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A novel synthesis of 1,2,4-oxadiazoles and isoxazoles

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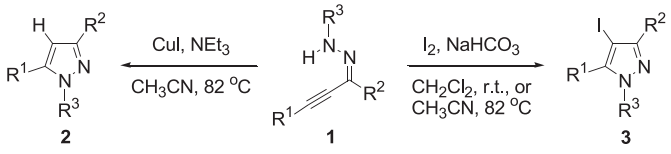
ABSTRACT

A novel synthesis of 1,2,4-oxadiazoles and isoxazoles is described by utilizing the reactions between amidoximes and α,β-alkynic aldehydes and/or ketones. Conjugate addition products, obtained from amidoximes and α,β-alkynic aldehydes and/or ketones, afford 1,2,4-oxadiazoles and isoxazoles when treated with bases and acids, respectively. 1,2,4-Oxadiazoles can also be synthesized directly from amidoximes and α,β-alkynic aldehydes in a one-pot manner under basic conditions. The reactions are general for a variety of starting compounds and tolerate the presence of aryl, heteroaryl and alkyl groups.

1. Introduction

Recently, α,β-alkynic aldehydes and ketones have emerged as valuable substrates in organic synthesis since they have two electrophilic centers and, when treated with binucleophiles, they can undergo cyclocondensation to afford a variety of important heterocycles, including pyrazoles,[1] isoxazoles,[2] pyridines,[3] pyrimidines,[4] thiophenes,[5] pyridopyrimidinones,[6] and quinolines.[7] In this regard, we have recently reported the synthesis of α,β-alkynic hydrazones **1** and their regioselective conversion into pyrazole derivatives **2** and **3** (Scheme 1).[8] When treated with copper(I) iodide or molecular iodine, α,β-alkynic hydrazones **1** undergo electrophilic cyclization to afford pyrazoles **2** and 4-iodopyrazoles **3**, respectively, in good to excellent yields.



Scheme 1. Synthesis of pyrazoles and 4-iodopyrazoles via electrophilic cyclization.

Amidoximes are known as popular binucleophilic reagents and have been extensively used in organic synthesis,[9] especially in the preparation of 1,2,4-oxadiazoles,[10] and pyrimidinones and/or their tautomer pyrimidines.[11] We reasoned that the reaction of amidoximes with α,β-alkynic aldehydes and ketones could lead to the formation of important heterocycles. Surprisingly, a search of the literature revealed very few reports concerning such reactions, which are displayed in Scheme 2. Naidu and Sorenson showed that the treatment of the in situ generated alkylamidoxime **4** with a propargyl ketone provided 1,2,4-oxadiazoline **5**.[12] A group of researchers employed the reactions between properly substituted amidoximes **6** and propargyl ketones to synthesize medicinally important pyrimidine derivatives **7**.[13] In the first step of this synthesis, amidoximes **6** are converted to the corresponding amidinium salts, which then react with propargyl ketones to afford pyrimidines **7**. It is noteworthy to mention that the reaction of amidoximes **6** with acetylenic diesters, followed by the thermal rearrangement of the resulting Michael adducts, affords pyrimidinones **8** and/or their tautomer pyrimidines **9**.[11] To the best of our knowledge, the reaction of amidoximes with α,β-alkynic aldehydes is not known.

We anticipated that the reaction of amidoximes with α,β-alkynic aldehydes and ketones could lead to the formation of 1,2,4-oxadiazepine derivatives **12** via cyclocondensation of the intermediate conjugate addition products **11** (Scheme 3). In fact, compared to other heterocyclic compounds, oxadiazepines are less known and less explored,[14] although they have great potential for both pharmaceutical[15] and agricultural[16] benefits. To the best of our knowledge, 1,2,4-oxadiazepines are not known although the examples of their bridged, benzo, hydro, and/or oxadiazepinone derivatives are known.[17] Unfortunately, the reaction of amidoximes **6** with α,β-alkynic aldehydes **10** did not produce the expected 1,2,4-oxadiazepines **12** and, from these reactions, conjugate addition products **11** were isolated (Scheme 3). Even at high temperatures,

