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A facile and efficient synthesis of enyne-reaction precursors by multicomponent reactions

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Abstract—Using improved reaction protocols for three-component coupling reactions of aldehydes, dienophiles, and amides (AAD-reaction) or anhydrides (ANAD-reaction) or orthoesters (ALAD-reaction), a variety of functionalized hexahydroisoindolo derivatives were synthesized and fully characterized. Condensation of ubiquitous available aldehydes with unsaturated amides or anhydrides or orthoesters and subsequent Diels–Alder reactions with electron deficient dienophiles furnishes *endo*-selective enyne-reaction precursors in good to excellent yield.

1. Introduction

With regard to the development of sustainable chemical methods, new reactions should proceed with cheap and easily available substrates, at best in a common apparatus giving a quantitative yield at a fast rate and 100% atom economy. Clearly, for multi-step synthetic procedures the number of reaction and purification steps are among the most important criteria for the efficiency and practicability of the process and should be as low as possible. Concerning to these aspects, multicomponent[1] and domino reactions[2] offer significant advantages (Fig. 1).

As a special benefit to the classical step by step formation of individual bonds in the target molecule, MCRs (or domino reactions) take advantage of the simultaneous formation of several bonds in only one operational step. Moreover, this approach allows also for the avoidance of intermediate separation, changing the reaction conditions, or adding any further reagents. Since isolated products include structural features of all employed reactants, MCRs often enable the enhancement of structural diversity in an unprecedented way. In addition, opportunities arise for an easier synthesis of compound libraries. Therefore, in the last decade research both in academia and industry has increasingly emphasized the use of MCRs as well as domino reaction sequences for a broad range of products.[3]

In the past we were especially interested in the development of transition metal-catalyzed three- and four-component coupling reactions. For instance, our investigations include hydroaminomethylation of olefins,[4] and amidocarbonylation of aldehydes.[5]

With respect to the latter work,[6] we discovered the first multicomponent reaction of amides, aldehydes, and dienophiles (AAD-reaction). More recently, instead of amides also carboxylic acid anhydrides (ANAD-reaction) or alcohols as well as orthoesters (ALAD-reaction) have been used. Covering this broad range of substrates, we have actually synthesized more than 200 carbo- and heterocyclic compounds with high efficiency (Scheme 1).[7]

Based on a simple condensation reaction, the underlying mechanism takes advantage of the in situ formation of substituted 1,3-butadienes as key intermediates, which are subsequently converted with electron-deficient dienophiles in a Diels–Alder reaction to the corresponding products.

Several other groups have demonstrated the versatility of

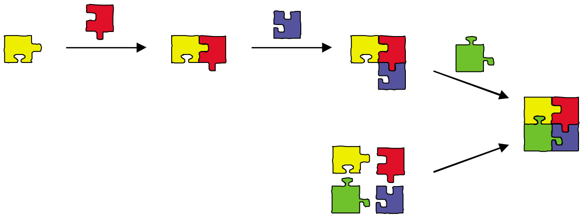

Figure 1. Schematic representation of multi-step versus multicomponent assembly.

Keywords: Enynes; Aldehydes; Diels–Alder reaction; Multicomponent coupling reaction.

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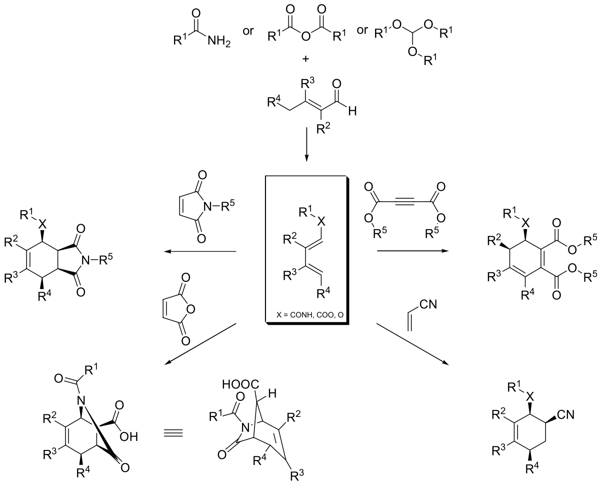
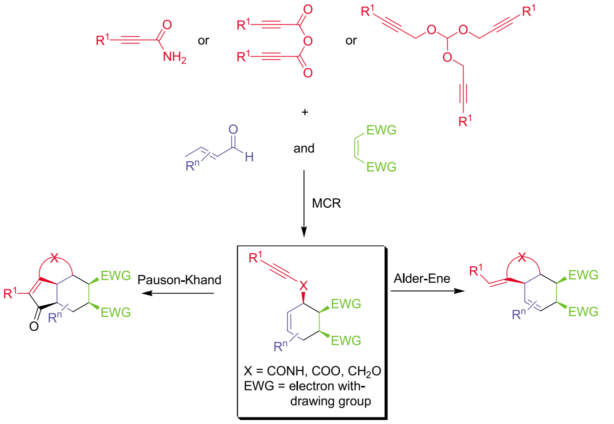


