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Diversity-oriented approach to unusual amino acid derivatives and heterocycles via methyl 2-acetamidoacrylate and its congeners

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Contents

1. Introduction

2-Acylaminoacrylic acid derivatives **1**–**5** (Fig. 1) are useful building blocks to design novel α-amino acids (AAAs) and heterocycles. There are some excellent accounts available in the literature[1] about the applications of these useful building blocks. We have included several examples from the recent literature (after 2000) where amidoacrylates are used to prepare unusual AAA derivatives and heterocycles and whenever required we have also included limited examples from old literature reports (before 2000). Methyl 2-acetamidoacrylate (**1**) and its derivatives are known to function as a moderate dienophile in Diels–Alder (DA) reaction, a dipolarophile and an electrophile in Michael-type reactions, and also a useful coupling partner in the Heck, Suzuki, and

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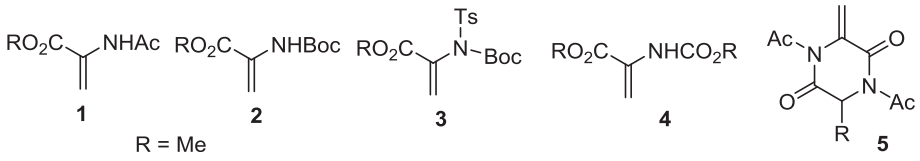
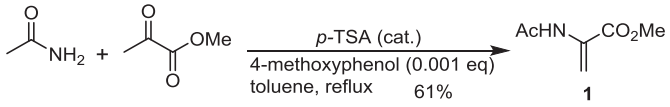


Fig. 1. Substituted amidoacrylate derivatives.

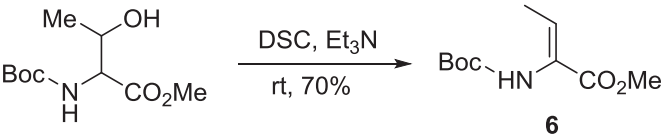
cycloaddition reactions. In some instances α-amidoacrylates also react with arenes under Friedel–Crafts conditions. Their synthetic utility stems from their easy accessibility and unique reactivity of the double bond. The presence of acylamino and ester groups on the same carbon of the double bond facilitates nucleophilic attack at the α-position (α-amidoalkylation) or at the β-position (Michael-type reactions) yielding in both cases an unusual AAAs that can be further synthetically manipulated. Cysteine derivatives have been prepared from 2-acylaminoacrylic acid synthon through radical addition sequence.[2] Several reports are available where these unsaturated compounds are subjected to asymmetric hydrogenation.[1] However, this aspect is not covered extensively in the present article.

Here, we have included some preparative methods to methyl 2-acetamidoacrylate (**1**). For example, acid-catalyzed condensation of acetamide with methyl pyruvate at toluene reflux temperature delivered compound **1** (Scheme 1).[3a]

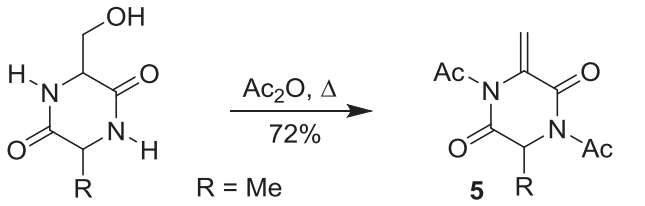


Scheme 1. Synthesis of methyl 2-acetamidoacrylate (**1**).

Similarly, protected methyl acrylate derivative such as **2** can be assembled from the activated cysteine. For example, cysteine derivatives are converted to nitroso compound, which on treatment with phosphine ligand gave the unsaturated compound **2** (Scheme 2).[3b]



Scheme 3. Synthesis of methyl (*Z*)-2-amino but-2-enoate.

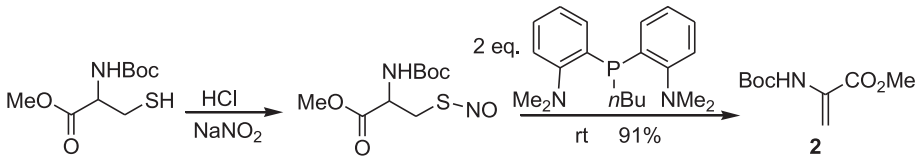


Scheme 4. Synthesis of 1,4-diacetyl-3-subtituted-6-methylenepiperazine-2,5-dione.

Alternatively, dehydroamino acid derivatives are generated via Erlenmeyer reaction. Thus, different glycine equivalents (Fig. 2) on condensation with aromatic/aliphatic/ferrocenyl aldehydes in the presence of a base followed by base hydrolysis gave dehydroamino acid derivatives.[7]

For example, Bautista and co-workers[8] reported the synthesis of dehydroamino acids starting with glycine derivatives. Thus, condensation of a suitably protected glycine derivative with carbonyl compounds in the presence of a base gave the oxazoline derivative, which on treatment with a strong base (e.g., NaOH) at reflux temperature gave the α,β-dehydro amino acid derivative **7** (Scheme 5).

Dehydroamino acid derivatives are assembled by a similar



Scheme 2. Synthesis of methyl 2-[(*tert*-butoxycarbonyl)amino]acrylate.

A general method based on β-elimination process is one of the simple ways to generate dehydroamino acid derivatives. The substrates containing β-substitution with suitable leaving groups (e.g., hydroxy, tosyl, acetyl, halo, arylselenyl, and sulfoxide derivatives) under thermal or oxidative elimination conditions generate dehydroamino acids.[4] For example, Ogura and co-workers[5] have demonstrated the synthesis of acrylate derivative **6** by elimination of β-hydroxyl moiety with equimolar quantities of di-succinimidyl carbonate (DSC) and triethylamine at rt (Scheme 3).

Similarly, Burkett and Chai have reported dehydration as a key step to prepare dehydroamino acids. To this end, cyclic 3-(hydroxymethyl)-piperazine-2,5-dione was treated with acetic anhydride to afford the corresponding 1,4-diacetyl-3-subtituted-6-methylenepiperazine-2,5-dione (**5**) (Scheme 4).[6]

strategy by condensation of an amine with a carbonyl compound to form the imine. Later, the imine is rearranged via isomerization in acidic medium to give the dehydroamino acids. Schmidt and Poisel[9a] reported a useful method to dehydroamino acids starting with protected amino acids. Here, the amino acid derivative has been converted to *N*-haloamine with alkoxyhalide. Later, the *N*-haloamine underwent dehydrochlorination with base (e.g., DBU) followed by isomerization with HCl to give the dehydroamino acid derivative **8** (Scheme 6).[9]

Wittig reaction is an effective tool for assembling dehydroamino acid derivatives. For example, phosphonate ester is condensed with an aldehyde in basic medium to generate acrylate derivative.[10] Along these lines, Williams and Fegley[11] reported the synthesis of benzylidene-2-oxomorpholines (**9**). In this regard, initially, lactone