Review

Synthesis of Oxygen Heterocycles via Aromatic C-O Bond Formation Using Arynes

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Abstract: Most of the synthetic approaches to the benzo-fused heterocycles containing an oxygen atom have involved the use of phenol derivatives as a starting material. This review highlights the new synthetic approaches involving the aromatic C-O bond-forming process using arynes. The insertion of arynes into the C=O bond gives the unstable intermediates, [2 + 2] cycloaddition-type adducts, which can be easily converted into a variety of oxygen atom-containing heterocycles in a single operation. In this review, the syntheses of oxygen heterocycles, such as coumarin, chromene, xanthene, dihydrobenzofuran and benzofuran derivatives, via the insertion of arynes into the C=O bond of aldehydes or formamides are summarized.

Keywords: oxygen heterocycles; arynes; synthesis; multi-component reaction

1. Introduction

Oxygen atom-containing heterocycles are an important class of the organic heterocyclic compounds. In particular, the benzo-fused oxygen heterocycles, in which oxygen heterocyclic ring is fused to benzene ring, are found as a key structural unit in natural products, pharmaceuticals and biologically active compounds (Figure 1) [1–3]. Therefore, benzo-fused oxygen heterocycles are of great synthetic interest. However, most of the synthetic approaches are based on the construction of oxygen heterocyclic ring from various phenol derivatives. Thus, the development of new approaches based on aromatic C-O bond formation continues to attract much interest.
As an representative example, the synthetic approaches to benzofurans and 2,3-dihydrobenzofurans are shown in Figure 2. Many reported approaches have involved the use of oxygen atom-containing arenes such as phenol, 2-bromophenol or salicylaldehyde derivatives as a starting material [4–8]. As an approach based on aromatic C-O bond formation, the intramolecular transition metal-catalyzed ipso substitution of aryl halide with an alcohol moiety was studied [9–16]. More recently, the oxidative aromatic C-O bond forming methods were developed [17]. Yu reported the oxidative approach to dihydrobenzofurans 2 from alcohols 1 via Pd(II)-catalyzed and hydroxyl-directed C-H bond activation followed by C-O bond formation [18]. Zhao reported that FeCl₃-mediated oxidative aromatic C-O bond forming cyclization of ketones 3 gave the benzofurans 4 [19].

Figure 2. Synthetic approaches to benzofurans and 2,3-dihydrobenzofurans.
The use of aryynes as the highly reactive intermediates in organic synthesis has attracted substantial attention [20–27]. The recent dramatic progress in aryne-based chemistry is summarized in the review articles [28–45]. The studies on the insertion of aryynes into the π-bond are limited [37,46]. This review highlights the new synthetic approaches to oxygen heterocycles via the aromatic C-O bond-forming process based on the insertion of aryynes into the C=O bond (Figure 3). When carbonyl compounds are employed, the insertion of aryne A into the C=O bond proceeds to give the unstable intermediate [2 + 2] cycloaddition-type adduct D, which isomerizes to the intermediate quinone methide E [47]. The subsequent trapping reaction of intermediate E with the reactant B having both nucleophilic and electrophilic sites gives oxygen atom-containing heterocycle C in a single operation.

**Figure 3.** Method for aromatic C-O bond formation using aryynes.

As shown in Figure 4, the insertion of aryne A into the C=O bond giving the [2 + 2] cycloaddition-type adduct D is assumed to proceed via the stepwise [2 + 2] mechanism involving the zwitterionic specie as an intermediate.

