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Base-Promoted Tandem Reaction Involving Insertion into Carbon–Carbon σ-Bonds: Synthesis of Xanthone and Chromone Derivatives

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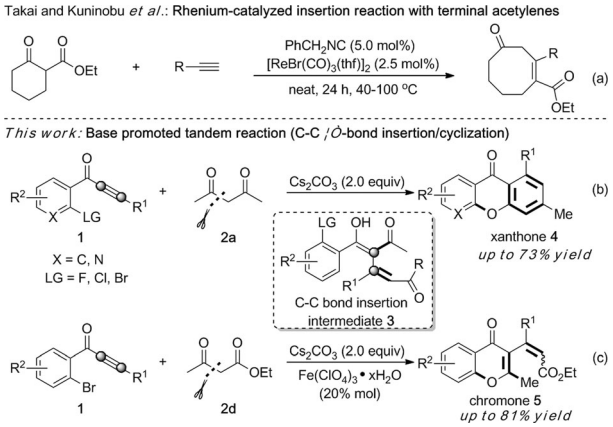
Abstract: Tandem reactions using base-promoted processes have been developed for the synthesis of xanthone and chromone derivatives. The first examples of base-promoted insertion reactions of isolated carbon–carbon triple bonds into carbon–carbon σ-bonds have been reported. Using these approaches, polycyclic structures can be prepared. This reaction has the potential to become a general synthetic protocol for the preparation of multi-substituted xanthones and chromones due to the abundance of easily accessible starting materials possessing diverse substituent groups.

Chemical transformations starting from selective carbon–carbon bond cleavage and subsequent functionalization are important and highly efficient methods in organic chemistry because C–C bonds constitute the fundamental skeletons of organic compounds. However, these chemical transformations are challenging because of the inert and stable properties of C–C bonds (both kinetically and thermodynamically). Over the past few decades, significant progress has been made in this area, particularly for transition-metal-catalyzed reactions of strained systems.[1] With regards to unstrained systems, insertion reactions involving acetylenes are limited to rhenium or nickel catalysis.[2] The Takai and Kuninobu groups[2b–e] have developed excellent rhenium-catalyzed insertion reactions using unstrained cyclic compounds; terminal acetylenes[2e] and internal alkynes[2d] insert into a carbon–carbon single bond positioned next to a carbonyl group (Scheme 1 a). However, transition-metal-free carbon–carbon σ-bond-insertion reactions with internal alkynes are rare, with the exception of highly reactive arynes.[3] Utilizing the properties of dicarbonyl compounds, we developed a base-promoted and transition-metal-free insertion reaction of internal alkynes with β-diketone compounds to give xanthone derivatives **4** (Scheme 1 b). When β-keto esters were employed in place of β-diketones, chromone derivatives **5** were obtained. The addition of $Fe(ClO_4)_3 \cdot xH_2O$ was able to significantly improve the yields of chromone **5** (Scheme 1 c).



Scheme 1. Insertion reactions into a carbon–carbon σ-bond.

Xanthone (9*H*-xanthen-9-one) and chromone derivatives are prevalent in natural products and are widely recognized as candidates for drug development due to their excellent biological and pharmacological activities. For example, siamchromones[4] with anti-tobacco mosaic virus (anti-TMV) and anti-HIV-1 activities, and α-mangiferin,[5] which has potent anti-bacterial, anti-tumor and anti-allergy properties (Figure 1). Thus, the synthesis of such xanthone and chromone substructures are synthetically attractive.[6,7]

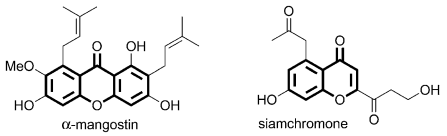


Figure 1. Chemical structures of natural products containing core xanthone and chromone skeletons.

