Aryne Chemistry

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A Multicomponent Coupling Reaction Induced by Insertion of Arynes into the C=O Bond of Formamide**

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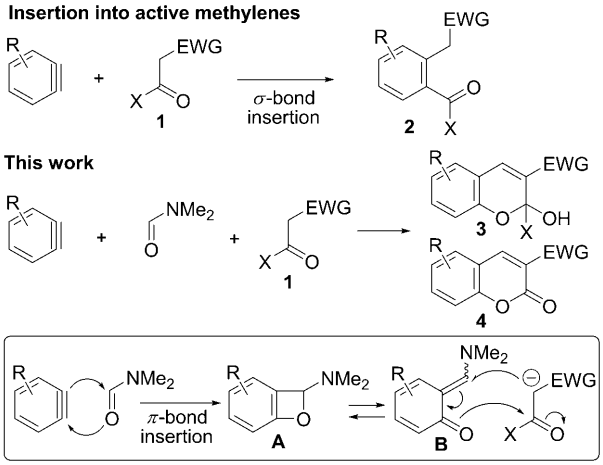
Aryne compounds are highly reactive intermediates that have been widely used in organic synthesis.[1,2] In recent years, studies on aryne-based reactions have achieved some remarkable success, particularly in sequential reactions with a nucleophile and an electrophile for the preparation of complex *ortho*-disubstituted arene derivatives,[3–5] which are difficult to synthesize by other methods. Most importantly, these advances have shown that the insertion of aryne compounds into various element–element σ-bonds can be achieved even under transition-metal-free conditions.[6,7] In contrast, less is known about the corresponding π-bond insertion,[8] except for the studies by Suzuki and co-workers on the insertion into the C=C bond to give stable benzocyclobutenes.[9] The synthetically useful insertion into the C=O bond was recently achieved by Yoshida et al.[10]

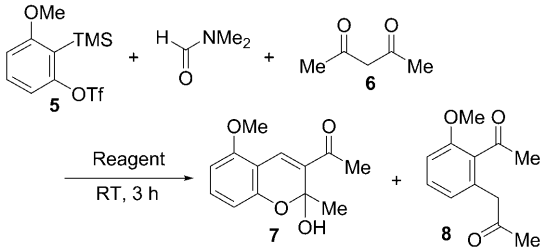
In general, the diversity observed in the reaction of arynes with amides is limited to N–C σ-bond insertion.[11] Recently, our research group reported the efficient insertion into the C=O π-bond of sterically less-hindered formamide compounds and the subsequent trapping process of the intermediates with dialkylzinc reagents.[12,13] Herein, we report a three-component coupling reaction leading to the cyclic products **3** and **4** through the insertion into a π-bond of *N*,*N*-dimethylformamide (DMF; Scheme 1). In this manner, the active methylenes **1** were employed as a second nucleophile for trapping the unstable intermediates **A** or **B**. However, it is important to notice that the active methylenes **1** have an excellent reactivity toward aryne compounds. The research groups of Stoltz[14] as well as Yoshida and Kunai[15] independently reported that the insertion into the C–C σ-bond of **1** leads to *ortho*-disubstituted arenes **2** and proceeds with good chemical efficiency by use of β-keto ester and α-cyanocarbonyl compounds, and so on.[16] Therefore, the key requirement for the present cascade sequence is assumed to be the control of two competitive insertions between DMF and active methylenes **1** and the sufficient reactivity of active methylenes toward intermediates **A** or **B**.



Scheme 1. Insertion of aryne compounds into the C=O bond of an amide compounds. EWG = electron-withdrawing group.

Our experiments began with the investigation of three-component coupling reaction of an aryne precursor **5**, DMF, and acetylacetone **6** (Table 1).[17] The competitive insertion of the aryne compound into **6** to give the undesired product **8** was suppressed when DMF was employed as a solvent. In the

Table 1: Three-component coupling reaction using acetylacetone **6**.[a]



Entry	Reagent[b]	Acetylacetone **6** [equiv]	Yield [%][c]	
			7	**8**
1[d]	TBAF	1.05	83	trace
2[d]	TBAF	1.5	86	3
3[d]	TBAF	2.0	85	3
4[d]	CsF	1.5	65	6
5[d]	$TBAHF_2$	1.5	77	6
6[e]	TBAF	1.5	84	trace
7[f]	TBAF	1.5	74	4[g]

[a] Reactions were carried out in DMF at RT for 3 h. [b] 3.0 equivalents of the fluoride ion source was employed. [c] Yield of isolated product. [d] 0.1 M solution of **5**. [e] 0.033 M solution of **5**. [f] 0.33 M solution of **5**. [g] A small amount of a different adduct was observed. Tf = trifluoromethanesulfonyl, TMS = trimethylsilyl.