**Figure 4.** Stepwise mechanism.
2. Syntheses of Oxygen Heterocycles Using Insertion of Arynes into C=O Bond

2.1. Domino Reaction Starting from Insertion of Arynes into Aldehydes

Heaney studied the reaction of arynes with carbonyl compounds [48–50]. He reported a novel approach to the synthesis of 2H-chromenes based on the reaction of arynes with α,β-unsaturated aldehydes (Scheme 1) [48]. Tetrachloroanthranilic acid 5 was employed as an aryne precursor. In the presence of pentyl nitrite, treatment of 5 with α,β-unsaturated aldehydes 6a–e gave 2H-chromenes 7a–e. Although the yields obtained in the reaction with acrolein 6a, 2,3-dimethylacrolein 6c or 3,3-dimethylacrolein 6d were not good, the use of crotonaldehyde 6b and cinnamaldehyde 6e led to the formation of 2H-chromenes 7b and 7e in the reasonable yields. Initially, aryne F is generated via the diazotization reaction of precursor 5 with pentyl nitrite. The insertion of aryne F into the C=O bond of aldehydes 6a–e gives the formal [2 + 2]-type adduct G. The ring opening of [2 + 2]-type adduct G gives the intermediate quinone methide H which could undergo the intramolecular Diels-Alder reaction to afford 2H-chromenes 7a–e.

![Scheme 1](image_url)

Scheme 1. Reaction of aryne precursor 5 with α,β-unsaturated aldehydes.

Next, tetrachlorobenzenediazonium-2-carboxylate hydrochloride 8 and 3,4,5,6-tetrachloro-2-(3,3-dimethyltriazeno)benzoic acid 9 were employed as an aryne precursor (Scheme 2). When aryne precursor 8 was heated at 60 °C in chloroform containing an excess of cinnamaldehyde 6e, 2H-chromene 7e was obtained in 58% yield. Similarly, heating precursor 9 at 120 °C in tetrachloroethylene containing cinnamaldehyde 6e gave 2H-chromene 7e in 35% yield. Interestingly, the isomerization of 2H-chromene 7e into 4H-chromene 10 was also observed. 4H-Chromene 10 was formed in 22% yield when the
reaction of 9 with 6e was carried out at 200 °C in the absence of a solvent. The effective isomerization of 7e into 10 was achieved by the preparative layer chromatography using neutral alumina.

Scheme 2. Reaction of precursors 8 and 9 with cinnamaldehyde 6e.

The reaction of benzyne with an excess amount of benzaldehyde was studied by Heaney and Nakayama, independently [50,51]. Nakayama reported that heating benzyne precursor 11 at 160 °C in benzaldehyde 12a gave cis- and trans-2,4-diphenyl-1,3-benzodioxines 13 and 14 accompanied by the basic compound 15 (Scheme 3). Two isomeric cyclic products 13 and 14 are formed through the [2 + 2]-type reaction of benzyne, generated from precursor 11, with the C=O bond of benzaldehyde 12a followed by the trapping reaction of the intermediate quinone methide I with benzaldehyde 12a. In contrast, 2-dimethylaminobenzhydrol 15 is obtained as a result of the reaction of benzyne with HNMe2 generated from precursor 11. Additionally, It is reported that the reaction of benzenediazonium-2-carboxylate with benzaldehyde 12a in CH2Cl2 at 40 °C afforded cis-isomer 13 exclusively. Thus, the trapping reaction of quinone methide I with benzaldehyde 12a would take place concertedly in syn fashion with the endo orientation.

Scheme 3. Reaction of aryne precursor 11 with benzaldehyde 12a.

A straightforward method for the synthesis of xanthene derivatives was developed by Yoshida and Kunai’s group (Scheme 4) [52]. They reported that the 2:1 coupling reaction of two molar amounts of
aryne and one molar amount of aryl aldehyde gave 9-arylxanthenes derivatives. The reaction was carried out in THF at 0 °C using o-trimethylsilylphenyl triflate 16 (0.45 mol) and aryl aldehydes 12a–e (0.15 mol) in the presence of KF and 18-crown-6. The reaction of benzylene, generated from 16 and KF/18-crown-6, with variously substituted aryl aldehydes 12b–e gave the 9-arylxanthenes 17b–e in reasonable yields, although low yield was observed in the reaction with simple benzaldehyde 12a. The reactions using naphthaldehydes 18a–c or other substituted precursors are also reported. As shown in Scheme 4, the substituted naphthaldehydes 18b and 18c worked well to give the bulky xanthenes 19b and 19c in 66% and 70% yields, respectively.

Scheme 4. 2:1-Coupling reaction of aryne precursor 16 with various aldehydes.