Initially, the reaction conditions were investigated using 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**1 a**) and pentane-2,4-dione (**2 a**) as the model substrates. The ratio of **1 a**:**2 a** was screened from 1.0:0.6 to 1.0:2.0 and the amount of base varied (see the Supporting Information, Table S1, entries 1–10). When the reaction was performed with a ratio of **1 a**:**2 a** = 1.0:1.0 in

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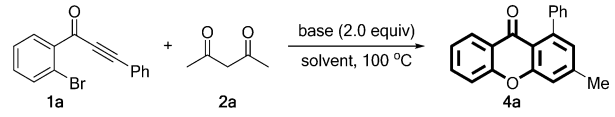
DMF using Cs_2CO_3 (2.0 equiv) as the base in air at 100 °C, xanthone **4a** was obtained in 73% isolated yield within 3 h. In addition, decreasing the reaction temperature to 50 °C resulted in a longer reaction time (30 h) with the desired product being obtained in moderate yield. However, reaction activity did not increase with an increased reaction temperature (see the Supporting Information, Table S1, entries 11 and 12). The effect of different bases and solvents was studied at 100 °C in air (Table 1).

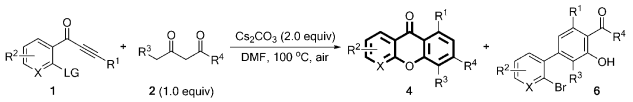
Table 1. Screening of bases and solvents.[a]



Entry	Base	Solvent	Time [h]	Yield [%][b]
1	Cs_2CO_3	DMF	3	73
2	K_2CO_3	DMF	6	49
3	K_3PO_4	DMF	3	56
4	NaOH	DMF	3	50
5	*t*BuOK	DMF	3	13
6	NaH	DMF	1	6
7	DABCO	DMF	8	complex mixture
8	DMAP	DMF	8	complex mixture
9	Cs_2CO_3	DMA	3	56
10	Cs_2CO_3	DMSO	3	65
11	Cs_2CO_3	toluene	8	41
12	Cs_2CO_3	1,4-dioxane	8	trace

[a] Reactions were conducted on a 0.6 mmol scale with the ratio of **1a**:**2a** = 1:1 in 5.0 mL of solvent at 100 °C in air. [b] Isolated yield.

Table 2. Synthesis of xanthone derivatives **4**.[a]



Entry	4	Time [h]	Yield of **4** [%][b]	Yield of **6** [%][b]
1	**4a** R^1 = Ph	3	73	10
2	**4b** R^1 = *p*Me-C_6H_4	2	59	11
3	**4c** R^1 = *o*Me-C_6H_4	3	63	16
4	**4d** R^1 = *p*MeO-C_6H_4	2	61	11
5	**4e** R^1 = *p*Cl-C_6H_4	3	54	15
6	**4f** R^1 = 1-naphthyl	3	47	33
7	**4g** R^1 = *n*Bu	27	20	–[c]
8	**4h** R^1 = *t*Bu	8	63	–[c]
9	**4i** R^1 = Ph, R^2 = 7-F	4	55	20
10	**4j** R^1 = Ph, R^2 = 6,7-*di*MeO	4	57	4
11	**4k** R^2 = 6,7-*di*MeO, R^1 = 3,4,5-*tri*MeO-C_6H_2	5	74	4
12	**4l** X = CH, R^3 = Me, R^4 = Et	3	52	–[c]
13	**4m** X = N, R^3 = H, R^4 = Me	2	49	–[c]

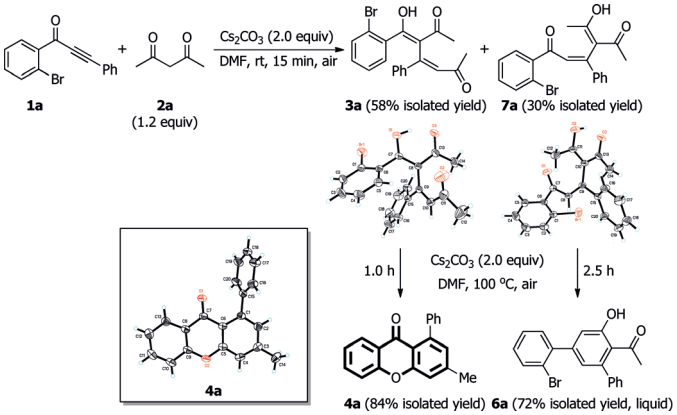
[a] Reactions were conducted on a 0.6 mmol scale with the ratio of **1**:**2** = 1:1 in 5.0 mL of DMF at 100 °C in air. [b] Isolated yield. [c] Not detected.