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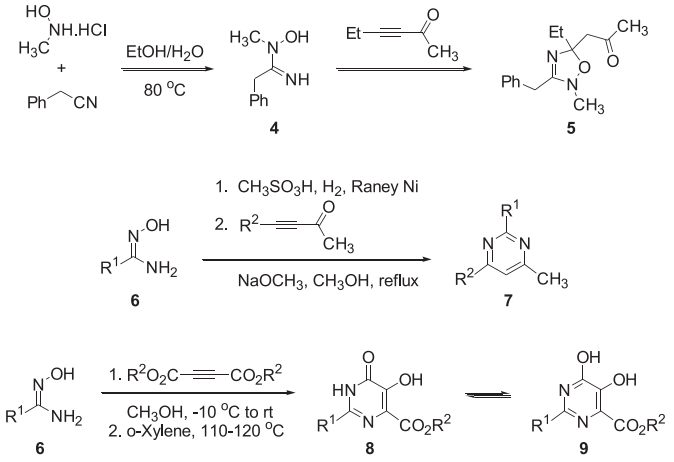
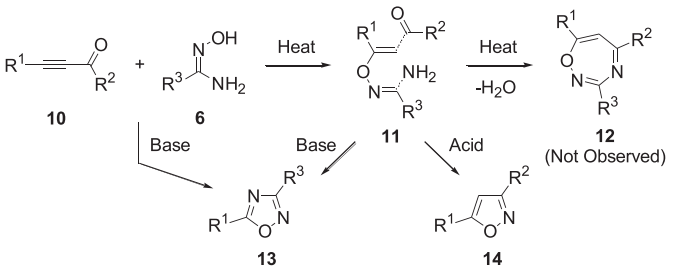


Scheme 2. Reaction of amidoximes with α,β-alkynic ketones and esters.

thermolysis of the conjugate addition products **11** did not yield 1,2,4-oxadiazepines **12**, and starting compounds were recovered with some decomposition. Interestingly, during these studies, we found that under basic and acidic conditions, conjugate addition products **11** afford 1,2,4-oxadiazoles **13** and isoxazoles **14** in good to high yields, respectively,[18] which are unprecedented reactions. We have also displayed that 1,2,4-oxadiazoles **13** can be synthesized directly from amidoximes **6** and propargyl aldehydes **10** in a one-pot manner under basic conditions (Scheme 3).

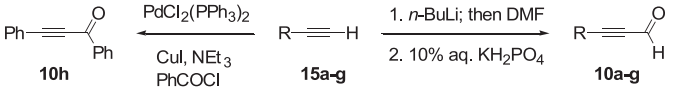


Scheme 3. Synthetic strategy for 1,2,4-oxadiazepines, 1,2,4-oxadiazoles, and/or isoxazoles.

In fact, 1,2,4-oxadiazoles and isoxazoles have been intensely studied in recent decades as important classes of heterocycles, and still receive great attention due to their growing significance in both bioactive compounds and materials.[19,20] 1,2,4-Oxadiazoles and isoxazoles have been reported to exhibit a wide range of biological properties, such as analgesic,[21] anti-asthmatic,[22] anti-diabetic,[23] anthelmintic,[24] diuretic,[25] anti-inflammatory,[26] antiparasitic,[27] anti-HIV,[28] and/or antitumor[29] activities. Briefly, 1,2,4-oxadiazoles and isoxazoles are prominent targets for synthetic chemists primarily because of their diverse and potent biological properties. Over the years, numerous methods have been developed for the synthesis of these compounds,[30,31] and new variants continue to appear since they have a noteworthy impact as intermediates in the synthesis of various drugs and natural products. As part of a program to synthesize pharmaceutically important heterocycles,[11,8,32] we have investigated the reaction of amidoximes with α,β-alkynic aldehydes and ketones, which afforded 1,2,4-oxadiazoles and isoxazoles depending upon the reaction conditions (Scheme 3). We herein report the full details of this study.