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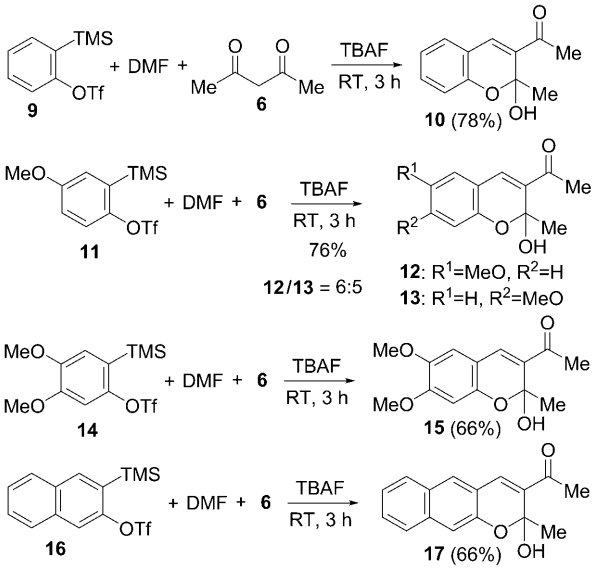
presence of anhydrous TBAF (tetra-*n*-butylammonium fluoride), treatment of triflate **5** with **6** in DMF predominantly gave the desired 2*H*-chromene **7** (Table 1, entries 1–3). The 2*H*-chromene **7** was obtained in 86% yield by using 1.5 equivalents of **6** (Table 1, entry 2). The replacement of anhydrous TBAF with CsF or tetrabutylammonium bifluoride ($TBAHF_2$) led to a decrease in the chemical yields (Table 1, entries 4 and 5). The concentration of the reaction was adjusted and 0.1M solution of **5** gave the best result (Table 1, entries 2, 6, and 7). The insertion into the C=O π-bond proceeded with excellent regioselectivity without the formation of regioisomers.[18,19]

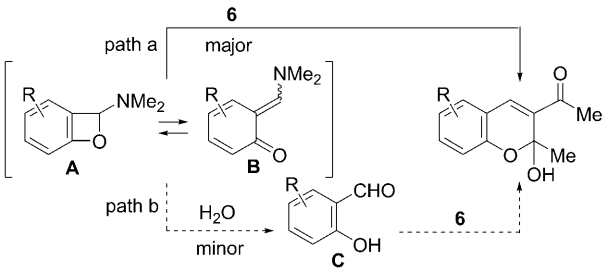
Several aryne precursors were next examined (Scheme 2). A good yield was obtained in the reaction of simple triflate **9** with **6**. Having a substituent on the aryne compound had an



Scheme 2. Reaction of several aryne compounds with DMF and acetylacetone **6**.

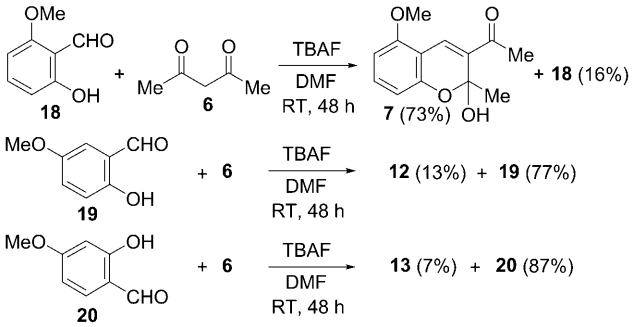
impact on regioselectivity, with 4-methoxytriflate **11** leading to regioisomers **12** and **13** in a 6:5 ratio (on the basis of ^{1}H NMR analysis). This observation indicated the formation of an aryne compound as an intermediate. Triflate **14** worked well and afforded the 2*H*-chromene **15**. This result indicates that the nucleophilicity of the carbonyl oxygen atom of DMF was sufficient to bring about insertion of an aryne compound bearing two methoxy groups. In the case of triflate **16**, the three-component coupling product **17** was isolated in 66% yield, and was accompanied by the competitive formation of the thia-Fries rearrangement product in 9% yield.[20]

We consider that the electrophilicity of the four-membered intermediate **A** would be increased by strain energy. Therefore, we propose a pathway involving the addition of an enolate anion to unstable intermediates **A** or **B** and the elimination of dimethylamine (path a in Scheme 3). However, the route via salicylaldehyde **C**, generated by the hydrolysis of **A** or **B**, cannot be excluded even under the careful anhydrous reaction conditions (path b).



Scheme 3. Reaction pathway.

