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The Oxygen-Containing Fused Heterocyclic Compounds

*Hillemane Venkatachalam
and Nanjangud Venkatesh Anil Kumar*

Abstract

The oxygen-containing heterocycles are an important class of compounds in organic chemistry. These compounds are used as drugs (coumarin and oxazole), solvent (tetrahydrofuran), flavors, and fragrances (lactones). The fusion of aromatic ring to the oxygen-heterocycle will change the electron density; thereby, the physical/chemical/biological properties will alter. Also, the preparation of these fused molecules will require a different strategy/method/reaction condition. The topics covered in this chapter are the general synthetic methods and uses of fused heterocyclic compounds containing oxygen as a heteroatom. The derivatization of the primary scaffold is excluded from this chapter. Some of the fused compounds are coumarin (benzopyrans) and piclozotan (benzoxazepines).

Keywords: heterocycles, oxygen heteroatom, fused molecules, coumarin, a flavonoid

1. Introduction

The oxygen-containing heterocycles are an important class of compounds in organic chemistry mainly because of their natural abundance and diverse biological functions. Natural and semi-synthetic oxygen heterocyclic compounds such as Taxol [1] (anticancer), Digoxin (CHF treatment), Cyclosporine-A (immunosuppressant) and Lovastatin (hypolipidemic) are well known used as promising therapeutic compounds [2]. Kaur et al. reviewed the oxygen heterocycles wherein saturated and unsaturated compounds are considered. They discussed the classification and chemistry of each of those compounds [1]. Reports are available wherein the synthesis of natural products containing oxygen as heteroatom is reviewed by Cossy and Guérinot [2]. Also, Rowlands and Farley chaptered the book on the anion radicals from oxygen-containing heterocycles [3]. None of these reports target the oxygen-containing heterocyclic compounds where fused rings are taken into consideration.

2. Classification of oxygen heterocycles

The oxygen-containing heterocycles can be classified in several ways like the classification based on (a) the number of oxygen atoms, (b) saturation level, (c) aromaticity or (d) abundance. For the clarity of the concept, the classification

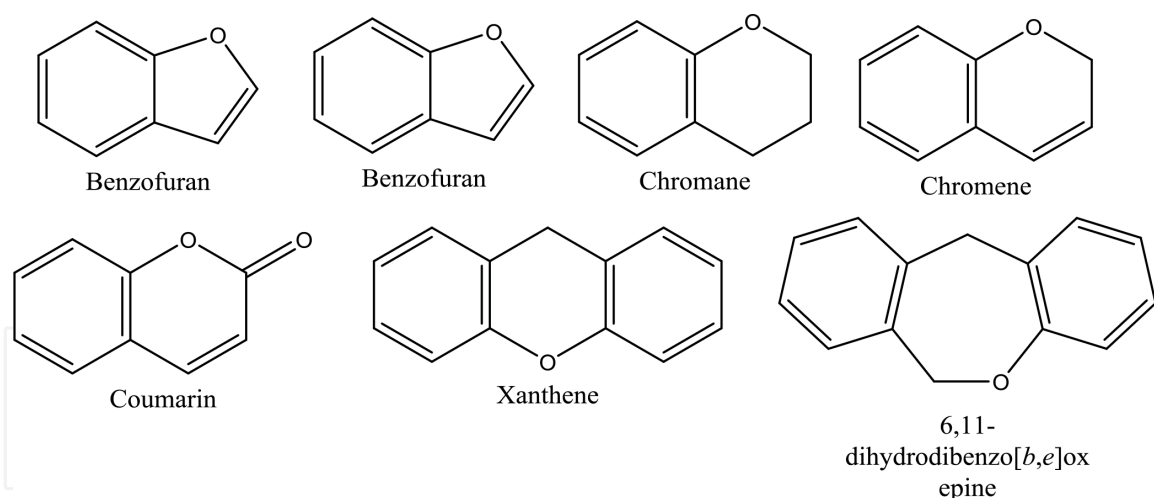


Figure 1.
Mono-oxygen containing fused heterocyclic compounds.

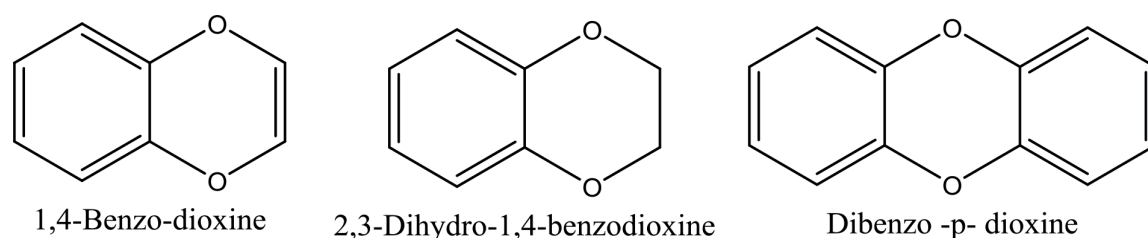


Figure 2.
Di-oxygen containing fused heterocyclic compounds.

based on a number of oxygen atoms is used. The benzene fused furan and pyrans are listed in **Figure 1**, whereas **Figure 2** represents the compounds with two oxygen atoms in the ring system.

