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An efficient one-pot synthesis of 3-aryl-5-methylisoxazoles from aryl aldehydes

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Dedicated with affection to Professor Theodore Cohen of University of Pittsburgh on the occasion of his 80th birthday

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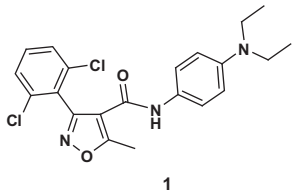
ABSTRACT

An efficient protocol for the one-pot preparation of alkyl 3-aryl-5-methylisoxazole-4-carboxylates from aryl aldehydes is described. This method is readily amenable to the large scale preparation of isoxazoles as well as the parallel synthesis of isoxazole libraries.

1. Introduction

Isoxazole derivatives have been widely studied as potential pharmaceutical agents.[1] For example, structures containing the 3-aryl-5-methylisoxazole-4-carboxamide moiety have been reported as modulators of the ghrelin receptor (**1**),[2] selective antagonists of the α_{1a} adrenergic receptor (**2**),[3] and allosteric metabotropic glutamate receptor **7** antagonists (isoxazolopyridone **3** was prepared from **4** in two steps).[4] Isoxazoles have also served as versatile building blocks in organic synthesis.[5]



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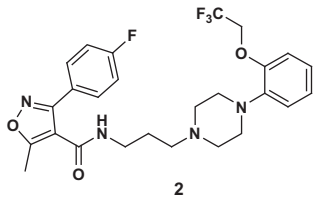

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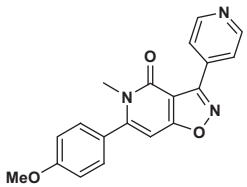

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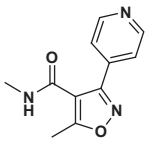

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A frequently-cited and robust synthetic route to 3-aryl-5-methylisoxazole carboxylates is the 1,3-dipolar cycloaddition of alkenes and alkynes with nitrile oxides.[5b] This procedure involves three discrete steps: (1) conversion of an aldehyde to the corresponding oxime; (2) α-chlorination of the oxime using *N*-chlorosuccinimide (NCS), usually initiated by HCl gas; and (3) reaction of the resulting hydroximinoyl chloride with a dipolarophile such as an alkyne,[6] the enolate of a β-ketoester or β-ketoamide[7] or the enamine of a β-ketoester.[8] As shown in Scheme 1 for the reaction with the enamine of a β-ketoester, a different solvent (or solvent mixture) is used in each of the three reactions: (1) water/ethanol; (2) DMF; and (3) ethanol. In practice, the oxime and hydroximinoyl chloride intermediates are usually isolated via extraction and used in the next step without further purification. Although this three-step procedure is quite general, we found that the chemistry was not amenable to the parallel synthesis of libraries of isoxazoles due to the number of extraction, filtration, and solvent evaporation steps. We sought a one-pot procedure to overcome these limitations.

Our initial breakthrough in this effort was the discovery that the final step (dipolar cycloaddition) could be carried out in an EtOH/DMF solvent mixture. This allowed us to combine the chlorination and the 1,3-dipolar cycloaddition steps and eliminate the isolation of hydroximinoyl chlorides from DMF. Our standard procedure involved adding a solution of the enamine of ethyl acetoacetate and triethylamine in ethanol to the chlorination reaction mixture.[9] Further efficiency was gained by generating the oximes in DMF rather than an ethanol/water mixture. In order to promote oxime formation, it was necessary to add triethylamine to the mixture of

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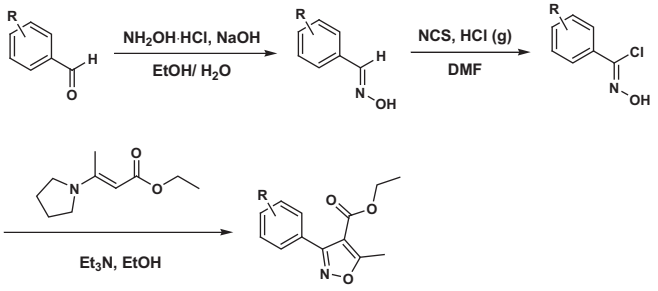
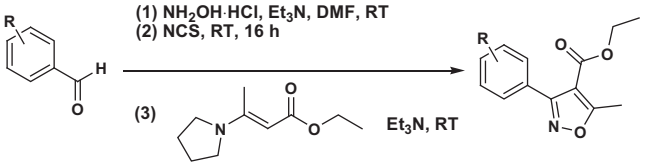


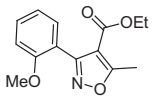
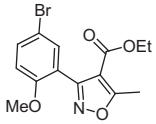
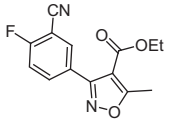
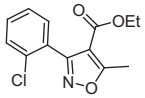
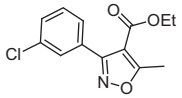
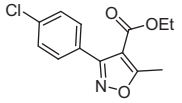
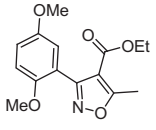
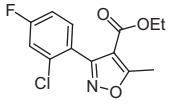
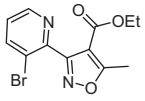
Scheme 1.

aldehyde and hydroxylamine hydrochloride in DMF. These solvent changes provided an efficient one-pot synthesis of isoxazoles from aldehydes (Eq. 1). The oxime-forming step is usually complete within 1 h at room temperature. The chlorination was done by simply adding *N*-chlorosuccinimide all at once to the oxime reaction mixture. It is not necessary to add NCS slowly in portions or use HCl gas or heat[10] to initiate the reaction and the chlorination is complete overnight. We generally use a slight excess of NCS to drive the chlorination step to completion. Finally, a solution of the enamine of ethyl acetoacetate and triethylamine in ethanol was added. The 1,3-dipolar cycloaddition can take from 2 to 16 h. All three reaction steps can be conveniently monitored by LC/MS. The overall yield of isoxazoles generated in the one-pot synthesis is usually higher than the yield obtained via the three-step procedure described previously. This is exemplified by direct comparison of the yield of the same isoxazoles (compounds **1**, 4 and **5**) synthesized by our one-pot method and that reported in Ref. [8b]. We have achieved yields very similar to those reported in the literature when we carried out the synthesis following the three-step procedure.



(1)

Table 1
Isoxazoles prepared from aldehydes by one-pot synthesis

Compd No.	Structure of product	Yield (%)[a] of one-pot syn.	Yield (%) of multi-step syn.	Purity (%)
1		93[b]	40[d], (100,78,51)	98.1
2		84[c]		99.2
3		79[c]		99.3
4		90	68[d], (96,94,75)	99.6
5		79	47[d], (69, 90,75)	99.0
6		69		98.3
7		60		99.7
8		67		99.4
9		85		98.5

[a] Isolated yields for products purified by preparative HPLC unless noted otherwise.
[b] Yield of crude product.
[c] Products purified by flash chromatography.
[d] Yields for individual steps in parentheses as reported in Ref. 8b.