To gain further insight into the feasibility of a path b, the reactions of salicylaldehyde derivatives **18**–**20** with **6** were evaluated under similar reaction conditions (Scheme 4). The



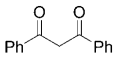
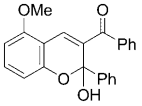
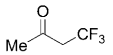
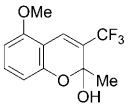
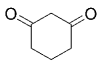
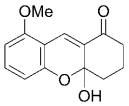
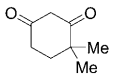
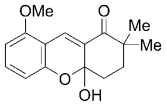
Scheme 4. Reaction of salicylaldehyde derivatives with **6**.

three-component coupling reaction using DMF was usually performed over 3 hours (Table 1 and Scheme 2). Although the prolonged reaction of **18** with **6** led to the formation of **7**, a significant amount of starting material was recovered after 3 hours. In the case of **19** and **20**, sufficient conversion was not observed even after 48 hours. These experimental outcomes support our proposal that path a should be the major pathway.

Further investigations using several ketones **21**–**24** were performed (Table 2). In the cases of **21** and **22** the reaction rates were lower; thus, all reaction times were changed to 12 hours. Under the optimized reaction conditions, the bulky 1,3-diketone **21** bearing two phenyl groups showed good reactivity (Table 2, entry 1). The acetone **22** having an α-CF_3 group also acted as a nucleophile and trapped the unstable intermediates to give the corresponding product **26** in 40% yield (Table 2, entry 2), even though salicylaldehyde **18** was also obtained by hydrolysis of the intermediates. The cyclic 1,3-diketones produced the tricyclic compounds, thereby allowing facile incorporation of structural variety (Table 2, entries 3 and 4). In particular, the three-component coupling reaction with **23** proceeded with good chemical efficiency, and produced **27** in 83% yield (Table 2, entry 3). In the case of unsymmetrical diketone **24**, tricyclic compound **28** was obtained as the major regioisomer (Table 2, entry 4).

Next, we directed our attention to the investigation of β-keto esters as a second nucleophile to trap the unstable intermediates **A** or **B** (Table 3).[21] As expected, coumarin

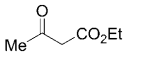
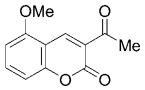
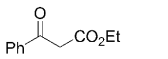
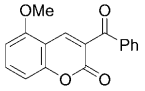
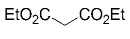
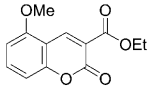
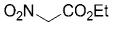
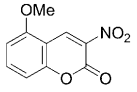
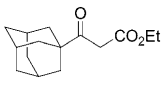
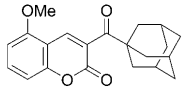
Table 2: Reaction of **5** and DMF with ketones **21**–**24**.[a]

Entry	Ketone (equiv)		Product (yield [%])[b]	
1		**21** (1.5)		**25** (79)
2		**22** (1.5)		**26** (40)[c]
3		**23** (1.0)		**27** (83)
4		**24** (1.0)		**28** (56)

[a] Reactions were carried out in DMF in the presence of anhydrous TBAF (3.0 equiv) at RT for 12 h. [b] Yield of isolated product. [c] Salicylaldehyde **18** was obtained in 35% yield.

derivative **34** was synthesized in 77% yield by employing β-keto ester **29** (Table 3, entry 1). β-Keto ester **30** bearing a phenyl group worked well (Table 3, entry 2). A high chemical

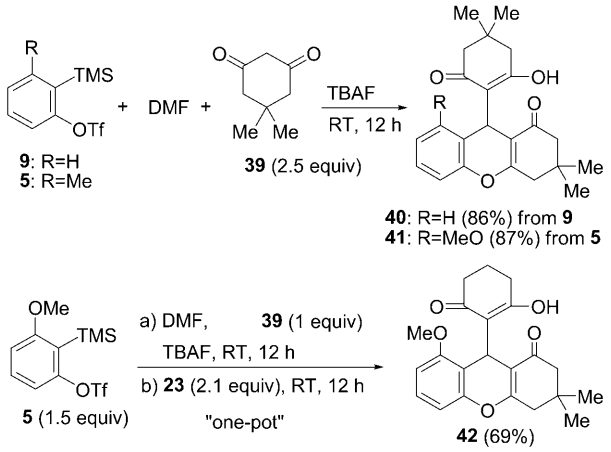
Table 3: Reaction of **5** and DMF with esters **29**–**33**.[a]

Entry	β-Keto ester (equiv)		Product (yield [%])[b]	
1		**29** (1.5)		**34** (77)
2		**30** (1.5)		**35** (83)
3		**31** (1.5)		**36** (86)
4		**32** (1.5)		**37** (27) + **5** (40)
5		**33** (1.5)		**38** (56)

[a] Reactions were carried out in DMF at RT for 12 h. [b] Yield of isolated product.

yield was also observed in the reaction using diethyl malonate **31** (Table 3, entry 3). The reaction of ester **32** having a nitro group proceeded, albeit with a relatively lower yield (Table 3, entry 4). Coumarin derivative **38** was isolated in 56% yield even when β-keto ester **33**, having a bulky adamantyl group, was employed (Table 3, entry 5).