3. Synthesis of benzofurans

3.1 Mono-substituted benzofurans

3.1.1 Substitution on furan ring

The ortho-hydroxystilbenes are cyclized in 70–90% yield in a metal-free environment using hypervalent iodine and 1 eq. of (diacetoxyiodo) benzene to get 2-substituted benzofurans [4]. The acids are converted to 2,4,6- trichloro-1,3,5-triazine esters, which are subsequently added to toluene, 2-hydroxybenzyl triphenylphosphonium bromide (1 eq.), and NEt_3 and irradiated at 110°C for two cycles of 30 min to get the 2-substituted benzofurans having a chiral stereocenter adjacent to the heterocycle in 60–80% yield [5]. Pd-catalyzed cyclisation of 2-chloroaryl alkynes using KOH at 100°C for 8 h resulted in the formation of benzofurans [6]. All three reactions are as shown in **Figure 3**.

3.1.2 Substitution on the benzene ring

Also, the substituted 1-allyl-2-allyloxybenzenes cyclizes to give substituted benzofurans by isomerization followed by ring-closure metathesis reaction using 5 mol.% catalyst [7]. The homologous members of benzofurans can be prepared by 0.1 eq. of Ru-catalyzed cycloisomerization of homo- and bis-homopropargylic alcohols in presence of pyridine at 90°C for 1–6 h [8] as shown in **Figure 4**.

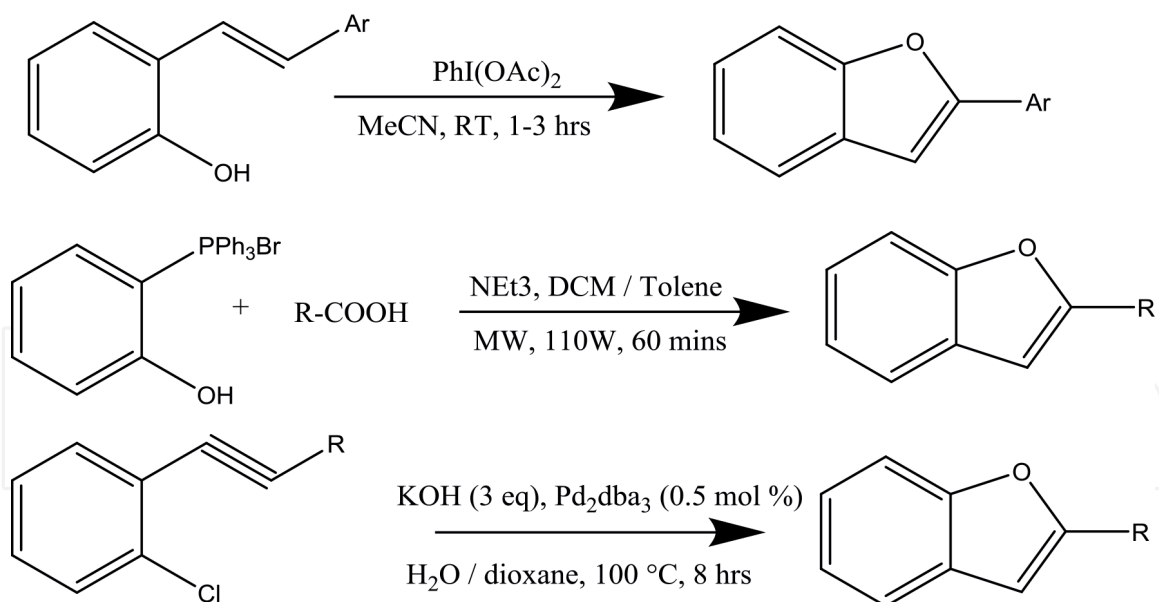


Figure 3.
 Preparation of mono-substituted benzofuran.

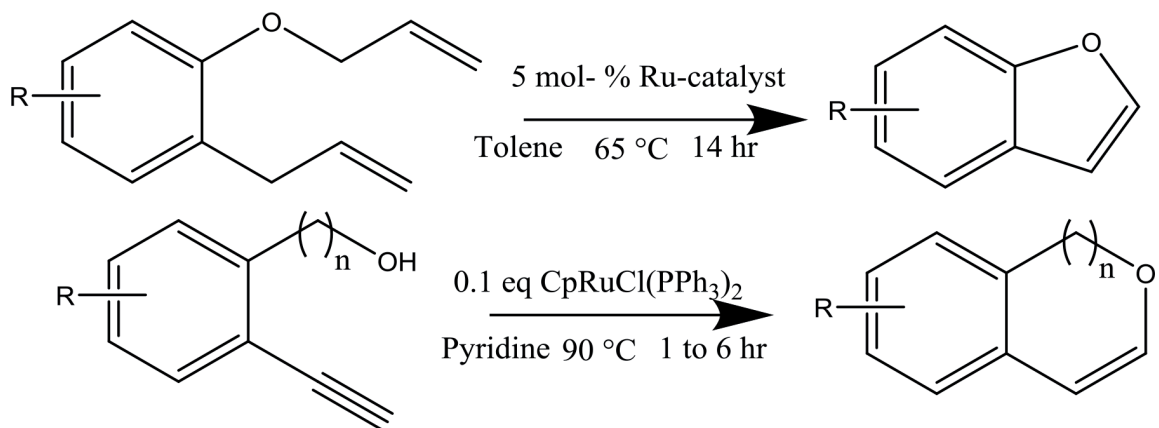


Figure 4.
 Benzene ring substituted benzofuran.