### 2.2. Domino Reaction Starting from Insertion of Arynes into Formamides

Domino reactions starting from the insertion of arynes into the C=O bond of formamides provide the new synthetic approaches to the benzo-fused heterocycles containing an oxygen atom. In 1965, Yaroslavsky reported that benzylene, generated from precursor 20, reacted with N,N-dimethylformamide (DMF) to give salicylaldehyde 21 in 32% yield (Scheme 5) [53]. Recently, Miyabe studied the trapping reaction of the intermediates generated by the reaction of precursor 22 with formamides [54,55]. He reported that diethyllzinc trapped the intermediates L with good chemical efficiencies to give the aminophenols 23a–23c. The mechanism involving the formation of formal [2 + 2]-type adducts K and quinone methides L is proposed.
Okuma reported that the 2:1 coupling reaction of two molar amounts of benzyne and one molar amount of DMF gave 9-hydroxyxanthene (Scheme 6) [56]. In the presence of CsF and K₂CO₃, the reaction of precursor 16 (1.2 mol) with DMF (0.5 mol) in CH₃CN at room temperature afforded 9-hydroxyxanthene 24 in 52% yield. 9-Hydroxyxanthene 24 would be formed by the reaction of salicylaldehyde 21 with benzyne. The formation of xanthenes and xanthones through the disproportionation of 9-hydroxyxanthene 24 is also reported.

A method for preparing 2H-chromene derivatives was developed by Miyabe (Scheme 7) [57]. Three-component coupling reaction leading 2H-chromenes 26a–c was achieved by the use of active methylene compounds 25a–c as a nucleophile for trapping the unstable intermediate M. In the presence of anhydrous TBAF as fluoride ion source, treatment of precursor 22 with acetylacetone 25a in DMF at room temperature gave the 2H-chromene 26a in 86% yield. Similarly, the bulky 1,3-diketone 25b bearing two phenyl groups and the acetone 25c having an α–CF₃ group acted as a nucleophile trapping quinone methide M to give the corresponding 2H-chromenes 26b and 26c in 79% and 40% yields, respectively.
The tricyclic 2H-chromene derivatives 28a and 28b were obtained when cyclic 1,3-diketones 27a and 27b were employed as a nucleophile (Scheme 8) [57]. Three-component coupling reaction with 27a at room temperature produced tricyclic compound 28a in 83% yield. In the case of unsymmetrical diketone 27b, the compound 28b was obtained as a major regioisomer. The formation of tricyclic 2H-chromene derivatives was also observed when cyclohexenone derivatives 29a and 29b were employed as a nucleophile [57]. In the presence of KF, the reaction using precursor 22 and cyclohexenone 29a was carried out in DMF at 80 °C to give the tricyclic product 30a in 40% yield. Under the similar reaction conditions, the desired compound 30b was obtained in 34% yield even when bulky nucleophile 29b was employed. This transformation would involve the trapping reaction of the intermediate M with anions O generated from cyclohexenones 29a and 29b.

Miyabe reported the synthesis of 4H-chromene derivatives (Scheme 9) [58]. Three-component coupling reaction involving the hetero Diels-Alder reaction of the transient intermediate M with dienophiles was investigated. In the presence of CsF, the reaction using precursor 22 and acetylenedicarboxylic acid dimethyl ester 31a in DMF proceeded effectively at 25 °C. The 4H-chromene 32a was obtained in 80%
yield after being stirred 2 h. The heating activation at 50 °C accelerated the reaction to give 32a in 79% for 15 min. Under analogous reaction conditions, diethyl ester of acetylenedicarboxylic acid 31b has shown the good reactivity. Moreover, bulky acetylenedicarboxylic acid di-tert-butyl ester 31c worked well to give the product 32c in 71% yield. The reaction of aryne precursor 33 was also reported.

