH, the yield increased to 52% (Table 1, entry 4). To our delight, the yield of **3a** further increased to 76% by carrying out the reaction at room temperature for 3 h (Table 1, entry 5). When reducing the phase transfer reagent TBAC to 1 or 0.5 equiv, the tandem reaction yielded **3a** in 68% yield (Table 1, entries 6 and 7). It indicates the reaction could be catalyzed by the transfer reagent. Reducing the phase transfer reagent TBAC to 0.2 equiv could decrease the reaction yield apparently (Table 1, entry 8). Subsequently, among the different phase transfer reagents explored, TBAC is the best (Table 1, entries 9–11). Also, by reducing the base to 1 equiv, the yield of product deceased to 33% (Table 1, entry 12). An exploration of different solvents uncovered the observation that *t*-BuOH is more suitable for this tandem process (Table 1, entries 13–17). In summary, optimized conditions involve reaction in *t*-BuOH at room temperature for 3 h in the presence of 2.0 equiv of *n*-Bu_4NCl (TBAC) and a saturated solution of KOH respectively.

To extend the scope of this tandem reaction, various substrates of **1** were used (Scheme 3). When R^1 was an aromatic group on the acetylene moiety, products **3a–3c** were obtained in 54–76% yields. It was noted that an electron-withdrawing group on the aromatic ring was unfavorable in the

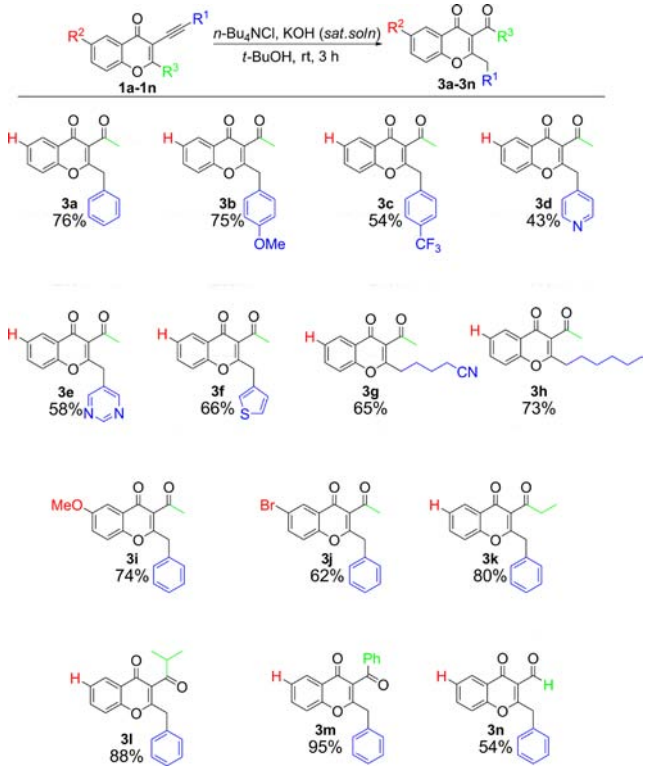
Table 1. Optimization of Reaction Conditions for the Formation of 3-Acyl-2-substituted Chromone 3a[a]



entry	additive	base; solvent	temp	yield(%)[d]
1	TBAC (2.0 equiv)	*t*-BuOK; DMF	110 °C; 10 min	40
2[b]	TBAC (2.0 equiv), H_2O	*t*-BuOK; DMF	110 °C; 10 min	63
3	TBAC (2.0 equiv)	KOH(*sat.soln*); DMF	110 °C; 10 min	33
4	TBAC (2.0 equiv)	KOH(*sat.soln*); *t*-BuOH	110 °C; 10 min	52
5	TBAC (2.0 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	76
6	TBAC (1.0 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	68
7	TBAC (0.5 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	68
8	TBAC (0.2 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	28
9	TBAF (0.5 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	50
10	TBAB (0.5 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	20
11	TBAI (0.5 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	22
12[c]	TBAC (0.5 equiv)	KOH(*sat.soln*); *t*-BuOH	rt; 3 h	33
13	TBAC (2.0 equiv)	KOH(*sat.soln*); EtOH	rt; 3 h	12
14	TBAC (2.0 equiv)	KOH(*sat.soln*); isopropanol	rt; 3 h	64
15	TBAC (2.0 equiv)	KOH(*sat.soln*); DMSO	rt; 3 h	trace
16	TBAC (2.0 equiv)	KOH(*sat.soln*); dioxane	rt; 3 h	13
17	TBAC (2.0 equiv)	KOH(*sat.soln*); THF	rt; 3 h	trace

[a]Unless otherwise noted, reactions were carried out with **1a** (0.5 mmol) and 2 equiv of base. [b]The reaction was carried out with 10 equiv of H_2O. [c]The reaction was carried out with 1 equiv of KOH. [d]Yield of isolated product based on **1a**.

Scheme 3. Synthesis of 3-Acyl-2-substituted Chromones 3[a]



[a]Unless otherwise noted, reactions were carried out under the optimized reaction conditions; isolated yield.