3.2 Di-substituted benzofurans

3.2.1 Substitution on furan and benzene ring of benzofuran

The reaction between 1 eq. of 2-(2-hydroxyphenyl)acetonitriles with 2 eq of aryl boronic acids along with $\text{Pd}(\text{OAc})_2$ (5 mol.%), bpy (10 mol.%), TFA (10 eq.), with TFA as solvent heated to 80°C for 36 h resulted in benzofuran derivatives with more than 80% yield [9]. Sonogashira cross-coupling reaction of halide with terminal alkynes followed by cyclization of the resulting 2-alkynylphenols in one-pot method results in benzofuran. The method employs the t-BuOH, $\text{PdCl}_2\text{-(CH}_3\text{CN)}_2$ (2 mol.%), t-BuOLi (3.6 eq.) and 2-chlorophenol (1 eq.), alkyne (1.5 eq.) were taken in a sealed tube and heated to 110°C for 22 h to get benzofuran [10]. Reaction of N-tosylhydrazones and terminal alkyne in a ligand free environment, using 10 mol.% of CuBr and 3 eq. of Cs_2CO_3 at 100°C for 4 h resulted in the formation of benzofurans with 38–91% yield [11]. Reductive cyclization of 1-(2-hydroxyphenyl)-propargyl alcohols in presence of $\text{Pd}(\text{OAc})_2$ (5 mol.%), t-BuNC (1.2 eq.), Cs_2CO_3 (1.2 eq.) and MeCN as solvent gives benzofurans [12]. These reaction schemes are as shown in **Figure 5**.

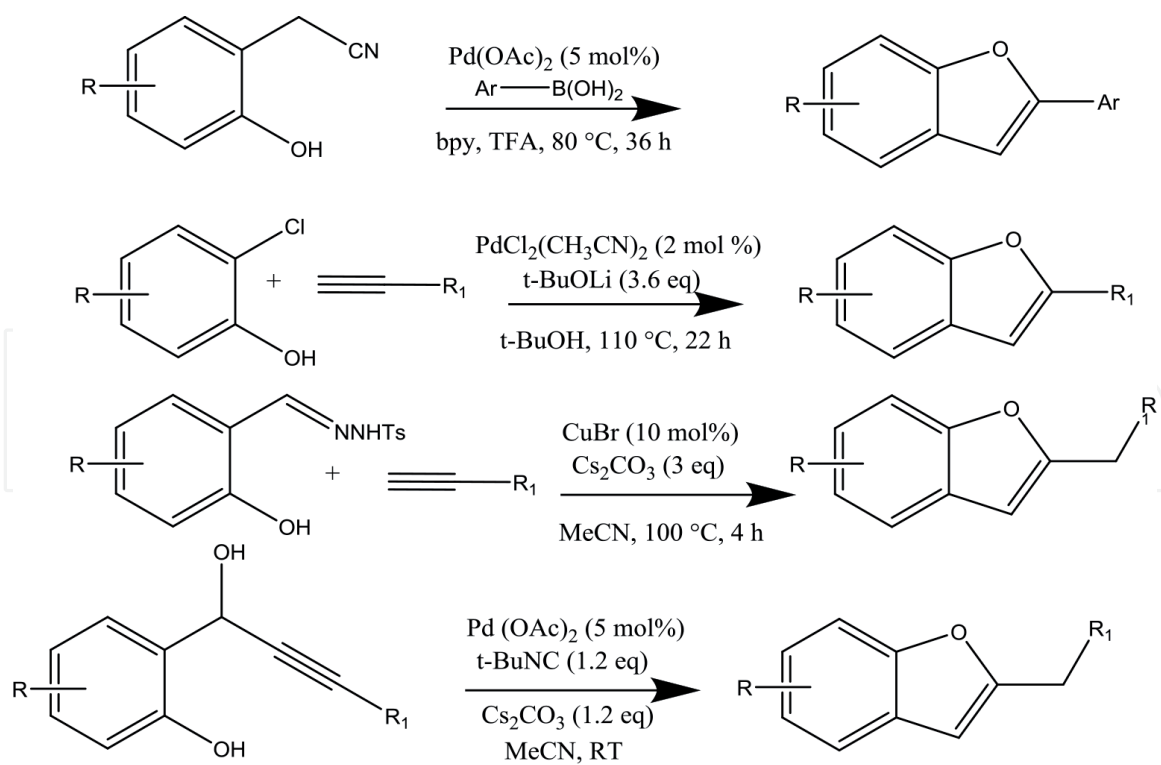


Figure 5.
Di-substituted benzofurans.