The reaction was determined by the alkalinity of the base. Full conversion of **1a** was observed within 1 h using sodium hydride as a base, but unfortunately the yield of xanthone **4a** decreased to 6% (Table 1, entry 6). When K_2CO_3 was employed in the reaction, a longer reaction time (6 h) was required and the desired product was obtained in moderate yield (49%) (Table 1, entry 2). The results were slightly better when K_3PO_4 (3 h, 56%) or NaOH (3 h, 50%) were used (Table 1, entries 3,4). Conversely, organic bases such as DABCO (1,4-diazabicyclo[2.2.2]octane) and DMAP (4-dimethylaminopyridine) were ineffective, requiring long reactions times and giving complex reaction mixtures (Table 1, entries 7 and 8). Next, solvents were screened using Cs_2CO_3 (2.0 equiv) as a base. From those tested, DMF proved to be the most effective (Table 1, entries 1,9–12). Xanthone **4a** was obtained in moderate to good yields if the reaction was performed in DMA (dimethylacetamide), DMSO or toluene, although a longer reaction time was required with toluene solvent (8 h, 41%). Only a trace amount of product was obtained when the reaction was performed in 1,4-dioxane.

With the optimized reaction conditions in hand (Table 1, entry 1), we next looked to expand the substrate scope to synthesize substituted xanthone derivatives **4** (Table 2). In some cases, the desired xanthones **4** were obtained with the accompanying *p*-acetyl arylols **6**. Different leaving groups (LG = Br, F, Cl) on substrate **1** (X = CH, R^1 = Ph, R^2 = H) were investigated for reaction with pentane-2,4-dione (**2a**) under the optimized reaction conditions. Xanthones **4a** (LG = F, 53%; Cl, 55%) were obtained in moderate yields. An insignificant quantity of *p*-acetyl arylol **6a** was detected when fluoride was the leaving group, *p*-acetyl arylol **6a** was obtained with isolated yields of 10% (LG = Br, entry 1) and 15% (LG = Cl), respectively. Overall, 1-(2-bromophenyl)-3-phenylprop-2-yn-1-one (**1a**) with a bromide leaving group gave the desired product **4a** in higher yield and greater chemoselectivity. Thus, the following investigations concerning substituents effects were carried out using substrate **1** bearing the bromide leaving group.

Various multisubstituted xanthone derivatives **4** were obtained in moderate to good yields. Firstly, the effect of the substituent R^1 of the alkynyl functional group was explored (Table 2, entries 1–8). Both electron-donating and -withdrawing groups on the aryl substituent R^1 were tolerated under the tested conditions with yields ranging between 63 and 54%. Additionally, *ortho*- and *para*-substituents made little difference to the selectivity and reactivity (Table 2, entries 2–5) in the reaction. Ring-fused substituents such as 1-naphthyl could also be successfully employed, although the ratio of the desired xanthone derivative **4f** to *p*-acetyl arylol **6f** was 4:3 (Table 2, entry 6). Notably, substrates **1g** and **1h** bearing an alkyl R^1 substituent selectively gave xanthones **4g** and **4h**, with no *p*-

