Multicomponent reactions (MCRs) of acetylenic compounds with isocyanides or triphenylphosphine–A Mini review

Maryam Ghazvini*, Ashraf Sadat Shahvelayati2, Meghdad Karimi3

1* Department of Chemistry, Payame Noor University (PNU), P.O. Box: 19395-4697, Tehran, Iran
2Department of Chemistry, Yadegar-e-Imam Khomeini (RAH) Shahre-rey Branch, Islamic Azad University, Tehran, Iran.
3Department of Chemistry, Tarbiat Modares University, Tehran, Iran.

Abstract

Acetylenic esters such as dimethylacetylenedicarboxylate (DMAD), diethyl acetylenedicarboxylate (DEAD) and alkyl propiolates are esters in which the ester groups are conjugated with a C-C triple bond. As such, these molecules are highly electrophilic, and are mainly used as a dienophile in cycloaddition reactions. They have been used in multicomponent reactions in the presence of nucleophilic compounds such as Isocyanides, Isoquinoline, Quinoline, Triphenylphosphine, trialkyl (aryl) phosphites and NH-acidic or OH-acidic compounds. This review mainly focuses on the research work reported in the scientific literature on the reaction this compounds with Isocyanides and Triphenylphosphine.

1. Introduction

Acetylenic esters such as dimethyl acetylenedicarboxylate (DMAD), diethyl acetylenedicarboxylate (DEAD) and alkyl propiolates are esters in which the ester groups are conjugated with a C-C triple bond. These kind of molecules are highly electrophilic, and are mainly used as a dienophile in cycloaddition reactions [1]. The other uses of these compounds are the multi-component reactions (MCRs), that they are consist of a single synthetic operation. MCRs are widely used in organic synthesis and chemical and pharmaceutical chemistry [2-12]. Because organic material is consumed and incorporated into the purpose of the combination, it is usually easy to clean products from MCRs. Maximum returns, reduced waste and eco-friendly products are the benefits of multi-component reactions. Therefore, start significant MCRs to prepare complex molecules of available materials. There are many ongoing efforts to develop new MCRs and many new 3- and 4-component reactions [13-14]. Acetylenic esters are reactive systems taking part in many chemical synthesis, for example, as Michael acceptors [15-18]. In recent years, there has been increasing interest in the application of acetylenic esters for multi-component synthesis [19-23]. Usually in addition to nucleophiles lacking an acidic hydrogen atom, it leads to a zwitterionic 1:1 mediator [24-29]. It can finally lead to a stabilized product by further transformation [30-33]. It has been convincingly argued the formation of zwitterions from pyridine, amines, triphenylphosphine, dimethyl sulfoxide, isocyanides and phosphoranes. Triphenylphosphine and Isocyanide based on MCRs are very important in this regard [34-39].

2. Reactions with Isocyanids

It has reported, that the reaction of alkyl isocyanides with dimethyl acetylenedicarboxylate (DMAD) and N, N’ dimethylbarbituric acid can lead to the formation of 4H-pyrazo [3, 2-d] pyrimidine derivatives. The isomeric
products dimethyl 7-(2,6-dimethylphenylamino)-1,3-dimethyl-2,4-dioxo-4H-pyran[3,2-d]pyrimidine-5,6-dicarboxylate 4 and dimethyl (E)-2-((2,6-dimethylphenylamino)-(1,3-dimethyl-2,4,6-trioxopyrimidine-5-ylidene)-methyl)-but-2-enedioate 5 in a nearly 1:1 ratio can be obtained from the reaction of 2,6-dimethylphenyl isocyanide 1 with DMAD 2 in the presence of N,N' dimethylbarbituric acid 3 (Scheme 1) [40].

![Scheme 1](image1.png)

We’ve had a lot of work in the field of multi-component reactions [41-44]. Continue this, we have recently described the synthesis of highly substituted 3-oxo-2,3-dihydro-5H-thiazolo [3,2-a] pyrimidines 9 via the one-pot, three-component reaction of an isocyanide 6 with a dialkyl acetylenedicarboxylate (DAAD) 7 and 2-imino-1,3-thiazolidin-4-one 8 in good yields (Scheme 2) [45].

![Scheme 2](image2.png)

A tentative mechanism for this transformation is proposed (figure 1):
The synthesis of novel tricyclic fused pyrano[2,3-d]pyrido[1,2-a]pyrimidines 11 containing both biologically active pyridopyrimidine and pyranopyrimidine scaffolds, via the reaction of 2-Hpyrido[1,2-a]pyrimidine-2,4(3H)-dione 10, isocyanides, and dialkylacetylenedicarboxylates are reported (Scheme 3) [46].

