ORGANIC LETTERS

2010
Vol. 12, No. 3
616−618

# Synthesis of Polysubstituted 5-Aminooxazoles from α- Diazocarbonyl Esters and α-Isocyanoacetamides

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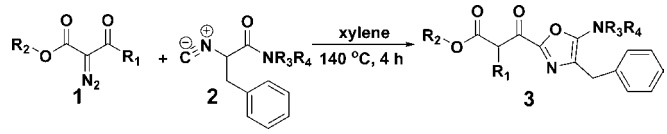
**Received December 10, 2009**

## ABSTRACT




**A novel and efficient reaction for the synthesis of 2-keto-5-aminooxazoles is developed. The entire sequence is realized by simply heating a xylene solution of α-diazocarbonyl esters and α-isocyanoacetamides without any promoters. A possible mechanism for the entire sequence is proposed.**

The oxazole group is an important heterocyclic unit that is widely present in medicinal, agrochemical, and natural products.[1,2] It is also present in applications for optical materials such as scintillant molecules and fluorescent dyes.[3] Thus, various synthetic methods of oxazole derivatives have been developed. Currently, the main synthetic methods of oxazoles include cyclodehydration reactions,[4] oxidations of oxazolines,[5] direct derivation of the parent oxazole,[6] and metal-catalyzed cross-coupling reactions.[7] The most common method for the preparation of oxazoles is the cyclodehydration, but this method provides low yields of oxazoles.[8] However, the lesser utilized methods of oxidations of oxazolines, direct derivation of the parent oxazole, and metal-catalyzed cross-coupling reactions are greatly limited by the substrate.

Isocyanide-based multicomponent reactions (IMCRs) such as the classic Passerini (P-3CR)[9] and Ugi[10] (U-4CR) reactions have been widely used for generating molecular complexity and molecular diversity.[11] Zhu et al. reported a novel multicomponent synthesis of polysubstituted 5-aminooxazoles by the reaction of isocyanoacetamides with aldehydes, amines in the presence of 1 equiv of ammonium chloride as a promoter, and its subsequent use as a chemical platform to generate new scaffolds.[12] However, the multicomponent reaction cannot occur in the absence of promoters (weak Brønsted and Lewis acids).[13] Moreover, none of the existing methods could satisfy the green-chemistry charac-

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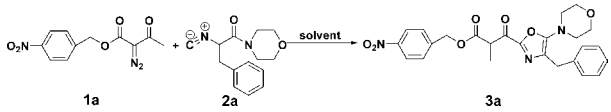
10.1021/ol902850a © 2010 American Chemical Society
**Published on Web 01/05/2010**

teristic of being ecologically benign as well as economical in atom count.[14] Thus developing a simple and effective method to synthesize polysubstituted 5-aminooxazole from simple and readily available starting materials is essential. Furthermore, the 2-keto-5-aminooxazole compounds are extraordinarily potent and selective inhibitors of fatty acid amide hydrolase (FAAH) which is the primary catabolic regulator of several bioactive lipid amides in vivo.[15] Thus we report herein a novel and efficient reaction for the synthesis of 2-keto-5-aminooxazoles from α-isocyanoacetamides and α-diazocarbonyl esters without the use of promoters. The process is economical in atom count and ecologically benign since only a molecule of nitrogen was lost in this entire sequence.

**Scheme 1.** Synthesis of 2-Keto-5-aminooxazoles




Initially. the reaction conditions were optimized using α-diazocarbonyl ester (**1a**) and α-isocyanoacetamide (**2a**) as starting substrates (Scheme 1, Table 1). When the reaction

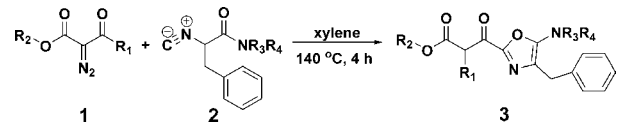
**Table 1.** Optimization of the Reaction Conditions: Synthesis of 2-Keto-5-aminooxazoles[a]

| entry | solvent | additive | temp (°C)/time (h) | yield (%)[b] |
|---|---|---|---|---|
| 1 | toluene | none | Reflux/4 | 20 |
| 2 | toluene | none | Reflux/12 | 48 |
| 3 | xylene | none | 140/4 | 88 |
| 4 | xylene | none | Reflux/4 | 87 |
| 5 | xylene | $NH_4Cl$ | 140/4 | 78 |
| 6 | xylene | LiBr | 140/4 | <5 |
| 7 | xylene | CSA | 140/4 | <5 |
| 8 | xylene | none | 140/8 | 89 |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), additive (1.0 mmol), solvent (10 mL), $N_2$. [b] The yield of the isolated product.