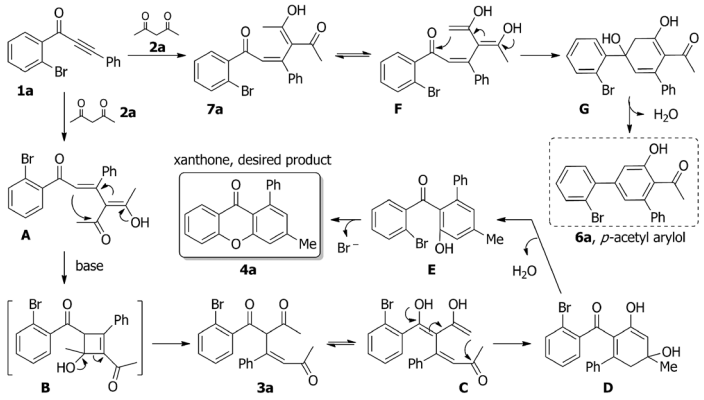
acetyl arylol being detected even with prolonged reaction times (Table 2, entries 7 and 8). Subsequently, the R^2 substituent on the aryl ring was explored (Table 2, entries 9–11). The introduction of an electron-withdrawing substituent (R^2 = 7-F) in substrate **4i** led to an increase of the yield of the *p*-acetyl arylol product **6i** (**4i**: 55%, **6i**: 20%). Conversely, the substrates **4j** and **4k** possessing electron-donating substituents (R^2 = 6,7-OMe) limited the yield of *p*-acetyl arylols to 4%. In addition, **6k** was obtained as a yellow solid and characterized by X-ray crystallography[8] (see the Supporting Information, including CIF files). In the case of heptane-3,5-dione (**2b**), the reaction proceeded smoothly to give a moderate yield of the desired xanthone **4l** (Table 2, entries 12). Reaction of 1-(2-bromopyridin-3-yl)-3-phenylprop-2-yn-1-one (**1m**) also proceeded, affording the desired product **4m** in 49% yield within 2 h (Table 2, entry 13).



Scheme 2. Mechanistic investigation.

The mechanism of this process was investigated and is shown in Scheme 2. To identify intermediates in this reaction, the experiment was carried out using the optimized reaction conditions at room temperature. Full conversion of **1a** occurred within 15 min as monitored by TLC. Intermediates **3a** and **7a**, the structures of which were characterized by X-ray crystallography[9] (see the Supporting Information, including CIF files), were isolated in 58 and 30% yield, respectively. These intermediates were used separately as starting materials and subjected to the general reaction conditions of our system. Products, **4a** and **6a** were thus obtained in 84 and 72% yield, respectively. This indicates that once the intermediate **7a** is formed, the formation of *p*-acetyl arylol **6a** cannot be avoided.

On the basis of the reported work[3] and our experimental results, a plausible mechanism for this reaction has been proposed (Scheme 3). The substrate **1a** is first attacked by the nucleophilic diketone **2a** to give intermediate **A**, which presumably undergoes an intramolecular nucleophilic addition/fragmentation cascade resulting in an alkyne insertion into the α,β carbon–carbon σ-bond of the diketone to give **3a**.[3c] After

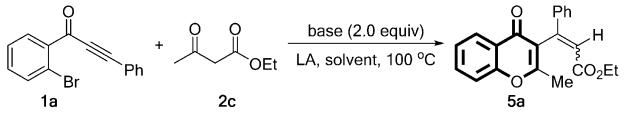


Scheme 3. Plausible reaction mechanism.

enolization, intramolecular nucleophilic addition occurs, followed by dehydration to give intermediate **E**, bearing a multisubstituted aryl ring with a hydroxyl group. Nucleophilic aromatic substitution (S_NAr)[10] leads to the desired product xanthone **4a**. An alternative pathway involving the nucleophilic addition of **1a** gives the *p*-acetyl arylol **6a** by cyclization.