Resulted zwitterionic intermediate formed from reaction of isocyanides and dimethyl acetylenedicarboxylate (DMAD), because of significant reactivity of isocyanide toward DMAD, can undergo next reactions with different class of electrophilic reagent. This fact is a way to synthesis of more complex dompounds. These reactions have been studied by many number of research groups [47-49]. As an example for application of this class of reaction, a simple synthesis of trichloromethylated iminofuranes explained [50-52]. Trichloromethylated iminofuranes is produced by reaction of isocyanide and DMAD in the presence of hexachoroacetone (HCA) 12 in dry dichloromethane as solvent. In this reaction dimethyl 5-(tert-butylimino)-2, 2-bis (trichloromethyl)-2,5-dihydrofuran- 3,4-dicarboxylate 13 produced in 95% isolated yield (Scheme 4) [53].

In spite of extensive developments in the chemistry of modified ketenes and isocyanates [54-55], little attention has been paid to the synthesis of ketenimines. A simple one-pot preparation of stable ketenimines was reported as a proton source nucleophile. In the preparation alkyl isocyanidesand dialkyl acetylenedicarboxylat is usedin the presence of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (methyl Meldrum's acid) 14. This three-component condensation reaction produces stable ketenimines 15 in fairly good yields (Scheme 5) [56].
In continuation of current interest in the development of new routes to heterocyclic and carbocyclic systems [57-61], a simple one-pot synthesis of functionalized alizarin derivatives was reported. Thus, the reactions of isocyanides with dialkyl acetylenedicarboxylates in the presence of alizarin 16 produces new functionalized dihydro-4H-naphtho [2, 3-g] - chromenes 17 in good yields (Scheme 6) [62].

3. Reactions with Triphenylphosphine
Aligned with the use of acetylene esters for the synthesis of new compounds [63-67], herein, we report a simple and efficient one-step procedure for the synthesis of novel dibenzofuran derivatives. In this regard, we use the Diels–Alder reaction of euparin, a natural product isolated from the roots of Petasites hybridus, and different activated acetylenes in the presence of catalytic PPh₃ (Scheme 7). The reaction between euparin 18, a natural product isolated from the roots of Petasites hybridus, and dimethyl dialkyl acetylenedicarboxylate or alkyl propiolate 19 in the presence of PPh₃ affords the corresponding dibenzofuran 20 derivatives in high to excellent yields (Scheme 7) [68].

A proposed mechanism for this evolution is shown (figure 2):
For preparation of stable phosphorus ylides, it has been reported a new method on the base of reaction between PPh₃, electron-deficient acetylenic compounds (for example dimethyl acetylenedicarboxylate) and different nucleophiles (N-H, O-H, or C-H acids like benzoylhydrazones) [69-72]. For example the corresponding ylide 22 was prepared via the reaction of benzoylhydrazones 21 with dimethyl acetylenedicarboxylate with triphenylphosphine (Scheme 8) [73].

For developing of MCRs by use of zwitterion species, the reaction probability of 1, 3- dipoles with aryl aldehydes were studied. In this case, instead of expected products unsaturated γ-butyrolactones and highly substituted enones with PPh₃ created. In these reactions, the role of PPh₃ is a mediator [74-75]. Reaction between aryl aldehyde 23, dimethyl acetylenedicarboxylate in the presence of Ph₃P is done as well at room temperature in dichloromethane as solvent at 24h. The presence of two products (unsaturated γ-butyrolactone 24 and highly substituted enone 25) is indicated according to ¹H-NMR and ¹³C- NMR (Scheme 9).

Product 27 also is resulted of reaction between DMAD and p-hydroxybenzaldehyde 26 in the presence of PPh₃ in moderate yield (Scheme 10) [76].
As part of current studies on synthesis of sulfur-containing organic compounds [77-79], an efficient procedure for chemoselective synthesis of functionalized thiazol-2(5H)-ones from reaction between thiazolidine-2, 4-diones and acetylenic esters in the presence of triphenylphosphine (Ph₃P) was reported. The reaction of dialkyl acetylenedicarboxylates with thiazolidine-2, 4-dione 28 in the presence of Ph₃P at r.t. in ethyl acetate was completed within a few hours, and phosphoranes 29 were produced in good yields. The ¹H-NMR spectra of the reaction mixtures clearly showed the formation of the phosphorane 29, and no other products could be detected. These ylides were subjected to intramolecular Wittig reaction in boiling toluene, without further purification, to produce dialkyl 2-(2, 5-dihydro-2-oxothiazol-4-yl) fumigates 30 in good yields (Scheme 11) [80-81]. The reaction of thiazolidine-2,4-dione 28 with alkyl propiolates in the presence of Ph₃P proceeded spontaneously at r.t. in toluene and was finished within 1-4 h. ¹H and ¹³C-NMR spectra of the reaction mixtures clearly indicated the presence of product 31 (Scheme 12) [82].

