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Microwave mediated synthesis of 2-aminooxazoles

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ABSTRACT

A microwave mediated synthesis of 2-aminooxazoles at 150 °C was developed, providing products with a variety of functional groups. The reaction takes 5 min and provides product with a simple precipitation at moderate to good yields without the need for recrystallization or flash chromatography.

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Introduction

The 2-aminooxazole scaffold has been found to have a wide variety of applications including the potential to treat chronic inflammatory skin disorders as a 5-lipooxygenase inhibitor [1] and treating infection caused by the human immunodeficiency virus (HIV) by acting as a potent inhibitor of HIV reverse transcriptase [2]. In addition, this scaffold can be used to synthesize inhibitors of kinase CLK1, suppressing cell growth and inducing apoptosis in cancer [3]. The related 1,3-thiazole moiety has also been used as an inhibitor of Valosin-containing protein, functioning as a potential cancer therapeutic [4]. Outside of medicinal chemistry usage, 2-aminooxazoles have also been studied as intermediates to prebiotic syntheses [5,6]. We became interested in synthesizing 2-aminooxazoles with the goal of developing potent inhibitors targeting human kinase STK16. In order to prepare a novel and diverse inhibitor library, we sought to develop a reliable and rapid method to synthesize 2-aminooxazoles.

Results and discussion

A number of reported methods exist for the preparation of 2-aminooxazoles, including the reaction of a terminal alkyne and a nitrile with a gold catalyst [7], the reaction of an isocyanide with thionyl chloride and an aldehyde [8] and the reaction of an α-bromoketone with urea [9]. However, the most common method used for the preparation of 2-aminooxazoles involves the reaction between an isothiocyanate, a β-keto azide and triphenylphosphine, as this method has been used to prepare many highly functionalized compounds [1,3,10]. Despite the popularity of this method, however, there are many aspects of the reaction which are poorly understood. It is generally assumed that the azide and triphenylphosphine react in an analogous manner to the Staudinger reaction to generate an iminophosphorane [11], which subsequently reacts with the isothiocyanate to form a carbodiimide intermediate [12], followed by an intramolecular cyclization to provide the product 2-aminooxazole (Scheme 1).

The general reported synthetic procedure for this reaction is to combine the starting reagents in a solvent (usually dioxane) and reflux until consumption of starting material is noted by TLC, then the crude material is purified through flash chromatography, providing the products with good to modest yields. It has also been

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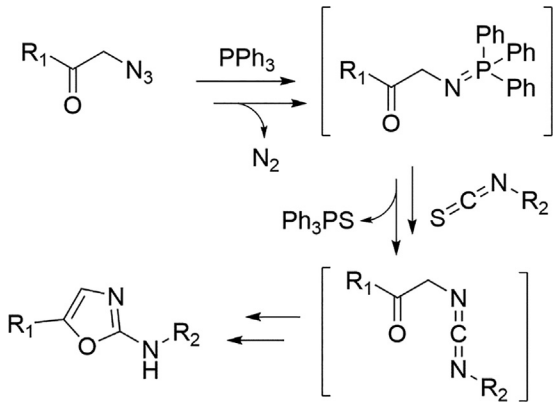
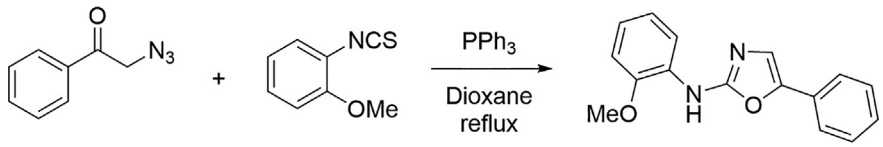


Scheme 1. Putative intermediates formed during the preparation of 2-aminooxazoles from a β-keto azide, triphenylphosphine and an isothiocyanate.

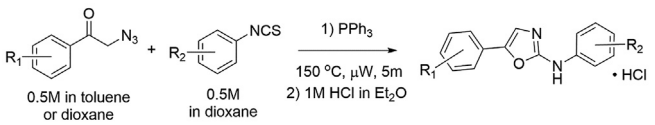
reported that lower yields are observed when electron withdrawing groups are present on the β-keto azide and when the reaction is run at room temperature (versus reflux) [12]. We were particularly interested in the effect of temperature on the reaction, as our group has used microwave heating to prepare a number of scaffolds quickly and with minimal workup, including pyrazole-5-amines [13] and tetrahydro-β-carbolines [14].

To better monitor the reaction at different temperatures, we decided to use ^{31}P NMR. The advantage of ^{31}P NMR is that the starting triphenylphosphine (^{31}P δ = -6 ppm) and the triphenylphosphine sulfide (^{31}P δ = 42 ppm) formed at the end of the reaction are both easily distinguishable. We first combined triphenylphosphine, 1-isothiocyanato-2-methoxybenzene and 2-azido-1-phenylethan-1-one in dioxane according to Scheme 2 and refluxed the solution for 30 min, at which time TLC indicated full consumption of starting materials.



Scheme 2. Synthesis of N-(2-methoxyphenyl)-5-phenyl-1,3-oxazol-2-amine for 31P NMR studies.

Table 1
2-Aminoxazoles prepared via microwave radiation.