We next expanded the reaction scope to oxobutanoate compounds. The first attempt utilized ethyl 3-oxobutanoate (**2c**) as the model substrate using the aforementioned optimized reaction conditions, from which chromone **5a** was obtained with an isolated yield of 43% within 3 h (Table 3, entry 1). To improve the yield of chromone **5a**, different solvents were screened (see the Supporting Information, Table S2, entries 8–14). When DMA was used, the desired product **5a** was obtained in 48% yield in air and 53% yield under N_2 (Table 3, entries 2 and 3). The addition of the Lewis acid, $Fe(ClO_4)_3 \cdot xH_2O$ (20% mol), resulted in a dramatic increase in the yield to 81% (Table 3, entries 4–9). Additionally, the alkalinity

Table 3. Screening of reaction conditions.[a]



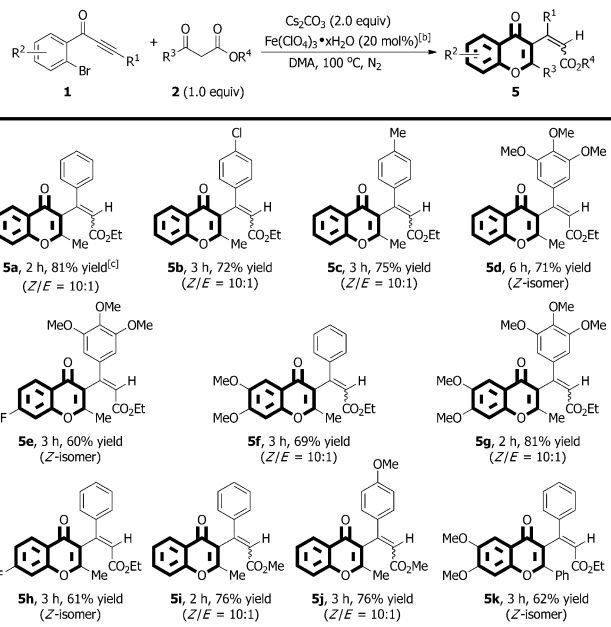
Entry	Lewis Acid	Base	Solvent	Time [h]	Yield [%][b]
1[c]	–	Cs_2CO_3	DMF	3	43
2[c]	–	Cs_2CO_3	DMA	2	48
3	–	Cs_2CO_3	DMA	2	53
4	CuI (10 mol%)	Cs_2CO_3	DMA	2	35
5	$FeCl_3 \cdot 6H_2O$ (10 mol%)	Cs_2CO_3	DMA	2	66
6	$Fe(acac)_3$ (10 mol%)	Cs_2CO_3	DMA	2	46
7[d]	$Fe(ClO_4)_3 \cdot xH_2O$ (10 mol%)	Cs_2CO_3	DMA	2	76
8[d]	$Fe(ClO_4)_3 \cdot xH_2O$ (20 mol%)	Cs_2CO_3	DMA	2	81
9[d]	$Fe(ClO_4)_3 \cdot xH_2O$ (5 mol%)	Cs_2CO_3	DMA	2	70
10[d]	$Fe(ClO_4)_3 \cdot xH_2O$ (20 mol%)	–	DMA	2	NR[e]

[a] Reactions were conducted on a 0.3 mmol scale with the ratio of **1a**:**2c** = 1.0:1.0 in 3.0 mL of DMA at 100 °C under N_2. [b] Isolated yield of mixture of *E*/*Z*-isomers. [c] In air. [d] The amount of Lewis acid was calculated as $Fe(ClO_4)_3 \cdot 9H_2O$. [e] No reaction.

and the amount of base greatly influenced reactivity; 2.0 equivalents of Cs_2CO_3 was essential for this process (see the Supporting Information, Table S2, entries 15–21). No reaction occurred in the absence of a base (Table 3, entry 10).

With the optimized reaction conditions in hand (Table 3, entry 8), we next engaged in the synthesis of a series of chromone derivatives **5** bearing different substituents (Table 4).

Table 4. Synthesis of chromone derivatives **5**.[a]



[a] Reactions were conducted on a 0.3 mmol scale with the ratio of **1**:**2** = 1.0:1.0 in 3.0 mL of DMA at 100 °C under N_2. [b] The amount of Lewis acid was calculated as $Fe(ClO_4)_3 \cdot 9H_2O$. [c] Isolated yield of mixture of *E*/*Z*-isomers.