was carried out in toluene at reflux under nitrogen in the absence of any promoters for 4 h, it gave relatively low yields of 2-keto-5-aminooxazole (entry 1). Increasing the reaction time to 12 h did not satisfactorily increase yields (entry 2). When using xylene as solvent at 140 °C in the absence of any promoters for 4 h, the yield was raised to 88% (entry 3). A further increase in the reaction temperature somewhat decreased the yield (entry 4). We unexpectedly found that

**Table 2.** Synthesis of 2-Keto-5-aminooxazoles in the Optimal Reaction Conditions[a]




| entry | $R_1$ | $R_2$ | $NR_3R_4$ | product | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $CH_3$ | 4-$NO_2PhCH_2$ | morpholinyl | **3a** | 88 |
| 2 | $CH_3$ | $C_2H_5$ | morpholinyl | **3b** | 78 |
| 3 | Ph | $C_2H_5$ | morpholinyl | **3c** | 70 |
| 4 | $CH_3$ | $CH(CH_3)_3$ | morpholinyl | **3d** | 78 |
| 5 | $PhCH_2$ | $C_2H_5$ | morpholinyl | **3e** | 84 |
| 6 | $CH3(CH_2)_2$ | $C_2H_5$ | morpholinyl | **3f** | 73 |
| 7 | *p*-$ClC_6H_5$ | $CH_3$ | morpholinyl | **3g** | 71 |
| 8 | *p*-$CH_3C_6H_5$ | $CH_3$ | morpholinyl | **3h** | 66 |
| 9 | $CH_3$ | 4-$NO_2PhCH_2$ | piperidinyl | **3i** | 85 |
| 10 | $CH_3$ | $CH(CH_3)_3$ | piperidinyl | **3j** | 73 |
| 11 | Ph | $C_2H_5$ | piperidinyl | **3k** | 68 |
| 12 | $PhCH_2$ | $C_2H_5$ | piperidinyl | **3l** | 81 |
| 13 | $CH3(CH_2)_2$ | $C_2H_5$ | piperidinyl | **3m** | 69 |
| 14 | *p*-$ClC_6H_5$ | $CH_3$ | piperidinyl | **3n** | 67 |
| 15 | *p*-$CH_3C_6H_5$ | $CH_3$ | piperidinyl | **3o** | 63 |
| 16 | $CH_3$ | 4-$NO_2PhCH_2$ | pyrrolidinyl | **3p** | 87 |
| 17 | $PhCH_2$ | $C_2H_5$ | pyrrolidinyl | **3q** | 83 |
| 18 | $CH3(CH_2)_2$ | $C_2H_5$ | pyrrolidinyl | **3r** | 71 |
| 19 | Ph | $C_2H_5$ | pyrrolidinyl | **3s** | 69 |
| 20 | $CH_3$ | $CH(CH_3)_3$ | pyrrolidinyl | **3t** | 76 |
| 21 | *p*-$ClC_6H_5$ | $CH_3$ | pyrrolidinyl | **3u** | 63 |
| 22 | *p*-$CH_3C_6H_5$ | $CH_3$ | pyrrolidinyl | **3v** | 60 |

[a] Reaction conditions: **1a** (1.0 mmol), **2a** (1.0 mmol), solvent (10 mL), $N_2$. [b] The yield of the isolated product.

utilizing ammonium chloride (entry 5) slightly lowered the product yield, while the addition of lithium bromide and camphorsulfonic acid (CSA) was detrimental to the desired transformation (entries 6 and 7). Prolonging the reaction time to 8 h did not increase yields (entry 8). Thus, the optimal reaction condition was obtained under the conditions outlined in entry 3. This reaction occurred in xylene in the absence of any promoters, which is intriguing, as most Passerini-like reactions are sluggish and afford products in low yields unless using an acidic promoter.[16]

