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A 'one-pot' synthesis of α-1,2,4-oxadiazolo esters from malonic diesters and amidoximes under solvent-free conditions

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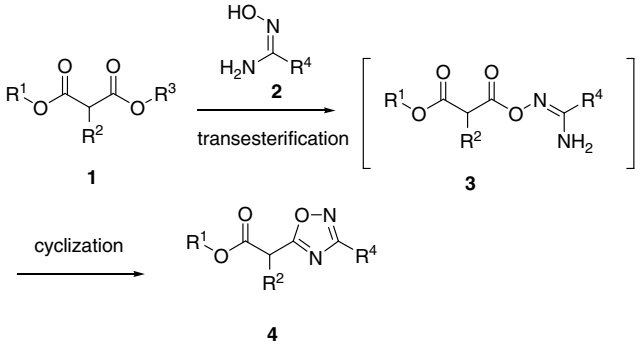
Abstract—A 'one-pot' procedure for synthesis of α-1,2,4-oxadiazolo esters from malonic diesters and amidoximes under solvent-free conditions is described. It is likely that this reaction goes through a ketene intermediate generated from the malonic diester by elimination of a molecule of alcohol.

α-Aryl esters are important building blocks in organic chemistry. Their synthesis has been a long-standing target for synthetic chemists.[1] Many methods for the synthesis of α-aryl esters are available, including recently developed palladium catalyzed direct α-arylation of esters.[2] Among a wide variety of aryl groups, 1,2,4-oxadiazole is a heteroaryl group that is often used in medicinal chemistry. It is considered to be a bioisostere of carboxylic functionalities and can be used to replace an ester group to achieve compounds that are resistant to enzyme catalyzed hydrolysis.[3]

1,2,4-Oxadiazoles are usually synthesized by 1,3-dipolar cycloaddition of cyano compounds or dehydration of acyl amidoxime.[4] Compared to the large number of syntheses of 1,2,4-oxadiazole containing compounds, the syntheses of α-oxadiazolo esters are quite limited. The known methods include 1,3-dipolar cycloaddition of nitrile oxides to α-cyano esters,[5] alcohololysis of 5-cyanomethyl oxadiazole[6] and derivatization of malonic acid. The latter method is a straight forward approach since the synthesis of 1,2,4-oxadiazole by cyclization/dehydration of acyl amidoxime is well known. It has been reported that α-1,2,4-oxadiazolo esters can be prepared from a monomalonic acid and an amidoxime through a coupling reaction followed by a base catalyzed cyclization.[7] However, only a small number of monomalonic acids are commercially available. Very often, the needed 2-substituted monomalonic acids need to be prepared from commercially available 2-substituted malonic diesters by monohydrolysis.[8] Thus, it will take three steps (monohydrolysis of a commercial malonic diester, coupling reaction, and cyclization) to prepare a substituted α-1,2,4-oxadiazolo esters. A more concise synthesis would be reaction of a malonic diester **1** and an amidoxime **2** through a transesterification to give an acyl amidoxime **3** in one step followed by cyclization/dehydration to give the desired α-1,2,4-oxadiazo esters **4** (Scheme 1). In general, both transesterification and acyl amidoxime cyclizations are facilitated by elevated temperature, and therefore these two steps may proceed in one-pot. Direct synthesis of 1,2,4-oxadiazole from an ester and amidoxime through transesterification in the presence of strong bases such as NaH[9] or NaOMe[10] has been reported in the literature, but its application in synthesis of α-oxadiazolo ester was only minimally explored.[11]



Scheme 1.

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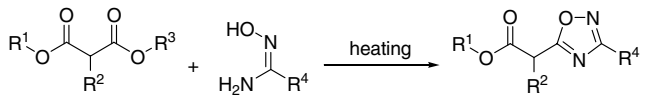
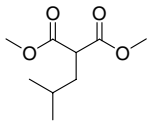
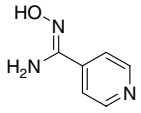
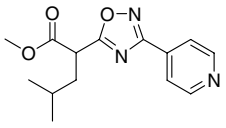
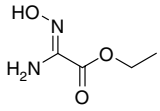
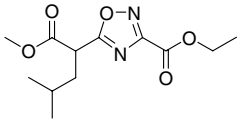
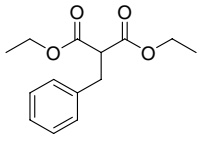
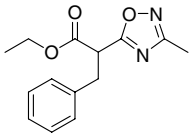
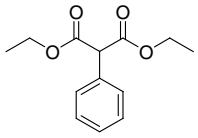
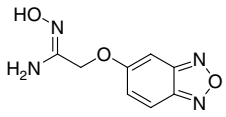
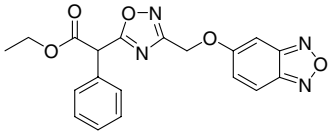
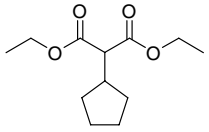
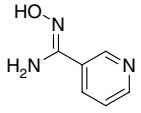
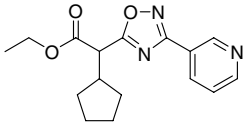
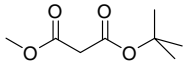
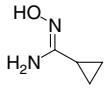
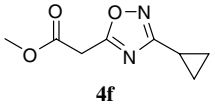
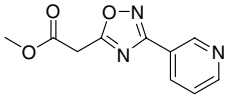
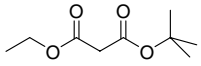
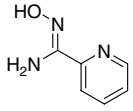
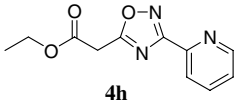
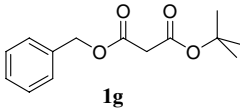
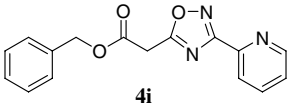
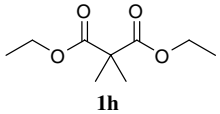
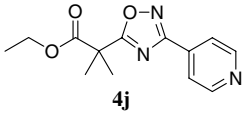
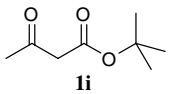
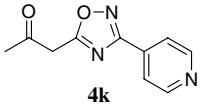
Table 1.