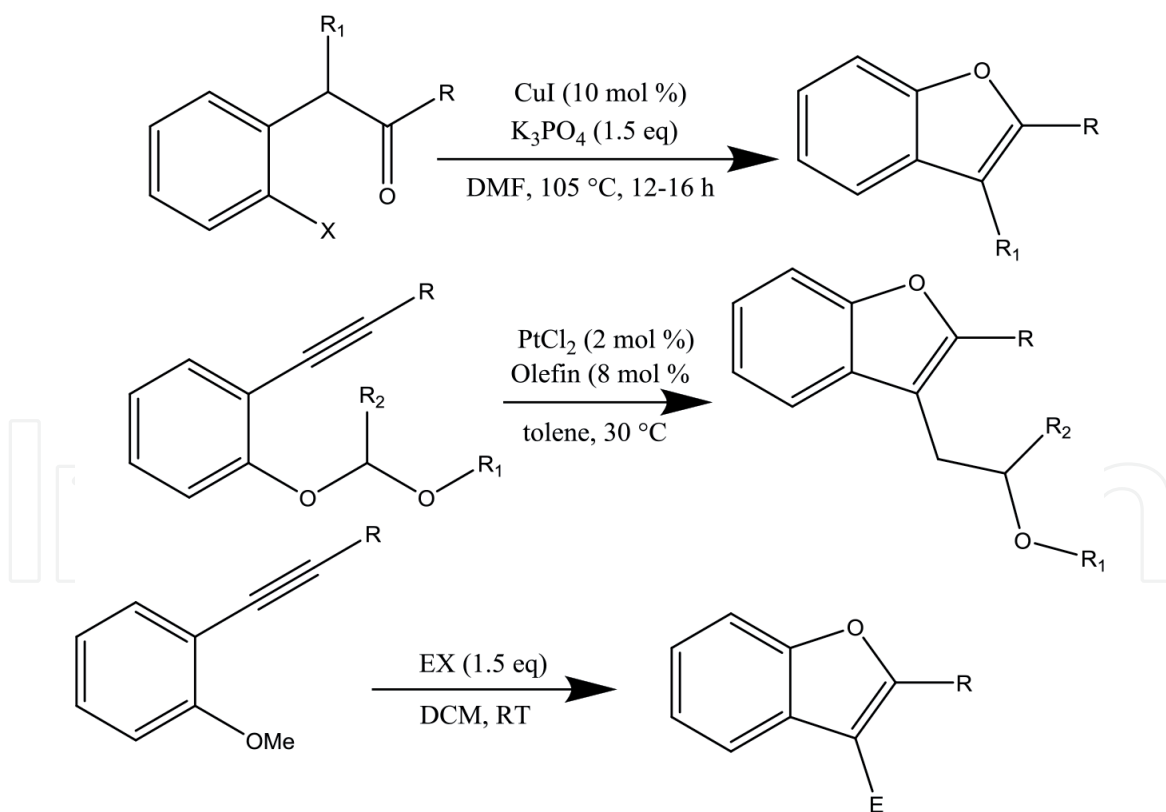


Figure 6.
Preparation of di-substituted benzofuran.

3.2.2 2,3-Substituted benzofuran

Ring closure of 2-haloaromatic ketones (1 eq.) in presence of K_3PO_4 (1.5 eq.), CuI (10 mol.%) and DMF at 105°C for 12–16 h results in di-substituted benzofurans [13]. The good yield coupled with atom economy was achieved, when o-alkynyl

phenyl acetals are cyclized using PtCl_2 (2 mol.%), olefin (8 mol.%) in toluene at 30°C [14]. Cyclization of *o*-iodoanisoles and terminal alkynes under mild conditions using an electrophile (EX like PhSeCl or $p\text{-O}_2\text{NC}_6\text{H}_4\text{SCl}$) (1.5 eq.), DCM at room temperature for 2–6 h yields 2,3-disubstituted benzofurans [15]. These reaction schemes are as shown in **Figure 6**.

Selective dehydrative C—H alkylation reaction of alkenes with alcohols using $[(\text{C}_6\text{H}_6)(\text{PCy}_3)(\text{CO})\text{RuH}]\text{BF}_4$, cyclopentene, toluene at 100°C for 6–12 h results in 2,3-substituted benzofurans [16]. *O*-Arylhydroxylamine hydrochloride (1 eq.) with cyclic or acyclic ketones (1 eq.) in the presence of methanesulfonic acid (2 eq.), THF at 60°C for 2–24 h yields benzofurans in 40–90% yield [17]. Ketones (1 eq.) on treatment with Grignard reagents (3 eq.), benzofurans are formed, in a regioselective manner via [1,2]-aryl migration [18]. These reactions are depicted in **Figure 7**.