In continuation of current interest in the development of new routes to heterocyclic and carbocyclic systems [83-85], a simple one-pot synthesis of functionalized alizarin derivatives was reported. Thus, the reaction of alizarin 32 with dialkyl acetylenedicarboxylates in the presence of Ph₃P produced functionalized dihydro-2H-naphtho [2, 3-g] - chromenes 33 in good yields (Scheme 12). When alkyl propiolates were employed as the acetylenic component, the reaction afforded 34 (Scheme 13 and 14) [86].
In continuation of our studies in using according to green chemistry for the synthesis of organic compounds, we report the condensation reaction between α-oximino ketone 35 and dialkyl acetylenedicarboxylate in the presence of triphenylphospine to afford substituted pyrroles 36 under ionic liquid conditions in good yields. The advantages of the present procedure are decrease reaction time, high yield products, green and recyclable solvent for the synthesis of oximes and pyrroles. (Scheme 15) [87].

In 2014 Sheikhi and et al reported products 38 through the standard Michael addition of the triphenylphosphine to the b-carbon of the electron-deficient alkyne (alkyle propiolate) and isatin derivatives 37 leads to products 38 under the correct reaction condition in satisfactory yields (Scheme 16) [88].

M. Anary-Abbasinejad and et al in 2012 reported One-pot, three-component reaction of different phenacyl bromides 39 and dialkylacetylenedicarboxylates was carried out with triphenylphosphine and functionalized oxodihydrofuran derivatives 40 in excellent yields. Nucleophilic addition of triphenylphosphine to activated acetylene is well known to produce a reactive zwiterion intermediate, [89-91] which may be trapped by acidic organic compounds such an alcohols. Reaction between dimethyl acetylenedicarboxylate and triphenylphosphine in the presence of alcohols has been reported to produce phosphorus ylide as an intermediate or final product. When a-hydroxy carbonyl compounds were used, the intramolecular Wittig reaction of the ylide intermediate afforded oxygen heterocycles.[92-93] Similar reactions have been developed for the synthesis of a variety of carbocycles and heterocycles, using N-H, [94] O-H, S-H [95] and C-H [96] acidic compounds to trap the zwiterionic DMAD-PPh3 intermediate in condition of our precision studies on the reaction of PPh3-DMAD zwiterions with organic acidic compounds [97]. Here was reported that the reaction of different phenacyl bromides, dialkyl acetylenedicarboxylates, and triphenylphosphine afforded oxodihydrofuran derivatives in good yields. Treatment of dimethyl acetylenedicarboxylate (DMAD) with triphenylphosphate and 4-chlorophenacyl bromide in dichloromethane at room temperature after 24 h afforded methyl 2-(bromomethyl)2-(4-chlorophenyl)4-methoxy-5-oxo-2,5-dihydrofuran-3-carboxylate 40 in 88% yield (Scheme 17) [98].
Mohebati and et al in 2016 reported the three-component and chemoselective reaction between dialkylacetylenedicarboxylates and triphenylphosphine in the presence of carbendazim \(\text{41}\) produces highly functionalized, phosphorus ylides \(\text{42}\) and \(\text{43}\) in excellent yields (Scheme 18) [99].

Shikholeslami-Farahani and et al in 2014 reported the synthesis of thiopyran derivatives \(\text{45}\) via three-component reaction of alkyl propiolate, benzoylisothiocyanate \(\text{44}\) and \(\alpha\)-haloketones in the presence of triphenylphosphine under solvent-free conditions at 70 °C (Scheme 19) [100].

Yavari and et al in 2010 reported a one-pot synthesis of alkyl 3, 4-dihydro-4-Oxo-2H-1, 3-thiazine-6-carboxylates \(\text{47}\) from dialkyl acetylenedicarboxylates and \(\text{N,N-}\) dialkylthioureas \(\text{46}\) in the presence of triphenylphosphine (Scheme 19) [101].

4. Conclusion

Acetylenic esters such as dimethyl acetylenedicarboxylat (DMAD), diethyl acetylenedicarboxylat (DEAD) and alkyl propiolates are esters in which the ester groups are conjugated with a C-C triple bond. As such, these molecules are highly electrophilic, and widely employed as a dienophile in cycloaddition reactions. They have been used in multicomponent reactions in the presence of nucleophilic compounds such as Isocyanides, Triphenylphosphine, trialkyl (aryl) phosphites. That can lead to heterocyclic products or open chain products in good yield.