



Digest paper

Radical reactions of aryl alkynoates in organic synthesis: Recent advances

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ABSTRACT

Aryl alkynoate is an important intermediate and powerful synthetic tool in organic chemistry, because it contains acetylene bond which can be easily introduced of different functional groups. During the past decades, several types of reactions and coupling partners have been developed for the functionalization of aryl alkynoates. In this review, we summarize the recent advances on the reactions of aryl alkynoates, including direct cyclization, ester group migration/cyclization, aryl migration/decarboxylation, ipso-cyclization/dearomatization, and other reactions in the past decade.

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Introduction

In the past few decades, radical initiated cascade reactions have been experienced a period of rapid development, and have been widely applied in the synthesis of natural products and bioactive compounds.¹ Among these methodologies, radical addition to

C–C triple bond occupies a special position and could not be neglected, because the activated C–C triple bond is a very ideal radical receptor.² Aryl alkynoate contains acetylene motif and ester group, thus, represents an important and extremely valuable synthetic block in organic synthesis. In recent years, the reactions of aryl alkynoates have received wide attentions from organic chemists, which can easily couple with radical partners and allows the various introductions of different functional groups.^{3,4} Until now, a great amount of transformations have been realized,

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including cyclization, rearrangement, dearomatization etc. In this review, we would like to highlight some recent advances using aryl alkynoate as a radical accepter in the past decade.

Direct cyclization with *ortho*-C(sp²) of aryl alkynoates

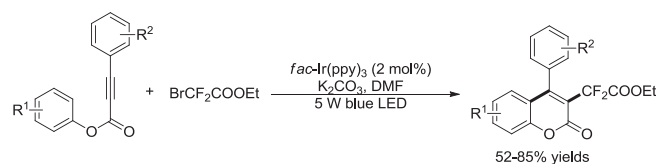
The construction of heterocyclic molecules via free radical tandem reactions has received much attention in recent years. Unlike traditional methods, the approach based on aryl alkynoates allows the rapid construction of multiple chemical bonds in just one step. Coumarin derivatives widely exist in natural products and drugs, and also are very basic organic chemical raw materials.⁵ The construction of coumarin skeletons by the addition of free radicals to aryl alkynoates have attracted more and more attentions in the past few years, because one additional functional group is introduced into the product along with the formation of coumarin at the same time. This section will cover some examples on the synthesis of coumarins through cyclization with *ortho*-C(sp²) of aryl alkynoates.

Synthesis of coumarins via introduction of fluorine functional groups

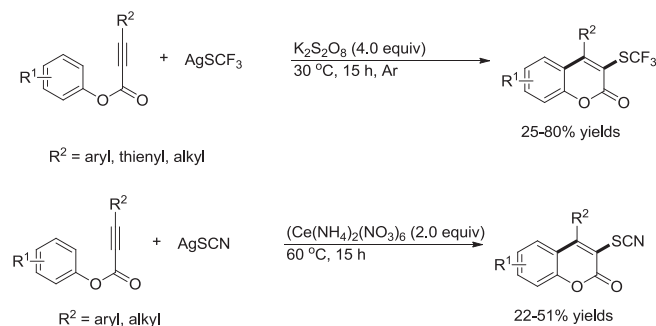
In 2014, Ding and co-workers reported a copper-catalyzed direct trifluoromethylation of aryl alkynoates with Togni's reagent I as trifluoromethyl radical precursor, affording a series of trifluoromethylated coumarins in moderate yields (Scheme 1).⁶ This reaction showed low reactivity for the alkyl substituted acetylenic ester, and only 26% yield was obtained.

The authors also provided a possible mechanism for this copper-catalyzed radical cyclization reaction. As shown in Scheme 2. First, the CF₃ radical is generated from the Togni's reagent promoted by copper catalyst. Then, the CF₃ radical adds to the C—C triple bond forming the intermediate **1**. Subsequent cyclization of **1** forms the intermediate **2**, which is followed by a SET process to generate the intermediate **3**. Finally, a further aromatization gives the final coumarin product **4**.

In 2015, the Fu group reported a novel and convenient visible light-induced cyclization method for the synthesis of 3-difluoroacetylated coumarins via radical cascade reaction between aryl alkynoates and ethyl bromodifluoroacetate (Scheme 3).⁷ The alkyl substituted acetylenic ester did not work in this reaction, and almost no corresponding product was found. The regioselectivity



Scheme 3.



Scheme 4.

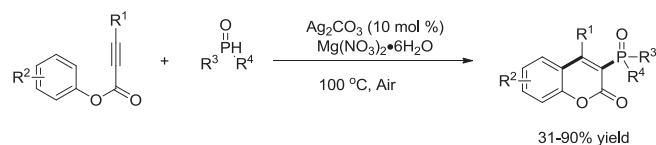
of this reaction was examined by use of a substrate bearing *meta*-substituted phenyl ester, and moderate regioselectivity (4:1) was found. The author also tried ethyl bromodifluoroacetate and diethyl bromodifluoromethylphosphonates as the radical coupling partners for phenyl alkynoate, however, no desired products were detected.

In 2016, the Wang group disclosed a similar strategy for the synthesis of various 3-trifluoromethylthiolated or 3-thiocyanated coumarins via oxidative radical reactions of aryl alkynoates with AgSCF₃ or AgSCN as the radical precursors (Scheme 4).⁸ These two reactions provided the corresponding products in low to moderate chemical yields. Also, the alkyl substituted substrates were not well tolerated in the current system, and only 25% yield was found. The reaction used different oxidants for these two silver salts, K₂S₂O₈ for AgSCF₃ substrate and (Ce(NH₄)₂(NO₃)₆ for AgSCN respectively. This process proceeds through the similar radical addition/cyclization to give the desired coumarins.

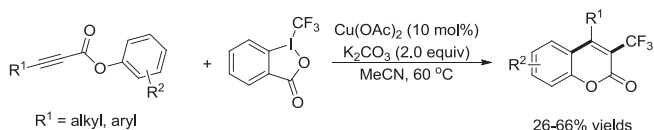
Synthesis of coumarins via C—S, C—P, C—Se bond formation

Organophosphorus compound is an important class of organic compounds owing to their potential applications in drug discovery and material chemistry. Countless efficient methods for constructing C—P bond have been reported in the past few decades. The use of phosphorus radicals to add unsaturated bonds has received much attention in recent years.

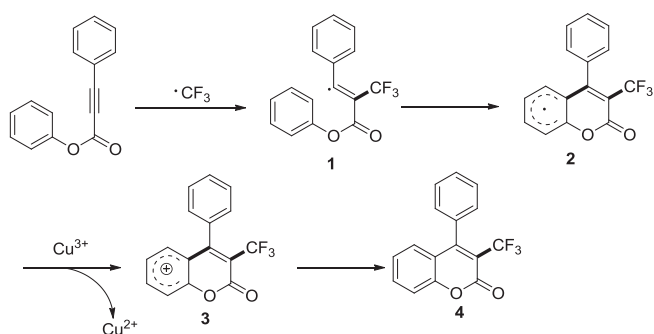
In 2014, Wu and co-workers reported a novel Ag-catalyzed approach via tandem radical reaction to synthesize 3-phosphonated coumarins with a wide range of substrate scope (Scheme 5).⁹ In the presence of additive Mg(NO₃)₂, the reaction proceeds via a single-electron transfer (SET) process to generate the active phosphinoyl radical without use of any peroxides, affording the corresponding product in 31–90% chemical yields. Although varieties



Scheme 5.



Scheme 1.



Scheme 2.

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