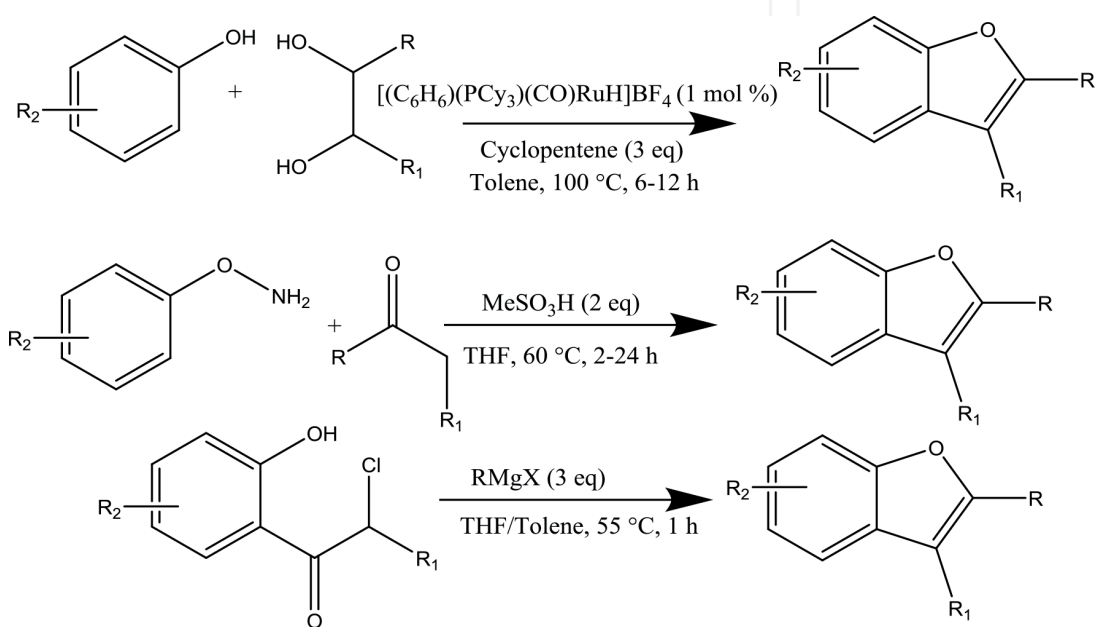


Figure 7.
Substituted benzofurans.

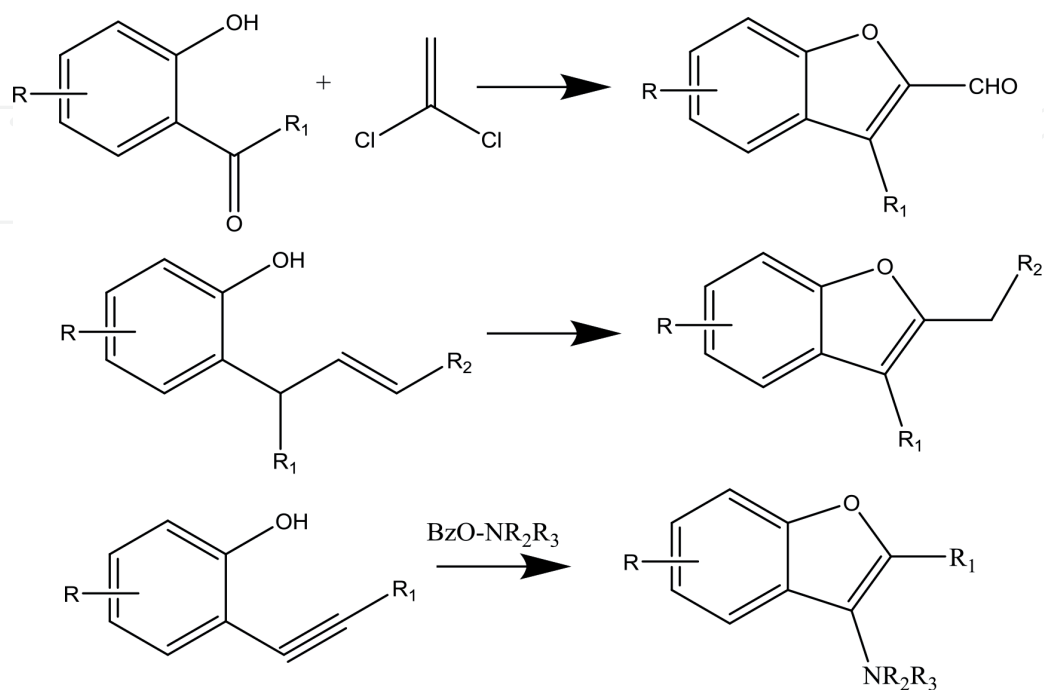


Figure 8.
Substituted benzofuran carbaldehydes.

Base-catalyzed, the condensation of o-hydroxyphenones with 1,1-dichloroethylene, gives substituted benzofuran carbaldehydes [19].

Similarly, o-cinnamyl phenols, on oxidative cyclisation, results in 2-benzyl benzofurans [20], while o-alkylphenols, on annulative reaction, gives 3-aminobenzofurans [21] (Figure 8).

4. Synthesis of benzofuranones

Alkenylphenols and phenyl formate reacts to give benzofuranones [22], while phenylacetic acids undergo cyclisation to give benzofuranones [23] (Figure 9).

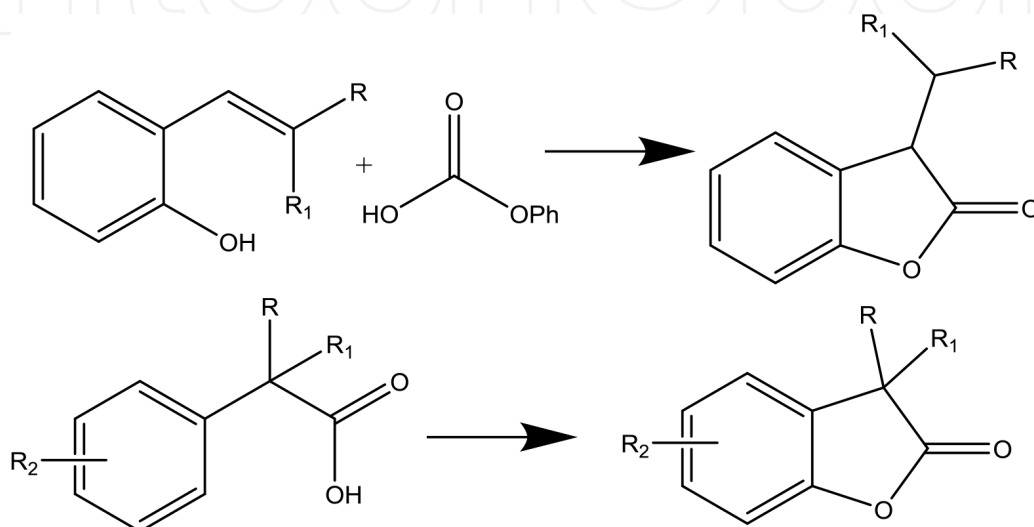


Figure 9.
Synthesis of benzofuranones.