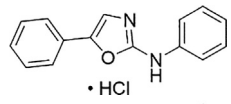
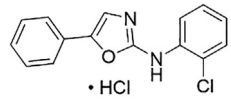
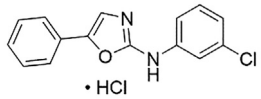
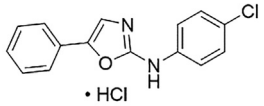
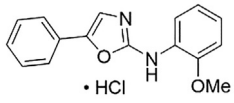
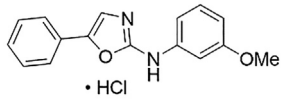
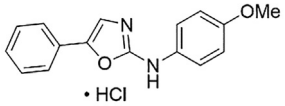
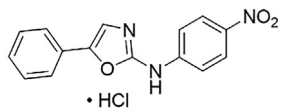
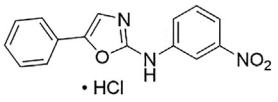
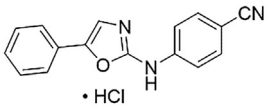
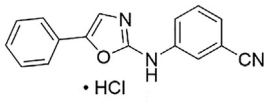
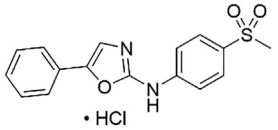
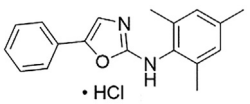
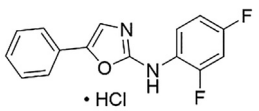
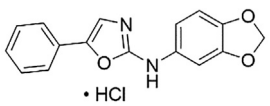
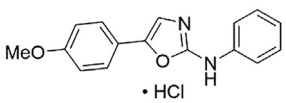
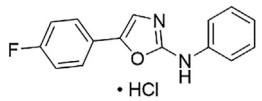
Entry	Product	Isolated Yield (%)
1		74
2		47
3		65
4		70
5		87
6		55
7		60
8		-[a]

Table 1 (*continued*)

Entry	Product	Isolated Yield (%)
9		-[a]
10		-[a]
11		-[a]
12		-[a]
13		-[a]
14		72
15		76
16		78
17		62

[a] Complex mixture of byproducts as indicated by ^{1}H NMR.

The ^{31}P NMR spectrum of the reaction solution showed a major peak at 42 ppm corresponding to triphenylphosphine sulfide, while an additional minor peak from an unidentified compound was present at 24 ppm (see supporting information). We next repeated the procedure at room temperature, monitoring by TLC until completion at 5 h. The ^{31}P NMR spectrum for the room temperature reaction was markedly different, with only a minor peak present for the triphenylphosphine sulfide side product and multiple peaks from unknown species present in the 18–34 ppm range (see supporting information). These ^{31}P NMR spectra suggested that lower temperatures lead to more unwanted side products, possibly explaining why previously reported room temperature reaction methods have led to lower yields [12]. The identity of these unwanted byproducts is unknown, but we decided to see if even higher temperatures achieved with microwave radiation could also provide the desired 2-aminooxazoles as cleanly as reflux conditions but with shorter heating periods. We were pleased to find that running the reaction described in Scheme 2 at 150 °C gave full consumption of the starting reactants within 5 min as indicated by TLC. The ^{31}P NMR spectrum of an aliquot from the microwave reaction solution was nearly identical to the ^{31}P NMR spectrum taken from the aliquot of the 30 min conventional reflux reaction, indicating successful product formation with minimal side products present (see supporting information).

Once we had our microwave heating conditions identified, we found that the product could be quickly isolated by precipitating the desired 2-aminooxazole with HCl in diethyl ether without the need for flash chromatography. In addition, we found that the reaction provided product in similar yields using toluene, acetonitrile or THF as the solvent (data not shown). However, we found the optimal solvent to be a 1:1 mixture of toluene and dioxane or pure dioxane alone, as these solvents provided a smooth heating profile in the microwave, were able to dissolve all tested reagents and minimized the pressure observed when heating (<5 bar). We found that increasing the temperature in the microwave above 150 °C did not result in significant changes in isolated yields, however we did observe significantly higher pressures as expected. Longer heating times likewise resulted in no significant changes in observed yields.

With our final procedure in hand, we proceeded to test it with a variety of substituted β-keto azides and isothiocyanates, with our results detailed in Table 1.

Entries 8–12, all of which featured a substrate with an electron withdrawing group, resulted in a complex mixture of byproducts as indicated by ^{1}H NMR and TLC, agreeing with previously observed difficulties in synthesizing 2-aminooxazoles with electron withdrawing groups [12]. A di-*ortho* substituted analogue (Entry 13) also failed to provide product, presumably due to steric issues. However, all other tested substitutions were well tolerated and provided the products in yields ranging from 47 to 87% after only 5 min of irradiation. Compared to other reported methods of synthesizing 2-aminooxazoles, this method provides a much quicker route and a simplified purification scheme.

Conclusion

The microwave reaction of an isothiocyante, a β-keto azide and triphenylphosphine at 150 °C provides 2-aminooxazoles in 5 min, with minimal work-up needed to isolate the products in moderate to good yields (47–87%). Substrates with an electron withdrawing group resulted in a complex mixture of byproducts, consistent with previous findings [12]. For products with suitable functional groups, this procedure is much quicker than previously reported procedures and utilizes a simple isolation that requires neither recrystallization nor chromatography.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2021.153555.

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