Good to moderate yields and selectivities (*Z*/*E* = 10:1) of chromone **5** were obtained irrespective of the presence of electron-donating or -withdrawing groups on the aryl ring of the chromone skeleton, or on the R^1 substituent. In addition, the desired products could be obtained as single *Z*-isomers in the cases of substrates **5d** (71% yield), **5e** (60% yield), **5h** (61% yield), and **5k** (62% yield). Structural identification of *Z*-**5f** was carried out by X-ray crystallography[11] (see Supporting Information, including CIF files). When methyl 3-oxobutanoate (**2d**) was employed, a slight decrease in the yield of the corresponding products was observed (**5i**: 76 vs. **5a**: 81%). The reaction also proceeded smoothly with methyl 3-oxo-3-phenylpropanoate (**2e**), giving only the corresponding product *Z*-**5k** in 62% isolated yield within 3 h.

In summary, we have developed a practical procedure for the synthesis of multisubstituted xanthone and chromone derivatives by a base-promoted, one-pot tandem reaction. An insertion reaction into a carbon–carbon σ-bond is a key step of the process. This methodology represents the first example of a base promoted insertion reaction of isolated internal alkynes into carbon–carbon σ-bonds. Xanthones and chromones were obtained in good to moderate yields using easily prepared starting materials. A plausible mechanism for this process has been proposed for the formation of xanthones and *p*-acetyl arylols when pentane-2,4-diones are used as substrates. This reaction provides a new strategy for the preparation of xanthone and chromone core structures and has the potential to be used widely in organic synthesis.

Experimental Section

Preparation of xanthone derivatives 4

In a Schlenk tube 1-aryl-3-phenylprop-2-yn-1-one **1** (0.6 mmol), pentane-2,4-dione **2** (0.6 mmol), and Cs_2CO_3 (391.0 mg, 1.2 mmol) in DMF (5.0 mL) was stirred at 100 °C in air. After the reaction was complete as monitored by thin-layer chromatography, the reaction mixture was then cooled to room temperature, water was added and the crude product was extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (appropriate mixture of petroleum ether/ethyl acetate/dichloromethane) to afford the corresponding xanthone derivative **4**.

Preparation of chromone derivatives 5

In a Schlenk tube 1-aryl-3-phenylprop-2-yn-1-one **1** (0.3 mmol), 3-oxobutanoate **2** (0.3 mmol), and Cs_2CO_3 (195.5 mg, 0.6 mmol) in DMF (3.0 mL) was stirred at 100 °C under N_2. After the reaction was complete as monitored by thin-layer chromatography, the reaction mixture was then cooled to room temperature, water was added and the crude product was extracted with ethyl acetate (3× 10 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by chromatography on silica gel (appropriate mixture of petroleum ether/ethyl acetate/dichloromethane) to afford the corresponding chromone derivative **5**.

Acknowledgements

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Keywords: base-promoted reaction · C–C activation · insertion · tandem reactions · xanthone

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[8] CCDC 1447958 contains the supplementary crystallographic data for **6k**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[9] CCDC 1447937, 1447944, and 1447940 for **3a**, **4a**, and **7a**, respectively, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Heterocycles

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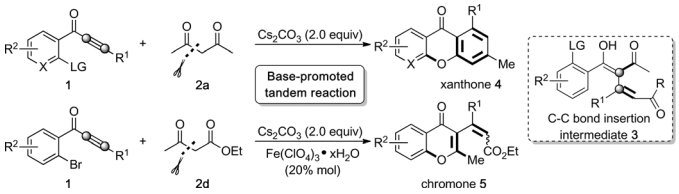
Base-Promoted Tandem Reaction Involving Insertion into Carbon–Carbon σ-Bonds: Synthesis of Xanthone and Chromone Derivatives



Tandem partners: Tandem reactions using a base-promoted process have been developed for the synthesis of xanthone and chromone derivatives (see scheme). These reactions represent the first examples of base-promoted insertion reactions of isolated internal alkynes into carbon–carbon σ-bonds. Polycyclic structures can be prepared using this process.