With the optimized conditions in hand, we next probed the generality of this reaction. A variety of starting materials including eight α-diazocarbonyl esters and three α-isocyanoacetamides were examined (Table 2). The α-diazocarbonyl esters were readily prepared from *β*-keto esters and methanesulfonyl azide according to a previous report by Taber.[17] Aliphatic and aromatic substituents of α-diazocarbonyl esters with different steric and electronic properties were tolerated in this reaction. They reacted with the α-isocyanoacetamides to provide the corresponding 2-keto-5-aminooxazoles in moderate to good isolated yields. Aro-

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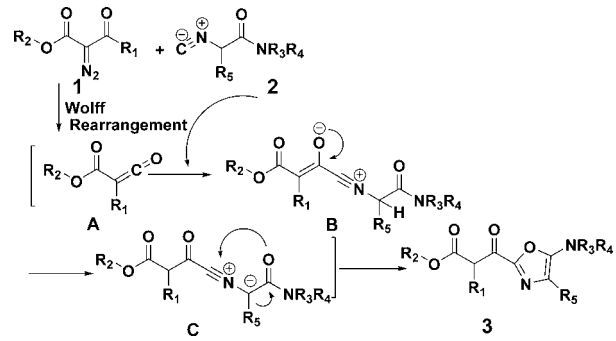
matic substitutive α-diazocarbonyl esters ($R_1$ = aryl) gave a lower yield (entries 3, 7, 8, 11, 14, 15, 19, 21, and 22). Aromatics containing an electron-withdrawing group provided higher yields than that with electron-donating groups (entries 7, 8, 14, 15, 21, and 22). Lengthening the carbon chain ($R_1$ = alkyl) decreased the yield (entries 6, 13, and 18). The benzyl group gave a good yield (entries 5, 12, and 17). The $R_2$ group had a rare effect on yields even with electronic and steric effects (entries 1, 2, and 4). The amine part of the oxazole ring can be varied by simply changing the structure of the isocyanoacetamides.[18,19] Substituents such as morpholinyl, piperidinyl, and pyrrolidinyl were successfully introduced into the C-5 position of the oxazole ring. The amino group influenced the reaction efficiency and the stability of products. 5-Piperidinyl-oxazoles are less stable than the morpholinyl and pyrrolidinyl compounds. So piperidinyl isocyanoacetamide gave lower yields than the morpholinyl and pyrrolidinyl isocyanoacetamides (entries 9−15). To the best of our knowledge, this procedure represents the first direct construction of 2-keto-5-aminooxazoles from simple and readily available starting materials. Moreover, in this entire sequence only a molecule of nitrogen was lost. After completing the reaction, the solvent was removed under reduced pressure and could be collected. Thus, the entire process is economical in atom count and ecologically benign.

On the basis of these results, we proposed the following possible mechanism for this reaction, as shown in Scheme 2. First, α-diazocarbonyl ester **1** transforms to ketene A through the Wolff rearrangement reaction.[20] Then ketene A reacts with isocyanoacetamide **2** to produce the nitrilium intermediate B. This intermediate B after tautomerization will cyclize to produce the desired 2-keto-5-aminooxazole **3**.

**Scheme 2.** Proposed Mechanism for the Synthesis of 2-Keto-5-aminooxazole




In conclusion, we have developed a novel and efficient reaction for the synthesis of 2-keto-5-aminooxazoles from α-isocyanoacetamides and α-diazocarbonyl esters. The entire sequence was realized under very simple conditions without the use of promoters. Moreover, the synthesis is economical in atom count and ecologically benign since only a molecule of nitrogen is lost in this entire sequence.

**Acknowledgment.** We thank the National Natural Science Foundation of China (No. 30772652 and No. 90813026) and National key Tech project for Major Creation of New Drugs (No. 2009ZX09501-010).

**Supporting Information Available:** Experimental procedures, characterization data, and copies of $^1$H and $^{13}$C NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL902850A

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