1 **2** **4**

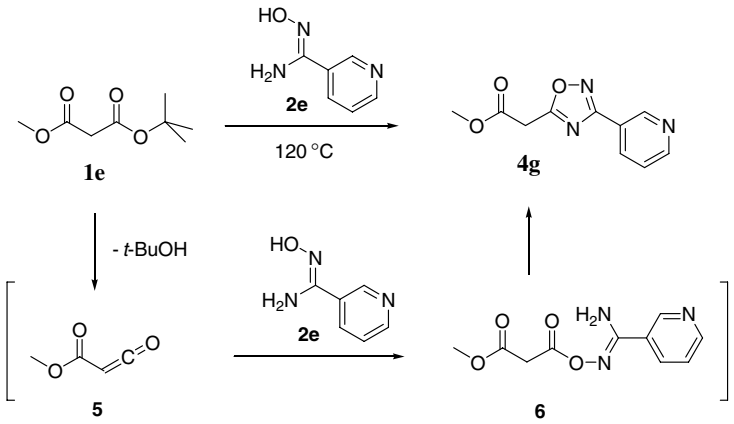
Entry	Malonate **1**	Amidoxime **2**	Product **4**	Yield
1	 **1a**	 **2a**	 **4a**	62%
2	**1a**	 **2b**	 **4b**	51%
3	 **1b**	 **2c**	 **4c**	77%
4	 **1c**	 **2d**	 **4d**	63%
5	 **1d**	 **2e**	 **4e**	47%
6	 **1e**	 **2f**	 **4f**	86%
7	**1e**	**2e**	 **4g**	71%
8	 **1f**	 **2h**	 **4h**	82%
9	 **1g**	**2h**	 **4i**	89%
10	 **1h**	**2a**	 **4j**	0
11	 **1i**	**2a**	 **4k**	91%

We report herein a one-pot synthesis of various substituted α-1,2,4-oxadiazolo esters from malonic diesters and amidoximes under solvent-free conditions. Dimethylisobutyl malonate **1a** was first refluxed with 4-pyridylamidoxime **2a** in toluene for 24 h, but the reaction only gave the desired oxadiazole product **4a** in 2% yield. Microwave was then applied to accelerate the reaction. Irradiation of a toluene solution of **1a** and **2a** in a sealed tube with microwave at 130 °C for 2 h only yielded trace of the desired oxadiazole product. When dioxane was used to enhance the solubility of **2a**, most of amidoxime still remained under the same reaction conditions. Same result was obtained when additives such as 4-DMAP, diisopropylethylamine and Cs_2CO_3 were added. Finally, the reaction was tested under solvent-free conditions. Neat **1a** and **2a** were well mixed and then heated to 130 °C, the solid amidoxime **2a** melted and the reaction mixture became a homogeneous liquid. After heating for 2 h, the reaction yielded the desired oxadizaole product **4a** in 62% yield.

Organic reactions under solvent-free conditions are attractive because they are more economical, easy to work up, environmentally friendly, and, in many cases give better yields in shorter time than traditional solution phase reactions. As an important branch of the emerging field of green chemistry, solvent-free synthesis has recently received much attention,[12] and has been further combined with microwave irradiation.[13] However, when neat **1a** and **2a** were irradiated with microwave in a sealed tube, the reaction only gave trace product.