2. Results and discussion

The required α,β-acetylenic aldehydes and ketones can be easily prepared according to known literature procedures, as depicted in Scheme 4. The lithiation of terminal alkynes **15a**–**g** with *n*-BuLi, followed by the formylation of the in situ generated lithium acetylides with DMF, affords α,β-acetylenic aldehydes **10a**–**g** in good to excellent yields.[8,33] It is noteworthy that a reverse quench into a phosphate buffer has proved to be the key for these high yielding formylation reactions. Diphenylpropynone (**10h**) can be prepared directly from phenylacetylene and benzoyl chloride by a palladium-catalyzed coupling reaction.[8,34]



Scheme 4. Synthesis of α,β-alkynic aldehydes and ketones.

The necessary amidoximes **6** were readily synthesized according to a standard literature protocol in one-pot way as illustrated in Table 1. The reaction of nitriles **16** with hydroxylamine hydrochloride in the presence of triethylamine in refluxing ethanol provided the desired amidoximes **6**.[35] As seen in Table 1, a variety of amidoximes **6** were prepared from the corresponding nitriles **16** in moderate to good yields.

Subsequently, we investigated the reactions between amidoximes **6** and α,β-acetylenic aldehydes and ketones **10**. At moderate temperatures, these reactions exclusively produced conjugate addition products **11**. The results are given in Table 2. Best results were obtained in refluxing methanol. The progress of the reaction was monitored by TLC and it was seen that in most cases, the reaction went to completion in almost 2 h. Higher temperatures, such as in dioxane at 100 °C did not increase the yields significantly. As seen in Table 2, a variety of conjugate addition products were synthesized in good to high yield. Due to the presence of double bonds, four possible stereoisomers can exist for the conjugate addition products **11** but these reactions afforded only one stereoisomer of **11** as indicated by the TLC analysis and NMR spectroscopy. However, the exact stereochemistry of these isomers could not be identified. As mentioned before, thermolysis of the conjugate addition products in refluxing dioxane or *p*-xylene did not provide 1,2,4-oxadiazepines **12**, which requires further investigation. These studies will be reported in due course.

The reactions of conjugate addition products **11** were investigated in the presence of bases and acids as well. First the reactions of conjugate addition products **11** were examined in the presence of bases, and for this purpose, KOH and NaH were employed (Table 3). Initially, conjugate addition product **11a** was treated with KOH in DCM at room temperature but no reaction occurred. However, the same reaction in refluxing dioxane afforded 3,5-diphenyl-1,2,4-oxadiazole (**13a**) (Table 3, entry 1). Subsequently, the reaction of conjugate addition product **11a** was performed in the presence of NaH in acetonitrile at room temperature, which also afforded oxadiazole **13a** (Table 3, entry 2). In summary, we discovered a novel oxadiazole-forming reaction from conjugate addition products **11**. As seen in Table 3, a variety of conjugate addition products **11** were employed and all yielded the expected oxadiazoles **13** in good to high yields (68–95%), except that isoxazole **13f** was obtained in a moderate yield (47%). Notably, NaH was more effective than KOH since NaH-mediated reactions went to completion at room temperature and mostly in shorter reaction times (Table 3, Entries 5–8, 15 and 16). However, the yields of oxadiazoles **13** obtained by both bases were found to be comparable. The reaction is surprisingly general for a diversity of conjugate addition products **11** without regard to the type of base and tolerates the presence of aryl, heteroaryl, and alkyl groups. Interestingly, these reactions also furnish acetaldehyde (Table 3, Entries 1–14) or acetophenone (Table 3, Entries 15 and 16), depending