5. Synthesis of dibenzofurans

Iododiaryl ether cyclizes under mild conditions to yield dibenzofurans [24]. Ortho-diazonium salts of diaryl ethers undergo intramolecular cyclisation,

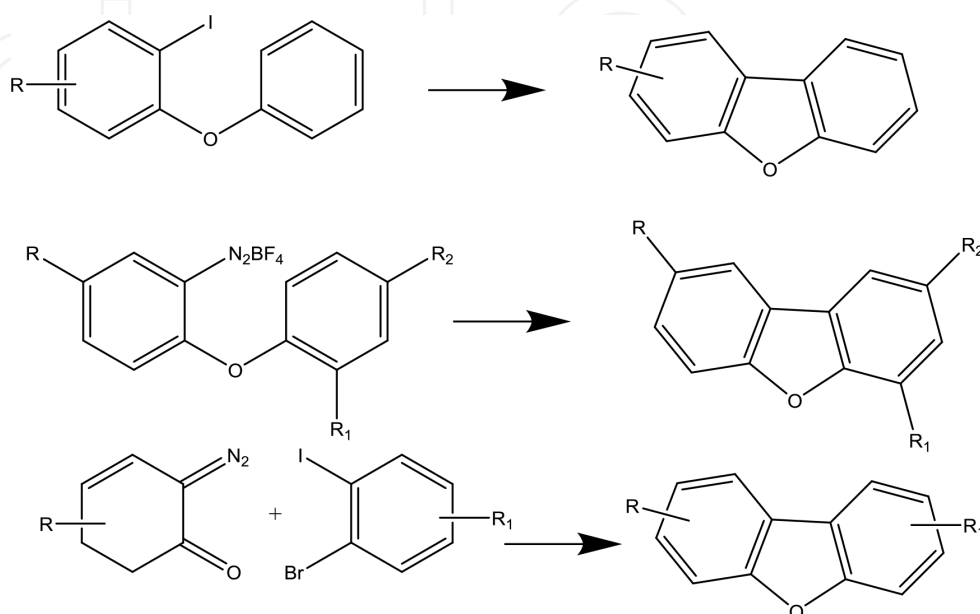


Figure 10.
Mono substituted dibenzofurans.

resulting in dibenzofurans [25]. Cross-coupling of 6-diazo-2-cyclohexenones and ortho-haloiodobenzenes gives substituted dibenzofuran [26] (Figure 10).

6. Synthesis of coumarins

Phenols react with beta-keto esters to give coumarins [27]. If phenolic acetates are used, then, acrylates are used [28]. Aromatic alkynoate undergoes cyclisation with aldehydes to form 3-acyl-4-arylcoumarins [29] (Figure 11).

Substituted 2-hydroxybenzaldehydes react with phenylacetic acids resulting in substituted 3-aryl coumarins [30]. With dialkyl acetylenedicarboxylate, 2-hydroxybenzaldehydes gives 4-carboxyalkyl-8-formyl coumarins [31]. 2-Hydroxybenzaldehydes (or 2-hydroxybenzaldehydes) cyclizes with aryl acetic acids to give 3-aryl coumarins (or 3-aryl-4-methyl-coumarins) [32] (Figure 12).

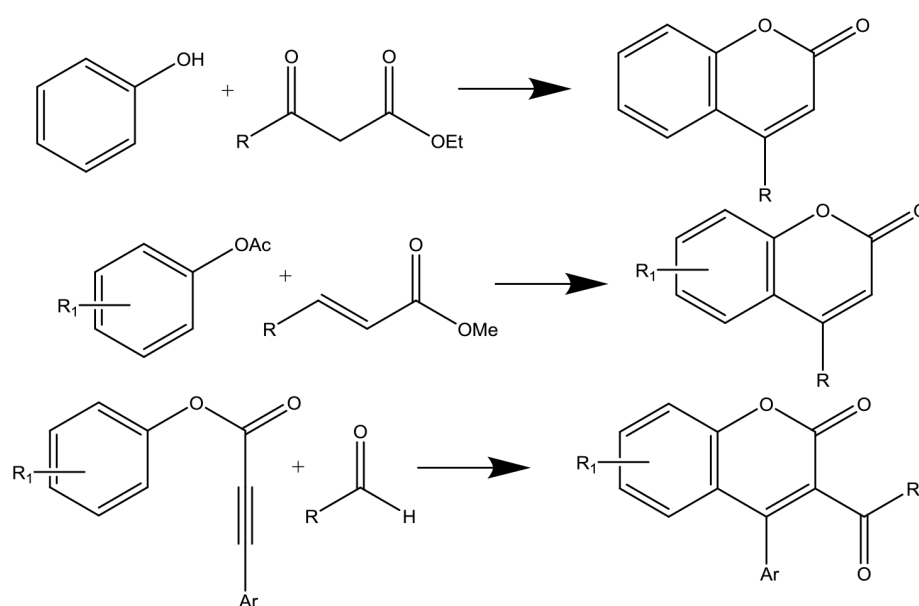


Figure 11.
Coumarin synthesis using phenol derivatives.