![Chemical structure of 4H-chromene derivatives](image)

**Scheme 9.** Synthesis of 4H-chromene derivatives.

The synthesis of coumarin derivatives was studied by Miyabe and Yoshida, independently [57,59]. Miyabe reported three-component coupling reaction using β–keto esters as a nucleophile trapping the intermediate quinone methide (Scheme 10) [57]. When β–keto ester 35a was employed, coumarin 36a was synthesized in 77% yield. High chemical yields were observed in the reactions using β–keto ester 35b having a phenyl group or diethyl malonate 35c. In contrast, the reaction of ester 35d having a nitro group proceeded, albeit with relatively lower yield.

![Chemical structure of coumarin derivatives](image)

**Scheme 10.** Synthesis of coumarin derivatives.

Yoshida studied three-component coupling reaction for the synthesis of coumarin derivatives [59]. The efficient method for preparing the coumarins substituted an aryl group at 3 position was reported (Scheme 11). In the presence of KF, the reaction using acetates 37a–c having an aryl group was carried out in DMF at 80 °C to give the coumarins 38a–c. Interestingly, acetonitriles 39a–c having aryl group acted as a nucleophile under similar conditions. The reaction using precursor 16 and phenylacetonitrile 39a in DMF proceeded at 80 °C to afford the coumarin 40a in 60% yield after being stirred 6.5 h.
Although the reaction of bulky 1-naphthylacetonitrile 39c resulted in a low yield, 2-naphthylacetonitrile 39b effectively participated in the reaction to give 40b in 66% yield.

**Scheme 11.** Synthesis of coumarin derivatives having an aryl group.

Coumarin 36c was effectively synthesized by the use of debrominated metal enolate P, which was *in situ* generated by a combination of α-bromomalonate 41 and Me₃Al (Scheme 12) [60]. In the presence of anhydrous TBAF, precursor 22 was reacted with 41 and Me₃Al in DMF at room temperature to give the desired coumarin 36c in 85% yield. Interestingly, the formation of coumarin 36a was observed when ethyl 2-butyrate 42 was used [58]. In this transformation, the anion Q would be generated by the addition of fluoride ion to butyrate 42. The trapping reaction of quinone methide M with anion Q would lead to the formation of coumarin 36a.

**Scheme 12.** Synthesis of coumarin derivatives using reactants 41 and 42.
Three-component coupling reaction for preparing 2H-chromenes as shown in Scheme 7 was successfully applied to four-component coupling reaction for the convenient synthesis of xanthene derivatives (Scheme 13) [57]. In the presence of anhydrous TBAF, treatment of aryne precursor 16 (1.0 equiv.) with dimedone 43 (2.5 equiv.) in DMF at room temperature gave xanthene derivative 44 in 86% yield. In this transformation, three-component coupling product 2H-chromene 45 reacted again with an excess amount of dimedone 43 to give 44 in one-pot. Four-component coupling reaction using two different 1,3-diketones also proceeded by a one-pot procedure. When 2-hydroxy-1,4-naphthoquinone 46 was used as a nucleophilic reactant, the direct one-pot synthesis of xanthene derivative 47 from precursor 22 was achieved [61]. These transformations involve the three C-C and two C-O bond-forming processes under mild neutral conditions.

Scheme 13. Multicomponent coupling reaction.

For the construction of the five-membered oxygen heterocyclic rings such as dihydrobenzofurans and benzofurans, the intermediate quinone methide M must be trapped with C1-units having a nucleophilic and electrophilic carbon atom (Figure 5).

Figure 5. Method for the synthesis of dihydrobenzofurans and benzofurans.
Miyabe used α-halogenated enolates as a nucleophilic and electrophilic C1-unit for trapping the intermediate M (Scheme 14) [60,62]. He reported that the desired α-halogenated enolate R was effectively prepared by a combination of α-chloromalonate 48 and Et2Zn. In the presence of CsF and Et2Zn, treatment of precursor 22 with α-chloromalonate 48 in DMF at -40 °C to room temperature gave 2,3-dihydrobenzofuran 49a in 86% yield. Under similar reaction conditions, dihydrobenzofuran 49b having N-methyl and N-allyl groups was obtained from unsymmetrical formamide. Additionally, 1-formylpiperidine worked well to give 2,3-dihydrobenzofuran 49c. Moreover, three-component coupling reaction using ethyl α-chlorophenylacetate 50 took place to afford two diastereomers 51a and 51b in acceptable yields.