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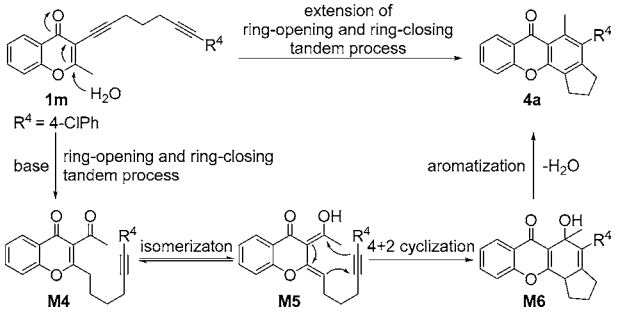
domino process. The reactions also proceeded smoothly when R^1 was a heterocycle or an aliphatic chain. However, there are obvious electronic effects on the R^2 substituent. When R^2 was an electron-donating group, the desired product **3i** could be obtained in good yield. An electron-withdrawing group such as a Br substituent could reduce the nucleophilicity of the oxygen anion for the ring-closing process and decrease the yield of the product. In addition, when R^3 was an ethyl, isopropyl, or phenyl group, the desired products were obtained in excellent yields respectively, which indicated that the steric effects of the R^3 position did not influence this tandem process. Finally, when R^3 was hydrogen, a product containing a formyl group was also achieved successfully in moderate yield. Recently, Siegel and co-workers reported a similar reaction to form the aldehyde intermediates for the synthesis of Vinaxanthone and its derivatives through ynone coupling reactions.[7]

In order to expand further application of this ring-opening and ring-closing tandem reaction, we envisioned that substance **1m** might undergo a further intramolecular 4 + 2 cyclization to afford M6,[7] which then could be transformed to a novel tetracyclic chromone scaffold via an aromatization (Scheme 4).

Scheme 4. Proposed Mechanism To Form Novel Tetracyclic Chromone Scaffold



After brief work designed to examine the reaction conditions for the formation of novel tetracyclic chromone **4a** (see Supporting Information, Table S1), the optimized reaction conditions were determined to involve 2.0 equiv of *t*-BuOK, using 2.0 equiv of *n*-Bu_4NCl in place of *n*-Bu_4NF, and 1.0 equiv of phenylacetonitrile **5** as an anion transfer reagent[6b] in DMSO at 110 °C for 20 min under microwave irradiation. Additionally, the structure of **4a** was unambiguously established by X-ray crystal structure analysis (Figure 1).[8]

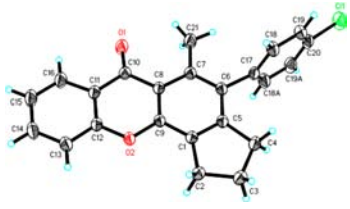
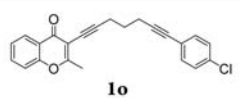
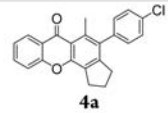
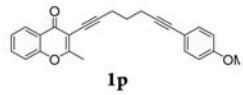
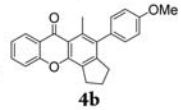
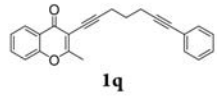
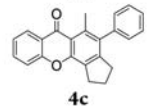
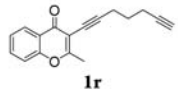
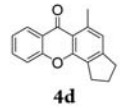
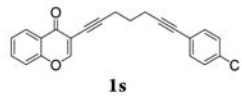
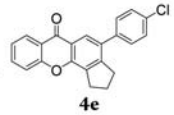
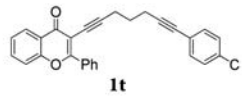
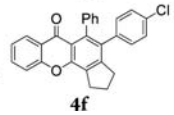


Figure 1. X-ray structure of tetracyclic chromone **4a**.[7]

Subsequently, the scope of this reaction was explored under the optimized reaction conditions, and the results were displayed in Table 2. We obtained the desired novel tetracyclic chromone derivatives mostly in good yields. There are no obvious electronic effects on an aromatic group of R^4 (Table 2, entries 1−3). But when R^4 was H, the corresponding product **4d** was found in 40% yield (Table 2, entry 4). Notably, the

Table 2. Synthesis of Novel Tetracyclic Chromones 4[a]

entry	substrate	product	yield(%)[a]
1	 1o	 4a	80
2	 1p	 4b	70
3	 1q	 4c	76
4	 1r	 4d	40
5	 1s	 4e	68
6	 1t	 4f	28

[a]Unless otherwise noted, reactions were carried out under the optimized reaction conditions; isolated yield.

reactions also proceed smoothly when R^3 was H (Table 2, entry 5). However, when R^3 was a phenyl group (Table 2, entry 6), the desired product was obtained in low yield, which may due to the steric effect of two phenyl groups at the ortho-position.

In conclusion, a novel and efficient phase transfer reagent promoted tandem ring-opening and ring-closing reaction of 3-(1-alkynyl)chromones with H_2O has been developed for the generation of functionalized 3-acyl-2-substituted chromones. This cascade process is mild and has a broad scope without the need for a transition metal catalyst. It is an efficient supplement for the synthetic approaches of diverse 3-acyl-2-substituted chromones which may be applied in drug discovery and materials engineering. Meanwhile, this tandem reaction has also been further explored to construct novel tetracyclic chromones via an anion transfer reagent, which included phenylacetonitrile modulating further cyclization reactions. Further library generation and biological evaluation of the diversified 3-acyl-2-substituted chromones and tetracyclic chromones are under investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and spectral data for all new compounds and crystal structure data for **4a** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) CCDC 1038732 (**4a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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