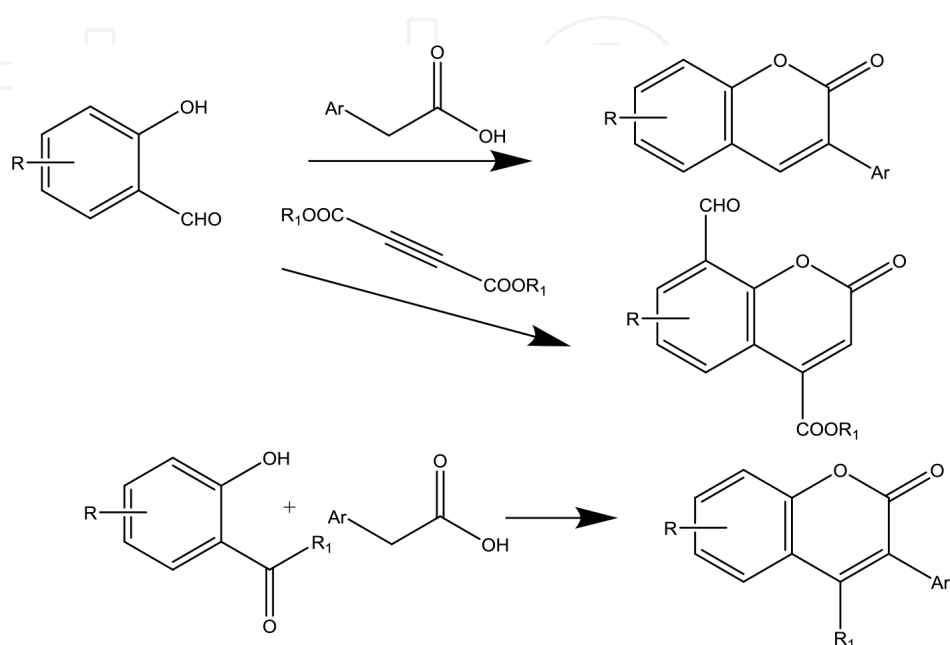


Figure 12.
Coumarin synthesis using benzaldehyde derivatives.

7. Synthesis of isocoumarins

Bromoalkynes reacts with benzoic acid and produces 3-substituted isocoumarins [33]. *o*-Halobenzoic acids and 1,3-diketones reacts to give 3-substituted isocoumarins [34]. 2-Halobenzoates and ketones react to give the same product [35]. *o*-Halobenzoic acids add to alkynes resulting in isocoumarin derivatives [36] (**Figure 13**).

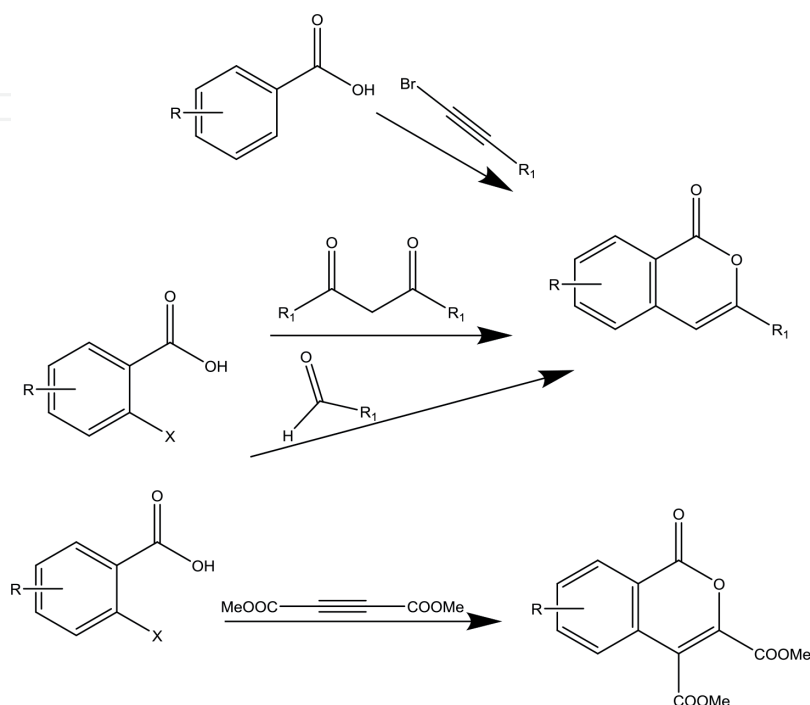


Figure 13.
Synthesis of isocoumarins.

8. Synthesis of flavones and flavonols

8.1 Baker-Venkataraman rearrangement

The chemical reaction between 2-hydroxyacetophenone and acid chloride in the presence of base yields 1,3-diketone which undergo rearrangement and