Scheme 14. Synthesis of 2,3-dihydrobenzofurans having a dimethylamino group.

The synthesis of 2,3-dihydrobenzofuran 53 having a hydroxy group was also reported (Scheme 15) [60]. When α-bromomalonate 52 was used as a C1-unit together with a small amount of water, the desired dihydrobenzofuran 53 was obtained in 77% yield instead of dihydrobenzofuran 49a having a dimethylamino group.

Scheme 15. Synthesis of 2,3-dihydrobenzofuran having a hydroxy group.
The conversion of 2,3-dihydrobenzofurans into benzofurans was studied (Scheme 16) [60]. Treatment of dihydrobenzofuran 29a with 2.5 equivalents of EtMgBr in THF at −40 °C to room temperature followed by SiO2 in AcOEt at room temperature gave benzofuran 55 in 77% yield. This transformation was carried out by one-pot procedure without the isolation of adduct 54. The desired benzofuran 55 is formed via the retro-aldol type reaction of 54 followed by the elimination of a dimethylamino group of intermediate S.

Scheme 16. Conversion of 2,3-dihydrobenzofuran 49a into benzofuran 55.

As an alternative approach for the synthesis of benzofurans, another effective transformation of 2,3-dihydrobenzofuran 53 having a hydroxy group into benzofuran 55 was reported (Scheme 17) [60]. This transformation would involve the decarboxylation of the cyclic intermediate T [63]. The base had an impact on the chemical efficiency of this transformation. LiHMDS and NaHMDS were less effective. When KHMDS was employed as a base in THF at −40 °C, benzofuran 55 was obtained in 96% yield.

Scheme 17. Conversion of dihydrobenzofuran 53 having a hydroxy group.

Direct synthesis of benzofurans from arylene precursors was also investigated [60,62]. The method using ethyl iodoacetate 56 as a C1-unit is shown in Scheme 18 [60]. In the presence of CsF, the reaction of precursor 22 with 56 was carried out in DMF at 100 °C to give the benzofuran 55 in 40% yield. When the same reaction was carried out at room temperature, simple O-alkylated product 57 was formed. Additionally, the formation of benzofuran 55 was observed in heating O-alkylated product 57 at 100 °C. Based on these results, two possible reaction pathways are proposed. As a direct pathway, benzofuran 55 is obtained from the intermediate U, which is generated by the trapping reaction of quinone methide M with ethyl iodoacetate 56. Another pathway is the formation of benzofuran 55 from O-alkylated product 57.
The direct one-pot synthesis of benzofurans through the retro-aldol type reaction was reported (Scheme 19) [62]. For this transformation, the α-halogenated active methines having a ketone group were used as a C1-unit, since the reaction of ketone moiety with Et₂Zn leads to the retro-aldol type process. In the presence of CsF, treatment of active methines 58a and 58b with Et₂Zn and precursor 22 at −60 °C to room temperature led to the direct formation of benzofurans 59a and 59b. This transformation proceeds via the addition of an ethyl anion to a ketone group of V followed by the retro-aldol type reaction of W. The methine 58c having a bulky phenyl ketone group worked well to give benzofuran 59c.

3. Concluding Remarks

The recent aryne-based chemistry has achieved some remarkable success. Particularly, the insertion of arynes into the C=O bond has been studied as a powerful method for preparing the benzo-fused oxygen heterocycles. These aromatic C-O bond forming reactions proceed under mild transition metal-free
conditions. Moreover, synthetic strategies involving multicomponent coupling reaction offer the advantage of multiple carbon-carbon and/or carbon-heteroatom bond formations in a single operation. In addition to the insertion of arynes into various element-element $\sigma$-bonds, the corresponding $\pi$-bond insertion disclosed a broader aspect of the utility of arynes in synthetic organic chemistry. This domain offers opportunities for further exploration with intriguing possibilities in aryne chemistry. I hope that this review will inspire new creative contributions by organic chemists.

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Conflicts of Interest

The author declares no conflict of interest.

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