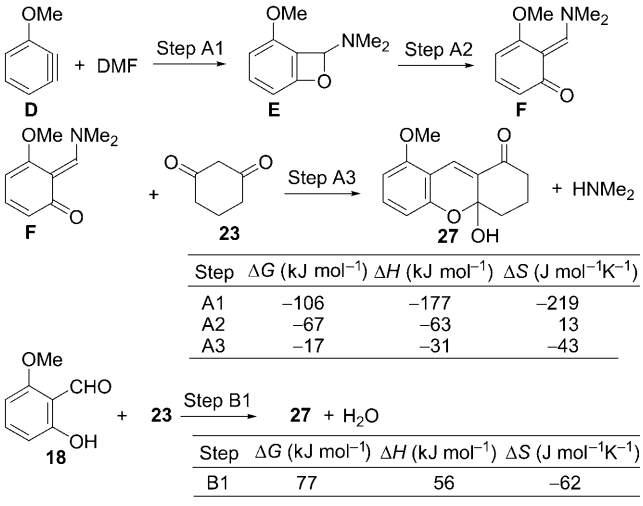
Our reaction was successfully applied to the convenient synthesis of a neuropeptide Y Y5 receptor antagonist, which was developed by Merck-Banyu researchers (Scheme 5).[22] In the presence of anhydrous TBAF, treatment of triflate **9** with dimedone **39** (2.5 equiv) in DMF gave the desired antagonist



Scheme 5. Multicomponent coupling reaction.

40 in 86% yield. Similarly, the reaction of **5** gave **41**. This transformation involves the formation of three C–C and two C–O bonds. In comparison with a previously reported method,[23] a favorable experimental feature of our method is that the reaction proceeds under neutral conditions at room temperature. Moreover, our method has enabled the new four-component coupling reaction using two different 1,3-diketones in a one-pot procedure, which readily gave the xanthene derivative **42**.

The multistep sequential reaction (Step A1 and Step A3) is obviously driven by high reactivity related to the strain energy of reactants (Scheme 6). The thermodynamic data, obtained by an ab initio molecular orbital calculation, indicate that Step A1 is remarkably exothermic ($\Delta H = -177\ \mathrm{kJ\,mol^{-1}}$) mainly as a result of the release of the strain energy of aryne **D**.[24] This enthalpy change sufficiently overcomes the entropy loss of the bimolecular coupling ($T\Delta S = -71\ \mathrm{kJ\,mol^{-1}}$). In total, the changes in Gibbs free energy of all steps mean that this sequential reaction is thermodynamically favorable ($\Delta G < 0\ \mathrm{kJ\,mol^{-1}}$). On the



Step	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1}K^{-1})
A1	−106	−177	−219
A2	−67	−63	13
A3	−17	−31	−43

Step	ΔG (kJ mol^{-1})	ΔH (kJ mol^{-1})	ΔS (J mol^{-1}K^{-1})
B1	77	56	−62

Scheme 6. Change in Gibbs free energy, enthalpy, and entropy at 325.15 K.

other hand, Step B1 (also see: path b in Scheme 3) from salicylaldehyde **18** is not favored because of thermodynamic considerations ($\Delta G = +77\ kJ\,mol^{-1}$), and is consistent with our experimental results described above.

In conclusion, we have developed the multicomponent coupling reaction based on the insertion of aryne compounds into DMF and subsequent trapping with active methylenes.

Experimental Section

General Procedure for the reaction of triflates, DMF, and acetylacetone **6**: Triflate (0.40 mmol) in DMF (1.0 mL) was added to a solution of anhydrous TBAF (314 mg, 1.2 mmol), acetylacetone **6** (62 μL, 0.60 mmol) in DMF (3.0 mL) under argon at RT. After stirring at RT for 3 h, silica gel (1.0 g) was added to the reaction mixture, and was subsequently concentrated under reduced pressure. Purification of the residue by flash column chromatography on silica gel (AcOEt/hexanes = 1:8–1:0 with 2% CH_2Cl_2) afforded the corresponding product.

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Keywords: 2*H*-chromenes · arynes · coumarins · insertion reaction · synthetic methods

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