Scheme 1. Schematic representation of the AAD-, ANAD-, ALAD-reaction protocol.

isolated functionalized 1,3-butadienes for Diels–Alder chemistry.[8] Prominent examples include the preparation of pumiliotoxin,[9] gephyrotoxin,[10] dendrobine,[11] and tabersonine.[12]

So far the synthetic utility of our domino sequence has been shown in the preparation of substituted anilines,[13] luminoles,[14] and phenanthridone[15] derivatives. The latter reaction is a nice example for the powerful combination of MCRs with subsequent catalytic reactions. In order to expand this concept further on we envisioned the application of acetylenic derivatives in AAD reactions with subsequent catalytic enyne-functionalizations (Scheme 2; see also following paper).

To the best of our knowledge there are no multicomponent reactions of aldehydes, dienophiles, and acetylenic derivatives known. Here, we wish to report on the successful application of our multicomponent coupling protocol for the straightforward synthesis of various hexahydroisoindole derivatives, which are functionalized by an additional alkyne group. These compounds represent valuable enyne-reaction precursors and constitute prominent substrates for additional ring closing reactions via Alder–Ene[16]- as well as Pauson–Khand[17]-reactions.



Scheme 2. Sequential AAD- and enyne reactions.

2. Results and discussion

Based on examinations of the three-component coupling reaction of amides, aldehydes, and dienophiles (AAD-reaction), we started synthesizing enyne-reaction precursors, using our recently improved 2nd generation MCR protocol.[18] Comprising toluene as suitable solvent, reactions were carried out in the presence of a catalytic amount of *p*-TSA and acetic acid anhydride as a water scavenging agent. To achieve full conversion, reactions were allowed to react for 24–120 h at 110 °C.

Initially, we studied the influence of differently substituted α,β-unsaturated aldehydes in the presence of 3-phenylpropynoic acid amide[19] and *N*-methylmaleimide. As a result of that, a variety of alkyl-substituted products were obtained in good yields ranging from 71 to 81% (Table 1, entries **1a**–**6a**). It is remarkable that the employed alkynoic acid amide reacts selectively in the desired fashion and not as a competing dienophile.

In the next set of experiments, we examined the influence of functionalized propiolamide derivatives on the conversion with crotonaldehyde, and *N*-methylmaleimide. Using propiolamide, terolic acid amide, and pent-2-ynenoic acid amide, the desired products were obtained in yields of 69, 60, and 80%, respectively (Table 1, entries **7a**–**9a**). In order to study also the influence of other dienophiles, acrylonitrile, dimethyl but-2-ynedioate, and 1,4-phenylene dimaleimide, were employed and gave yields of 58, 36, and 80%, respectively (Table 1, entries **10a**–**12a**).

In addition to amides, acetylenic carboxylic acid anhydrides (ANAD-reaction) and acetylenic orthoesters (ALAD-reaction) can serve as substrates and lead to an increase of structural diversity.[20] Following the previous ANAD-reaction protocol, initial experiments concentrated on the employment of phenyl propiolic acid anhydride, crotonaldehyde and *N*-methylmaleimide as starting materials. To our surprise the target product is not obtained at all, presumably due to the poor reactivity of the chosen anhydride. Changing the reaction conditions (140 °C, 24–48 h) led to no improvement. However, reaction of phenyl propiolic acid with oxalyl dichloride to the corresponding acid chloride, and subsequent addition of crotonaldehyde and potassium butoxide at −78 °C in THF, gave the buta-1,3-dienyl 3-phenylpropiolate as an intermediate (not isolated). After addition of *N*-methylmaleimide to the reaction mixture the desired product is isolated in 30% yield (Table 1, entry **13a**). Next, tris(prop-2-ynyloxy)-methane[21] was used for the synthesis of propargylic ether-substituted cyclohexenes. Depending on the choice of the aldehyde, the products were isolated in the range of 67–84% yield (Table 1, entries **14a**–**17a**).

To pursue ring closing reactions on nitrogen tethered enyne-precursors, it is often necessary to protect the heteroatom in an additional step for successful conversions.[22] Therefore, we studied also the protection of the synthesized enyne-AAD-products, using standard protocols with alkylating reagents.[23]

However, several approaches using strong bases like