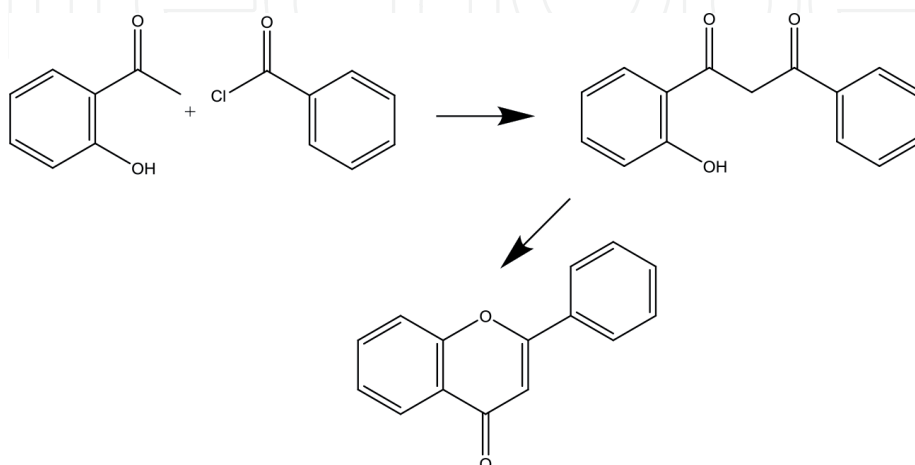


Figure 14.
Synthesis of flavone (from 1,3-diketone).

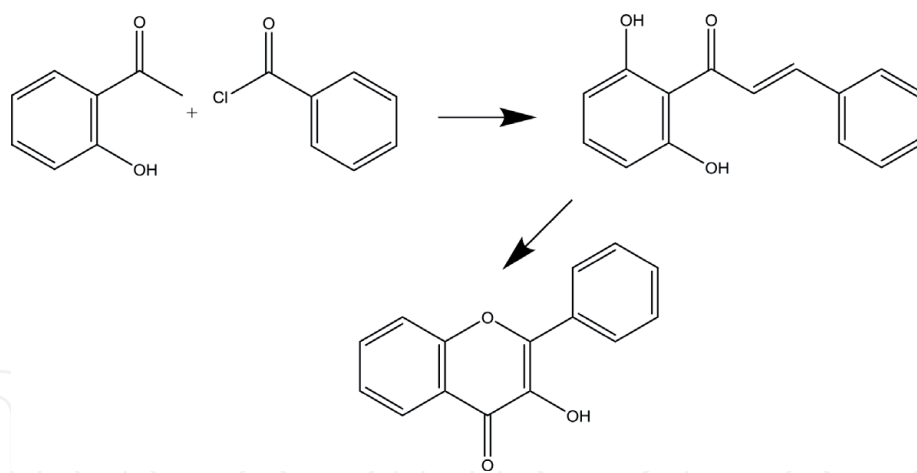


Figure 15.
Synthesis of flavone (from chalcone).

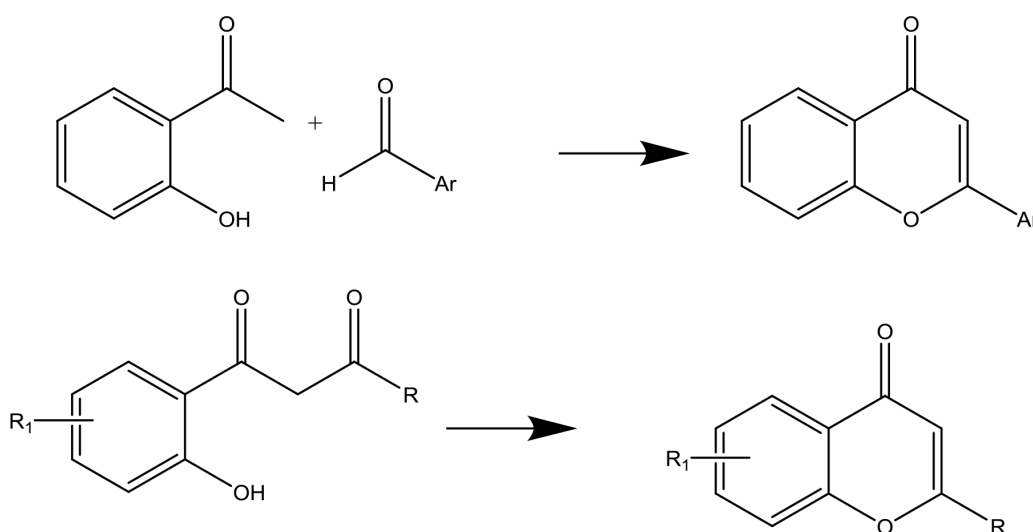


Figure 16.
Preparation of 2-phenyl γ -benzopyrones.

concomitant cyclisation to produce flavone [37]. This reaction is often used to synthesize chromones and flavones (**Figure 14**).

8.2 Algar-Flynn-Oyamada synthesis

In this method, chalcone (1,3-diaryl-2-propen-1-one) is produced by condensing 2-hydroxyacetophenone with an aryl aldehyde in alkaline medium (Claisen-Schmidt condensation) followed by oxidative cyclisation of chalcone to get flavone [38] (**Figure 15**).

A mixture of acetophenone and aromatic aldehyde when exposed to Microwave irradiation, 2-phenyl γ -benzopyrones are obtained [39]. The same compound can be prepared by cyclizing 1,3-diaryl propanediones (**Figure 16**).

9. Conclusions

In this chapter, the synthesis of fused heterocyclic compounds having oxygen as heteroatom is considered. The care is taken not to consider the reactions, where the reactions of the compounds leading to derivatizations are not included.

Benzofurans, benzofuranones, dibenzofurans, coumarins, isocoumarins, chromones, and flavones are the fused heterocyclic compounds considered in this chapter. Also, the reactions are indicative and not the detailed reaction conditions, and appropriate reagents are not included in this chapter.

Conflict of interest

No conflict of interest from both the authors.

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