The solvent-free conditions for **1a** and **2a** were then applied to other substrates and similar results were obtained (Table 1). An amidoxime and two equivalents of malonic diester were mixed in a test tube and were then gradually heated to 120–150 °C. The reaction was followed by TLC or LC-MS. After 2–6 h, the reaction was cooled to room temperature and applied to a silica gel column. Flash chromatography yielded the desired α-oxadiazolo ester in moderate to good yield.[14] In entry 2, malonate **1a** reacted with ethyl 2-oximinooxamate **2b** to give oxadiazole **4b** in 51% yield. The methyl ester in **1a** was more reactive than the ethyl esters in **2b** and **4b**. Another monosubstituted malonic ester, diethyl benzylmalonate **1b**, reacted with acetamide oxime **2c** to give oxadiazole **4c** in 77% yield. Reaction of phenyl substituted malonic ester **1c** and amidoxime **2d** yielded oxadiazole **4d.** Interesting regioselectivity was observed for malonic esters that have two different ester groups. The reaction between *tert*-butyl methyl malonate **1e** and amidoxime **2f** gave a methyl ester product **4f** in 86% yield. Apparently, the hindered *tert*-butyl ester was more reactive than the methyl ester in this reaction. Similar selectivity was observed on other *tert*-butyl malonates. As shown in entries 6–9, the bulky *t*-butyl ester reacted faster than less hindered esters such as methyl, ethyl and benzyl esters. Reaction of *tert*-butyl methyl malonate **1e** with amidoxime **2e** yielded methyl ester **4g** in 71% yield. *tert*-Butyl ethyl malonate **1f** and benzyl *t*-butyl malonate **1g** yielded ethyl ester **4h** and benzyl ester **4i**, respectively. The reaction was also applied to disubstituted malonic ester. Heating diethyl 2,2-dimethylmalonate **1h** with amidoxime **2a** at 150 °C for 12 h did not yield the desired product **4j**. These reaction conditions can also be extended to α-ketoesters. Reaction between *t*-butyl acetoacetate **1i** and amidoxime **2a** yielded β-keto oxadiazole **4k** in excellent yield.[15]

The results from entries 6–10 in Table 1 suggest that this one-pot reaction likely proceeds through a ketene intermediate. The proposed detailed reaction mechanism is showed in Scheme 2 using entry 7 as the example. The transesterification step between **1e** and **2e** likely first goes through a ketene intermediate **5** by elimination of one molecule of *t*-butyl alcohol. Direct substitution of the ester alkoxy group by an amidoxime is excluded because in such case, the replacement should have occurred on the less hindered methyl ester instead of the highly hindered *t*-butyl ester. Ketene **5** subsequently reacts with amidoxime **2e** to give acyl amidoxime **6**, which yields **4h** upon heating. Ketene formation by pyrolysis of a malonic ester has been documented.[16] It is also known that structurally similar α-ketoesters can undergo ketene intermediate transesterification.[17] In the α-ketoester substrates, the hindered *t*-butoxy group is 15–20 times faster than less hindered alkoxy group in formation of a ketene intermediate.[18] The ketene intermediate mechanism is consistent with the results from entries 6–10. *t*-Butoxy group is more easily



Scheme 2.

eliminated than the less hindered methoxy, ethoxy, and benzoxy groups to form the corresponding ketene intermediate due to its bulkiness. Disubstituted malonic ester **1h** is unable to form the ketene intermediate because of the gem-dimethyl group. Thus, non-enolizable malonic esters such as **1h** are inert under these reaction conditions.

In conclusion, we present here a practical 'one-pot' synthesis of α-1,2,4-oxadiazolo esters from malonic esters and amidoximes under neutral and solvent-free conditions. This reaction likely goes through a ketene intermediate formed by elimination of a molecule of alcohol. The ester from a bulky alcohol is more reactive than the ester from a less hindered alcohol under the same reaction conditions due to facile ketene formation. This method is both time and cost efficient compared to previously described methods. Further studies on utilizing the thermally generated ketene intermediate is currently ongoing and will be reported in due courses.

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14. Representative experimental procedure using compound **4g** as an example: amidoxime **2e** (140 mg, 1 mmol) and *t*-butyl methyl malonate **1e** (348 mg, 2 mmol) were mixed in a test tube with a stir bar. The test tube was then placed in an oil bath and heated to 120 °C for 2 h with stirring. After the reaction was completed, the reaction mixture was applied to a silica gel column. Flash chromatography yielded compound **4g** as white solid (156 mg) in 71% yield. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.14 (1H, d, $J = 1.6$ Hz), 8.59 (1H, dd, $J = 5.1$, 1.6 Hz), 8.19 (1H, dt, $J = 8$, 1.8 Hz), 7.28 (1H, dd, $J = 8$, 4.3 Hz), 3.99 (2H, s), 3.65 (3H, s); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.9, 166.4, 165.8, 151.8, 148.2, 134.3, 123.3, 122.4, 52.7, 32.5. The spectroscopy data of other products are consistent with their structures.
15. ^{1}H NMR of compound **4k** in $CDCl_3$ showed that **4k** is a 4:1 mixture of the ketone form and its enolate form.
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